

Conviban

Oral solution

Topiramate 25mg / ml

1 INDICATIONS AND USAGE

1.1 Monotherapy Epilepsy

CONVIBAN is indicated as initial monotherapy for the treatment of partial-onset or primary generalized tonic-clonic seizures in patients 2 years of age and older.

1.2 Adjunctive Therapy Epilepsy

CONVIBAN is indicated as adjunctive therapy for the treatment of partial-onset seizures, primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome in patients 2 years of age and older.

1.3 Migraine

CONVIBAN is indicated for the preventive treatment of migraine in patients 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing in Monotherapy Epilepsy

Adults and Pediatric Patients 10 Years of Age and Older

The recommended dose for CONVIBAN monotherapy in adults and pediatric patients 10 years of age and older is 400 mg/day in two divided doses. The dose should be achieved by titration according to the following schedule (Table 1):

Table 1: Monotherapy Titration Schedule for Adults and Pediatric Patients 10 years and older

	Morning Dose	Evening Dose
Week 1	25 mg	25 mg
Week 2	50 mg	50 mg
Week 3	75 mg	75 mg
Week 4	100 mg	100 mg
Week 5	150 mg	150 mg
Week 6	200 mg	200 mg

Pediatric Patients 2 to 9 Years of Age

Dosing in patients 2 to 9 years of age is based on weight. During the titration period, the initial dose of CONVIBAN is 25 mg/day nightly for the first week. Based upon tolerability, the dosage can be increased to 50 mg/day (25 mg twice daily) in the second week. Dosage can be increased by 25–50 mg/day each subsequent week as tolerated. Titration to the minimum maintenance dose should be attempted over 5–7 weeks of the total titration period. Based upon tolerability and clinical response, additional titration to a higher dose (up to the maximum maintenance dose) can be attempted at 25–50 mg/day weekly increments. The total daily dose should not exceed the maximum maintenance dose for each range of body weight (Table 2).

Table 2: Monotherapy Target Total daily Maintenance Dosing for Patients 2 to 9 Years of Age

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

2.2 Dosing in Adjunctive Therapy Epilepsy

Adults (17 Years of Age and Older)

The recommended total daily dose of CONVIBAN as adjunctive therapy in adults with partial onset seizures or Lennox-Gastaut Syndrome is 200 to 400 mg/day in two divided doses, and 400 mg/day in two divided doses as adjunctive treatment in adults with primary generalized tonic-clonic seizures. CONVIBAN should be initiated at 25 to 50 mg/day, followed by titration to an effective dose in increments of 25 to 50 mg/day every week. Titrating in increments of 25 mg/day every week may delay the time to reach an effective dose. Doses above 400 mg/day have not been shown to improve responses in adults with partial-onset seizures.

Pediatric Patients 2 to 16 Years of Age

The recommended total daily dose of CONVIBAN as adjunctive therapy for pediatric patients 2 to 16 years of age with partial-onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome is approximately 5 to 9 mg/kg/day in two divided doses. Titration should begin at 25 mg/day (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses), to achieve optimal clinical response. Dose titration should be guided by clinical outcome. The total daily dose should not exceed 400 mg/day.

2.3 Dosing for the Preventive Treatment of Migraine

The recommended total daily dose of CONVIBAN as treatment for patients 12 years of age and older for the preventive treatment of migraine is 100 mg/day administered in two divided doses (Table 3). The recommended titration rate for CONVIBAN for the preventive treatment of migraine is as follows:

Table 3: Preventive Treatment of Migraine Titration Schedule for Patients 12 years and older

	Morning Dose	Evening Dose
Week 1	None	25 mg
Week 2	25 mg	25 mg
Week 3	25 mg	50 mg
Week 4	50 mg	50 mg

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

2.4 Administration Information

CONVIBAN can be taken without regard to meals.

A calibrated measuring device is recommended to measure and deliver the prescribed dose accurately. A household teaspoon or tablespoon is not an adequate measuring device.

Discard the unused portion after 90 days .

2.5 Dosing in Patients with Renal Impairment

In patients with renal impairment (creatinine clearance less than 70 mL/min/1.73 m²), one-half of the usual adult dose of CONVIBAN is recommended .

2.6 Dosing in Patients Undergoing Hemodialysis

To avoid rapid drops in topiramate plasma concentration during hemodialysis, a supplemental dose of CONVIBAN may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed .

