AUSTRALIAN PRODUCT INFORMATION

TAMATE®

(topiramate) tablet

1 NAME OF THE MEDICINE

Topiramate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25 mg, 50 mg, 100 mg, or 200 mg of Topiramate as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

TAMATE 25 mg: White, round, biconvex, film-coated tablet debossed with "G" on one side and "TO" over "25" on the other.

TAMATE 50 mg: Yellow, round, biconvex, film-coated tablet debossed with "G" on one side and "TO" over "50" on the other.

TAMATE 100 mg: Yellow, round, biconvex, film-coated tablet debossed with "G" on one side and "TO" over "100" on the other.

TAMATE 200 mg: Red, round, biconvex, film-coated tablet debossed with "G" on one side and "TO" over "200" on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Epilepsy

TAMATE is indicated in adults and children, 2 years and over:

- as monotherapy in patients with newly diagnosed epilepsy
- for conversion to monotherapy in patients with epilepsy
- as add-on therapy in partial onset seizures (with or without secondary generalised seizures), primary generalised tonic-clonic seizures or drop attacks associated with Lennox-Gastaut syndrome.

Migraine

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Method of administration

TAMATE tablets should be swallowed whole.

TAMATE can be taken without regard to meals.

Dosage (dose and interval)

For optimum seizure control in both adults and children, it is recommended that therapy should be initiated at a low dose followed by slow titration to an effective dose. Dose titration should be guided by clinical outcome.

The recommended dosages of TAMATE in adults and children for epilepsy are summarised in Table 1.

Epilepsy - Monotherapy

In newly diagnosed epileptic patients, TAMATE monotherapy should be initiated at a low dose (see Table 1).

In patients who are being converted to TAMATE monotherapy, consideration should be given to the effects of seizure control when withdrawing concomitant antiepileptic agents (AEDs). 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 (see Drug withdrawal and Dosage reduction and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). When enzyme inducing drugs are withdrawn, topiramate levels will increase. A decrease in TAMATE dosage may be required if clinically indicated.

Adults: Titration for monotherapy should begin at 25 mg as a single (nightly) dose for one week or longer. The dosage should then be increased by 25 to 50 mg/day at weekly or longer intervals to the recommended target dose of 100 mg/day. If the patient is unable to tolerate the titration regimen, smaller increments or longer intervals between increments can be used. The maximum recommended dose is 500 mg/day. Some patients with refractory forms of epilepsy have tolerated doses of 1,000 mg/day. The daily dosage should be taken as two divided doses.

Children (2 years and over): Titration for monotherapy should begin at 0.5 to 1 mg/kg as a single (nightly) dose for the first week. The dosage should then be increased by 0.5 to 1 mg/kg/day at weekly or longer intervals to the recommended target dose of 3 to 6 mg/kg/day. If the child is unable to tolerate the titration regimen, smaller increments or longer intervals between dose increments can be used. Some children with recently diagnosed partial onset seizures have received doses of up to 500 mg/day. The daily dosage should be given as two divided doses.

Epilepsy Add-on therapy

Adults: Titration for add-on therapy should begin at 25 to 50 mg as a single (nightly) or divided dose for one week or longer. The dosage should then be increased by 25 to 100 mg/day at weekly or longer intervals to the target dose of 200 to 400 mg/day. The maximum recommended dose should not exceed 1000 mg/day. The daily dosage should be taken as two divided doses.

Children (2 years and over): Titration for add-on therapy should begin at 1 to 3 mg/kg/day up to 25 mg/day as a single (nightly) dose for the first week. The dosage should then be increased by 1 to 3 mg/kg/day at weekly or longer intervals to the recommended total daily dose of 5 to 9 mg/kg/day. Daily doses up to 30 mg/kg have been studied and were generally well tolerated. The daily dosage should be given as two divided doses.

Table 1: Recommended dosages in adults and children

		Monotherapy	**Add-on therapy**
Adults	**Starting dose**	25 mg as a single (nightly) dose for one week (or longer).	25 to 50 mg as a single (nightly) or divided dose for one week (or longer).
	Escalation dose	Increase by 25 to 50 mg/day at weekly or longer intervals.	Increase by 25 to 100 mg/day at weekly or longer intervals.
	Target dose	100 mg/day	200 to 400 mg/day
	Maximum dose	Up to 500 mg/day[1]	Up to 1000 mg/day
Children 2 years & over	**Starting dose**	0.5 to 1 mg/kg as a single (nightly) dose for the first week.	1 to 3 mg/kg/day up to 25 mg/day as a single (nightly) dose for the first week.
	Escalation dose	Increase by 0.5 to 1 mg/kg/day at weekly or longer intervals.	Increase by 1 to 3 mg/kg/day at weekly or longer intervals.
	Target dose	3 to 6 mg/kg/day	5 to 9 mg/kg/day
	Maximum dose	Up to 500 mg/day	Up to 30 mg/kg/day

Note: Daily doses greater or equal to 50 mg should be taken as two divided doses.
[1] Some patients with refractory epilepsy have tolerated doses of 1000 mg/day.

It is not necessary to monitor topiramate plasma concentrations to optimise TAMATE therapy. For patients receiving concomitant phenytoin and carbamazepine, dosage adjustment for TAMATE may be required (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Migraine

Adults

Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased weekly in increments of 25 mg/day. If the patient is unable to tolerate the titration regimen, longer intervals between dose adjustments can be used.

The recommended total daily dose of TAMATE as treatment for prophylaxis of migraine headache is 100 mg/day administered in two divided doses. 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 should be guided by clinical outcome.

Use in the elderly

Caution is advised during titration in the elderly with renal disease and/or hepatic impairment (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Use in patients with hepatic and/or renal impairment

Caution is advised during titration in patients with renal disease and/or hepatic impairment (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Patients with moderate and severe renal impairment may require a dose reduction. Half of the usual starting and maintenance dose is recommended (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Use in patients undergoing haemodialysis

Topiramate is cleared by haemodialysis. To avoid rapid reduction in topiramate plasma concentration during haemodialysis, a supplemental dose of TAMATE 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 Section 5.2 PHARMACOKINETIC PROPERTIES).

The actual adjustment should take into account:

- the duration of the dialysis period,
- the clearance rate of the dialysis system being used, and
- the effective renal clearance of topiramate in the patient being dialysed.

Drug withdrawal and Dosage reduction

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

4.3 CONTRAINDICATIONS

Hypersensitivity to any component of this product.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Withdrawal of Topiramate

In patients with or without a history of seizures or epilepsy, antiepileptic medicines including topiramate should be gradually withdrawn to minimise 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.

