Do not print pink colour line.

- Space for 15 Digit Sequential 2D Data matrix Barcode shall be printed by the vendor.
- 2D data matrix should be minimum 8mm to 10mm height & width.
- 2D data matrix should be printed in the middle of the blank space in the folded Outsert.

Between text matter to 2D Code the blank space should be min. 5mm.

Position / Orientation shall be changed depending upon the Printer's Machine suitability.

Topiramate Capsules (Sprinkle)
1054468

Topiramate Capsules (Sprinkle)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TOPIRAMATE CAPSULES (SPRINKLE) safely and effectively. See full prescribing information for TOPIRAMATE CAPSULES (SPRINKLE).

TOPIRAMATE capsules (sprinkle), for oral use
Initial U.S. Approval: 1996

----------------------RECENT MAJOR CHANGES-----------------

Contraindications (4) 3/2026
Warnings and Precautions (5.11, 5.13) 3/2026

---------------------INDICATIONS AND USAGE----------------

Topiramate is indicated for:

- Epilepsy: initial monotherapy for the treatment of partial-onset or primary generalized tonic-clonic seizures in patients 2 years of age and older (1.1); adjunctive therapy for the treatment of partial-onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome in patients 2 years of age and older (1.2)
- Preventive treatment of migraine in patients 12 years of age and older (1.3)

----------------DOSAGE AND ADMINISTRATION----------------

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

----------------DOSAGE FORMS AND STRENGTHS-------------

- Capsules (Sprinkle): 15 mg, 25mg, and 50 mg (3)

----------------------CONTRAINDICATIONS---------------------

History of hypersensitivity reaction to topiramate, or any of the inactive ingredients of topiramate (4, 5.13)

---------------WARNINGS AND PRECAUTIONS-----------------

- Acute myopia and secondary angle closure glaucoma: can lead to permanent visual loss; discontinue topiramate as soon as possible (5.1)
- Visual field defects: consider discontinuation of topiramate (5.2)
- Oligohidrosis and hyperthermia: monitor decreased sweating and increased body temperature, especially in pediatric patients (5.3)
- Metabolic acidosis: baseline and periodic measurement of serum bicarbonate is recommended; consider dose reduction or discontinuation of topiramate if clinically appropriate (5.4)
- Suicidal behavior and ideation: antiepileptic drugs increase the risk of suicidal behavior or ideation (5.5)
- Cognitive/neuropsychiatric adverse reactions: use caution when operating machinery including cars; depression and mood problems may occur (5.6)
- Fetal Toxicity: use during pregnancy can cause major congenital malformations, including but not limited to cleft lip and/or palate, and being small for gestational age (5.7)
- Withdrawal of AEDs: withdraw topiramate gradually (5.8)
- Decrease in Bone Mineral Density: has been shown to decrease bone mineral density and bone mineral content in pediatric patients (5.9)
- Negative effects on growth (height and weight): may slow height increase and weight gain; carefully monitor children receiving prolonged therapy (5.10)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity, serious skin reactions (SJS or TEN), anaphylaxis, and angioedema: Discontinue topiramate if an alternative etiology cannot be established (5.11, 5.12, 5.13)
- Hyperammonemia/encephalopathy: measure ammonia if encephalopathic symptoms occur (5.14)
- Kidney stones: avoid use with other carbonic anhydrase inhibitors, drugs causing metabolic acidosis, or in patients on a ketogenic diet (5.15)
- Hypothermia has been reported with and without hyperammonemia during topiramate treatment with concomitant valproic acid use (5.16)

------------------------ADVERSE REACTIONS---------------------

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

Migraine: Most common (≥5% more frequent than placebo) adverse reactions in adult and pediatric patients were: paresthesia, anorexia, weight loss, difficulty with memory, taste perversion, diarrhea, hypoesthesia, nausea, abdominal pain and upper respiratory tract infection (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Strides Pharma Inc. at 1-877-244-9825 or go to www.strides.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------------------DRUG INTERACTIONS----------------------

- Contraceptives: decreased contraceptive efficacy and increased breakthrough bleeding, especially at doses greater than 200 mg/day (7.4)
- Monitor lithium levels if lithium is used with high-dose topiramate (7.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Monotherapy Epilepsy

Topiramate 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

Topiramate 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

Topiramate 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 topiramate 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 topiramate 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 topiramate 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. Topiramate 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 topiramate 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 topiramate 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 topiramate for the preventive treatment of migraine is as follows:

Table 3: Preventive Treatment of Migraine Titration Schedule for Patients 12 Years of Age 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

Topiramate can be taken without regard to meals.

Topiramate Capsules (Sprinkle)

Topiramate capsules (sprinkle) may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoon) of soft food. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use.

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 topiramate is recommended *[see Use in Specific Populations (8.5, 8.6), Clinical Pharmacology (12.3)]*.

2.6 Dosing in Patients Undergoing Hemodialysis

To avoid rapid drops in topiramate plasma concentration during hemodialysis, a supplemental dose of topiramate may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Topiramate Capsules (Sprinkle) are available containing 15 mg, 25 mg or 50 mg of topiramate, USP.

- Hard gelatin capsule size "2", clear transparent cap imprinted with "TPC" and flesh opaque body imprinted with "15" axially in black ink filled with white to off white beads.
- Hard gelatin capsule size "1", clear transparent cap imprinted with "TPC" and flesh opaque body imprinted with "25" axially in black ink filled with white to off white beads.
- Hard gelatin capsule size "0", clear transparent cap imprinted with "TPC" and flesh opaque body imprinted with "50" axially in black ink filled with white to off white beads.

4 CONTRAINDICATIONS

Topiramate is contraindicated in patients with a history of hypersensitivity reaction to topiramate, or any of the inactive ingredients of topiramate. Anaphylaxis and angioedema have occurred *[see Warnings and Precautions (5.13)]*.

