1.4.3 Package Insert

1. NAME OF THE MEDICINAL PRODUCT

Topiron 25mg film-coated tablets
Topiron 50mg film-coated tablets
Topiron 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg of topiramate.
Excipients: Each 25 mg tablet contains 28.93 mg of lactose.

Each tablet contains 50 mg of topiramate.
Excipients: Each 50 mg tablet contains 57.86 mg of lactose.

Each tablet contains 100 mg of topiramate.
Excipients: Each 100 mg tablet contains 115.71 mg of lactose.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

25 mg tablets are white, round and convex.
50 mg tablets are yellow, round and convex.
100 mg tablets are yellow, round and convex.

4. CLINICAL PARTICLULARS

4.1. Therapeutic indications

Topiramate is indicated as monotherapy in adults and children with partial onset seizures and generalised seizures including tonic-clonic seizures.

Topiramate is indicated as adjunctive therapy for adults and children with partial onset seizures or generalized tonic-clonic seizures and seizures associated with Lennox-Gastaut syndrome.

Topiramate is also indicated in adults for the prophylaxis of migraine headache. The usefulness of Topiramate in the acute treatment of migraine headache has not been studied.

4.2. Posology and method of administration

General

For optimal seizure control in both adults and children, it is recommended that therapy be initiated at a low dose followed by titration to an effective dose.

Topiron is available in a film-coated tablet formulation. It is recommended that film-coated tablets not be broken.

Topiron can be taken without regard to meals.

Monotherapy epilepsy

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When concomitant antiepileptic drugs (AEDs) are withdrawn to achieve monotherapy with topiramate, consideration should be given to the effects this may have on seizure control.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

When enzyme inducing drugs are withdrawn, topiramate levels will increase.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

Adults

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

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

Paediatric population (aged 2 years and above)

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

The recommended initial target dose range for topiramate monotherapy in children aged 2 years and above is 3 to 6 mg/kg/day. Children with recently diagnosed partial onset seizures have received doses of up to 500 mg/day.

Adjunctive therapy epilepsy

Adults

Therapy should begin at 25-50 mg nightly for one week. Subsequently, at weekly or bi-weekly intervals, the dose should be increased by 25-50 mg/day and taken in two divided doses. Dose titration should be guided by clinical outcome. Some patients may achieve efficacy with once-a-day dosing.

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

These dosing recommendations apply to all adults, including the elderly, in the absence of underlying renal disease (see section 4.4).

Paediatric population (children aged 2 years and above)

The recommended total daily dose of topiramate as adjunctive therapy is approximately 5 to 9 mg/kg/day in two divided doses. Titration should begin at 25 mg (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.

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

Migraine

The recommended total daily dose of topiramate for prophylaxis of migraine headache is 100 mg/day administered in two divided doses. Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased in increments of 25 mg/day administered at 1-week intervals. If the patient is unable to tolerate the titration regimen, longer intervals between dose adjustments can be used. Some patients may experience a benefit at a total daily dose of 50 mg/day. Patients have received a total daily dose up to 200 mg/day. Dose and titration rate should be guided by clinical outcome.

General dosing recommendations for Topiron in special patient populations

Renal impairment

Patients with moderate and severe renal impairment may require a dose reduction. Half of the usual starting and maintenance dose is recommended (see Pharmacokinetic Properties).

Hemodialysis

Since topiramate is removed from plasma by haemodialysis, a supplemental dose of Topiramate equal to approximately one-half the daily dose should be administered on haemodialysis days. The supplemental dose should be administered in divided doses at the beginning and completion of the haemodialysis procedure. The supplemental dose may differ based on the characteristics of the dialysis equipment being used (see Pharmacokinetic Properties).

Hepatic impairment

Topiramate should be administered with caution in patients with hepatic impairment (see Pharmacokinetic Properties).

4.3. Contraindications

Migraine prophylaxis: in pregnancy and in women of childbearing potential if not using a highly effective method of contraception.

Hypersensitivity to the active substance or to any of the excipients.

4.4. Special warnings and precautions for use

Withdrawal of topiramate

In patients with or without a history of seizures or epilepsy, antiepileptic drugs including topiramate should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency. In clinical trials, daily dosages were decreased in weekly intervals by 50-100 mg in adults with epilepsy and by 25-50 mg in adults receiving topiramate at doses up to 100 mg/day for migraine prophylaxis. In clinical trials of children, topiramate was gradually withdrawn over a 2-8 week period. In situations where rapid withdrawal of topiramate is medically required, appropriate monitoring is recommended.

Renal impairment

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

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

Hydration

Adequate hydration while using topiramate is very important. Hydration can reduce the risk of nephrolithiasis (see below). Proper hydration prior to and during activities such as exercise or exposure to warm temperatures may reduce the risk of heat-related adverse reactions (see section 4.8).

Mood disturbances/depression

An increased incidence of mood disturbances and depression has been observed during topiramate treatment.

Suicide/suicide ideation

Antiepileptic drugs (AEDs), including Topiramate, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. A meta-analysis of randomised placebo-controlled trials of anti-epileptic drugs has shown an increased risk of suicidal ideation and behaviour (0.43% on anti-epileptic drugs versus 0.24% on placebo). The mechanism of this risk is not known.

In double blind clinical trials, suicide related events (SREs) (suicidal ideation, suicide attempts and suicide) occurred at a frequency of 0.5% in topiramate treated patients (46 out of 8,652 patients treated) compared to 0.2% treated with placebo (8 out of 4,045 patients treated). One completed suicide was reported in a bipolar disorder double-blind trial in a patient on topiramate.

Patients therefore should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and, when appropriate, caregivers of patients) should be advised to seek immediate medical advice should signs of suicidal ideation or behaviour emerge.

Nephrolithiasis

Some patients, especially those with a predisposition to nephrolithiasis, may be at increased risk for renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain.

Risk factors for nephrolithiasis include prior stone formation, a family history of nephrolithiasis and hypercalciuria. None of these risk factors can reliably predict stone formation during topiramate treatment. In addition, patients taking other medicinal products associated with nephrolithiasis may be at increased risk.

Decreased hepatic function

In hepatically-impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased. (see “Posology and Method of Administration” and “Pharmacokinetic Properties”).