3 DOSAGE FORMS AND STRENGTHS

CONVIBAN oral solution 25 mg/mL is supplied as Colorless to slightly yellow colored clear solution

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Myopia and Secondary Angle Closure Glaucoma Syndrome

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving topiramate. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include some or all of the following: myopia, mydriasis, anterior chamber shallowing, ocular hyperemia (redness), choroidal detachments, retinal pigment epithelial detachments, macular striae, and increased intraocular pressure. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating CONVIBAN therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in pediatric patients as well as adults. The primary treatment to reverse symptoms is discontinuation of topiramate as rapidly as possible, according to the judgment of the treating physician. Other measures, in conjunction with discontinuation of topiramate, may be helpful.

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

5.2 Visual Field Defects

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

5.3 Oligohidrosis and Hyperthermia

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

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

5.4 Metabolic Acidosis

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

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

Manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fractures. A one-year, active-controlled study of pediatric patients treated with topiramate demonstrated that topiramate decreased lumbar spine bone mineral density and that this lumbar spine bone mineral density decrease was correlated (using change from baseline for lumbar spine Z score at final visit versus lowest post-treatment serum bicarbonate) with decreased serum bicarbonate, a reflection of metabolic acidosis. Chronic metabolic acidosis in pediatric patients may also reduce growth rates, which may decrease the maximal height achieved. Long-term, open-label treatment of pediatric patients 1 to 24 months old with intractable partial epilepsy, for up to 1 year, showed reductions from baseline in length, weight, and head circumference compared to age and sex-matched normative data, although these patients with epilepsy are likely to have different growth rates than normal 1 to 24 month old pediatric patients.

Reductions in length and weight were correlated to the degree of acidosis . Topiramate treatment that causes metabolic acidosis during pregnancy can possibly produce adverse effects on the fetus and might also cause metabolic acidosis in the neonate from possible transfer of topiramate to the fetus .

Measurement of Serum Bicarbonate in Epilepsy and Migraine Patients

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

5.5 Suicidal Behavior and Ideation

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

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

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

Table 4 shows absolute and relative risk by indication for all evaluated AEDs.

Table 4: Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events per 1000 Patients	Drug Patients with Events per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

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

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

5.6 Cognitive/Neuropsychiatric Adverse Reactions

CONVIBAN can cause cognitive/neuropsychiatric adverse reactions. The most frequent of these can be classified into three general categories: 1) Cognitive-related dysfunction (e.g., confusion, psychomotor slowing, difficulty with concentration/attention, difficulty with memory, speech or language problems, particularly word-finding difficulties); 2) Psychiatric/behavioral disturbances (e.g., depression or mood problems); and 3) Somnolence or fatigue.

Adult Patients

Cognitive-Related Dysfunction

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

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

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

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

Psychiatric/Behavioral Disturbances

Psychiatric/behavioral disturbances (e.g., depression, mood) were dose-related for both the adjunctive epilepsy and migraine populations.

Somnolence/Fatigue

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

Pediatric Patients

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

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

The risk for cognitive/neuropsychiatric adverse reactions was dose-dependent, and was greatest at the

highest dose (200 mg). This risk for cognitive/neuropsychiatric adverse reactions was also greater in younger patients (6 to 11 years of age) than in older patients (12 to 17 years of age). The most common cognitive/neuropsychiatric adverse reaction in these trials was difficulty with concentration/attention. Cognitive adverse reactions most commonly developed during titration and sometimes persisted for various durations after completion of titration.

5.7 Fetal Toxicity

Topiramate can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate in utero have an increased risk of major congenital

malformations, including but not limited to cleft lip and/or cleft palate (oral clefts) and for being small for gestational age (SGA). When multiple species of pregnant animals received topiramate at clinically relevant doses, structural malformations, including craniofacial defects, and reduced fetal weights occurred in offspring.

Consider the benefits and the risks of topiramate when administering this drug in women of childbearing potential, particularly when topiramate is considered for a condition not usually associated with permanent injury or death. Topiramate should be used during pregnancy only if the potential benefit outweighs the potential risk. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

5.8 Withdrawal of Antiepileptic Drugs

In patients with or without a history of seizures or epilepsy, antiepileptic drugs, including topiramate, should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency. In situations where rapid withdrawal of topiramate is medically required, appropriate monitoring is recommended.