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 topiramate therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in pediatric patients as well as adults. The primary treatment to reverse symptoms is discontinuation of 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 postmarketing experience in patients receiving topiramate. In clinical trials, most of these events were reversible after topiramate discontinuation. If visual problems occur at any time during 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 ≤ 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 *[see Warnings and Precautions (5.9, 5.15)]*. 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 *[see Warnings and Precautions (5.9), Use in Specific Populations (8.4)]*. 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 months old pediatrics. Reductions in length and weight were correlated to the degree of acidosis *[see Use in Specific Populations (8.4)]*. 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 *[see Warnings and Precautions (5.7), Use in Specific Populations (8.1)]*.

Measurement of Serum Bicarbonate in Epilepsy and Migraine Patients

Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing 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.

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

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

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

Table 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

Topiramate 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 *[see Warnings and Precautions (5.5)]*.

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.

The Cambridge Neuropsychological Test Automated Battery (CANTAB) was administered to adolescents (12 to 17 years) to assess the effects of topiramate on cognitive function at baseline and at the end of the Study 13 *[see Clinical Studies (14.3)]*. Mean change from baseline in certain CANTAB tests suggests that topiramate treatment may result in psychomotor slowing and decreased verbal fluency.

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 of 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 *[see Use in Specific Populations (8.1)]*.

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 *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*. 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 *[see Use in Specific Populations (8.1)]*.

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 *[see Clinical Studies (14)]*. 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 *[see Use in Specific Populations (8.4)]*. 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 *[see Warnings and Precautions (5.4)]*. 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) *[see Use in Specific Populations (8.4)]*. 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 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity Reactions

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, has been reported in patients taking topiramate. DRESS may be fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Topiramate should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

5.12 Serious Skin Reactions

Serious skin reactions (Stevens-Johnson Syndrome [SJS] and Toxic Epidermal Necrolysis [TEN]) have been reported in patients receiving topiramate. Topiramate 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.

5.13 Anaphylaxis and Angioedema

Hypersensitivity reactions, including anaphylaxis and angioedema, have occurred in patients treated with topiramate in the postmarketing setting. If a hypersensitivity reaction occurs, discontinue topiramate and initiate appropriate therapy *[see Contraindications (4)]*.

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

Topiramate treatment can cause hyperammonemia with or without encephalopathy *[see Adverse Reactions (6.2)]*. The risk for hyperammonemia with topiramate appears dose-related. Hyperammonemia has been reported more frequently when topiramate is used concomitantly with valproic acid. Postmarketing cases of hyperammonemia with or without encephalopathy have been reported with topiramate and valproic acid in patients who previously tolerated either drug alone *[see Drug Interactions (7.1)]*.

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.

5.15 Kidney Stones

Topiramate 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 *[see Use in Specific Populations (8.4)]*.

Topiramate is a carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors can promote stone formation by reducing urinary citrate excretion and by increasing urinary pH *[see Warnings and Precautions (5.4)]*. The concomitant use of 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 *[see Use in Specific Populations (8.4)]*. This increased ratio of urinary calcium/citrate increases the risk of kidney stones and/or nephrocalcinosis.

5.16 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 *[see Drug Interactions (7.1)]*. 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 *[see Warnings and Precautions (5.1)]*
- Visual Field Defects *[see Warnings and Precautions (5.2)]*
- Oligohidrosis and Hyperthermia *[see Warnings and Precautions (5.3)]*
- Metabolic Acidosis *[see Warnings and Precautions (5.4)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.5)]*
- Cognitive/Neuropsychiatric Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Decrease of Bone Mineral Density *[see Warnings and Precautions (5.9)]*
- Negative Effects on Growth (Height and Weight) *[see Warnings and Precautions (5.10)]*
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity Reactions *[see Warnings and Precautions (5.11)]*
- Serious Skin Reactions *[see Warnings and Precautions (5.12)]*
- Anaphylaxis and Angioedema *[see Warnings and Precautions (5.13)]*
- Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid [VPA] Use) *[see Warnings and Precautions (5.14)]*
- Kidney Stones *[see Warnings and Precautions (5.15)]*
- Hypothermia with Concomitant Valproic Acid (VPA) Use *[see Warnings and Precautions (5.16)]*

The data described in the following sections were obtained using topiramate tablets.

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.

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 (≥ 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 (≥ 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 (Study 1) that occurred in pediatric patients in the 400 mg/day topiramate group and at an incidence higher (≥ 10%) than in the 50 mg/day group were fever and weight loss (see Table 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 (≥ 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.

Table 5: Adverse Reactions in the High Dose Group As Compared to the Low Dose Group, in Monotherapy Epilepsy Trial (Study 1) in Adult and Pediatric Patients

	Age Group			
	Pediatric (6 to 15 Years)		Adult (Age ≥16 Years)	
	Topiramate Daily Dosage Group (mg/day)			
	50	400	50	400
Body System / Adverse Reaction	(N=74) %	(N=77) %	(N=160) %	(N=159) %
Body as a Whole - General Disorders				
Asthenia	0	3	4	6
Fever	1	12		
Leg pain			2	3
Central & Peripheral Nervous System Disorders				
Paresthesia	3	12	21	40
Dizziness			13	14
Ataxia			3	4
Hypoesthesia			4	5
Hypertonia			0	3
Involuntary muscle contractions	0	3		
Vertigo	0	3		
Gastro-Intestinal System Disorders				
Constipation			1	4
Diarrhea	8	9		
Gastritis			0	3
Dry mouth			1	3
Liver and Biliary System Disorders				
Increase in gamma-GT			1	3
Metabolic and Nutritional Disorders				
Weight loss	7	17	6	17
Platelet, Bleeding & Clotting Disorders				
Epistaxis	0	4		
Psychiatric Disorders				
Anorexia			4	14
Anxiety			4	6
Cognitive problems	1	6	1	4
Confusion	0	3		
Depression	0	3	7	9
Difficulty with concentration or attention	7	10	7	8
Difficulty with memory	1	3	6	11
Insomnia			8	9
Decrease in libido			0	3
Mood problems	1	8	2	5
Personality disorder (behavior problems)	0	3		
Psychomotor slowing			3	5
Somnolence			10	15
Red Blood Cell Disorders				
Anemia	1	3		
Reproductive Disorders, Female				
Intermenstrual bleeding	0	3		
Vaginal hemorrhage			0	3
Resistance Mechanism Disorders				
Infection	3	8	2	3
Viral infection	3	6	6	8
Respiratory System Disorders				
Bronchitis	1	5	3	4
Upper respiratory tract infection	16	18		
Rhinitis	5	6	2	4
Sinusitis	1	4		
Skin and Appendages Disorders				
Alopecia	1	4	3	4
Pruritus			1	4
Rash	3	4	1	4
Acne			2	3
Special Senses Other, Disorders				
Taste perversion			3	5
Urinary System Disorders				
Cystitis			1	3
Micturition frequency	0	3		
Renal calculus			0	3
Urinary incontinence	1	3		
Vascular (Extracardiac) Disorders				
Flushing	0	5		