Acute myopia and secondary angle closure glaucoma

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving topiramate. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperaemia (redness) and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating topiramate therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in paediatric patients as well as adults. Treatment includes discontinuation of topiramate, as rapidly as possible in the judgment of the treating physician, and appropriate measures to reduce intraocular pressure. These measures generally result in a decrease in intraocular pressure.

Visual field defects

Visual field defects have been reported in patients receiving topiramate independent of elevated intraocular pressure. 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.

Oligohydrosis and Hyperthermia

Oligohydrosis (decreased sweating), infrequently resulting in hospitalization, has been reported in association with topiramate use. Decrease sweating and an elevation in body temperature above normal characterized these cases. Some of these cases were reported after exposure to elevated environmental temperature. The majority of these reports have been in children. Patients, especially paediatric 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 prescribed 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.

Metabolic acidosis

Hyperchloremic, non-anion gap, metabolic acidosis (i.e. decreased serum bicarbonate below the normal reference range in the absence of respiratory alkalosis) is associated with topiramate treatment. This decrease in serum bicarbonate is due to the inhibitory effect of topiramate on renal carbonic anhydrase. Generally, the decrease in bicarbonate occurs early in treatment although it can occur at any time during treatment. These decreases are usually mild to moderate (average decrease of 4 mmol/l at doses of 100 mg/day or above in adults and at approximately 6 mg/kg/day in paediatric patients). Rarely, patients have experienced decreases to values below 10 mmol/l. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhoea, surgery, ketogenic diet, or certain drugs) may be additive to the bicarbonate lowering effects of topiramate.

Chronic metabolic acidosis in paediatric patients can reduce growth rates. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated in paediatric or adult populations.

Depending on underlying conditions, appropriate evaluation including serum bicarbonate levels is recommended with topiramate therapy. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering).

Chronic, untreated metabolic acidosis may increase the risk of nephrolithiasis or nephrocalcinosis.

Serious skin reactions

Serious skin reactions (Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)) have been

reported in patients receiving topiramate. The majority of cases have occurred in patients concurrently taking other medications that are known to be associated with SJS and TEN. There have also been several cases in patients receiving monotherapy. It is recommended that patients be informed about the signs of serious skin reactions. If SJS or TEN are suspected, use of topiramate should be discontinued.

Nutritional supplementation

A dietary supplement or increased food intake may be considered if the patient is losing weight while on topiramate.

Lactose intolerance

Topiramate contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medication.

Women of childbearing potential

Topiramate may cause fetal harm when administered to a pregnant woman. There is an increased risk of pre-term labor and premature delivery associated with the use of AEDs, including topiramate.

Before the initiation of treatment with topiramate in a woman of childbearing potential, pregnancy testing should be performed and a highly effective contraceptive method used. The patient should be fully informed of the risks related to the use of topiramate during pregnancy (see Pregnancy and Breast Feeding).

For migraine prophylaxis, topiramate is contraindicated in pregnancy and in women of childbearing potential if a highly effective method of contraception is not used (see Contraindications and Interactions).

Topiramate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see Contraindications, Pregnancy and Breast Feeding).

4.5. Interaction with other medicinal products and other forms of interaction

For purposes of this section, a no effect dose is defined as a $\leq$ 15% change.

Effects of Topiramate on other antiepileptic medicinal products

The addition of topiramate to other antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no effect on their steady-state plasma concentrations, except in the occasional patient, where the addition of topiramate to phenytoin may result in an increase of plasma concentrations of phenytoin. This is possibly due to inhibition of a specific enzyme polymorphic isoform (CYP2C19). Consequently, any patient on phenytoin showing clinical signs or symptoms of toxicity should have phenytoin levels monitored.

A pharmacokinetic interaction study of patients with epilepsy indicated the addition of topiramate to lamotrigine had no effect on steady state plasma concentration of lamotrigine at topiramate doses of 100 to 400 mg/day. In addition, there was no change in steady state plasma concentration of topiramate during or after removal of lamotrigine treatment (mean dose of 327 mg/day).

Effects of other antiepileptic medicinal products on topiramate

Phenytoin and carbamazepine decrease the plasma concentration of topiramate. The addition or withdrawal of phenytoin or carbamazepine to topiramate therapy may require an adjustment in dosage of the latter. This should be done by titrating to clinical effect. The addition or withdrawal of valproic acid does not produce

clinically significant changes in plasma concentrations of topiramate and, therefore, does not warrant dosage adjustment of topiramate.

The results of these interactions are summarized below:

AED Coadministered	AED Concentration	Topiramate Concentration
Phenytoin	↔**	↓ (48%)
Carbamazepine (CBZ)	↔	↓ (40%)
Valproic acid	↔	↔
Lamotrigine	↔	↔
Phenobarbital	↔	NS
Primidone	↔	NS

↔ = No effect on plasma concentration (≤ 15% change)
** = Plasma concentrations increase in individual patients
↓ = Plasma concentrations decrease
NS = Not studied
AED = antiepileptic drug

Other medicinal product interactions

Digoxin

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

CNS depressants

Concomitant administration of topiramate and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. It is recommended that topiramate not be used concomitantly with alcohol or other CNS depressant drugs.

Oral contraceptives

In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 µg ethinyl estradiol (EE), topiramate given in the absence of other medications at doses of 50 to 200 mg/day was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. In another study, exposure to EE was statistically significantly decreased at doses of 200, 400, and 800 mg/day (18%, 21%, and 30%, respectively) when given as adjunctive therapy in patients taking valproic acid. In both studies, topiramate (50-800 mg/day) did not significantly affect exposure to NET. Although there was a dose dependent decrease in EE exposure for doses between 200-800 mg/day, there was no significant dose dependent change in EE exposure for doses of 50-200 mg/day. The clinical significance of the changes observed is not known. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with topiramate. Patients taking estrogen containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding.

Lithium

In healthy volunteers, there was an observed reduction (18% for AUC) in systemic exposure for lithium during concomitant administration with topiramate 200 mg/day. In patients with bipolar disorder, the pharmacokinetics of lithium were unaffected during treatment with topiramate at doses of 200 mg/day; however, there was an observed increase in systemic exposure (26% for AUC) following topiramate doses of up to 600 mg/day. Lithium levels should be monitored when co-administered with topiramate.