Topiramate has not been studied in patients with a history of psychiatric disorders. Given the reported association of certain antiepileptic agents and psychiatric disturbances, topiramate should be used with caution in patients with a prior psychiatric history.

Hydration

Maintaining adequate hydration whilst using topiramate is very important. Hydration can reduce the risk of nephrolithiasis. Proper hydration prior to and during activities such as exercise or exposure to warm temperatures may reduce the risk of heat-related adverse events.

Suicidal Behaviour and Ideation

Antiepileptic drugs (AEDs), including topiramate, increase the risk of suicidal thoughts or behaviour 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 behaviour, and/or any unusual changes in mood or behaviour.

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 behaviour compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour 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 behaviour 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 behaviour 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 behaviour beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analysed. 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 analysed.

Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2: 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 behaviour 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.

In double-blind clinical trials with topiramate in approved and investigational indications, suicide related events (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.

Anyone considering prescribing topiramate or any other AED must balance the risk of suicidal thoughts or behaviour 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 behaviour. Should suicidal thoughts and behaviour 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.

Patients, and, when appropriate, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour or the emergence of suicidal thoughts, behaviour or thoughts about self-harm. Behaviours of concern should be reported immediately to the treating doctor.

Serious Skin Reactions

Serious skin reactions (Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)) have been reported in patients receiving topiramate (Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). 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.

Nephrolithiasis

Patients, especially those with a predisposition to nephrolithiasis, may be at increased risk for renal stone formation (none of 216 placebo patients versus 1.6% of 1446 patients who had received topiramate were reported to have nephrolithiasis) 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 (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Metabolic acidosis and sequelae), and gender (male). None of these risk factors can reliably predict stone formation during topiramate treatment. In addition, patients taking other medication associated with nephrolithiasis may be at increased risk.

Oligohydrosis and Hyperthermia

Oligohydrosis (decreased sweating) and anhidrosis, 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 temperature.

The majority of the 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.

Patients, especially paediatric patients, treated with topiramate should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather.

Use in patients with 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.

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

Use in patients with hepatic impairment

In hepatically-impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased.

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. Ophthalmological findings can include some or all of the following: myopia, mydriasis, anterior chamber shallowing, ocular hyperaemia (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 paediatric patients as well as adults. Treatment includes discontinuation of topiramate as rapidly as possible in the judgement of the treating physician and appropriate measures to reduce intraocular pressure. These measures generally result in a decrease in intraocular pressure.

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

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 however, some cases were not. In a large proportion of post marketing case reports reversibility was unknown, but in cases where an outcome was reported, the majority were reversible. If visual problems occur at any time during topiramate treatment, consideration should be given to discontinuing the drug.

Metabolic acidosis and sequelae

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 as 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 medicines) may be additive to the bicarbonate lowering effects of topiramate.

Chronic, untreated metabolic acidosis may increase the risk of nephrolithiasis or nephrocalcinosis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Nephrolithiasis).

In adults, the incidence of persistent treatment-emergent decreases in serum bicarbonate (levels of <20 mmol/L at two consecutive visits or at the final visit) in controlled clinical trials for adjunctive treatment of epilepsy was 32% for 400 mg/day, and 1% for placebo. Metabolic acidosis has been observed at doses as low as 50 mg/day. The incidence of a markedly abnormally low serum bicarbonate (i.e. absolute value <17 mmol/L and >5 mmol/L decrease from pre-treatment) in these trials was 3% for 400 mg/day, and 0% for placebo. Serum bicarbonate levels have not been systematically evaluated at daily doses greater than 400 mg/day.

The incidence of persistent treatment-emergent decreases in serum bicarbonate in placebo-controlled trials for adults for prophylaxis of migraine was 44% for 200 mg/day, 39% for 100 mg/day, 23% for 50 mg/day, and 7% for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mmol/L and >5 mmol/L decrease from pre-treatment) in these trials was 11% for 200 mg/day, 9% for 100mg/day, 2% for 50 mg/day, and <1% for placebo.

In paediatric patients (<16 years of age), the incidence of persistent treatment-emergent decreases in serum bicarbonate in placebo-controlled trials for adjunctive treatment of Lennox-Gastaut syndrome or refractory partial onset seizures was 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 mmol/L and >5 mmol/L decrease from pre-treatment) in these trials was 11% for topiramate and 0% for placebo. Cases of moderately severe metabolic acidosis have been reported in patients as young as 5 months old, especially at daily doses above 5 mg/kg/day.

Some 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 paediatric patients) and/or osteoporosis with an increased risk for fractures. Chronic metabolic acidosis in paediatric patients can 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 in adult populations. A one year, open-label study in paediatric patients aged 6 to 15 years including 63 subjects with recent or new onset of epilepsy was conducted to assess the effects of topiramate (28 subjects) versus levetiracetam on growth, development, and bone mineralization. Continued growth was observed in both treatment groups but the topiramate group showed statistically significant reductions in mean annual change from baseline in body weight and bone mineral density compared to the levetiracetam group. A similar trend was also observed for height and height velocity but were not statistically significant. Growth-related changes were not clinically significant nor treatment limiting. Other confounding factors cannot be excluded.

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 (by using dose tapering).

Hyperammonemia and encephalopathy

Hyperammonemia with or without encephalopathy has been reported with topiramate treatment (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). The risk for hyperammonemia with topiramate appears dose-related. Hyperammonemia has been reported more frequently when topiramate is used concomitantly with valproic acid (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy. In most cases, hyperammonemic encephalopathy abated with discontinuation of treatment. In patients who develop unexplained lethargy, or changes in mental status associated with topiramate monotherapy or adjunctive therapy, it is recommended to consider hyperammonemic encephalopathy and measuring ammonia levels.

Mood Disturbances/Depression

An increased incidence of mood disturbances and depression has been observed during topiramate treatment. Psychiatric/behavioural disturbances (depression or mood problems) in the majority of affected patients were dose related for both the add-on epilepsy and migraine populations.

Women of childbearing potential

Topiramate may cause fetal harm when administered to a pregnant woman. There is an increased risk of pre-term labour, premature delivery and congenital malformations 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 Section 4.6 FERTILITY, PREGNANCY and LACTATION).

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 Section 4.3 CONTRAINDICATIONS and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS)

Topiramate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see Section 4.3 CONTRAINDICATIONS and Section 4.6 FERTILITY, PREGNANCY and LACTATION).

Use in the Elderly

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Use in the elderly.