5.9 Decrease in Bone Mineral Density

Results of a one-year active-controlled study in pediatric patients (N=63) demonstrated negative effects of topiramate monotherapy on bone mineral acquisition via statistically significant decreases in bone mineral density (BMD) measured in lumbar spine and in total body less head. Twenty-one percent of topiramate-treated patients experienced clinically important reductions in BMD (Z score change from baseline of -0.5 or greater) compared to 0 patients in the control group. Although decreases in BMD occurred across all pediatric age subgroups, patients 6 to 9 years of age were most commonly affected. The sample size and study duration were too small to determine if fracture risk is increased. Decreased BMD in the lumbar spine was correlated with decreased serum bicarbonate, which commonly occurs with topiramate treatment and reflects metabolic acidosis, a known cause of increased bone resorption. Although small decreases in some markers of bone metabolism (e.g., serum alkaline phosphatase, calcium, phosphorus, and 1,25-dihydroxyvitamin D) occurred in topiramate-treated patients, more significant decreases in serum parathyroid hormone and 25-hydroxyvitamin D, hormones involved in bone metabolism, were observed, along with an increased excretion of urinary calcium.

5.10 Negative Effects on Growth (Height and Weight)

Results of a one-year active-controlled study of pediatric patients (N=63) demonstrated negative effects of topiramate monotherapy on growth (i.e., height and weight). Although continued growth was observed in both treatment groups, the topiramate group showed statistically significant reductions in mean annual change from baseline in body weight compared to the control group. A similar trend of attenuation in height velocity and height change from baseline was also observed in the topiramate group compared to the control group. Negative effects on weight and height were seen across all topiramate age subgroups.

Growth (height and weight) of children receiving prolonged topiramate therapy should be carefully

monitored.

5.11 Serious Skin Reactions

Serious skin reactions (Stevens-Johnson Syndrome [SJS] and Toxic Epidermal Necrolysis [TEN])

have been reported in patients receiving topiramate. CONVIBAN should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered. Inform patients about the signs of serious skin reactions.

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

CONVIBAN treatment can cause hyperammonemia with or without encephalopathy . The risk for hyperammonemia with topiramate appears dose-related. Hyperammonemia has been reported more frequently when topiramate is used concomitantly with valproic acid. Post-marketing cases of hyperammonemia with or without encephalopathy have been reported with topiramate and valproic acid in patients who previously tolerated either drug alone .

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 the preventive treatment of migraine 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 treatment or an interaction of concomitant topiramate 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.

5.13 Kidney Stones

CONVIBAN increases the risk of kidney stones. During adjunctive epilepsy trials, the risk for kidney stones in 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. Topiramate is not approved for treatment of epilepsy in pediatric patients less than 2 years old .

Topiramate is a carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors can promote stone formation by reducing urinary citrate excretion and by increasing urinary pH . The concomitant use of topiramate 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.

An increase in urinary calcium and a marked decrease in urinary citrate was observed in topiramate-treated pediatric patients in a one-year active-controlled study . This increased ratio of urinary calcium/citrate increases the risk of kidney stones and/or nephrocalcinosis.

5.14 Hypothermia with Concomitant Valproic Acid Use

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

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 Syndrome . Visual Field Defects .
- Oligohidrosis and Hyperthermia .
- Metabolic Acidosis .
- Suicidal Behavior and Ideation .
- Cognitive/Neuropsychiatric Adverse Reactions .
- Decrease of Bone Mineral Density .
- Negative Effects on Growth (Height and Weight) .
- Serious Skin Reactions .
- Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid [VPA] Use) .
- Kidney Stones.
- Hypothermia with Concomitant Valproic Acid (VPA) Use .

6.1 Clinical Trials Experience

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

The safety data described below were obtained from clinical trials of patients treated with topiramate tablets or sprinkle capsules .

Monotherapy Epilepsy

Adults 16 Years of Age and Older

The most common adverse reactions in the controlled clinical trial (Study 1) that occurred in adults in the 400 mg/day topiramate group and at an incidence higher ($\geq 10\%$) than in the 50 mg/day group

were: paresthesia, weight loss and anorexia (see Table 5).

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 ($\geq 2\%$ 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 to 15 Years of Age

The most common adverse reactions in the controlled clinical trial that occurred in pediatric patients in the 400 mg/day topiramate group and at an incidence higher ($\geq 10\%$) than in the 50 mg/day group were fever and weight loss (see Table 5).

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 ($\geq 2\%$ more frequent than low-dose 50 mg/day topiramate) adverse reactions resulting in discontinuation were difficulty with concentration/attention, fever, flushing, and confusion.

Table 5 presents the incidence of adverse reactions occurring in at least 3% of adult and pediatric patients treated with 400 mg/day topiramate and occurring with greater incidence than 50 mg/day topiramate.