Risperidone

Drug-drug interaction studies conducted under single dose conditions in healthy volunteers and multiple dose conditions in patients with bipolar disorder, yielded similar results. When administered concomitantly with topiramate at escalating doses of 100, 250 and 400 mg/day there was a reduction in risperidone (administered at doses ranging from 1 to 6 mg/day) systemic exposure (16% and 33% for steady-state AUC at the 250 and 400 mg/day doses, respectively). Minimal alterations in the pharmacokinetics of the total active moiety (risperidone plus 9-hydroxyrisperidone) and no alterations for 9-hydroxyrisperidone were observed. There were no clinically significant changes in the systemic exposure of the risperidone total active moiety or of topiramate, therefore this interaction is not likely to be of clinical significance.

Hydrochlorothiazide (HCTZ)

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg q24h) and topiramate (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that topiramate C_{max} increased by 27% and AUC increased by 29% when HCTZ was added to topiramate. The clinical significance of this change is unknown. The addition of HCTZ to topiramate therapy may require an adjustment of the topiramate dose. Clinical laboratory results indicated decreases in serum potassium after topiramate or HCTZ administration, which were greater when HCTZ and topiramate were administered in combination.

Metformin

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

When topiramate is added or withdrawn in patients on metformin therapy, careful attention should be given to the routine monitoring for adequate control of their diabetic disease state.

Pioglitazone

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

Glyburide

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

When topiramate is added to glyburide therapy or glyburide is added to topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Other forms of interactions

Agents predisposing to nephrolithiasis

Topiramate, when used concomitantly with other agents predisposing to nephrolithiasis, may increase the risk of nephrolithiasis. While using topiramate, agents like these should be avoided since they may create a physiological environment that increases the risk of renal stone formation.

Valproic acid

Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse reaction is not due to a pharmacokinetic interaction. An association of hyperammonemia with topiramate monotherapy or concomitant treatment with other anti-epileptics has not been established.

Additional pharmacokinetic drug interaction studies

Clinical studies have been conducted to assess the potential pharmacokinetic drug interaction between topiramate and other agents. The changes in C_{max} or AUC as a result of the interactions are summarized below. The second column (concomitant drug concentration) describes what happens to the concentration of the concomitant drug listed in the first column when topiramate is added. The third column (topiramate concentration) describes how the coadministration of a drug listed in the first column modifies the concentration of topiramate.

Summary of Results from Additional Clinical Pharmacokinetic Drug Interaction Studies

Concomitant Drug	Concomitant Drug Concentration[a]	Topiramate Concentration[a]
Amitriptyline	↔ 20% increase in C_{max} and AUC of nortriptyline metabolite	NS
Dihydroergotamine (Oral and Subcutaneous)	↔	↔
Haloperidol	↔ 31% increase in AUC of the reduced metabolite	NS
Propranolol	↔ 17% increase in C_{max} for 4-OH propranolol (TPM 50 mg q12h)	9% and 16% increase in C_{max}, 9% and17% increase in AUC (40 and 80 mg propranolol q12h respectively)
Sumatriptan (Oral and Subcutaneous)	↔	NS
Pizotifen	↔	↔
Diltiazem	25% decrease in AUC of diltiazem and 18% decrease in DEA, and ↔ for DEM*	20% increase in AUC
Venlafaxine	↔	↔
Flunarizine	16% increase in AUC (TPM 50 mg q12h)[b]	↔

[a] % values are the changes in treatment mean C_{max} or AUC with respect to monotherapy
↔ = No effect on C_{max} and AUC (≤ 15% change) of the parent compound
NS = Not studied
*DEA = des acetyl diltiazem, DEM = N-demethyl diltiazem
[b] Flunarizine AUC increased 14% in subjects taking flunarizine alone. Increase in exposure may be attributed to accumulation during achievement of steady state.

4.6. Pregnancy and Lactation

Use during pregnancy

Studies in animals have shown reproductive toxicity (see Pharmacokinetic Properties). As with other antiepileptic drugs, topiramate was teratogenic in mice, rats and rabbits. In rats, topiramate crosses the placental barrier.

There are no adequate and well-controlled studies with topiramate in pregnant women.

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 congenital malformations (e.g., craniofacial defects, such as cleft lip/palate, hypospadias, and anomalies involving various body systems) and neurodevelopmental disorders (e.g., autism spectrum disorders and intellectual disability). This has been reported with topiramate monotherapy and topiramate as part of a polytherapy regimen.

Data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry indicate an increased risk of oral clefts in infants exposed to topiramate monotherapy during the first trimester of pregnancy. The prevalence of oral clefts was 1.2% compared to a prevalence of 0.39% - 0.46% in infants exposed to other AEDs, and a prevalence of 0.12% in infants of mothers without epilepsy or treatment with other AEDs. For comparison, the Centers for Disease Control and Prevention (CDC) reviewed available data on oral clefts in the United States and found a similar background rate of 0.17%. The relative risk of oral clefts in topiramate-exposed pregnancies in the NAAED Pregnancy Registry was 9.6 (95% Confidence Interval = CI 3.6 – 25.7) as

compared to the risk in a background population of untreated women. The UK Epilepsy and Pregnancy Register reported a similarly increased prevalence of oral clefts of 3.2% among infants exposed to topiramate monotherapy. The observed rate of oral clefts was 16 times higher than the background rate in the UK, which is approximately 0.2%.

Compared with a reference group not taking antiepileptic drugs, registry data for Topiramate monotherapy showed a higher prevalence of low birth weight (<2500 grams). A causal relationship has not been established. In addition, data from these registries and other studies indicate that, compared with monotherapy, there is an increased risk of teratogenic effects associated with the use of anti-epileptic drugs in combination therapy.

Epilepsy indication
It is recommended to consider alternative therapeutic options in women of childbearing potential. If topiramate is used in women of childbearing potential, it is recommended that highly effective contraception be used (see Interactions), and that the woman is fully informed of the known risks of uncontrolled epilepsy to the pregnancy and the potential risks of the medicinal product to the fetus. If a woman plans a pregnancy, a preconceptional visit is recommended in order to reassess the treatment, and to consider other therapeutic options. In case of administration during the first trimester, careful prenatal monitoring should be performed.

Migraine prophylaxis indication
Topiramate is contraindicated in pregnancy and in women of childbearing potential if a highly effective method of contraception is not used (see Contraindications and Interactions).

Risk related to epilepsy and AEDs in general
Specialist advice should be given to women who are of childbearing potential. The need for treatment with AEDs should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, sudden discontinuation of AED therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child. Monotherapy should be preferred whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated antiepileptics.