Paediatric Use

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Children (2 years and over).

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Studies in mice receiving concomitant administration of topiramate and carbamazepine or phenobarbital showed synergistic anticonvulsant activity, while combination with phenytoin showed additive anticonvulsant activity.

Effects of topiramate on other antiepileptic drugs

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.

Effects of other antiepileptic drugs on topiramate

The metabolic breakdown of topiramate is increased in patients receiving concomitant antiepileptic therapy with agents that are inducers of drug metabolising enzymes. The increased metabolic breakdown results in up to 1.5 times higher clearance of 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 summarised in Table 3.

Table 3: Summary of AED interactions with topiramate

AED Co-administered	AED Concentration	Topiramate Concentration
Phenytoin	↔ *	↓** (48%)
Carbamazepine (CBZ)	↔	↓ (40%)
Valproic Acid	↔	↔
Phenobarbital	↔	N
Primidone	↔	N
Lamotrigine	↔	↔

↔ = No effect on plasma concentration
* = Plasma concentrations increase in occasional patients
↓ = Plasma concentrations decrease
** = Approximately 35% decrease in plasma C_{maxss} and 57% decrease in plasma C_{minss} concentrations
N = Not studied
AED = antiepileptic drug
NOTE: No data are available on the use of topiramate with lamotrigine, gabapentin or vigabatrin.

No data are available on the use of topiramate with vigabatrin.

Other drug 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.

Contraceptives

In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethisterone (NET) plus 35 mcg ethinylestradiol (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 mg/day to 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 contraceptive products with topiramate. Patients taking oestrogen 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.

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 and multiple dose conditions in healthy volunteers and 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. The clinical relevance of the observed, apparently not statistically significant changes in the systemic exposure of the total active moiety (risperidone plus 9-hydroxyrisperidone) or of topiramate is not known.

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 $AUC_{t, ss}$ 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 $AUC_{t, ss}$ respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in $C_{max, ss}$ and $AUC_{t, ss}$ 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.

Glibenclamide

A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glibenclamide (5 mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 25% reduction in glibenclamide AUC24 during topiramate administration. Systemic exposure of the active metabolites, 4-trans-hydroxy-glibenclamide (M1) and 3-cis-hydroxyglibenclamide (M2), were also reduced by 13% and 15%, respectively. The steady-state pharmacokinetics of topiramate were unaffected by concomitant administration of glibenclamide. When topiramate is added to glibenclamide therapy or glibenclamide 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 (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). This adverse effect is not due to a pharmacokinetic interaction.

Hypothermia, defined as an unintentional drop in body core temperature to <35°C, has been reported in association with concomitant use of topiramate and valproic acid (VPA) both in conjunction with hyperammonemia and in the absence of hyperammonemia. This adverse event in patients using concomitant topiramate and valproate can occur after starting topiramate treatment or after increasing the daily dose of topiramate.

Vitamin K-antagonist anticoagulant medications

Decreased Prothrombin Time/International Normalized Ratio (PT/INR) responses have been reported following concomitant administration of topiramate with vitamin K-antagonist anticoagulant medications. Closely monitor INR during concomitant administration of topiramate therapy with vitamin K-antagonist anticoagulant medications.

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 in Table 4. 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.

Table 4: Summary of Results from Additional Clinical Pharmacokinetic Drug Interaction Studies

Concomitant Drug	Concomitant Drug Concentration	Topiramate Concentration
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 50mg q12h)	9% and 16% Increase in C_{max}, 9% and 17% increase in AUC (40 mg 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]	↔

↔ = No effect on C_{max} and AUC (≤ 15% change) of the parent compound

[b] = Flunarizine AUC increased 14% in subjects taking flunarizine alone. Increase in exposure may be attributed to accumulation during achievement of steady state.

NS = Not studied

*DEA = des acetyl diltiazem, DEM = N-demethyl diltiazem

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

There were no effects on fertility or reproductive parameters in rats following oral administration of topiramate at doses up to 100 mg/kg/day, with estimated exposures (plasma AUC) less than human exposure at the maximal recommended clinical dose. Oral administration of topiramate to juvenile rats did not affect subsequent reproductive development, mating or fertility (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Growth and Development).

Use in Pregnancy

Pregnancy Category: D

When administered orally during organogenesis, topiramate was teratogenic in mice, rats and rabbits at maternal exposures (plasma AUC) less than clinical exposure at the maximal recommended dose. In mice, the numbers of fetal malformations (primarily craniofacial abnormalities) were increased at all dose levels tested. The malformations in rats (limb reduction defects) and rabbits (axial and costal skeletal defects) were similar to those seen with carbonic anhydrase inhibitors in these species. Carbonic anhydrase inhibitors have not been associated with malformations in human beings.

There are no studies using topiramate in pregnant women. In post-marketing experience, cases of hypospadias have been reported in male infants exposed in-utero to topiramate, with or without other anticonvulsants. A causal relationship with topiramate has not been established.

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

Topiramate can cause fetal harm when administered to a pregnant woman. This has been reported with topiramate monotherapy and topiramate as part of a polytherapy regimen.

Congenital malformations

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).

Data from the North American AED (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 1.4% compared to a prevalence of 0.38% - 0.55% in infants exposed to other AEDs, and a prevalence of 0.07 % in infants of mothers without epilepsy or treatment with other AEDs. The relative risk of oral clefts in topiramate-exposed pregnancies in the NAAED Pregnancy Registry was 21.3 (95% Confidence Interval 7.9 – 57.1) 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%.

In addition, data from 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. The risk has been observed in all doses and effects were reported to be dose-dependent. In women treated with topiramate who have had a child with a congenital malformation, there appears to be an increased risk of malformations in subsequent pregnancies when exposed to topiramate. There is an increased risk of pre-term labour and premature delivery associated with the use of AEDs, including topiramate.

Small for gestational age (SGA)

Compared with a reference group not taking antiepileptic drugs, registry data for topiramate monotherapy showed a higher prevalence of low birth weight (<2500 grams). One pregnancy registry reported an increased frequency of infants who were small for gestational age (SGA; defined as birth weight below the 10th percentile corrected for their gestational age, stratified by sex) among those exposed to topiramate monotherapy in utero. SGA has been observed in all doses and is dose-dependent. The prevalence of SGA is greater in women who received higher doses of topiramate during pregnancy. In addition, the prevalence of SGA for women who continued topiramate use later in pregnancy is higher compared to women who stopped its use before the third trimester. The long-term consequences of the SGA findings could not be determined. A causal relationship for low birth weight and SGA has not been established.