Adverse Reactions in the High Dose Group as Compared to the Low Dose Group, in Monotherapy Epilepsy Trial in Adult and Pediatric Patients

Body as a Whole- General Disorders

Asthenia

Fever

Leg Pain

Central & Peripheral Nervous System Disorders

Paresthesia

Dizziness

Ataxia

Hypoesthesia

Hypertonia

Involuntary muscle contractions

Vertigo

Gastro-Intestinal System Disorders

Constipation

Diarrhea

Gastritis

Dry mouth

Liver and Biliary System Disorders

Increase in Gamma-GT

Metabolic and Nutritional Disorders

Weight loss

Platelet, Bleeding & Clotting Disorders

Epistaxis

Psychiatric Disorders

Anorexia

Anxiety
Cognitive problems
Confusion
Depression
Difficulty with concentration or attention
Difficulty with memory
Insomnia
Decrease in libido
Mood problems
Personality disorder (behavior problems)
Psychomotor slowing
Somnolence

Red Blood Cell Disorders

Anemia

Reproductive Disorders, Female

Intermenstrual bleeding
Vaginal hemorrhage

Resistance Mechanism Disorders

Infection
Viral infection

Respiratory System Disorders

Bronchitis
Upper respiratory tract infection
Rhinitis
Sinusitis

Skin and Appendages Disorders

Alopecia
Pruritus
Rash
Acne

Special Senses Other, Disorders

Taste perversion

Urinary System Disorders

Cystitis
Micturition frequency
Renal calculus
Urinary incontinence

Vascular (Extracardiac) Disorders

Flushing

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 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 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 ($\geq 10\%$) than in the placebo group were: dizziness, speech disorders/related speech problems, somnolence, nervousness, psychomotor slowing, and vision abnormal.

Table 6 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 mg – 1000 mg daily) compared to the incidence of these adverse reactions at the recommended dosing (200 mg to 400 mg daily) range.

Most Common Adverse Reactions in Pooled Placebo-Controlled, Adjunctive Epilepsy Trials in Adults *

Body as a Whole-General Disorders

Fatigue
Asthenia
Back pain
Chest pain
Influenza-like symptoms

Central & Peripheral Nervous System Disorders

Dizziness
Ataxia
Speech disorders/Related speech problems

Paresthesia
Nystagmus
Tremor
Language problems
Coordination abnormal
Gait abnormal

Gastro-Intestinal System Disorders

Nausea
Dyspepsia
Abdominal pain
Constipation

Metabolic and Nutritional Disorders

Weight loss

Psychiatric Disorders

Somnolence
Nervousness
Psychomotor slowing
Difficulty with memory
Confusion
Anorexia
Difficulty with concentration/attention
Mood problems

Agitation
Aggressive reaction
Emotional lability
Cognitive problems

Reproductive Disorders

Breast pain

Respiratory System Disorders

Rhinitis
Pharyngitis
Sinusitis

Vision Disorders

Vision abnormal
Diplopia

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

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

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 topiramate at dosages of 5 to 9 mg/kg/day (recommended dose 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 topiramate group with an incidence higher ($\geq 10\%$) than in the placebo group were: fatigue and somnolence.

below 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 dose range) of topiramate and was greater than placebo incidence.

Adverse Reactions in Pooled Placebo-Controlled, Adjunctive Epilepsy Trials in Pediatric Patients 2 to 15 Years of Age^{*,†}

Body as a Whole-General Disorders

Fatigue
Injury

Central & Peripheral Nervous System Disorders

Gait abnormal
Ataxia
Hyperkinesia
Dizziness
Speech disorders/Related speech problems

Gastro-Intestinal System Disorders

Nausea
Saliva increased
Constipation
Gastroenteritis

Metabolic and Nutritional Disorders

Weight loss

Platelet, Bleeding, & Clotting Disorders

Purpura

Epistaxis

Psychiatric Disorders

Somnolence

Anorexia

Nervousness

Personality disorder (behavior problems)

Difficulty with concentration/attention

Aggressive reaction

Insomnia

Difficulty with memory

Confusion

Psychomotor slowing

Resistance Mechanism Disorders

Infection viral

Respiratory System Disorders

Pneumonia

Skin and Appendages Disorders

Skin disorder

Urinary System Disorders

Urinary incontinence

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

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

None of the pediatric patients who received topiramate adjunctive therapy at 5 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 clinical trials for the preventive treatment of migraine (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 topiramate 100 mg in the clinical trials for the preventive treatment of migraine of predominantly adults that were seen at an incidence higher ($\geq 5\%$) than in the placebo group were: paresthesia, anorexia, weight loss, taste perversion, diarrhea, difficulty with memory, hypoesthesia, and nausea.