Topiramate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see Contraindications). In treating and counseling women of childbearing potential, the prescribing physician should weigh the benefits of therapy against the risks and consider alternative therapeutic options. 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 the fetus.

Use during lactation

Topiramate is excreted in the milk of lactating rats. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggest an extensive excretion of topiramate into breast milk. Since many drugs are excreted into human milk, a decision must be made whether to suspend breast-feeding or to discontinue topiramate therapy, taking into account the importance of the drug to the mother (section 4.4).

Pediatric use

Safety and effectiveness in patients below the age of 2 years have not been established. Topiramate is associated with metabolic acidosis. Chronic untreated metabolic acidosis in paediatric patients may cause osteomalacia (rickets) and may reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of Topiramate on growth and bone-related sequelae has not been systematically investigated.

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

Clinical Trial Data

The safety of topiramate was evaluated from a clinical trial database consisting of 4,111 patients (3,182 on topiramate and 929 on placebo) who participated in 20 double-blind trials and 2,847 patients who participated in 34 open-label trials, respectively, for the treatment of primary generalized tonic-clonic seizures, partial onset seizures, seizures associated with Lennox-Gastaut syndrome, newly or recently diagnosed epilepsy or migraine. The information presented in this section was derived from pooled data. The majority of ADRs were mild to moderate in severity.

Double-Blind, Placebo-Controlled Data, Adjunctive Epilepsy Trials – Adult Patients

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

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

System/Organ Class Adverse Reaction	Topiramate 200-400 mg/day (N=354) %	Topiramate 600-1000 mg/day (N=437) %	PLACEBO (N=382) %
Metabolism and Nutrition Disorders			
Anorexia	5.4	6.2	1.8
Decreased appetite	5.1	8.7	3.7
Psychiatric Disorders			
Bradyphrenia	8.2	19.5	3.1
Expressive language disorder	4.5	9.4	1.6
Confusional state	3.1	5.0	0.8
Depression	3.1	11.7	3.4
Insomnia	3.1	6.4	4.5
Aggression	2.8	3.2	1.8
Agitation	1.7	2.3	1.3
Anger	1.7	2.1	0.5
Anxiety	1.7	6.6	2.9
Disorientation	1.7	3.2	1.0
Mood altered	1.7	4.6	1.0
Nervous System Disorders			
Somnolence	17.8	17.4	8.4
Dizziness	16.4	34.1	13.6
Paresthesia	8.2	17.2	3.7
Coordination abnormal	7.1	11.4	4.2
Nystagmus	6.2	11.7	6.8
Lethargy	5.6	8.0	2.1
Dysarthria	5.4	6.2	1.0
Memory impairment	5.1	10.8	1.8
Disturbance in attention	4.5	11.9	1.8
Tremor	4.0	9.4	5.0
Amnesia	3.4	5.3	1.0
Balance disorder	3.4	3.9	2.4
Hypoesthesia	3.1	5.9	1.0
Intention tremor	3.1	4.8	2.9
Dysgeusia	1.4	4.3	0.8
Mental impairment	1.4	5.0	1.3
Speech disorder	1.1	2.7	0.5
Eye Disorders			
Diplopia	7.3	12.1	5.0
Vision blurred	5.4	8.9	2.4
Visual disturbance	2.0	1.4	0.3
Gastrointestinal Disorders			
Nausea	6.8	15.1	8.4
Diarrhea	5.1	14.0	5.2
Abdominal pain upper	3.7	3.9	2.1
Constipation	3.7	3.2	1.8
Stomach discomfort	3.1	3.2	1.3
Dyspepsia	2.3	3.0	2.1
Dry mouth	1.7	3.7	0.3
Abdominal pain	1.1	2.7	0.8

Musculoskeletal and Connective Tissue Disorders			
Myalgia	2.0	2.5	1.3
Muscle spasms	1.7	2.1	0.8
Musculoskeletal chest pain	1.1	1.8	0.3
General Disorders and Administration Site Conditions			
Fatigue	13.0	30.7	11.8
Irritability	9.3	14.6	3.7
Asthenia	3.4	3.0	1.8
Gait disturbance	1.4	2.5	1.3
Investigations			
Weight decreased	9.0	11.9	4.2

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

Double-Blind, Placebo-Controlled Data, Adjunctive Epilepsy Trials – Pediatric Patients

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

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

System/Organ Class Adverse Reaction	**Topiramate (N=104) %**	**PLACEBO (N=102) %**
Metabolism and Nutrition Disorders		
Decreased appetite	19.2	12.7
Anorexia	5.8	1.0
Psychiatric Disorders		
Aggression	8.7	6.9
Abnormal behavior	5.8	3.9
Confusional state	2.9	2.0
Mood altered	2.9	2.0
Nervous System Disorders		
Somnolence	15.4	6.9
Lethargy	13.5	8.8
Disturbance in attention	10.6	2.0
Balance disorder	5.8	2.0
Dizziness	4.8	2.9
Memory impairment	3.8	1.0
Respiratory, Thoracic and Mediastinal Disorders		

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

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

Double-Blind, Controlled Data, Monotherapy Epilepsy Trials – Adult Patients

ADRs reported in ≥1% of Topiramate-treated adult patients in doubleblind, controlled monotherapy epilepsy trials are shown in Table 3. ADRs that had an incidence >5% at the recommended dose (400 mg/day) in descending order of frequency included paraesthesia, weight decreased, fatigue, anorexia, depression, memory impairment, anxiety, diarrhoea, asthenia, dysguesia, and hypoesthesia.

Table 3: Adverse Reactions in Adults in Double-Blind, Controlled, Monotherapy Epilepsy Studies (≥1% in any group)

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

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

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

[a] topiramate 50 mg/day and topiramate 500 mg/day groups also include subjects whose baseline weight were no more than 50 kg and were randomized to receive topiramate 25 mg/day and topiramate 200 mg/day, respectively.

Double-Blind, Controlled Data, Monotherapy Epilepsy Trials – Pediatric Patients

ADRs reported in ≥2% of Topiramate-treated pediatric patients (6 to 16 years of age) in double-blind, controlled monotherapy epilepsy trials are shown in Table 4. ADRs that had an incidence >5% at the recommended dose (400 mg/day) in descending order of frequency included weight decreased, paraesthesia, diarrhoea, disturbance in attention, pyrexia, and alopecia.