Neurodevelopmental disorders

- Data from an observational US cohort study did not suggest an increased cumulative incidence of autism spectrum disorder by 8 years of age in 1030 children of mothers with epilepsy exposed to topiramate in utero, compared with children of mothers with epilepsy not exposed to topiramate, after adjustment for indication and other confounders.

- Data from two observational population-based registry studies undertaken in largely the same dataset from the Nordic countries suggest that there may be a 2- to 3-fold higher prevalence of autism spectrum disorders, intellectual disability or attention deficit hyperactivity disorder (ADHD) in almost 300 children of mothers with epilepsy exposed to topiramate in utero, compared with children of mothers with epilepsy not exposed to an AED.

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 Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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 Section 4.3 CONTRAINDICATIONS and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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 potential benefit justifies the potential risk to the fetus (see Section 4.3 CONTRAINDICATIONS). In treating and counselling women of childbearing potential, the prescribing physician should weigh the benefits of therapy against the risks. 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.

The risk of having an abnormal child as a result of antiepileptic medication is far outweighed by the danger to the mother and fetus of uncontrolled epilepsy.

It is recommended that:

- Women on antiepileptic drugs (AEDs) receive pregnancy counselling with regard to the risk of fetal abnormalities;
- AEDs should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication;
- Folic acid supplementation (5 mg) should be commenced four weeks prior to and continue for twelve weeks after conception;
- Specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.

Use in Lactation

Radioactivity was detected in milk following oral administration of radiolabelled topiramate to lactating rats. About 1.5% of the dose was recovered in milk in 24 hours, and milk and maternal plasma radioactivity concentrations were similar. The excretion of topiramate has not been evaluated in controlled studies. Limited observation in patients suggests an extensive excretion of topiramate in breast milk. Diarrhoea and somnolence have been reported in breastfed infants whose mothers receive topiramate treatment. Lactating women should be advised not to breastfeed during treatment with topiramate.

Growth and Development

In juvenile rats, 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, centrilobular 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. Exposure (plasma AUC) was up to 2-fold human exposure at the maximal recommended clinical dose.

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 events are potentially dangerous in patients driving a vehicle or operating machinery, particularly until the individual patient's experience with the drug is established.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Data

The safety of topiramate was evaluated from a clinical trial database consisting of 4111 patients (3182 on topiramate and 929 on placebo) who participated in 20 double-blind trials and 2847 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 all adverse reactions were mild to moderate in severity.

Increased risk for Bleeding

Topiramate treatment 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 event for topiramate than for placebo (4.5% versus 3.0% in adult patients, and 4.4% versus 2.3% in paediatric 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 paediatric patients.

Adverse bleeding reactions reported with topiramate ranged from mild epistaxis, ecchymosis, and increased menstrual bleeding to life-threatening haemorrhages. 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, non-steroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, or warfarin or other anticoagulants).

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 5. 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, nystagmus, lethargy, anorexia, dysarthria, vision blurred, decreased appetite, memory impairment and diarrhoea.

Table 5: Adverse Drug 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
Paraesthesia	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
Hypoaesthesia	3.1	5.9	1.0
Intention tremor	3.1	4.8	2.9
Dysgeusia	1.4	4.3	0.8

Table 5: Adverse Drug 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) %**
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
Diarrhoea	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
Adverse drug reactions reported by <1% of topiramate-treated adult patients in double-blind, placebo-controlled, adjunctive epilepsy trials included increased appetite, abnormal behaviour, apathy, depressed mood, distractibility, disturbance in sexual arousal, dysphemia, euphoric mood, flat affect, lack of spontaneous speech, mood swings, panic disorder, paranoia, reading disorder, sleep disorder, suicidal ideation, thinking abnormal, aphasia, cerebellar syndrome, cognitive disorder, dysaesthesia, dysgraphia, dyskinesia, formication, parosmia, psychomotor skills impaired, repetitive speech, sensory disturbance,			

Table 5: Adverse Drug 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) %**
sensory loss, stupor, unresponsive to stimuli, lacrimation increased, presbyopia, visual acuity reduced, deafness, deafness unilateral, hearing impaired, tinnitus, sinus bradycardia, dyspnoea, dyspnoea exertional, paranasal sinus hypersecretion, abdominal discomfort, abdominal tenderness, breath odour, flatulence, hypoaesthesia oral, paraesthesia oral, erythema, hypoaesthesia facial, skin odour abnormal, swelling face, calculus urinary, dysuria, haematuria, incontinence, pollakiuria, renal colic, renal pain, urinary, incontinence, erectile dysfunction, sexual dysfunction, feeling abnormal, feeling drunk, tandem gait test abnormal, and white blood cell count decreased. The recommended dose for adjunctive epilepsy therapy in adults is 200-400 mg/day.			

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

ADRs reported in >2% of topiramate-treated paediatric patients (2 to 16 years of age) in double-blind, placebo-controlled adjunctive epilepsy trials are shown in Table 6. 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 behaviour, anorexia, balance disorder, and constipation.

Table 6: Adverse Drug Reactions Reported by ≥ 2% of Topiramate-Treated Paediatric 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 behaviour	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

Table 6: Adverse Drug Reactions Reported by ≥ 2% of Topiramate-Treated Paediatric Patients in Double-Blind, Placebo-Controlled, Adjunctive Epilepsy Trials		
System/Organ Class Adverse Reaction	**Topiramate (N=104) %**	**Placebo (N=102) %**
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
Adverse drug reactions reported by <2% of topiramate-treated pediatric patients in double-blind, placebo-controlled, adjunctive epilepsy trials included leukopenia, lymphadenopathy, thrombocytopenia, increased appetite, anger, middle insomnia, perseveration, dysarthria, dysgeusia, paraesthesia, poor quality sleep, syncope, tremor, diplopia, lacrimation increased, vision blurred, sinus bradycardia, paranasal sinus hypersecretion, abdominal pain, flatulence, gastrooesophageal reflux disease, glossodynia, alopecia, skin discolouration, musculoskeletal stiffness, incontinence, pollakiuria, asthenia, feeling abnormal, malaise, and thirst. Nausea and headache were not considered ADRs based on case review which indicated that these events could be attributed to other causes, including concomitant use of other medications or an intervening illness 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 double-blind, controlled monotherapy epilepsy trials are shown in Table 7. 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, dysgeusia, and hypoesthesia.

