AUSTRALIAN PRODUCT INFORMATION – NOUMED TOPIRAMATE (topiramate film-coated tablets)

1. NAME OF THE MEDICINE

Topiramate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NOUMED TOPIRAMATE tablets contain 25 mg, 50 mg, 100 mg or 200 mg topiramate.

Excipients with known effects: sugars as lactose.

For the full list of excipients, see *Section 6.1 List of excipients*.

3. PHARMACEUTICAL FORM

NOUMED TOPIRAMATE tablets are available in the following presentations:

25 mg, white, round shaped, film-coated tablet, plain on both sides.

50 mg, yellow, round shaped, film-coated tablet, plain on both sides.

100 mg, white, round shaped, film-coated tablet, plain on both sides.

200 mg, yellow, round shaped, film-coated tablet, plain on both sides

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

EPILEPSY

Topiramate 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

Topiramate is indicated for the prophylaxis of migraine headache in adults.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

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 topiramate in adults and children for epilepsy are summarised in **Table 1**.

Monotherapy - Epilepsy

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

In patients who are being converted to topiramate 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 two 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 When enzyme inducing drugs are withdrawn, topiramate levels will increase.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

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.

Add-on therapy - Epilepsy

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 topiramate 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	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 and 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 dose great 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 therapy with this medicine. For patients receiving concomitant phenytoin and carbamazepine, dosage adjustment for topiramate 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 topiramate 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.

Method of administration

NOUMED TOPIRAMATE tablets should be swallowed whole and can be taken without regard to meals.

Dosage adjustment in:

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 topiramate should be added to the patient's normal daily dose as follows:

- Patients on Concomitant Enzyme Inducers: (phenytoin, carbamazepine, phenobarbitone and other barbiturates)

  A supplemental dose equal to 1/3 the patient's normal daily dose should be given on the day of haemodialysis. The supplemental dose should be divided so as to allow for administration of 1/4 of the supplemental dose at the start of haemodialysis. The remaining 3/4 of the supplemental dose should be administered at the completion of the haemodialysis.

- Patients Not on Concomitant Enzyme Inducers

  A supplemental dose equal to 1.6 times the patient's normal daily dose should be given on the day of haemodialysis. The supplemental dose should be divided so as to allow for administration of 1/3 of the supplemental dose at the start of haemodialysis. The remaining 2/3 of the supplemental dose should be administered at the completion of the haemodialysis.

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*).

Drug withdrawal and Dosage reduction

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 of increased seizure frequency. In situations where rapid withdrawal of topiramate 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 effective methods of contraception.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In patients with or without a history of seizures or epilepsy, antiepileptic drugs including topiramate should be gradually withdrawn to minimise the potential for seizures or increased seizure frequency. In clinical trials, daily dosages were decreased at 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

Adequate hydration while 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 Polled 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 (see *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 subsection below on *Metabolic Acidosis*), 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.

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. Ophthalmological 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 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 postmarketing 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

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

Chronic, untreated metabolic acidosis may increase the risk of nephrolithiasis or nephrocalcinosis (see subsection above on *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 50mg/day. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mmol/L and >5 mmol/L decrease from pretreatment) 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 100 mg/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 6mg/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 pretreatment) 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, non-specific 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 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).

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.

Nutritional supplementation

Some patients may experience weight loss whilst on treatment with topiramate. It is recommended that patients on topiramate treatment should be monitored for weight loss. A dietary supplement or increased food intake may be considered if the patient is losing weight while on topiramate.

Use in women of childbearing potential

Topiramate may cause foetal 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.

NOUMED TOPIRAMATE should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus (see *section 4.6 Fertility, pregnancy and lactation*).

Use in hepatic impairment

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

Use in 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 the elderly

Caution is advised during titration in the elderly with renal disease and/or hepatic impairment.

Paediatric use

See *section 4.2 Dose and method of administration*.

Effects on laboratory tests

Clinical trial data indicates that topiramate has been associated with an average decrease of 4mmol/L in serum bicarbonate level (see *section 4.4 Special warnings and precautions for use*). In double blind trials hypokalaemia, defined as serum potassium decline below 3.5 mmol/L, has been observed in 0.4% of subjects treated with topiramate compared to 0.1% of subjects treated with placebo.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

Effects of topiramate on other antiepileptic medicines

The addition of topiramate to other antiepileptic medicines (phenytoin, carbamazepine, valproic acid, phenobarbitone, 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 plasma levels monitored.