Below includes those adverse reactions that occurred in the placebo-controlled trials where the incidence in any topiramate treatment 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 daily) compared to the incidence of these adverse reactions at the recommended dosing (100 mg daily).

Adverse Reactions in Pooled, Placebo-Controlled, Migraine in Adults ^{*,†}

Body as a Whole-General Disorders

Fatigue

Injury

Central & Peripheral Nervous System Disorders

Paresthesia

Dizziness

Hypoesthesia

Language problems

Gastro-Intestinal System Disorders

Nausea

Diarrhea

Abdominal pain

Dyspepsia

Dry mouth

Gastroenteritis

Metabolic and Nutritional Disorders

Weight loss

Musculoskeletal System Disorders

Arthralgia

Psychiatric Disorders

Anorexia

Somnolence

Difficulty with memory

Insomnia

Difficulty with concentration/attention

Mood problems

Anxiety

Depression

Nervousness

Confusion

Psychomotor slowing

Reproductive Disorders, Female

Menstrual disorder

Reproductive Disorders, Male

Ejaculation premature

Resistance Mechanism Disorders

Viral infection

Respiratory System Disorders

Upper respiratory tract infection

Sinusitis

Pharyngitis

Coughing

Bronchitis

Dyspnea

Skin and Appendages Disorders

Pruritus

Special Sense Other, Disorders

Taste perversion

Urinary System Disorders

Urinary tract infection

Vision Disorders

Blurred vision ‡

* Includes 35 adolescent patients age 12 to 15 years.

† 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.

‡ Blurred vision was the most common term considered as vision abnormal. Blurred vision was an included term that accounted for >50% of reactions coded as vision abnormal, a preferred term.

Of the 1,135 patients exposed to topiramate in the adult placebo-controlled studies, 25% of topiramate-treated patients discontinued due to adverse reactions, compared to 10% of the 445 placebo-treated patients. The adverse reactions associated with discontinuing therapy in the topiramate-treated patients included paresthesia (7%), fatigue (4%), nausea (4%), difficulty with concentration/attention (3%), insomnia (3%), anorexia (2%), and dizziness (2%).

Patients treated with topiramate 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, topiramate 50, 100, and 200 mg groups, respectively.

Pediatric Patients 12 to 17 Years of Age

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

In four, fixed-dose, double-blind clinical trials for the preventive treatment of migraine in topiramate-treated pediatric patients 12 to 17 years of age, the most common adverse reactions with topiramate 100 mg that were seen at an incidence higher ($\geq 5\%$) than in the placebo group were: paresthesia, upper respiratory tract infection, anorexia, and abdominal pain. Below shows adverse reactions from the pediatric trial in which 103 pediatric patients were treated with placebo or 50 mg or 100 mg of topiramate, and three predominantly adult trials in which 49 pediatric patients (12 to 17 years of age) were treated with placebo or 50 mg, 100 mg or 200 mg of topiramate. Table 9 also shows adverse reactions in pediatric patients in the controlled migraine trials when the incidence in a topiramate dose group was at least 5 % or higher and greater than the incidence of placebo. Many adverse reactions shown in Table 9 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 topiramate dosing (200 mg daily) compared to the incidence of these adverse reactions at the recommended dosing (100 mg daily).

Adverse Reactions in Pooled Double-Blind Studies for the Preventive Treatment of Migraine in Pediatric Patients 12 to 17 Years of Age^{*,†,‡}

Body as a Whole-General Disorders

Fatigue

Fever

Central & Peripheral Nervous System Disorders

Paresthesia

Dizziness

Gastro-Intestinal System Disorders

Abdominal pain

Nausea

Metabolic and Nutritional Disorders

Weight loss

Psychiatric Disorders

Anorexia

Somnolence

Insomnia

Resistance Mechanism Disorders

Infection viral

Respiratory System Disorders

Upper respiratory tract infection

Rhinitis

Sinusitis

Coughing

Special Sense Other, Disorders

Taste perversion

Vision Disorders

Conjunctivitis

* 35 adolescent patients aged 12 to <16 years were also included in adverse reaction assessment for adults (Tables 11 and 12)

† Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events.

‡ Included studies MIG-3006, MIGR-001, MIGR-002 and MIGR-003

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

Increased Risk for Bleeding

Topiramate, the active ingredient in 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, topiramate was associated with changes in several clinical laboratory analytes in randomized, double-blind, placebo-controlled studies. 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 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 topiramate (vs placebo). Topiramate is not indicated for partial-onset seizures in pediatric patients less than 2 years of age.