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 (≥ 10%) than in the placebo group were: dizziness, speech disorders/related speech problems, somnolence, nervousness, psychomotor slowing, and vision abnormal (Table 6).

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.

Table 6: Most Common Adverse Reactions in Pooled Placebo-Controlled, Adjunctive Epilepsy Trials in Adults[a]

Body System / Adverse Reaction	Placebo (N=291)	Topiramate Dosage (mg/day) 200-400 (N=183)
Body as a Whole-General Disorders		
Fatigue	13	15
Asthenia	1	6
Back pain	4	5
Chest pain	3	4
Influenza-like symptoms	2	3
Central & Peripheral Nervous System Disorders		
Dizziness	15	25
Ataxia	7	16
Speech disorders/Related speech problems	2	13
Paresthesia	4	11
Nystagmus	7	10
Tremor	6	9
Language problems	1	6
Coordination abnormal	2	4
Gait abnormal	1	3
Gastro-Intestinal System Disorders		
Nausea	8	10
Dyspepsia	6	7
Abdominal pain	4	6
Constipation	2	4
Metabolic and Nutritional Disorders		
Weight loss	3	9
Psychiatric Disorders		
Somnolence	12	29
Nervousness	6	16
Psychomotor slowing	2	13
Difficulty with memory	3	12
Confusion	5	11
Anorexia	4	10
Difficulty with concentration/attention	2	6
Mood problems	2	4
Agitation	2	3
Aggressive reaction	2	3
Emotional lability	1	3
Cognitive problems	1	3
Reproductive Disorders		
Breast pain	2	4
Respiratory System Disorders		
Rhinitis	6	7
Pharyngitis	2	6
Sinusitis	4	5
Vision Disorders		
Vision abnormal	2	13
Diplopia	5	10

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

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 (≥ 10 %) than in the placebo group were: fatigue and somnolence (Table 7).

Table 7 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.

Table 7: Adverse Reactions in Pooled Placebo-Controlled, Adjunctive Epilepsy Trials in Pediatric Patients 2 to 15 Years of Age[a,b]

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

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

None of the pediatric patients who received topiramate adjunctive therapy at 5 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 (≥ 5 %) than in the placebo group were: paresthesia, anorexia, weight loss, taste perversion, diarrhea, difficulty with memory, hypoesthesia, and nausea (see Table 8).

Table 8 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).

Table 8: Adverse Reactions in Pooled, Placebo-Controlled, Migraine Trials in Adults[a,b]

		Topiramate Dosage (mg/day)	
Body System/ Adverse Reaction	Placebo (N=445) %	50 (N=235) %	100 (N=386) %
Body as a Whole-General Disorders			
Fatigue	11	14	15
Injury	7	9	6
Central & Peripheral Nervous System Disorders			
Paresthesia	6	35	51
Dizziness	10	8	9
Hypoesthesia	2	6	7
Language problems	2	7	6
Gastro-Intestinal System Disorders			
Nausea	8	9	13
Diarrhea	4	9	11
Abdominal pain	5	6	6
Dyspepsia	3	4	5
Dry mouth	2	2	3
Gastroenteritis	1	3	3
Metabolic and Nutritional Disorders			
Weight loss	1	6	9
Musculoskeletal System Disorders			
Arthralgia	2	7	3
Psychiatric Disorders			
Anorexia	6	9	15
Somnolence	5	8	7
Difficulty with memory	2	7	7
Insomnia	5	6	7
Difficulty with concentration/attention	2	3	6
Mood problems	2	3	6
Anxiety	3	4	5
Depression	4	3	4
Nervousness	2	4	4
Confusion	2	2	3
Psychomotor slowing	1	3	2
Reproductive Disorders, Female			
Menstrual disorder	2	3	2
Reproductive Disorders, Male			
Ejaculation premature	0	3	0
Resistance Mechanism Disorders			
Viral infection	3	4	4
Respiratory System Disorders			
Upper respiratory tract infection	12	13	14
Sinusitis	6	10	6
Pharyngitis	4	5	6
Coughing	2	2	4
Bronchitis	2	3	3
Dyspnea	2	1	3
Skin and Appendages Disorders			
Pruritus	2	4	2
Special Sense Other, Disorders			
Taste perversion	1	15	8
Urinary System Disorders			
Urinary tract infection	2	4	2
Vision Disorders			
Blurred vision[c]	2	4	2

[a] Includes 35 adolescent patients age 12 to 15 years.
[b] Values represent the percentage of patients reporting a given adverse reaction. Patients may have reported more than one adverse reaction during the study and can be included in more than one adverse reaction category.
[c] 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 (≥5%) than in the placebo group were: paresthesia, upper respiratory tract infection, anorexia, and abdominal pain (see Table 9). Table 9 shows adverse reactions from the pediatric trial (Study 13 *[see Clinical Studies (14.3)]*) 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).