Effects of other antiepileptic medicines 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	↔	↔
Phenobarbitone	↔	N
Primidone	↔	N
Lamotrigine	↔	↔

↔ = No effect on plasma concentration
⇑ = Plasma concentrations increase in occasional patients
↓ = Plasma concentrations decrease
N = Not studied
AED = antiepileptic drug
* = Approximately 35% decrease in plasma C_{maxss} and 57% decrease in plasma C_{minss} concentrations
Note: 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.

St John's Wort (Hypericum perforatum)

A risk of decreased plasma concentrations resulting in a loss of efficacy could be observed with co-administration of topiramate and St John's Wort. There have been no clinical studies evaluating this potential interaction.

Oral Contraceptives

In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1mg norethisterone (NET) plus 35 microgram ethinyl oestradiol (EO), topiramate given in the absence of other medications at doses of 50 to 200mg/day was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. In another study, exposure to EO 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 EO exposure for doses between 200-800mg/day, there was no significant dose dependent change in EO exposure for doses of 50-200mg/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 oestrogen 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 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 6mg/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 q24 h) and topiramate (96 mg q12 h) 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 the administration of topiramate or HCTZ individually, 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, $C_{max,ss}$ and $AUC_{t,ss}$, of the active hydroxy-metabolite decreased by 13% and 16%, respectively, and $C_{max,ss}$ and $AUC_{t,ss}$ of the active keto-metabolite decreased by 60%. 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 AUC_{24} 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. This adverse event 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 conjuntion 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 when administering topiramate concomitantly with these 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 50 mg q12h)	9% and 16% increase in C_{max}, 9% and 17% increase in AUC (40mg and 80mg proporaolol 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)†	↔

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

† = 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 100mg/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 subsection below on *Growth and Development*).

Use in pregnancy

Category D [1]

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 foetal 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.

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.

[1] Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

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

Topiramate can cause foetal 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). This has been reported with topiramate monotherapy and topiramate as part of a polytherapy regimen.

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 these registries and other studies suggest that, compared with monotherapy, there may be 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.

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 yet been established. 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.

Topiramate should be used during pregnancy only if potential benefit justifies the potential risk to the foetus. In treating and counselling women of childbearing potential, the prescribing doctor 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 foetus.

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

It is recommended that:

- Women on antiepileptic drugs (AEDs) receive pregnancy counselling with regard to the risk of foetal 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 continued 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 radio labelled 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. 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, 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. 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 medicine 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.

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, nonsteroidal 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, decreased weight, bradyphrenia, paresthesias, diplopia, abnormal coordination, nausea, nystgamus, lethargy, anorexia, dysarthria, blurred vision, 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

System/Organ Class Adverse Reaction	Topiramate 200-400 mg/day (N=354) %	Topiramate 600-1000 mg/day (N=437) %	PLACEBO (N=382) %
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
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

System/Organ Class Adverse Reaction	Topiramate 200-400 mg/day (N=354) %	Topiramate 600-1000 mg/day (N=437) %	PLACEBO (N=382) %
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, abnormal thinking, aphasia, cerebellar syndrome, cognitive disorder, dysaesthesia, dysgraphia, dyskinesia, formication, parosmia, impaired psychomotor skills, repetitive speech, sensory disturbance, sensory loss, stupor, unresponsive to stimuli, increased lacrimation, presbyopia, reduced visual acuity, deafness, unilateral deafness, impaired hearing, tinnitus, sinus bradycardia, dyspnoea, dyspnoea exertional, paranasal sinus hypersecretion, abdominal discomfort, abdominal tenderness, breath odour, flatulence, oral hypoaesthesia, oral paraesthesia, erythema, facial hypoaesthesia, abnormal skin odour, swelling face, urinary calculus, dysuria, haematuria, urinary incontinence, pollakiuria, renal colic, renal pain, erectile dysfunction, sexual dysfunction, feeling abnormal, feeling drunk, abnormal tandem gait test, and decreased white blood cell count.

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 pediatric 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, decreased weight, aggression, rash, abnormal behaviour, anorexia, balance disorder, and constipation.

Table 6: Adverse Drug 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 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
Respiratory, Thoracic and Mediastinal Disorders		
Epistaxis	4.8	1.0

System/Organ Class Adverse Reaction	TOPIRAMATE (N=104) %	PLACEBO (N=102) %
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, increased lacrimation, blurred vision, 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, decreased weight, 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 50mg/day (N=257) %	TOPIRAMATE 400mg/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
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

System/Organ Class Adverse Reaction	TOPIRAMATE 50mg/day (N=257) %	TOPIRAMATE 400mg/day (N=153) %
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
Pruritus	0.4	3.3
Hypoaesthesia facial	0.4	2.0
Pruritus 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
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, localised urticaria, 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 pediatric 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 decreased weight, paraesthesia, diarrhoea, disturbance in attention, pyrexia, and alopecia.