In pediatric patients (ranging from 6–17 years of age) receiving topiramate for the preventive treatment of migraine, there was an increased incidence for an increased result (relative to normal analyte reference range) associated with 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. Topiramate is not indicated for the preventive treatment of migraine 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 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, hyperammonemia, hyperammonemic encephalopathy, hypothermia with concomitant valproic acid.

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, nephrocalcinosis.

Vision Disorders: acute myopia, secondary angle closure glaucoma, maculopathy.

Hematological Disorders: decrease of the International Normalized Ratio (INR) or prothrombin time when given concomitantly with vitamin K antagonist anticoagulant medications such as warfarin.

7 DRUG INTERACTIONS

7.1 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.

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.

7.2 Other Carbonic Anhydrase Inhibitors

Concomitant use of CONVIBAN, a carbonic anhydrase inhibitor, with any other carbonic anhydrase inhibitor (e.g., zonisamide or acetazolamide) may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. Therefore, patients given CONVIBAN concomitantly with another carbonic anhydrase inhibitor should be monitored particularly closely for the appearance or worsening of metabolic acidosis.

7.3 CNS Depressants

Concomitant administration of topiramate and alcohol or other CNS depressant drugs 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, CONVIBAN should be used with extreme caution if used in combination with alcohol and other CNS depressants.

7.4 Contraceptives

The possibility of decreased contraceptive efficacy and increased breakthrough bleeding may occur in patients taking combination oral contraceptive products with topiramate. Patients taking estrogen containing or progestin-only contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding.

7.5 Hydrochlorothiazide (HCTZ)

Topiramate C_{max} and AUC increased when HCTZ was added to topiramate. The clinical significance of this change is unknown. The addition of HCTZ to topiramate may require a decrease in the topiramate dose.

7.6 Pioglitazone

A decrease in the exposure of pioglitazone and its active metabolites were noted with the concurrent use of pioglitazone and topiramate in a clinical trial. The clinical relevance of these observations is unknown; however, when topiramate is added to pioglitazone therapy or pioglitazone is added to topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

7.7 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 topiramate.

7.8 Amitriptyline

Some patients may experience a large increase in amitriptyline concentration in the presence of topiramate and any adjustments in amitriptyline dose should be made according to the patient's clinical response and not on the basis of plasma levels.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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 an increased risk of major congenital malformations, including but not limited to cleft lip and/or cleft palate (oral clefts) and for being small for gestational age (SGA). SGA has been observed at all doses and appears to be dose-dependent. The prevalence of SGA is greater in infants of women who received higher doses of topiramate during pregnancy. In addition, the prevalence of SGA in infants of women who continued topiramate use until later in pregnancy is higher compared to the prevalence in infants of women who stopped topiramate use before the third trimester.

In multiple animal species, topiramate produced developmental toxicity, including increased incidences of fetal malformations, in the absence of maternal toxicity at clinically relevant doses.

All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

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, 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.

Topiramate treatment can cause metabolic acidosis. 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. Newborns of mothers treated with topiramate should be monitored for metabolic acidosis because of transfer of topiramate to the fetus and possible occurrence of transient metabolic acidosis following birth.

Based on limited information, topiramate has also been associated with pre-term labor and premature delivery.

developmental toxicity in mice was not identified. The lowest dose tested, which was associated with

8.2 Lactation

Risk Summary

Topiramate is excreted in human milk. The effects of topiramate on milk production are unknown. Diarrhea and somnolence have been reported in breastfed infants whose mothers receive topiramate treatment.

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

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 of oral clefts and SGA.

8.4 Pediatric Use

Adjunctive Treatment for Epilepsy

Pediatric Patients 2 Years of Age and Older

The safety and effectiveness of Convivan as adjunctive therapy for the treatment of partial-onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome have been established in pediatric patients 2 years of age and older

Pediatric Patients Below the Age of 2 Years

Safety and effectiveness 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 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 were assessed. After 20 days of double-blind treatment, topiramate (at fixed doses of 5, 15, and 25 mg/kg/day) did not demonstrate efficacy compared with placebo in controlling seizures.

In general, the adverse reaction profile for 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/toxicities (not previously observed in older pediatric patients and adults; i.e., growth/length retardation, certain clinical laboratory abnormalities, and other adverse reactions/toxicities 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 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.

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. The significance of these findings is uncertain.

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. 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.

Treatment with topiramate for up to 1 year was associated with reductions in Z SCORES for length, weight, and head circumference.

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).