Table 9: Adverse Reactions in Pooled Double-Blind Studies for the Preventive Treatment of Migraine in Pediatric Patients 12 to 17 Years of Age[a,b,c]

		Topiramate Dosage	
Body System/ Adverse Reaction	Placebo (N=45) %	50 mg/day (N=46) %	100 mg/day (N=48) %
Body as a Whole - General Disorders			
Fatigue	7	7	8
Fever	2	4	6
Central & Peripheral Nervous System Disorders			
Paresthesia	7	20	19
Dizziness	4	4	6
Gastrointestinal System Disorders			
Abdominal pain	9	7	15
Nausea	4	4	8
Metabolic and Nutritional Disorders			
Weight loss	2	7	4
Psychiatric Disorders			
Anorexia	4	9	10
Somnolence	2	2	6
Insomnia	2	9	2
Resistance Mechanism Disorders			
Infection viral	4	4	8
Respiratory System Disorders			
Upper respiratory tract infection	11	26	23
Rhinitis	2	7	6
Sinusitis	2	9	4
Coughing	0	7	2
Special Senses Other, Disorders			
Taste perversion	2	2	6
Vision Disorders			
Conjunctivitis	4	7	4

[a] 35 adolescent patients aged 12 to <16 years were also included in adverse reaction assessment for adults (Tables 11 and 12)
[b] Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events.
[c] 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 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 *[see Warnings and Precautions (5.4, 5.14)]*. 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, blood urea nitrogen (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) *[see Use in Specific Populations (8.4)]*. 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 *[see Use in Specific Populations (8.4)]*. 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: immediate hypersensitivity reactions (including anaphylaxis and angioedema) *[see Warnings and Precautions (5.13)]*, delayed hypersensitivity reactions (including facial swelling, lip swelling, periorbital swelling, tongue swelling), oligohydrosis and hyperthermia *[see Warnings and Precautions (5.3)]*, hyperammonemia, hyperammonemic encephalopathy *[see Warnings and Precautions (5.14)]*, hypothermia with concomitant valproic acid *[see Warnings and Precautions (5.16)]*

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) *[see Warnings and Precautions (5.12)]*, pemphigus, urticaria

Urinary System Disorders: kidney stones, nephrocalcinosis *[see Warnings and Precautions (5.4, 5.15)]*

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

To report SUSPECTED ADVERSE REACTIONS, contact Strides Pharma Inc. at 1-877-244-9825 or go to www.strides.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Medication Guide

Topiramate Capsules (Sprinkle)
(toe pir' a mate)

What is the most important information I should know about topiramate?

Topiramate may cause eye problems. Serious eye problems include:

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

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

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

Sometimes people with metabolic acidosis will:

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

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

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

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

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

Do not stop topiramate without first talking to a healthcare provider.

- Stopping topiramate suddenly can cause serious problems.
- Suicidal thoughts or actions can be caused by things other than medicines.

If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

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

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

Topiramate can harm your unborn baby.

- If you take topiramate during pregnancy, your baby has a higher risk for birth defects including cleft lip and cleft palate. These defects can begin early in pregnancy, even before you know you are pregnant.
- Birth defects may happen even in children born to women who are not taking any medicines and do not have other risk factors.
- There may be other medicines to treat your condition that have a lower chance of birth defects.
- All women of childbearing age should talk to their healthcare providers about using other possible treatments instead of topiramate. If the decision is made to use topiramate, you should use effective birth control (contraception) unless you are planning to become pregnant. You should talk to your doctor about the best kind of birth control to use while you are taking topiramate.
- Tell your healthcare provider right away if you become pregnant while taking topiramate. You and your healthcare provider should decide if you will continue to take topiramate while you are pregnant.
- If you take topiramate during pregnancy, your baby may be smaller than expected at birth. The long-term effects of this are not known. Talk to your healthcare provider if you have questions about this risk during pregnancy.
- Metabolic acidosis may have harmful effects on your baby. Talk to your healthcare provider if topiramate has caused metabolic acidosis during your pregnancy.
- Pregnancy Registry: If you become pregnant while taking topiramate, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of topiramate and other antiepileptic drugs during pregnancy.

Topiramate may decrease the density of bones when used over a long period.

Topiramate may slow height increase and weight gain in children and adolescents when used over a long period.

What is topiramate?

Topiramate is a prescription medicine used:

- to treat certain types of seizures (partial-onset seizures and primary generalized tonic-clonic seizures) in adults and children 2 years and older,
- with other medicines to treat certain types of seizures (partial-onset seizures, primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome) in adults and children 2 years and older,
- to prevent migraine headaches in adults and adolescents 12 years and older.

Who should not take topiramate?

Do not take topiramate if you are allergic to topiramate, or any of the ingredients in topiramate. See the end of this Medication Guide for a complete list of ingredients in topiramate.

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

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

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Topiramate and other medicines may affect each other causing side effects.

Especially tell your healthcare provider if you take:

- Valproic acid (such as DEPAKENE or DEPAKOTE).
- any medicines that impair or decrease your thinking, concentration, or muscle coordination.
- birth control that contains hormones (such as pills, implants, patches or injections). Topiramate may make your birth control less effective. Tell your healthcare provider if your menstrual bleeding changes while you are using birth control and topiramate.

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

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

How should I take topiramate?