Table 7: Adverse Drug Reactions Reported by ≥ 1% of Topiramate-Treated Adult Patients in Double-Blind, Controlled Monotherapy Epilepsy Trials		
System/Organ Class Adverse Reaction	**Topiramate 50 mg/day (N=257) %**	**Topiramate 400 mg/day (N=153) %**
Blood and Lymphatic System Disorders		
Anaemia	0.8	2.0
Metabolism and Nutrition Disorders		
Anorexia	3.5	12.4
Decreased appetite	2.3	2.6
Psychiatric Disorders		
Depression	4.3	8.5

Table 7: Adverse Drug Reactions Reported by ≥ 1% of Topiramate-Treated Adult Patients in Double-Blind, Controlled Monotherapy Epilepsy Trials		
System/Organ Class Adverse Reaction	**Topiramate 50 mg/day (N=257) %**	**Topiramate 400 mg/day (N=153) %**
Anxiety	3.9	6.5
Bradyphrenia	2.3	4.6
Expressive language disorder	3.5	4.6
Depressed mood	0.8	2.6
Mood altered	0.4	2.0
Mood swings	1.6	2.0
Nervous System Disorders		
Paraesthesia	18.7	40.5
Memory impairment	1.2	7.2
Dysgeusia	2.3	5.9
Hypoaesthesia	4.3	5.2
Balance disorder	1.6	3.3
Dysarthria	1.6	2.6
Cognitive disorder	0.4	2.0
Lethargy	1.2	2.0
Mental impairment	0.8	2.0
Psychomotor skills impaired	0	2.0
Sedation	0	1.3
Visual field defect	0.4	1.3
Eye Disorders		
Dry eye	0	1.3
Ear and Labyrinth Disorders		
Ear pain	0	1.3
Tinnitus	1.6	1.3
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnoea	1.2	2.0
Rhinorrhoea	0	1.3
Gastrointestinal Disorders		
Diarrhoea	5.4	6.5
Paraesthesia oral	1.2	3.3
Dry mouth	0.4	2.6
Gastritis	0.8	2.6
Abdominal pain	1.2	2.0
Gastroesophageal reflux disease	0.4	2.0
Gingival bleeding	0	1.3
Skin and Subcutaneous Tissue Disorders		
Rash	0.4	3.9
Alopecia	1.6	3.3
Pruritis	0.4	3.3
Hypoaesthesia facial	0.4	2.0
Pruritis generalised	0	1.3
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	2.7	3.3
Arthralgia	1.9	2.0
Muscle twitching	0.4	1.3
Renal and Urinary Disorders		
Nephrolithiasis	0	2.6
Dysuria	0.8	2.0

Table 7: Adverse Drug Reactions Reported by ≥ 1% of Topiramate-Treated Adult Patients in Double-Blind, Controlled Monotherapy Epilepsy Trials		
System/Organ Class Adverse Reaction	**Topiramate 50 mg/day (N=257) %**	**Topiramate 400 mg/day (N=153) %**
Pollakiuria	0.8	2.0
Reproductive System and Breast Disorders		
Erectile dysfunction	0.8	1.3
General Disorders and Administration Site Conditions		
Fatigue	15.2	14.4
Asthenia	3.5	5.9
Irritability	3.1	3.3
Investigations		
Weight decreased	7.0	17.0
Adverse drug reactions reported by <1% of topiramate-treated adult patients in double-blind, controlled monotherapy epilepsy trials included lymphadenopathy, increased appetite, polydipsia, agitation, anger, dysphemia, euphoric mood, initial insomnia, suicidal ideation, drooling, hypogeusia, poor quality sleep, sensory disturbance, accommodation disorder, amblyopia, diplopia, palpitations, abdominal discomfort, breath odour, glossodynia, stomach discomfort, anhidrosis, urticaria localised, muscular weakness, and thirst. The recommended dose for monotherapy therapy in adults is 400 mg/day.		

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

ADRs reported in ≥2% of topiramate-treated paediatric patients (10 to 16 years of age) in double-blind, controlled monotherapy epilepsy trials are shown in Table 8. 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 8: Adverse Drug Reactions Reported by ≥ 2% of Topiramate-Treated Paediatric Patients in Double-Blind, Controlled Monotherapy Epilepsy Trials		
System/Organ Class Adverse Reaction	**Topiramate 50 mg/day (N=77) %**	**Topiramate 400 mg/day (N=63) %**
Metabolism and Nutrition Disorders		
Decreased appetite	1.3	4.8
Psychiatric Disorders		
Bradyphrenia	0	4.8
Mood altered	1.3	4.8
Depression	0	3.2
Nervous System Disorders		
Paraesthesia	3.9	15.9
Disturbance in attention	3.9	7.9

Table 8: Adverse Drug Reactions Reported by ≥ 2% of Topiramate-Treated Paediatric Patients in Double-Blind, Controlled Monotherapy Epilepsy Trials		
System/Organ Class Adverse Reaction	**Topiramate 50 mg/day (N=77) %**	**Topiramate 400 mg/day (N=63) %**
Ear and Labyrinth Disorders		
Vertigo	0	3.2
Respiratory, Thoracic and Mediastinal Disorders		
Epistaxis	0	3.2
Gastrointestinal Disorders		
Diarrhoea	3.9	9.5
Vomiting	3.9	4.8
Skin and Subcutaneous Tissue Disorders		
Alopecia	0	6.3
General Disorders and Administration Site Conditions		
Pyrexia	0	6.3
Asthenia	0	4.8
Investigations		
Weight decreased	7.8	20.6
Social Circumstances		
Learning disability	0	3.2
Adverse drug reactions reported by <2% of topiramate-treated paediatric patients in double-blind, controlled monotherapy epilepsy trials included eosinophilia, hypersensitivity, increased appetite, abnormal behaviour, apathy, confusional state, crying, distractibility, expressive language disorder, insomnia, mood swings, lethargy, mental impairment, poor quality sleep, diplopia, nasal congestion, rhinorrhoea, abdominal discomfort, gastritis, pruritus, rash, skin discolouration, urticaria, arthralgia, micturition urgency, pollakiuria, feeling abnormal, and hyperthermia. The recommended dose for monotherapy therapy in children 10 years and older is 400 mg/day.		

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

ADRs reported in ≥1% of topiramate-treated adult patients in double-blind, placebo-controlled migraine prophylaxis trials are shown in Table 9. ADRs that had an incidence >5% at the recommended dose (100 mg/day) in descending order of frequency included paraesthesia, fatigue, nausea, diarrhoea, weight decreased, dysgeusia, anorexia, decreased appetite, insomnia, hypoesthesia, disturbance in attention, anxiety, somnolence, and expressive language disorder.