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 topiramate treatment, because the background mortality rate for a similar, significantly refractory, young pediatric population (1–24 months) with partial epilepsy is not known.

Monotherapy Treatment for Epilepsy

The safety and effectiveness of EPRONTIA as monotherapy for the treatment of partial-onset seizures or primary generalized tonic-clonic seizures have been established in pediatric patients aged 2 years and older.

Pediatric Patients 2 Years of Age and Older

A one-year, active-controlled, open-label study with blinded assessments of bone mineral density (BMD) and growth in pediatric patients 4 to 15 years of age, including 63 patients with recent or new onset of epilepsy, was conducted to assess effects of topiramate (N=28, 6-15 years of age) versus levetiracetam (N=35, 4-15 years of age) monotherapy on bone mineralization and on height and weight, which reflect growth. Effects on bone mineralization were evaluated via dual-energy X-ray absorptiometry and blood markers. Table 10 summarizes effects of topiramate at 12 months for key safety outcomes including BMD, height, height velocity, and weight. All Least Square Mean values for topiramate and the comparator were positive. Therefore, the Least Square Mean treatment differences shown reflect a topiramate-induced attenuation of the key safety outcomes. Statistically significant effects were observed for decreases in BMD (and bone mineral content) in lumbar spine and total body less head and in weight. Subgroup analyses according to age demonstrated similar negative effects for all key safety outcomes (i.e., BMD, height, weight).

Table 10: Summary of Topiramate Treatment Difference Results at 12 Months for Key Safety Outcomes

Safety Parameter	Treatment Difference in Least Square Means (95 % Confidence Interval)
Annual Change in BMD Lumbar Spine (g/cm ²)	-0.036 (-0.058, -0.014)
Annual Change in BMD TBLH* (g/cm ²)	-0.026 (-0.039, -0.012)
Annual Change in Height (cm) (4-9 years, Primary Analysis Population for Height) **	-0.84 (-2.67, 0.99)
Annual Change in Height (cm) (4-15 years)	-0.75 (-2.21, 0.71)
Annual Change in Height (cm) (10-15 years)	-1.01 (-3.64, 1.61)
Height Velocity (cm/year) (4-9 years)	-1.00 (-2.76, 0.76)
Height Velocity (cm/year) (4-15 years)	-0.98 (-2.33, 0.37)
Height Velocity (cm/year) (10-15 years)	-0.96 (-3.24, 1.32)
Annual Change in Weight (kg)	-2.05 (-3.66, -0.45)
* TBLH=total body less head	
** Whereas no patients were randomized to 2-5 year age subgroup for topiramate, 5 patients (4-5 years) were randomized to the active control group.	

Metabolic acidosis (serum bicarbonate < 20 mEq/L) was observed in all topiramate-treated patients at some time in the study. Over the whole study, 76% more topiramate-treated patients experienced persistent metabolic acidosis (i.e., 2 consecutive visits with or final serum bicarbonate < 20 mEq/L) compared to levetiracetam-treated patients. Over the whole study, 35% more topiramate-treated patients experienced a markedly abnormally low serum bicarbonate (i.e., absolute value < 17 mEq/L and ≥ 5 mEq/L decrease from pre-treatment), indicating the frequency of more severe metabolic acidosis, compared to levetiracetam-treated patients. The decrease in BMD at 12 months was correlated with decreased serum bicarbonate, suggesting that metabolic acidosis was at least a partial factor contributing to this adverse effect on BMD.

Topiramate-treated patients exhibited an increased risk for developing an increased serum creatinine and an increased serum glucose above the normal reference range compared to control patients.

Pediatric Patients Below the Age of 2 Years

Safety and effectiveness in patients below the age of 2 years have not been established for the monotherapy treatment of epilepsy.

Preventive Treatment of Migraine in Pediatric Patients 12 to 17 Years of Age

Safety and effectiveness of topiramate for the preventive treatment 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 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, 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 for the preventive treatment of migraine 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 the preventive treatment of migraine in pediatric patients 12 to 17 years of age is demonstrated for a 100 mg daily dose in Study 13. Efficacy of topiramate (2 to 3 mg/kg/day) for the preventive treatment of migraine 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 topiramate, the most common adverse reactions with 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.

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.

Markedly abnormally low serum bicarbonate values indicative of metabolic acidosis were reported in topiramate-treated pediatric migraine patients.

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.

Notable changes (increases and decreases) from baseline in systolic blood pressure, diastolic blood pressure, and pulse were observed occurred more commonly in pediatric patients treated with topiramate compared to pediatric patients treated with placebo.