Table 4: Adverse Reactions in Children Age 6-16 Years Old in Double-Blind, Controlled, Monotherapy Epilepsy Studies (≥2% in any topiramate group)

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

Circadian rhythm sleep disorder	0	2.6	2.6	0	0
Disturbance in attention	3.9	2.6	15.4	9.6	0
Dysarthria	0	2.6	2.6	0	0
Hypoaesthesia	0	2.6	0	0	0
Lethargy	2.9	5.3	0	3.6	0
Nystagmus	0	2.6	2.6	0	0
Parosmia	0	0	2.6	0	0
Psychomotor skills impaired	1.0	0	2.6	0	0
Ear and labyrinth disorders	0	2.6	5.1	2.4	0
Ear pain	0	2.6	0	0	0
Vertigo	0	0	5.1	2.4	0
Cardiac disorders	0	2.6	0	0	0
Palpitations	0	2.6	0	0	0
Vascular disorders	0	0	2.6	0	0
Orthostatic hypotension	0	0	2.6	0	0
Respiratory, thoracic and mediastinal disorders	2.0	7.9	7.7	6.0	28.6
Nasal congestion	2.0	0	2.6	1.2	21.4
Epistaxis	0	5.3	5.1	3.6	14.3
Rhinorrhoea	0	2.6	0	1.2	0
Gastrointestinal disorders	10.8	23.7	10.3	14.5	28.6
Vomiting	5.9	10.5	5.1	6.0	14.3
Abdominal discomfort	0	0	0	1.2	7.1
Diarrhea	6.9	10.5	0	8.4	7.1
Stomach discomfort	0	0	2.6	0	7.1
Dry mouth	0	0	2.6	0	0
Gastritis	0	2.6	2.6	1.2	0
Gingival bleeding	0	2.6	0	0	0
Paraesthesia oral	0	2.6	0	0	0
Skin and subcutaneous tissue disorders	1.0	7.9	2.6	10.8	14.3
Rash	1.0	5.3	0	3.6	14.3
Alopecia	0	0	0	4.8	0
Pruritus	0	0	2.6	1.2	0
Urticaria	0	2.6	0	1.2	0
Musculoskeletal and connective tissue disorders	0	0	5.1	1.2	7.1
Arthralgia	0	0	5.1	1.2	7.1
Musculoskeletal stiffness	0	0	0	0	7.1
Myalgia	0	0	2.6	0	0
General disorders and administration site conditions	1.0	7.9	12.8	16.9	14.3
Asthenia	0	0	2.6	4.8	7.1
Pyrexia	1.0	5.3	7.7	7.2	7.1
Hyperthermia	0	0	0	3.6	0
Malaise	0	2.6	0	0	0
Sluggishness	0	0	2.6	0	0
Investigations	6.9	5.3	7.7	16.9	0
Weight decreased	6.9	5.3	7.7	16.9	0
Social circumstances	1.0	0	0	3.6	7.1
Learning disability	1.0	0	0	3.6	7.1

[a] topiramate 50 mg/day and topiramate 500 mg/day groups also include subjects from whose baseline weight were no more than 50 kg and were randomized to receive topiramate 25 mg/day and topiramate 200 mg/day, respectively.

Double-Blind, Placebo-Controlled Data, Migraine Prophylaxis Trials – Adult Patients

ADRs reported in ≥1% of Topiramate-treated adult patients in doubleblind, placebo-controlled migraine prophylaxis trials are shown in Table 5. ADRs that had an incidence >5% at the recommended dose (100 mg/day) in descending order of frequency included paraesthesia, fatigue, nausea, diarrhea, weight decreased,

dysguesia, anorexia, decreased appetite, insomnia, hypoesthesia, disturbance in attention, anxiety, somnolence, and expressive language disorder.

Table 5: Adverse Reactions Reported by ≥1% of Topiramate-Treated Adult Patients in Double-Blind, Placebo-Controlled Migraine Prophylaxis Trials

System/Organ Class Adverse Reaction	Topiramate 50 mg/day (N=227) %	Topiramate 100 mg/day (N=374) %	Topiramate 200 mg/day (N=501) %	PLACEBO (N=436) %
Metabolism and Nutrition Disorders				
Anorexia	3.5	7.5	7.2	3.0
Decreased appetite	5.7	7.0	6.8	3.0
Psychiatric Disorders				
Insomnia	4.8	7.0	5.6	3.9
Anxiety	4.0	5.3	5.0	1.8
Expressive language disorder	6.6	5.1	5.2	1.4
Depression	3.5	4.8	7.4	4.1
Depressed mood	0.4	2.9	2.0	0.9
Confusional state	0.4	1.6	2.0	1.1
Mood swings	1.8	1.3	1.0	0.2
Affect lability	0.4	1.1	0.2	0.2
Bradyphrenia	1.8	1.1	3.4	1.4
Nervous System Disorders				
Paresthesia	35.7	50.0	48.5	5.0
Dysgeusia	15.4	8.0	12.6	0.9
Hypoesthesia	5.3	6.7	7.4	1.4
Disturbance in attention	2.6	6.4	9.2	2.3
Somnolence	6.2	5.1	6.8	3.0
Memory impairment	4.0	4.5	6.2	1.6
Amnesia	3.5	2.9	5.2	0.5
Tremor	1.3	1.9	2.4	1.4
Balance disorder	0.4	1.3	0.4	0
Mental impairment	0.4	1.1	1.8	0.9
Eye Disorders				
Vision blurred	4.0	2.4	4.4	2.5
Ear and Labyrinth Disorders				
Tinnitus	0.4	1.3	1.6	0.7
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	1.3	2.7	1.6	1.4
Epistaxis	0.4	1.1	0.6	0.5
Gastrointestinal Disorders				
Nausea	9.3	13.6	14.6	8.3
Diarrhea	9.3	11.2	10.0	4.4
Dry mouth	1.8	3.2	5.0	2.5

Paresthesia oral	1.3	2.9	1.6	0.5
Constipation	1.8	2.1	1.8	1.4
Abdominal distension	0	1.3	0.2	0.2
Stomach discomfort	2.2	1.3	1.0	0.2
Gastroesophageal reflux disease	0.4	1.1	1.2	0.5
Musculoskeletal and Connective Tissue Disorders				
Muscle twitching	1.8	1.3	1.8	0.7
General Disorders and Administration Site Conditions				
Fatigue	15.0	15.2	19.2	11.2
Asthenia	0.9	2.1	2.6	0.5
Irritability	3.1	1.9	2.4	0.9
Thirst	1.3	1.6	1.0	0.5
Investigations				
Weight decreased	5.3	9.1	10.8	1.4

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

Other Clinical Trial Data

ADRs reported in double-blind controlled clinical trials in <1% of Topiramate-treated adult patients or at any rate in open-label clinical trials of Topiramate-treated adult patients are shown in Table 6.