Table 9: Adverse Drug 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				
Paraesthesia	35.7	50.0	48.5	5.0
Dysgeusia	15.4	8.0	12.6	0.9
Hypoaesthesia	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				
Dyspnoea	1.3	2.7	1.6	1.4
Epistaxis	0.4	1.1	0.6	0.5

Table 9: Adverse Drug 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) %**
Gastrointestinal Disorders				
Nausea	9.3	13.6	14.6	8.3
Diarrhoea	9.3	11.2	10.0	4.4
Dry mouth	1.8	3.2	5.0	2.5
Paraesthesia 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
Adverse drug reactions reported by <1% of topiramate-treated adult patients in double-blind, placebo-controlled migraine prophylaxis trials included hypersensitivity, polydipsia, aggression, agitation, anger, crying, disorientation, euphoric mood, hallucination, lack of spontaneous speech, libido decreased, listless, loss of libido, mood altered, panic attack, panic disorder, restlessness, tearfulness, aphasia, burning sensation, clumsiness, cognitive disorder, coordination abnormal, dizziness postural, dyskinesia, dysphasia, hypogeusia, hypokinesia, poor quality sleep, presyncope, psychomotor skills impaired, speech disorder, visual field defect, blepharospasm, diplopia, dry eye, night blindness, visual disturbance, ear discomfort, ear pain, palpitations, flushing, hot flush, dysphonia, nasal congestion, paranasal sinus hypersecretion, epigastric discomfort, gastritis, gingival bleeding, glossodynia, hypoaesthesia oral, alopecia, hypoaesthesia facial, pruritus generalised, urticaria, flank pain, muscular weakness, calculus urinary, micturition urgency, nephrolithiasis, renal pain, sexual dysfunction, feeling abnormal, gait disturbance, malaise, and peripheral coldness. The recommended dose for migraine prophylaxis is 100 mg/day.				

Other Clinical Trial Data

ADRs reported, rate unspecified, in open-label clinical trials of topiramate-treated adult patients are shown in Table 10.

Table 10: Adverse Drug Reactions Reported, Rate Unspecified, in Open-Label Clinical Trials of Topiramate-Treated Adult Patients
Nervous System Disorders
Apraxia, aura, complex partial seizure, convulsion, dystonia, grand mal convulsion
Eye Disorders
Glaucoma
Gastrointestinal Disorders
Pancreatitis

ADRs reported, rate unspecified, in open-label clinical trials of topiramate-treated paediatric patients are shown in Table 11.

Table 11: Adverse Drug Reactions Reported, Rate Unspecified, in Open-Label Clinical Trials of Topiramate-Treated Paediatric Patients
Nervous System Disorders
Convulsion, grand mal convulsion
Gastrointestinal Disorders
Pancreatitis

Post-marketing Data

Adverse events first identified as ADRs during post-marketing experience with topiramate, presented by frequency category based on spontaneous reporting rates are included in Table 12. 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 < 1/1000);

Very rare: (<1/10,000, including isolated reports)

Table 12: Adverse Drug Reactions Identified During Post-marketing 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 oedema
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 oedema
Very rare	Eye movement disorder
Very rare	Eyelid oedema
Very rare	Maculopathy
Very rare	Myopia
Frequency not known	Uveitis
Respiratory, Thoracic and Mediastinal Disorders	
Very rare	Cough
Skin and Subcutaneous Tissue Disorders	
Very rare	Erythema multiforme
Very rare	Periorbital oedema
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	Generalised oedema
Very rare	Influenza like illness
Investigations	
Very rare	Weight increased

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Signs and Symptoms

Ingestion of between 6 and 40 g topiramate have been reported in a few patients. Signs and symptoms included: headache, agitation, drowsiness, lethargy, convulsions, speech disturbances, blurred vision, diplopia, mentation impaired, abnormal coordination, stupor, hypotension, abdominal pain, dizziness, depression and hypokalaemia. The clinical consequences were not severe in most cases, but deaths have been reported after polydrug overdoses involving topiramate.

Topiramate overdose can result in severe metabolic acidosis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - METABOLIC ACIDOSIS AND SEQUELAE).

The highest topiramate overdose reported 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 the event of overdose, topiramate should be discontinued and general supportive treatment given until clinical toxicity has been diminished or resolved. Haemodialysis has been shown to be an effective means of removing topiramate from the body. The patient should be well hydrated.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Topiramate is classified as a sulfamate substituted monosaccharide. Three pharmacological properties of topiramate have been identified that may contribute to its anticonvulsant activity:

- Topiramate reduces the frequency at which action potentials are generated when neurons are subjected to a sustained depolarisation, which is indicative of a state dependent blockage of voltage sensitive sodium channels.
- Topiramate markedly enhances the activity of GABA at some types of GABAA receptors. 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 GABAA receptors. Because the antiepileptic profile of topiramate differs markedly from that of the benzodiazepines, it may modulate a benzodiazepine insensitive subtype of GABAA receptor.
- Topiramate antagonises the ability of kainate to activate the kainate/AMPA subtype of excitatory amino acid (glutamate) receptors but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype.

In addition, topiramate inhibits some isoenzymes of carbonic anhydrase. This pharmacological 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.

The mechanism(s) of action of topiramate in migraine prophylaxis is unknown.

Clinical Trials

Monotherapy Epilepsy

Three double-blind, randomised, parallel group clinical trials were conducted to evaluate the efficacy and safety of topiramate given as monotherapy. Study YI and EPMN-104 evaluated the safety and efficacy of topiramate monotherapy using a dose-response design by comparing the low dose regimen with the high dose

regimen. Study EPMN-105 compared topiramate monotherapy to carbamazepine or valproate in patients with newly diagnosed epilepsy.

In study YI, adults with refractory partial onset seizures (n = 48) were converted from their existing treatment to topiramate 100 mg/day or 1,000 mg/day as monotherapy. The high dose group was statistically superior to the low dose group for efficacy variables. 54% of high dose patients achieved monotherapy compared with 17% in the low dose group with the difference between the doses being statistically significant (p = 0.005). The mean time to exit was significantly greater in the high dose group (p = 0.002). The investigator and subject global evaluations of clinical response statistically favoured the high dose group (less than or equal to 0.002).