- Take topiramate exactly as prescribed.
- Your healthcare provider may change your dose. **Do not** change your dose without talking to your healthcare provider.
- Topiramate capsules (sprinkle) may be swallowed whole or may be opened and sprinkled on a teaspoon of soft food. Drink fluids right after eating the food and medicine mixture to make sure it is all swallowed. **Do not** chew the food and medicine mixture.
- **Do not** store any medicine and food mixture for later use.
- Topiramate can be taken before, during, or after a meal. Drink plenty of fluids during the day. This may help prevent kidney stones while taking topiramate.
- If you take too much topiramate, call your healthcare provider right away or go to the nearest emergency room.
- If you miss a single dose of topiramate, take it as soon as you can. However, if you are within 6 hours of taking your next scheduled dose, wait until then to take your usual dose of topiramate, and skip the missed dose. **Do not** double your dose. If you have missed more than one dose, you should call your healthcare provider for advice.
- **Do not** stop taking topiramate without talking to your healthcare provider. Stopping topiramate suddenly may cause serious problems. If you have epilepsy and you stop taking topiramate suddenly, you may have seizures

450 x 850 mm

Perforation not required.

MFG. LOCATION: KRSG

NON PRINTING COLOUR

ARTWORK DETAIL LABEL

Product	**Topiramate Capsules (Sprinkle)**		
Buyer/Country	STRIDES PHARMA INC - US	Component	Outsert
Dimension	**450 x 850 mm**	Pack	NA
New Item Code	**1054468**	Old Item Code	1052452
Colour Shades	BLACK	No. of Colours	1
Change Control No.	PC-ODF/2026/259 - Record Number: 492681	Artwork Version	2.0
Design/Style	Front and Back Side Printing, to be supplied in the folded booklet form with pasting and folded size: 38 x 38 mm.		
Substrate	30 GSM Bible Paper.		
Special Instructions	Printing clarity should be clear and sharp.		
Autocartonator Requirements	NA		

Caution to the printer: Before processing, please ensure that the ARTWORK received for printing is exactly in line with APPROVED ARTWORK provided to you. In case of any FONTS/DESIGN are Mis-matching with the APPROVED ARTWORK, please inform PDC for further action. **DO NOT MAKE ANY CHANGE TO THE ARTWORK WITHOUT WRITTEN INSTRUCTIONS FROM PDC.**

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that do not stop. Your healthcare provider will tell you how to stop taking topiramate slowly.

- Your healthcare provider may do blood tests while you take topiramate.

What should I avoid while taking topiramate?

- You should not drink alcohol while taking topiramate. Topiramate and alcohol can affect each other causing side effects such as sleepiness and dizziness.
- Do not drive a car or operate machinery until you know how topiramate affects you. Topiramate can slow your thinking and motor skills, and may affect vision.

What are the possible side effects of topiramate?

Topiramate may cause serious side effects including:

See **"What is the most important information I should know about topiramate?"**

- **Effects on thinking and alertness.** Topiramate may affect how you think and cause confusion, problems with concentration, attention, memory, or speech. Topiramate may cause depression or mood problems, tiredness, and sleepiness.
- **Dizziness or loss of muscle coordination.**
- **Severe multiorgan reactions.** Treatment with topiramate may cause a serious allergic reaction that may affect your skin or other parts of your body such as your liver, kidneys, heart, or blood cells. This allergic reaction can be life-threatening and can cause death, particularly if it is not treated as early as possible. Contact your healthcare provider or get medical help right away if you have:
  - blistering and peeling of your skin or skin rash
  - fever or swollen glands that do not go away
  - hives
  - swelling of your face, eyes, lips, tongue, or throat
  - sores in your mouth,
  - trouble swallowing or breathing
  - dark urine
  - yellowing of the skin or whites of the eyes
- **Serious skin reactions.** Topiramate may cause a severe rash with blisters and peeling skin, especially around the mouth, nose, eyes, and genitals (Stevens-Johnson syndrome). Topiramate may also cause a rash with blisters and peeling skin over much of the body that may cause death (toxic epidermal necrolysis). Call your healthcare provider right away if you develop a skin rash or blisters.
- **Allergic reactions.** Serious allergic reactions can happen after you take topiramate. Get emergency help right away if you have swelling of the face, lips, eyes, tongue, or throat, or trouble swallowing or breathing.
- **High blood ammonia levels.** High ammonia in the blood can affect your mental activities, slow your alertness, make you feel tired, or cause vomiting. This has happened when topiramate is taken with a medicine called valproic acid (DEPAKOTE). Call your healthcare provider right away if you develop unexplained tiredness, vomiting, slowing of your thinking or reaction time, or changes in your mental activities.
- **Kidney stones.** Drink plenty of fluids when taking topiramate to decrease your chances of getting kidney stones.
- **Low body temperature.** Taking topiramate when you are also taking valproic acid can cause a drop in body temperature to less than 95°F, or can cause tiredness, confusion, or coma.

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

The most common side effects of topiramate include:

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

Tell your healthcare provider about any side effect that bothers you or that does not go away. These are not all the possible side effects of topiramate. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to Strides Pharma Inc. at 1-877-244-9825.

How should I store topiramate?

- Store topiramate at room temperature between 20° to 25°C (68° to 77°F).
- Keep topiramate in a tightly closed container.
- Keep topiramate dry and away from moisture.

Keep topiramate and all medicines out of the reach of children.

General information about the safe and effective use of topiramate.

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

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

What are the ingredients in topiramate capsules (sprinkle)?

Active ingredient: topiramate

Inactive ingredients:

- **Capsules (sprinkle):** carboxymethylcellulose calcium, FD&C Red No. 40, gelatin, hypromellose, lactose monohydrate, microcrystalline cellulose, polyethylene glycol, povidone, saccharin sodium, sodium lauryl sulfate, talc and titanium dioxide. The imprinting ink contains shellac, black iron oxide and traces of potassium hydroxide.

Distributed by:
Strides Pharma Inc.
Bridgewater, NJ 08807

Revised: 04/2026

The brands listed are trademarks of their respective owners.

For more information, call contact Strides Pharma Inc. at 1-877-244-9825 or go to www.strides.com

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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 *[see Dosage and Administration (2.1), Clinical Pharmacology (12.3)]*.

Concomitant administration of valproic acid and topiramate has been associated with hypothermia and hyperammonemia with and without encephalopathy. Examine blood ammonia levels in patients in whom the onset of hypothermia has been reported *[see Warnings and Precautions (5.14, 5.16), Clinical Pharmacology (12.3)]*.