Table 6. Adverse Reactions Reported in Double-Blind Controlled Clinical Trials in <1% of Topiramate-Treated Adult Patients or at Any Rate in Open-Label Clinical Trials of Topiramate-Treated Adult Patients

Blood and Lymphatic System Disorders

Leukopenia, lymphadenopathy, thrombocytopenia

Immune System Disorders

Hypersensitivity

Metabolism and Nutrition Disorders

Acidosis hyperchloremic, hypokalemia, increased appetite, metabolic acidosis, polydipsia

Psychiatric Disorders

Abnormal behavior, anorgasmia, apathy, crying, distractibility, disturbance in sexual arousal, dysphemia, early morning awakening, elevated mood, euphoric mood, flat affect, hallucination, hallucination auditory, hallucination visual, hypomania, initial insomnia, lack of spontaneous speech, libido decreased, listless, loss of libido, mania, middle insomnia, orgasmic sensation decreased, panic attack, panic disorder, panic reaction, paranoia, perseveration, reading disorder, restlessness, sleep disorder, suicidal ideation, suicide attempt, tearfulness, thinking abnormal

Nervous System Disorders

Ageusia, akinesia, anosmia, aphasia, apraxia, aura, burning sensation, cerebellar syndrome, circadian rhythm sleep disorder, clumsiness, complex partial seizure, convulsion, depressed level of consciousness, dizziness postural, drooling, dysesthesia, dysgraphia, dyskinesia, dysphasia, dystonia, essential tremor, formication, grand mal convulsion, hyperesthesia, hypersomnia, hypogeusia, hypokinesia, hyposmia, neuropathy peripheral, parosmia, poor quality sleep, presyncope, repetitive speech, sensory disturbance, sensory loss, stupor, syncope, unresponsive to stimuli

Eye Disorders
Accommodation disorder, altered visual depth perception, amblyopia, blepharospasm, blindness transient, blindness unilateral, glaucoma, lacrimation increased, mydriasis, night blindness, photopsia, presbyopia, scintillating scotoma, scotoma, visual acuity reduced

Ear and Labyrinth Disorders
Deafness, deafness neurosensory, deafness unilateral, ear discomfort, hearing impaired

Cardiac Disorders
Bradycardia, sinus bradycardia, palpitations

Vascular Disorders
Flushing, hot flush, orthostatic hypotension, Raynaud's phenomenon

Respiratory, Thoracic, and Mediastinal Disorders
Dysphonia, dyspnea exertional, nasal congestion, paranasal sinus hypersecretion

Gastrointestinal Disorders
Abdominal discomfort, abdominal pain lower, abdominal tenderness, breath odor, epigastric discomfort, flatulence, glossodynia, hypoesthesia oral, oral pain, pancreatitis, salivary hypersecretion

Skin and Subcutaneous Tissue Disorders
Anhidrosis, dermatitis allergic, erythema, rash macular, skin discoloration, skin odor abnormal, swelling face, urticaria, urticaria localized

Musculoskeletal and Connective Tissue Disorders
Flank pain, muscle fatigue, muscular weakness, musculoskeletal stiffness

Renal and Urinary Disorders
Calculus ureteric, calculus urinary, hematuria, incontinence, micturition urgency, renal colic, renal pain, urinary incontinence

Reproductive System and Breast Disorders
Sexual dysfunction

General Disorders
Calcinosis, face edema, feeling abnormal, feeling drunk, feeling jittery, malaise, peripheral coldness, sluggishness

Investigations
Blood bicarbonate decreased, crystal urine present, tandem gait test abnormal, white blood cell count decreased

ADRs reported in double-blind controlled clinical trials in <2% of Topiramate-treated pediatric patients or at any rate in open-label clinical trials of Topiramate-treated pediatric patients are shown in Table 7.

Table 7. Adverse Drug Reactions Reported in Double-Blind Controlled Clinical Trials in <2% of Topiramate-Treated Pediatric Patients or at Any Rate in Open-Label Clinical Trials of Topiramate-Treated Pediatric Patients

Blood and Lymphatic System Disorders Eosinophilia, leukopenia, lymphadenopathy, thrombocytopenia
Immune System Disorders Hypersensitivity
Metabolism and Nutrition Disorders Acidosis hyperchloremic, hypokalemia, increased appetite
Psychiatric Disorders Anger, apathy, crying, distractibility, expressive language disorder, initial insomnia, insomnia, middle insomnia, mood swings, perseveration, sleep disorder, suicidal ideation, suicide attempt
Nervous System Disorders Circadian rhythm sleep disorder, convulsion, dysarthria, dysgeusia, grand mal convulsion, hypoesthesia, mental impairment, nystagmus, parosmia, poor quality sleep, psychomotor hyperactivity, psychomotor skills impaired, syncope, tremor
Eye Disorders Diplopia, lacrimation increased, vision blurred
Ear and Labyrinth Disorders Ear pain
Cardiac Disorders Palpitations, sinus bradycardia
Vascular Disorders Orthostatic hypotension
Respiratory, Thoracic, and Mediastinal Disorders Nasal congestion, paranasal sinus hypersecretion, rhinorrhea
Gastrointestinal Disorders Abdominal discomfort, abdominal pain, dry mouth, flatulence, gastritis, gastroesophageal reflux disease, gingival bleeding, glossodynia, pancreatitis, paresthesia oral, stomach discomfort

Musculoskeletal and Connective Tissue Disorders
Arthralgia, musculoskeletal stiffness, myalgia

Renal and Urinary Disorders
Incontinence, micturition urgency, pollakiuria

General Disorders
Feeling abnormal, hyperthermia, malaise, sluggishness

Postmarketing Data

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

Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1,000 to <1/100
Rare ≥1/10,000 to <1/1,000
Very rare <1/10,000, including isolated reports

In Table 8, ADRs are presented by frequency category based on spontaneous reporting rates.