In study EPMN-104, adult and paediatric patients with recently diagnosed epilepsy (n = 252) were randomised into the low dose (25 or 50 mg/day) or the high dose group (200 or 500 mg/day) based on their bodyweight. Overall, 54% of high dose patients and 39% of low dose patients were reported to be seizure free during the double-blind phase (p = 0.022). The high dose group was also superior to the low dose group with respect to seizure frequency distribution (p = 0.008) and the difference in time to first seizure across three plasma topiramate concentration strata (p = 0.015).

In study EPMN-105, patients with newly diagnosed epilepsy (n = 613) were randomised to receive either 100 or 200 mg/day of topiramate or standard epileptic treatment (carbamazepine or valproate).

Topiramate was at least as efficacious as carbamazepine or valproate in reducing seizures in these patients; the 95% confidence intervals for the difference between the two treatment groups were narrow and included zero, indicating that there was no statistically significant difference between both groups. The two treatment groups were also comparable with respect to all clinical utility and efficacy endpoints including time to exit, proportion of seizure free subjects and time to first seizure.

Patients (n = 207; 32 were aged less than or equal to 16 years) who completed the double-blind phase of study YI and EMPN-104 were enrolled in long-term extension studies with the majority or patients receiving topiramate for two to five years. In these studies, sustained efficacy was demonstrated with long-term administration of topiramate as monotherapy. There was no significant change in dosage during the extension period and no indication that effectiveness of topiramate monotherapy diminished with continued exposure.

The safety profile of topiramate in monotherapy trials is consistent with that of the add-on trials.

Add-on Therapy Epilepsy

Over 2,000 patients worldwide were involved in the clinical trials of topiramate as an add-on treatment in adults and children with the following type of epilepsy: partial onset seizures with or without secondary generalised seizures, primary generalised tonic-clonic seizures and seizures associated with Lennox-Gastaut syndrome. These trials were randomised, placebo controlled, double blind, multicentre, parallel group studies in which patients were given topiramate or placebo as add-on treatment while they were receiving phenytoin, carbamazepine, primidone, phenobarbital or valproic acid, as concomitant therapy.

These trials had 4 to 12 weeks as the ‘run in’ phases, several weeks of titration and then up to 12 weeks of stabilisation. Topiramate reduced monthly seizure rates and increased responder rates (fraction of patients with at least 50% seizure reduction) significantly compared to placebo. In addition, Topiramate significantly reduced seizure severity in patients with Lennox-Gastaut syndrome. No evidence of tolerance to Topiramate has been demonstrated in humans.

In a pooled analysis of two clinical trials involving patients with primary generalised tonic-clonic epilepsy, topiramate (n = 79) was statistically better than placebo (n = 81) (p = 0.004). In these two trials, 17 patients who were 16 years or younger received topiramate.

There is limited clinical experience with topiramate at or above daily dose of 1000 mg. Comparative data or data on the safety and efficacy of using topiramate with lamotrigine, gabapentin or vigabatrin are not available. Elderly patients and patients with known or suspected coronary artery disease did not participate in these studies.

Migraine

The clinical development program to evaluate the efficacy of topiramate in the prophylaxis of migraine included four double blind, placebo controlled, parallel group trials. Each trial started with a washout period (14 to 28 days) for subjects already taking prophylactic drugs, followed by a 28 day 'run in' phase, an eight week dose titration phase and a 12 or 18 week maintenance phase.

The pooled results of the two pivotal trials, evaluating topiramate doses of 50 (n = 233), 100 (n = 244) and 200 mg/day (n = 288), found a median percent reduction in average monthly migraine period rate of 35, 51% and 49% respectively, compared to 21% for the pooled placebo group (n = 229). Notably 27% of patients administered topiramate 100 mg/day achieved at least a 75% reduction in migraine frequency, while 52% achieved at least a 50% reduction.

Study MIGR-003 demonstrated that topiramate 100 mg/day was comparable in terms of efficacy to propranolol 160 mg/day. There was no statistically significant difference between the two groups in the primary efficacy endpoint or clinically significant 50% responder rate (43% for propranolol 160 mg/day, 37% for topiramate 100 mg/day (-6% difference, 95% CI (-17%, +6%), p = 0.28), 35% for topiramate 200 mg/day (-7% difference, 95% CI (-19%, +4%), p = 0.17)).

Results from each trial are summarised in Table 13.

Table 13: Responder Rates (at least a 50% reduction in average monthly migraine period compared to baseline –ITT)

Study	Placebo	Topiramate 50mg/day	Topiramate 100mg/day	Topiramate 200mg/day
MIGR-001	23%	36% p≤0.05* 12%[a] (1%, 24%)[b]	54% p≤0.001* 31%[a] (19%, 42%)[b]	52% p≤0.001* 29%[a] (17%, 41%)[b]
MIGR-002	23%	39% p≤0.05* 16%[a] (4%, 28%)[b]	49% p≤0.001* 26%[a] (15%, 38%)[b]	47% p≤0.001* 24%[a] (12%, 36%)[b]
MIGR-003	22%		37% p≤0.05* 15%[a] (4%, 25%)[b]	35% p≤0.05* 13%[a] (2%, 23%)[b]
CAPSS-155	34%			40% NS 6%[a] (-8%, 19%)[b]

*Nominal p values for comparison of topiramate with placebo.

[a] difference – treatment responder rate of topiramate minus placebo.

[b] 95% Confidence interval – pairwise difference of topiramate minus placebo.

NOTE: The overall safety profile of topiramate observed in the migraine studies was generally consistent with that established for epilepsy therapy.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic profile of topiramate compared to other antiepileptic drugs shows a long plasma elimination 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 metabolising enzymes. Routine monitoring of plasma topiramate concentrations is not necessary and it can be administered without regard to meals. In clinical studies, there was no consistent relationship between plasma concentrations and efficacy or adverse events.

Topiramate was rapidly and well absorbed and distributed in total body water following oral administration in animals. The same metabolic and elimination pathways were present as in human subjects. C_{max} values were similar to those obtained in human subjects but topiramate was more rapidly cleared in animals resulting in lower overall systemic exposure.

Absorption

Based on the recovery of radioactivity from urine in humans, the mean extent of absorption of a 100 mg dose of 14C-topiramate was at least 81%. Following oral administration of 100 mg topiramate to healthy subjects, a mean peak plasma concentration (C_{max}) of approximately 1.5 microgram/mL was achieved with two or three hours (T_{max}). The bioavailability of topiramate is not significantly affected by food.

In a separate study involving 24 normal, healthy, non-smoking male and female subjects under fasting conditions, the mean absorption rate of a 200 mg dose of topiramate was found to be approximately 132.65 microgram/mL. Following oral administration of 200 mg topiramate to healthy subjects, a mean peak plasma concentration (C_{max}) of approximately 4.5 microgram/mL was achieved within two hours of administration.