7.2 Other Carbonic Anhydrase Inhibitors

Concomitant use of topiramate, 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 topiramate concomitantly with another carbonic anhydrase inhibitor should be monitored particularly closely for the appearance or worsening of metabolic acidosis *[see Clinical Pharmacology (12.3)]*.

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, topiramate 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 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 *[see Clinical Pharmacology (12.3)]*.

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 *[see Clinical Pharmacology (12.3)]*.

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 *[see Clinical Pharmacology (12.3)]*.

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 *[see Clinical Pharmacology (12.3)]*.

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 *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to topiramate during pregnancy. Patients should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll-free number 1888-233-2334. Information about the North American Drug Pregnancy Registry can be found at http://www.aedpregnancyregistry.org/.

Risk Summary

Topiramate can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate *in utero* have an increased risk of major congenital malformations, including but not limited to cleft lip and/or cleft palate (oral clefts), and of being small for gestational age (SGA) *[see Human Data]*. 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 *[see Animal Data]*.

[illegible]

[see Warnings and Precautions (5.4), Adverse Reactions (6)].

In open-label, uncontrolled experience, increasing impairment of adaptive behavior was documented in behavioral testing over time in this population. There was a suggestion that this effect was dose-related. However, because of the absence of an appropriate control group, it is not known if this decrement in function was treatment-related or reflects the patient's underlying disease (e.g., patients who received higher doses may have more severe underlying disease) *[see Warnings and Precautions (5.6)]*.

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

Pediatric Patients 2 Years of Age and Older

The safety and effectiveness of topiramate 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 *[see Adverse Reactions (6.1), Clinical Studies (14.1)]*.

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 *[see Warnings and Precautions (5.4)]*. 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.

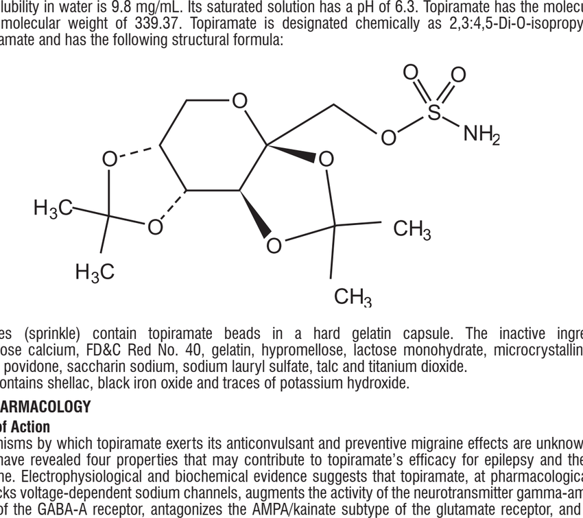
Preventive Treatment of Migraine

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 *[see Clinical Studies (14.3)]*, 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 *[see Clinical Studies (14.3)]*. 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 [illegible]

[illegible]



[illegible]

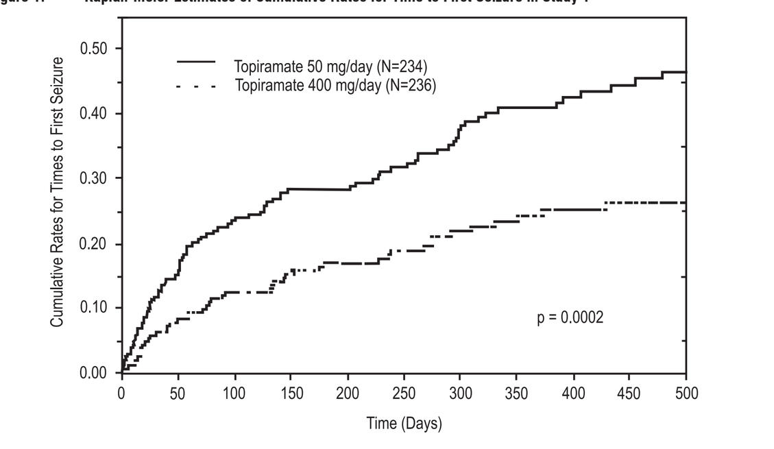
changes (increases and decreases) from baseline in vital signs (systolic blood pressure-SBP, diastolic blood pressure-DBP, pulse) occurred more frequently in pediatric patients (6 to 17 years) treated with various daily doses of topiramate (50 mg, 100 mg, 200 mg, 2 to 3 mg/kg) than in patients treated 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.

12.3 Pharmacokinetics

The sprinkle formulation is bioequivalent to the immediate-release tablet formulation and, therefore, may be substituted as a therapeutic equivalent.

[illegible]

Figure 1:



[illegible]

Following randomization, patients began the double-blind phase of treatment. Patients received active drug beginning at 25 or 50 mg/day; the dose was then increased by 25 mg to 150 mg/day increments every other week until the assigned dosage of 125, 175, 225, or 400 mg/day based on patients' weight to approximate a dosage of 6 mg/kg/day was reached, unless intolerance prevented increases. After titration, patients entered an 8-week stabilization period.

Patients With Primary Generalized Tonic-Clonic Seizures

The effectiveness of topiramate as an adjunctive treatment for primary generalized tonic-clonic seizures in patients 2 years of age and older was established in a multicenter, randomized, double-blind, placebo-controlled trial (Study 9), comparing a single dosage of topiramate and placebo (see Table 13).

Patients in Study 9 were permitted a maximum of two antiepileptic drugs (AEDs) in addition to topiramate or placebo. Patients were stabilized on optimum dosages of their concomitant AEDs during an 8-week baseline phase. Patients who experienced at least three primary generalized tonic-clonic seizures during the baseline phase were randomly assigned to placebo or topiramate in addition to their other AEDs.