Table 8: Adverse Reactions Identified During Postmarketing Experience with Topiramate by Frequency Category Estimated from Spontaneous Reporting Rates

Infections and Infestations	
Very rare	Nasopharyngitis
Blood and Lymphatic System Disorders	
Very rare	Neutropenia
Immune System Disorders	
Very rare	Allergic edema
Metabolism and Nutrition Disorders	
Very rare	Hyperammonemia
Very rare	Hyperammonemic encephalopathy
Psychiatric Disorders	
Very rare	Feeling of despair
Eye Disorders	
Very rare	Abnormal sensation in eye
Very rare	Angle closure glaucoma
Very rare	Conjunctival edema
Very rare	Eye movement disorder
Very rare	Eyelid edema
Very rare	Maculopathy
Very rare	Myopia
Very rare	Uveitis

Respiratory, Thoracic and Mediastinal Disorders	
Very rare	Cough
Skin and Subcutaneous Tissue Disorders	
Very rare	Erythema multiforme
Very rare	Periorbital edema
Very rare	Stevens-Johnson syndrome
Very rare	Toxic epidermal necrolysis
Musculoskeletal and Connective Tissue Disorders	
Very rare	Joint swelling
Very rare	Limb discomfort
Renal and Urinary Disorders	
Very rare	Renal tubular acidosis
Very rare	Nephrocalcinosis
General Disorders and Administration Site Reactions	
Very rare	Generalized edema
Very rare	Influenza like illness
Investigations	
Very rare	Weight increased

4.9. Overdose

Signs and symptoms

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

Topiramate overdose can result in severe metabolic acidosis (see section 4.4).

The highest topiramate overdose reported was calculated to be between 96 and 110 g and resulted in coma lasting 20 to 24 hours followed by full recovery after 3 to 4 days.

Treatment

In acute topiramate overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has been shown to adsorb topiramate *in vitro*. Treatment should be appropriately supportive and the patient should be well hydrated. Haemodialysis has been shown to be an effective means of removing topiramate from the body.

5. PHARMACOLOGICAL PROPRIETIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antiepileptics, antimigraine preparations, ATC code: N03AX11

Topiramate is classified as a sulfamate-substituted monosaccharide. The precise mechanism by which topiramate exerts its antiseizure and migraine prophylaxis effects are unknown. Electrophysiological and biochemical studies on cultured neurons have identified three properties that may contribute to the antiepileptic efficacy of topiramate.

Action potentials elicited repetitively by a sustained depolarization of the neurons were blocked by topiramate in a time-dependent manner, suggestive of a state-dependent sodium channel blocking action. Topiramate increased the frequency at which γ-aminobutyrate (GABA) activated $GABA_A$ receptors, and enhanced the ability of GABA to induce a flux of chloride ions into neurons, suggesting that topiramate potentiates the activity of this inhibitory neurotransmitter.

This effect was not blocked by flumazenil, a benzodiazepine antagonist, nor did topiramate increase the duration of the channel open time, differentiating topiramate from barbiturates that modulate $GABA_A$ receptors.

Because the antiepileptic profile of topiramate differs markedly from that of the benzodiazepines, it may modulate a benzodiazepine-insensitive subtype of $GABA_A$ receptor. Topiramate antagonized the ability of kainate to activate the kainate/AMPA (α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid) subtype of excitatory amino acid (glutamate) receptor, but had no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype. These effects of topiramate were concentration-dependent over a range of 1 µM to 200 µM, with minimum activity observed at 1 µM to 10 µM.

In addition, topiramate inhibits some isoenzymes of carbonic anhydrase. This pharmacologic effect is much weaker than that of acetazolamide, a known carbonic anhydrase inhibitor, and is not thought to be a major component of topiramate's antiepileptic activity.

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

Studies in mice receiving concomitant administration of topiramate and carbamazepine or phenobarbital showed synergistic anticonvulsant activity, while combination with phenytoin showed additive anticonvulsant activity. In well-controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations of topiramate and its clinical efficacy. No evidence of tolerance has been demonstrated in man.

5.2. Pharmacokinetic properties

The pharmacokinetic profile of topiramate compared to other antiepileptic drugs shows a long plasma half-life, linear pharmacokinetics, predominantly renal clearance, absence of significant protein binding, and lack of clinically relevant active metabolites.

Topiramate is not a potent inducer of drug metabolizing enzymes, can be administered without regard to meals, and routine monitoring of plasma topiramate concentrations is not necessary. In clinical studies, there was no consistent relationship between plasma concentrations and efficacy or adverse events.

Absorption
Topiramate is rapidly and well absorbed. Following oral administration of 100 mg topiramate to healthy subjects, a mean peak plasma concentration (C_{max}) of 1.5 µg/ml was achieved within 2 to 3 hours (T_{max}).

Based on the recovery of radioactivity from the urine the mean extent of absorption of a 100 mg oral dose of ^{14}C-topiramate was at least 81%. There was no clinically significant effect of food on the bioavailability of topiramate.

Distribution
Generally, 13 to 17% of topiramate is bound to plasma protein. A low capacity binding site for topiramate in/on erythrocytes that is saturable above plasma concentrations of 4 µg/ml has been observed. The volume of distribution varied inversely with the dose. The mean apparent volume of distribution was 0.80 to 0.55 l/kg for a single dose range of 100 to 1200 mg. An effect of gender on the volume of distribution was detected, with values for females circa 50% of those for males. This was attributed to the higher percent body fat in female patients and is of no clinical consequence.

Metabolism
Topiramate is not extensively metabolized (~20%) in healthy volunteers. It is metabolized up to 50% in patients receiving concomitant antiepileptic therapy with known inducers of drug metabolizing enzymes. Six metabolites, formed through hydroxylation, hydrolysis and glucuronidation, have been isolated, characterized and identified from plasma, urine and faeces of humans. Each metabolite represents less than 3% of the total

radioactivity excreted following administration of ^{14}C-topiramate. Two metabolites, which retained most of the structure of topiramate, were tested and found to have little or no anticonvulsant activity.

Elimination

In humans, the major route of elimination of unchanged topiramate and its metabolites is via the kidney (at least 81% of the dose). Approximately 66% of a dose of ^{14}C-topiramate was excreted unchanged in the urine within four days. Following twice a day dosing with 50 mg and 100 mg of topiramate the mean renal clearance was approximately 18 ml/min and 17 ml/min, respectively. There is evidence of renal tubular reabsorption of topiramate. This is supported by studies in rats where topiramate was co-administered with probenecid, and a significant increase in renal clearance of topiramate was observed. Overall, plasma clearance is approximately 20 to 30 ml/min in humans following oral administration.