Distribution

Generally 13 to 17% of topiramate is bound to plasma proteins. A low capacity binding site for topiramate in/on erythrocytes that is saturated at steady state has been observed. Following single dose administration, the volume of distribution varies inversely with dose. The mean apparent volume of distribution has been measured as 0.55 to 0.8 L/kg for a single dose of 100 to 1,200 mg. There is an effect of gender on the volume of distribution. Values for females are about 50% lower than those of males. This is attributed to the higher percent body fat in females and is of no clinical consequence.

Metabolism

Topiramate is not extensively metabolised (approximately 20%) in healthy volunteers. It is metabolised up to 50% in patients receiving concomitant antiepileptic therapy with known inducers of drug metabolising enzymes. Six metabolites formed through hydroxylation, hydrolysis and glucuronidation have been isolated, characterised and identified in plasma, urine and faeces of humans. Each metabolite represents less than 3% of the total radioactivity excreted following administration of 14C-topiramate. Two metabolites, which retained most of the structure of topiramate, were tested and found to have little to no anticonvulsant activity.

Excretion

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 14C-topiramate was excreted unchanged in the urine within four days. Following twice a day dosing with 50 and 100 mg of topiramate, the mean renal clearance was approximately 18 and 17 mL/minute 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/minute in humans following oral administration. Concomitant multiple dose administration of topiramate, 100 to 400 mg twice a day, with phenytoin and carbamazepine shows dose proportional increases in plasma concentrations of topiramate.

Topiramate exhibits low intersubject variability in plasma concentrations and therefore, has predictable pharmacokinetics. The pharmacokinetics of topiramate are linear at steady state with plasma clearance remaining constant and area under the plasma concentration curve (AUC) increasing in a dose proportional manner over a 200 to 800 mg daily oral dose range. Patients with normal renal function may take four to eight 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 microgram/mL. Following administration of multiple doses of 50 and 100 mg of topiramate twice a day, the mean plasma elimination half-life was approximately 21 hours.

Following administration of a single dose of 200 mg of topiramate in 24 subjects under fasting conditions, the mean plasma elimination half-life was approximately 28 hours.

Patients with renal impairment

The plasma and renal clearance of topiramate decreased in patients with moderate and severe impaired renal function (creatinine clearance < 70 mL/minute). As a result, higher steady-state plasma concentrations are expected for a given dose in renally impaired patients 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 (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Topiramate is effectively removed from plasma by haemodialysis. A prolonged period of haemodialysis 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 haemodialysis, 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 dialysed.

Patients with hepatic impairment

Plasma clearance of topiramate decreased a mean of 26% in patients with moderate to severe hepatic impairment. Therefore, topiramate should be administered with caution in patients with hepatic impairment.

Elderly

Plasma clearance of topiramate is unchanged in elderly subjects in the absence of underlying renal disease or hepatic impairment. Patients more than 71 years of age have not been studied.

Paediatric up to 12 years of age

The pharmacokinetics of topiramate are linear in children receiving the drug as add-on therapy. The clearance is independent of dose and steady-state plasma concentrations increase proportionally to dose. Hepatic enzyme inducing antiepileptic drugs decrease the steady-state plasma concentrations. In comparison to adults, however, children have a higher clearance and shorter elimination half-life when topiramate is used as adjunctive therapy to both enzyme inducing and non-enzyme inducing antiepileptic drugs. Consequently, the plasma concentrations of topiramate for the same mg/kg dose may be lower in children compared to adults.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Topiramate was not genotoxic in a series of assays for gene mutations, chromosomal damage or DNA damage.

Carcinogenicity

No evidence of carcinogenicity was seen in rats following oral administration of topiramate for 2 years at doses of 12 0mg/kg. An increased incidence of urinary bladder tumours of a proliferative nature was observed in mice following oral administration of topiramate for 22 months at doses of 300 mg/kg. These tumours probably resulted from chronic irritation and may lack clinical significance. The plasma concentration exposure obtained in the animal studies was less than the likely clinical exposure at the maximum recommended dose.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets also contain the following inactive excipients: microcrystalline cellulose, povidone, colloidal anhydrous silica, sodium starch glycollate type A, and magnesium stearate.

The coating contained in the tablets are as follows:

25 mg: OPADRY complete film coating system YS-1-7003 White (ID 11956)

50 mg: OPADRY complete film coating system 03B92164 Yellow (ID 12654)

100 mg: OPADRY complete film coating system 03B92180 Yellow (ID 12655)

200 mg: OPADRY complete film coating system 05B16131 Maroon (ID 12656)

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

TAMATE tablets should be stored in a dry place below 25°C and protected from light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: blister pack Al/Al

Pack sizes: 60’s

Australian Register of Therapeutic Goods (ARTG)

AUST R 150447 – TAMATE topiramate 25mg tablet blister pack

AUST R 150445 – TAMATE topiramate 50mg tablet blister pack

AUST R 150446 – TAMATE topiramate 100mg tablet blister pack

AUST R 150444 – TAMATE topiramate 200mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

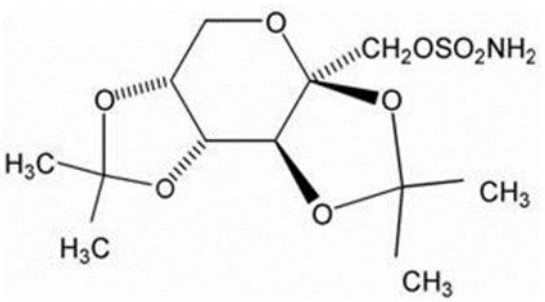
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Topiramate is a white crystalline powder with a bitter taste.

Topiramate is most soluble in alkaline solutions with a pH of 9 to 10, including those that contain sodium hydroxide or sodium phosphate. It is freely soluble in acetone, chloroform, dimethylsulfoxide and ethanol. The solubility in water is 9.8 mg/mL. Its saturated solution has a pH of 6.3.

Chemical Structure



Chemical Formula: 2,3:4,5-bis-0-(1-methylethylidene)-β-D-fructopyranose sulfamate

Molecular formula: $C_{21}H_{21}NO_8S$

Molecular weight: 339.36

CAS Number:

97240-79-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

01/06/2009

10 DATE OF REVISION

07/07/2025

Summary Table of Changes

Section Changed	Summary of New Information
4.4	Minor editorial correction

TAMATE® is a Viatris company trade mark

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