Following randomization, patients began the double-blind phase of treatment. Patients received active drug beginning at 50 mg/day for four weeks; the dose was then increased by 50 mg to 150 mg/day increments every other week until the assigned dose of 175, 225, or 400 mg/day based on patients' body weight to approximate a dosage of 6 mg/kg/day was reached, unless intolerance prevented increases. After titration, patients entered a 12-week stabilization period.

Patients With Lennox-Gastaut Syndrome

The effectiveness of topiramate as an adjunctive treatment for seizures associated with Lennox-Gastaut syndrome was established in a multicenter, randomized, double-blind, placebo-controlled trial (Study 10) comparing a single dosage of topiramate with placebo in patients 2 years of age and older (see Table 13).

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

The primary measures of effectiveness were the percent reduction in drop attacks and a parental global rating of seizure severity.

Table 12: Topiramate Dose Summary During the Stabilization Periods of Each of Six Double-Blind, Placebo-Controlled, Adjunctive Trials in Adults with Partial-Onset Seizures[a]

			Target Topiramate Dosage (mg/day)				
Study	Stabilization Dose	Placebo[b]	200	400	600	800	1,000
2	N	42	42	40	41	--	--
	Mean Dose	5.9	200	390	556	--	--
	Median Dose	6.0	200	400	600	--	--
3	N	44	--	--	40	45	40
	Mean Dose	9.7	--	--	544	739	796
	Median Dose	10.0	--	--	600	800	1,000
4	N	23	--	19	--	--	--
	Mean Dose	3.8	--	395	--	--	--
	Median Dose	4.0	--	400	--	--	--
5	N	30	--	--	28	--	--
	Mean Dose	5.7	--	--	522	--	--
	Median Dose	6.0	--	--	600	--	--
6	N	28	--	--	--	25	--
	Mean Dose	7.9	--	--	--	568	--
	Median Dose	8.0	--	--	--	600	--
7	N	90	157	--	--	--	--
	Mean Dose	8	200	--	--	--	--
	Median Dose	8	200	--	--	--	--

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

[b] Placebo dosages are given as the number of tablets. Placebo target dosages were as follows: Protocol 3 4 tablets/day; Protocols 1 and 4, 6 tablets/day; Protocols 5 and 6, 8 tablets/day; Protocol 2, 10 tablets/day.

In all adjunctive trials, the reduction in seizure rate from baseline during the entire double-blind phase was measured. The median percent reductions in seizure rates and the responder rates (fraction of patients with at least a 50% reduction) by treatment group for each study are shown below in Table 13. As described above, a global improvement in seizure severity was also assessed in the Lennox-Gastaut trial.

Table 13: Efficacy Results in Double-Blind, Placebo-Controlled, Adjunctive Epilepsy Trials

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

Comparisons with placebo: [a]$p=0.080$; [b]$p \le 0.010$; [c]$p \le 0.001$; [d]$p \le 0.050$; [e]$p=0.065$; [f]$p \le 0.005$; [g]$p=0.071$;

[h] Median % reduction and % responders are reported for PGTC seizures;

[i] Median % reduction and % responders for drop attacks, i.e., tonic or atonic seizures

[j] Percentage of subjects who were minimally, much, or very much improved from baseline.

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

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

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

14.3 Preventive Treatment of Migraine

Adult Patients

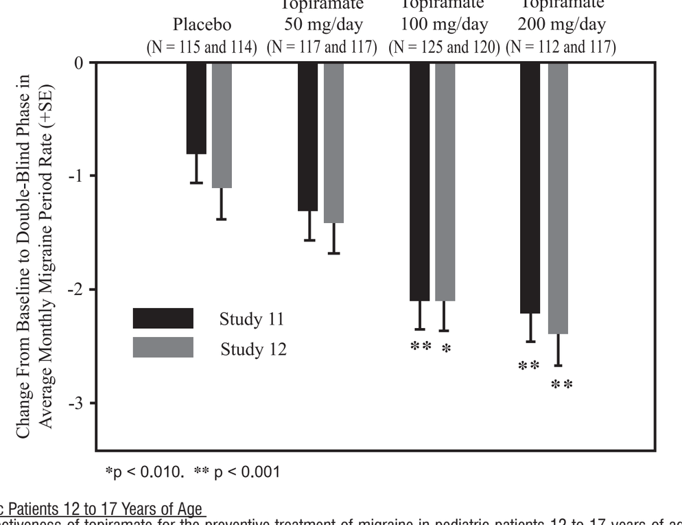
The results of 2 multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trials established the effectiveness of topiramate in the preventive treatment of migraine. The design of both trials (Study 11 was conducted in the U.S. and Study 12 was conducted in the U.S. and Canada) was identical, enrolling patients with a history of migraine, with or without aura, for at least 6 months, according to the International Headache Society (IHS) diagnostic criteria. Patients with a history of cluster headaches or basilar, ophthalmoplegic, hemiplegic, or transformed migraine headaches were excluded from the trials. Patients were required to have completed up to a 2-week washout of any prior migraine preventive medications before starting the baseline phase.

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

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

In Study 11, a total of 469 patients (416 females, 53 males), ranging in age from 13 to 70 years, were randomized and provided efficacy data. Two hundred sixty-five patients completed the entire 26-week double-blind phase. The median average daily dosages were 48 mg/day, 88 mg/day, and 132 mg/day in the target dose groups of topiramate 50, 100, and 200 mg/day, respectively.