Table 8: Adverse Drug Reactions Reported by ≥ 2% of Topiramate-Treated Pediatric Patients in Double-Blind, Controlled Monotherapy Epilepsy Trials

System/Organ Class Adverse Reaction	TOPIRAMATE 50mg/day (N=77) %	TOPIRAMATE 400mg/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
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 pediatric 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, decreased weight, 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 50mg/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
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

System/Organ Class Adverse Reaction	TOPIRAMATE 50mg/day (N=227) %	TOPIRAMATE 100 mg/day (N=374) %	TOPIRAMATE 200 mg/day (N=501) %	PLACEBO (N=436) %
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, decreased libido, listless, loss of libido, altered mood, panic attack, panic disorder, restlessness, tearfulness, aphasia, burning sensation, clumsiness, cognitive disorder, abnormal coordination, postural dizziness, dyskinesia, dysphasia, hypogeusia, hypokinesia, poor quality sleep, presyncope, impaired psychomotor skills, 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, oral hypoaesthesia, alopecia, facial hypoaesthesia, generalised pruritus, urticaria, flank pain, muscular weakness, urinary calculus , 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
General Disorders
Calcinosis

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

Table 11: Adverse Drug Reactions Reported, Rate Unspecified, in Open-Label Clinical Trials of Topiramate-Treated Pediatric Patients

Nervous System Disorders
Convulsion, grand mal convulsion
Gastrointestinal Disorders
Pancreatitis

Postmarketing Data

Adverse events first identified as ADRs during postmarketing 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 < 1/1,000
Very rare	< 1/10,000, including isolated reports

Table 12: Adverse Drug 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 oedema
Metabolism and Nutrition Disorders	
Very rare	hyperammonemia, hyperammonemic encephalopathy
Psychiatric Disorders	
Very rare	feeling of despair
Eye Disorders	
Very rare	abnormal sensation in eye, angle closure glaucoma, conjunctival oedema, eye movement disorder, eyelid oedema, maculopathy, myopia
Frequency not known	uveitis
Respiratory, Thoracic and Mediastinal Disorders	
Very rare	cough
Skin and Subcutaneous Tissue Disorders	
Very rare	erythema multiforme, periorbital oedema, Stevens-Johnson syndrome, toxic epidermal necrolysis
Musculoskeletal and Connective Tissue Disorders	
Very rare	joint swelling, limb discomfort
Renal and Urinary Disorders	
Very rare	renal tubular acidosis, nephrocalcinosis
General Disorders and Administration Site Reactions	
Very rare	generalized oedema, influenza like illness
Investigations	
Very rare	increased weight

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

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

Signs and Symptoms

Ingestion of between 6 and 40 g topiramate have been reported in a few patients. Clinical signs and symptoms included: headache, agitation, drowsiness, lethargy, convulsions, speech disturbances, blurred vision, diplopia, impaired mentation, 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*)

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

Treatment

Topiramate should be discontinued and general supportive measures given until clinical toxicity has been diminished or resolved. Hemodialysis has been shown to be an effective means of removing topiramate from the body. The patient should be well hydrated.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Topiramate is classified as a sulfamate substituted monosaccharide.

Mechanism of action

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 blockade of voltage-sensitive sodium channels.
- Topiramate markedly enhances the activity of gamma-aminobutyric acid (GABA) at some types of $GABA_A$ 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 $GABA_A$ 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 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 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.

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 1000 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 (≤0.002). In study EPMN-104, adult and paediatric patients with recently diagnosed epilepsy (n=252) were randomised into the low dose (25 or 50mg/day) or the high dose group (200 or 500 mg/day) based on their body weight. 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 200mg/day of topiramate or standard anti-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 were no statistically significant between-group difference. 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 ≤16 years) who completed the double-blind phase of study YI and EPMN-104 were enrolled in long term extension studies with the majority of patients receiving topiramate for 2 to 5 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 2000 patients worldwide were involved in clinical trials where topiramate was used 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, multi-centre, parallel group studies in which patients were given topiramate or placebo as add-on treatment while they were receiving phenytoin, carbamazepine, primidone, phenobarbitone 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 a daily dose of 1000 mg. Comparative data or data on the safety and efficacy of using topiramate with lamotrigine, vigabatrin or gabapentin is not available. Geriatric patients and patients with known or suspected coronary artery disease did not participate in these studies.

Migraine

The clinical development programme 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=228), 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, whilst 52% achieved at least a 50% reduction.