Pediatric Patients Below the Age of 12 Years of Age

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

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 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 placebo treated patients.

The risk for cognitive adverse reaction was greater in younger patients (6 to 11 years of age) than in older patients (12 to 17 years of age).

8.5 Geriatric Use

In clinical trials, 3% of patients were over age 60. No age-related differences in effectiveness or adverse effects were evident. However, clinical studies of topiramate did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently than younger subjects. Dosage adjustment may be necessary for elderly with age-related renal impairment (creatinine clearance rate $<70 \text{ mL/min/1.73 m}^2$) resulting in reduced clearance.

8.6 Renal Impairment

The clearance of topiramate is reduced in patients with moderate (creatinine clearance 30 to $69 \text{ mL/min/1.73 m}^2$) and severe (creatinine clearance $<30 \text{ mL/min/1.73 m}^2$) renal impairment. A dosage adjustment is recommended in patients with moderate or severe renal impairment.

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.

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.

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

In the event of overdose, Topiramate should be discontinued and general supportive treatment given until clinical toxicity has been diminished or resolved. Hemodialysis is an effective means of removing topiramate from the body.

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

The precise mechanisms by which topiramate exerts its anticonvulsant and preventive migraine effects are unknown; however, preclinical studies have revealed four properties that may contribute to topiramate's efficacy for epilepsy and the preventive treatment of migraine. 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.

11.2 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 GABAA 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 the preventive treatment of migraine. 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.

11.3 Pharmacokinetics

Peak topiramate plasma concentrations (C_{max}) occurred at approximately 0.5 hour after oral administration of Topiramate in healthy male subjects under fasting conditions. Oral administration of Topiramate with a high-fat and high calorie meal did not affect topiramate AUC_{0-t} and AUC_{0-∞}, but lowered the C_{max} by 28% and delayed the T_{max} by 5 hours. Overall, the impact of food-intake on topiramate pharmacokinetics is not expected to be clinically significant, and therefore, Topiramate can be administered without regard to food.

The pharmacokinetics of topiramate are linear with dose proportional increases in plasma concentration over the dose range studied (200 to 800 mg/day). The mean plasma elimination half-life is 21 hours after single or multiple doses. Steady-state is thus reached in about 4 days in patients with normal renal function. Topiramate is 15% to 41% bound to human plasma proteins over the blood concentration range of 0.5 to 250 µg/mL. The fraction bound decreased as blood concentration increased.

Carbamazepine and phenytoin do not alter the binding of topiramate. Sodium valproate, at 500 µg/mL (a concentration 5 to 10 times higher than considered therapeutic for valproate) decreased the protein binding of topiramate from 23% to 13%. 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 to 30 mL/min in adults following oral administration.

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/1.73 m²) and by 54% in subjects with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²) compared to subjects with normal renal function (creatinine clearance >70 mL/min/1.73 m²).

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 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.

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 .

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

Pediatric Pharmacokinetics

Pharmacokinetics of topiramate were evaluated in patients age 2 to <16 years. Patients received either no or a combination of other antiepileptic drugs. A population pharmacokinetic model was developed based on pharmacokinetic data from relevant topiramate clinical studies. This dataset contained data from 1217 subjects including 258 pediatric patients age 2 to <16 years (95 pediatric patients <10 years of age).

Pediatric patients on adjunctive treatment exhibited a higher oral clearance (L/h) of topiramate compared to patients on monotherapy, presumably because of increased clearance from concomitant enzyme inducing antiepileptic drugs. In comparison, topiramate clearance per kg is greater in pediatric patients than in adults and in young pediatric patients (down to 2 years) than in older pediatric patients. Consequently, the plasma drug concentration for the same mg/kg/day dose would be lower in pediatric patients compared to adults and 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Composition:

Each 1 ml oral solution contains:

Active ingredients:

Topiramate 25 mg

Inactive Ingredients

Methylparaben base

propylparaben base

Sucralose

Strawberry liquid flavor

Polyethylene Glycol 400

Glycerin

16.2 Shelf life:

See outer pack

16.3 Storage and Handling

Store at temperature not exceeding 30 °C. & at temperature below 30 °C for 3 months after first opening

Discard any unused portion after 3 months after first opening .

16.4 Pack

Carton box containing an amber (type III) glass bottle containing 120 ml oral solution , with white polypropylene closure cap containing white solid PE foam (low density polyethylene and carbon dioxide) inside + 5 ml graduated disposable plastic syringe composed of 3 parts with tip and plastic pierced stopper and insert leaflet.

Applicant & Manufacturer:

Marcyrl Pharmaceutical Industries