[illegible]



*p < 0.010. ** p < 0.001

Pediatric Patients 12 to 17 Years of Age

The effectiveness of topiramate for the preventive treatment of migraine in pediatric patients 12 to 17 years of age was established in a multicenter, randomized, double-blind, parallel-group trial (Study 13). The study enrolled 103 patients (40 male, 63 female) 12 to 17 years of age with episodic migraine headaches with or without aura. Patient selection was based on IHS criteria for migraines (using proposed revisions to the 1988 IHS pediatric migraine criteria [IHS-R criteria]). Patients who experienced 3 to 12 migraine attacks (according to migraines classified by patient reported diaries) and ≤ 14 headache days (migraine and non-migraine) during the 4-week prospective baseline period were randomized to either topiramate 50 mg/day, 100 mg/day, or placebo and treated for a total of 16 weeks (4-week titration period followed by a 12-week maintenance period). Treatment was initiated at 25 mg/day for one week, and then the daily dosage was increased by 25 mg increments each week until reaching the assigned target dose or maximum tolerated dose (administered twice daily). Approximately 80% or more patients in each treatment group completed the study. The median average daily dosages were 45 and 79 mg/day in the target dose groups of topiramate 50 and 100 mg/day, respectively.

Effectiveness of treatment was assessed by comparing each topiramate treatment group to placebo (ITT population) for the percent reduction from baseline to the last 12 weeks of the double-blind phase in the monthly migraine attack rate (primary endpoint). The percent reduction from baseline to the last 12 weeks of the double-blind phase in average monthly migraine attack rate is shown in Table 14. The 100 mg topiramate dose produced a statistically significant treatment difference relative to placebo of 28% reduction from baseline in the monthly migraine attack rate.

The mean reduction from baseline to the last 12 weeks of the double-blind phase in average monthly attack rate, a key secondary efficacy endpoint in Study 13 (and the primary efficacy endpoint in Studies 11 and 12, of adults) was 3.0 for 100 mg topiramate dose and 1.7 for placebo. This 1.3 treatment difference in mean reduction from baseline of monthly migraine rate was statistically significant (p = 0.0087).

Table 14: Percent Reduction from Baseline to the Last 12 Weeks of Double-Blind Phase in Average Monthly Attack Rate: Study 13 (Intent-to-Treat Analysis Set)

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

[a] P-values (two-sided) for comparisons relative to placebo are generated by applying an ANCOVA model on ranks that includes subject's stratified age at baseline, treatment group, and analysis center as factors and monthly migraine attack rate during baseline period as a covariate.

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

[c] Indicates p-value is <0.05 (two-sided).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Topiramate Capsules (Sprinkles)

1. 15 mg capsules:

Hard gelatin capsule size "2", clear transparent cap imprinted with "TPC" and flesh opaque body imprinted with "15" axially in black ink filled with white to off white beads.

NDC 64380-241-01
Bottle of 60 capsules
NDC 64380-241-02
Bottle of 500 capsules

2. 25 mg capsules:

Hard gelatin capsule size "1", clear transparent cap imprinted with "TPC" and flesh opaque body imprinted with "25" axially in black ink filled with white to off white beads.

NDC 64380-242-01
Bottle of 60 capsules
NDC 64380-242-02
Bottle of 500 capsules

3. 50 mg capsules:

Hard gelatin capsule size "0", clear transparent cap imprinted with "TPC" and flesh opaque body imprinted with "50" axially in black ink filled with white to off white beads.

NDC 64380-240-01
Bottle of 60 capsules
NDC 64380-240-02
Bottle of 500 capsules

16.2 Storage and Handling

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Protect from moisture.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

PHARMACIST: Dispense a Medication Guide with each prescription.

17 PATIENT COUNSELING INFORMATION

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

Eye Disorders

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

Oligohidrosis and Hyperthermia

Closely monitor topiramate-treated patients, especially pediatric patients, for evidence of decreased sweating and increased body temperature, especially in hot weather. Counsel patients to contact their healthcare professionals immediately if they develop a high or persistent fever, or decreased sweating *[see Warnings and Precautions (5.3)]*.

Metabolic Acidosis

Warn patients about the potential significant risk for metabolic acidosis that may be asymptomatic and may be associated with adverse effects on kidneys (e.g., kidney stones, nephrocalcinosis), bones (e.g., osteoporosis, osteomalacia, and/or rickets in children), and growth (e.g., growth delay/retardation) in pediatric patients, and on the fetus *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1)]*.

Suicidal Behavior and Ideation

Counsel patients, their caregivers, and families that AEDs, including topiramate, may increase the risk of suicidal thoughts and behavior, and advise of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior or the emergence of suicidal thoughts, or behavior or thoughts about self-harm. Instruct patients to immediately report behaviors of concern to their healthcare providers *[see Warnings and Precautions (5.5)]*.

Interference with Cognitive and Motor Performance

Warn patients about the potential for somnolence, dizziness, confusion, difficulty concentrating, or visual effects, and advise patients not to drive or operate machinery until they have gained sufficient experience on topiramate to gauge whether it adversely affects their mental performance, motor performance, and/or vision *[see Warnings and Precautions (5.6)]*.

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1054468

450 x 850 mm

Page 2 of 2 Back side

Perforation not required.

MFG. LOCATION: KRSG

NON PRINTING COLOUR

ARTWORK DETAIL LABEL

Product	**Topiramate Capsules (Sprinkle)**				
Buyer/Country	STRIDES PHARMA INC - US	Component	Outsert		
Dimension	**450 x 850 mm**			Pack	NA
New Item Code	**1054468**	Old Item Code	1052452		
Colour Shades	BLACK			No. of Colours	1

Change Control No.	PC-ODF/2026/259 - Record Number: 492681	Artwork Version	2.0
Design/Style	Front and Back Side Printing, to be supplied in the folded booklet form with pasting and folded size: 38 x 38 mm.		
Substrate	30 GSM Bible Paper.		
Special Instructions	Printing clarity should be clear and sharp.		
Autocartonator Requirements	NA		

Caution to the printer: Before processing, please ensure that the ARTWORK received for printing is exactly in line with APPROVED ARTWORK provided to you. In case of any FONTS/DESIGN are Mis-matching with the APPROVED ARTWORK, please inform PDC for further action. **DO NOT MAKE ANY CHANGE TO THE ARTWORK WITHOUT WRITTEN INSTRUCTIONS FROM PDC.**

RD/PD/003/F-08/R0