Topiramate exhibits low intersubject variability in plasma concentrations and, therefore, has predictable pharmacokinetics. The pharmacokinetics of topiramate are linear with plasma clearance remaining constant and area under the plasma concentration curve increasing in a dose-proportional manner over a 100 to 400 mg single oral dose range in healthy subjects. Patients with normal renal function may take 4 to 8 days to reach steady-state plasma concentrations. The mean C_{max} following multiple, twice a day oral doses of 100 mg to healthy subjects was 6.76 µg/ml. Following administration of multiple doses of 50 mg and 100 mg of topiramate twice a day, the mean plasma elimination half-life was approximately 21 hours.

Concomitant multiple-dose administration of topiramate, 100 to 400 mg twice a day, with phenytoin or carbamazepine shows dose proportional increases in plasma concentrations of topiramate.

The plasma and renal clearance of topiramate are decreased in patients with moderate and severe impaired renal function ($CL_{CR} \leq 70$ ml/min). As a result, higher steady-state topiramate plasma concentrations are expected for a given dose in renal-impaired patients as compared to those with normal renal function. In addition, patients with renal impairment will require a longer time to reach steady-state at each dose. In patients with moderate and severe renal impairment, half of the usual starting and maintenance dose is recommended (see Posology And Method Of Administration).

Topiramate is effectively removed from plasma by haemodialysis. A prolonged period of hemodialysis may cause topiramate concentration to fall below levels that are required to maintain an anti-seizure effect. 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.

Plasma clearance of topiramate decreased a mean 26% in patients with moderate to severe hepatic impairment. Therefore, topiramate should be administered with caution in patients with hepatic impairment. Plasma clearance of topiramate is unchanged in elderly subjects in the absence of underlying renal disease.

Paediatric population (pharmacokinetics, up to 12 years of age)

The pharmacokinetics of topiramate in children, as in adults receiving add-on therapy, are linear, with clearance independent of dose and steady-state plasma concentrations increasing in proportion to dose. Children, however, have a higher clearance and a shorter elimination half-life. Consequently, the plasma concentrations of topiramate for the same mg/kg dose may be lower in children compared to adults. As in adults, hepatic enzyme inducing anti-epileptic drugs decrease the steady-state plasma concentrations.

5.3. Preclinical safety data

Acute and long-term exposure of mice, rats, dogs and rabbits to topiramate was well tolerated. Hyperplasia of the gastric epithelial cells was observed only in rodents and in rats was reversible after 9 weeks without treatment.

Tumors of smooth muscle origin in the urinary bladder were seen only in mice (oral dosages up to 300 mg/kg for 21 months) and appear to be unique to the species. Since no human counterpart exists, they were not considered clinically relevant. No such findings occurred in the rat carcinogenicity study (oral dosages up to

120 mg/kg/day for 24 months). Other toxicologic and pathologic effects of topiramate observed in these studies may be related to the weak induction of drug metabolizing enzymes or weak carbonic anhydrase inhibition.

Despite maternal and paternal toxicity as low as 8 mg/kg/day, no effects on fertility were observed, in male or female rats with doses up to 100 mg/kg/day.

In preclinical studies, topiramate has been shown to have teratogenic effects in the species studied (mice, rats and rabbits). In mice, fetal weights and skeletal ossification were reduced at 500 mg/kg/day in conjunction with maternal toxicity. Overall numbers of fetal malformations in mice were increased for all drug-treated groups (20, 100 and 500 mg/kg/day), but no significant differences or dosage-response relationships were observed for overall or specific malformations, suggesting that other factors such as maternal toxicity may be involved.

In rats, dosage-related maternal and embryo/fetal toxicity (reduced fetal weights and/or skeletal ossification) were observed down to 20 mg/kg/day with teratogenic effects (limb and digit defects) at 400 mg/kg/day and above. In rabbits, dosage-related maternal toxicity was noted down to 10 mg/kg/day with embryo/fetal toxicity (increased lethality) down to 35 mg/kg/day, and teratogenic effects (rib and vertebral malformations) at 120 mg/kg/day.

The teratogenic effects seen in rats and rabbits were similar to those seen with carbonic anhydrase inhibitors, which have not been associated with malformations in humans. Effects on growth were also indicated by lower weights at birth and during lactation for pups from female rats treated with 20 or 100 mg/kg/day during gestation and lactation. In rats, topiramate crosses the placental barrier.

In juvenile rats, daily oral administration of topiramate at doses up to 300 mg/kg/day during the period of development corresponding to infancy, childhood, and adolescence resulted in toxicities similar to those in adult animals (decreased food consumption with decreased body weight gain, centrolobullar hepatocellular hypertrophy and slight urothelial hyperplasia in the urinary bladder). There were no relevant effects on long bone (tibia) growth or bone (femur) mineral density, preweaning and reproductive development, neurological development (including assessments on memory and learning), mating and fertility or hysterotomy parameters.

In a battery of *in vitro* and *in vivo* mutagenicity assays, topiramate did not show genotoxic potential.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet nucleus
Lactose monohydrate
Pregelatinized maize starch
Sodium starch glycolate Type A
Microcrystalline cellulose
Magnesium stearate

Tablet coating
Basic butylated methacrylate copolymer
Sodium laurilsulfate
Stearic acid
Magnesium stearate
Talc
Titanium dioxide (E171)
Yellow iron oxide (E 172) [only for 50mg and 100mg]

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

25mg – 24 months
50mg – 24 months
100mg – 24 months

6.4. Special precautions for storage

Store at or below 25˚C

6.5. Nature and contents of container

Tablets are packed in PVC/PCTFE/PVC and Aluminium blister.
Blister packs of 60 tablets.

6.6. Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novem Pharma Pte Ltd
23 New Industrial Road
#03-08 Solstice Business Center
Singapore 536209

8. MARKETING AUTHORISATION NUMBER(S)

Topiron 25mg film-coated tablets - SIN14132P
Topiron 50mg film-coated tablets - SIN14131P
Topiron 100 mg film-coated tablets – SIN14311P

9. DATE OF REVISION OF THE TEXT

Apr 2023