Study MIGR-003 demonstrated that topiramate 100 mg/day was comparable in terms of efficacy to propranolol 160mg/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 50 mg/day	Topiramate 100 mg/day	Topiramate 200 mg/day
MIGR-001	23%	36% p ≤ 0.05* 12%† (1%, 24%)‡	54% p ≤ 0.001* 31%† (19%, 42%)‡	52% p ≤ 0.001* 29%† (17%, 41%)‡
MIGR-002	23%	39% p ≤ 0.05* 16%† (4%, 28%)‡	49% p ≤ 0.001* 26%† (15%, 38%)‡	47% p ≤ 0.001* 24%† (12%, 36%)‡
MIGR-003	22%		37% p ≤ 0.05* 15%† (4%, 25%)‡	35% p ≤ 0.05* 31%† (2%, 23%)‡
CAPSS-155	34%			40% NS 6%† (-8%, 19%)‡

***** Nominal p values for comparison of topiramate with placebo.

† Difference - treatment responder rate of topiramate minus placebo.

‡ 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.

ITT = intention to treat

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. It 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.

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 recovery of radioactivity from urine in humans, the mean extent of absorption of a 100 mg dose of ^{14}C-topiramate was at least 81%. Following oral administration of 100 mg topiramate to healthy subjects, a mean peak plasma concentration (C_{max}) of approximately 2.4 micrograms/mL was achieved within approximately 4 hours (T_{max}). The bioavailability of topiramate is not significantly affected by food.

Distribution

Generally 13-17% 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 0.8 - 0.55 L/kg for a single dose range of 100 mg to 1200 mg. A gender effect on the volume of distribution was observed, with values for females being about 50% lower than those for males. This difference is attributed to the higher percent body fat in females and is of no clinical consequence.

Metabolism

Topiramate is not extensively metabolised (~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 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.

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 ^{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. Concomitant multiple-dose administration of topiramate (100 mg to 400 mg twice a day) with phenytoin or 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 increasing in a dose-proportional manner over a 200 mg 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 micrograms/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.

Patients with renal impairment

The plasma and renal clearance of topiramate decreased in patients with moderate and severe impaired renal function (CL_{CR} < 70 mL/min). As a result, higher steady-state 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.

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 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 over 71 years of age have not been studied.

Paediatric up to 12 years of age

The pharmacokinetics of topiramate in children receiving the drug as add-on therapy are linear. The clearance is independent of dose and steady-state plasma concentrations increase in proportion 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 two years at doses of 120 mg/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

All tablets contain the inactive ingredients lactose monohydrate, pregelatinised maize starch, microcrystalline cellulose, sodium starch glycollate, magnesium stearate, titanium dioxide, hypromellose, macrogol 400 and polysorbate 80. In addition, NOUMED TOPIRAMATE 50 mg and 200 mg tablets contain iron oxide yellow.

6.2 INCOMPATIBILITIES

Refer to *section 4.5 – Interactions with other medicines and other forms of interactions*.

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

Store below 25˚C.

6.5 NATURE AND CONTENTS OF CONTAINER

NOUMED TOPIRAMATE is supplied in either HDPE bottles with child resistant caps and desiccant or Al/Al blister packs containing 60 film-coated tablets each.*

*Not all presentations may be marketed.

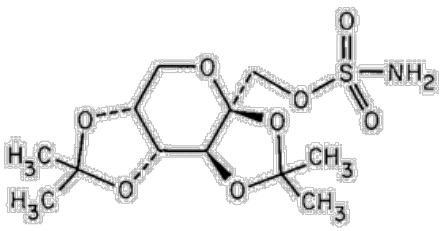
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Topiramate is a white crystalline powder with a bitter taste. It is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and has a pH of 9 to 10. 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:



Empirical formula:	$C_{12}H_{21}NO_8S$
Molecular weight:	339.36
CAS number:	97240-79-4

7. MEDICINE SCHEDULE (POISON STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Avallon Pharmaceuticals Pty Ltd
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Tel: 1800 930 999
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9. DATE OF FIRST APPROVAL

07 June 2017

10. DATE OF REVISION

05 July 2021

Summary table of changes

Section changed	Summary of new information
4.4	Added precautions on serious skin reactions; Added statement on consequences of chronic untreated metabolic acidosis; Added precaution regarding potential risks in women of childbearing potential.
4.5	Added potential effects of concomitant use with Vitamin K antagonist anticoagulants.
4.6	Added information on potential teratogenic effects during pregnancy.
4.8	Added adverse effects spontaneously reported during post-marketing.
4.9	Updated treatment recommendations for overdose.
6.5	Included both bottle and blister pack presentations.
8	Additional contact details for sponsor.