TOPAMAX®

TABLETS AND SPRINKLE CAPSULES

TOPIRAMATE

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

TOPAMAX® 25 mg, 50 mg, 100 mg & 200 mg film-coated tablets

TOPAMAX® Sprinkle 15 mg, 25 mg & 50 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TABLETS

Each tablet contains 25 mg, 50 mg, 100 mg or 200 mg of topiramate.

Excipient(s) with known effect:

Sugars as lactose

For a full list of excipients, see **section 6.1**.

SPRINKLE CAPSULES

Each capsule contains 15 mg, 25 mg or 50 mg of topiramate.

Excipients with known effect: Sugar

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

TABLETS

25 mg: Round, white, film-coated tablets, marked “TOP” on one side and “25” on the other.

50 mg: Round, light-yellow, film-coated tablets, marked “TOP” on one side and “50” on the other

100 mg: Round, yellow, film-coated tablets, marked “TOP” on one side and “100” on the other

200 mg: Round, salmon, film-coated tablets, marked “TOP” on one side and “200” on the other.

SPRINKLE CAPSULES

Hard capsules enclosing small, white to off-white spheres. Each gelatin capsule consists of a clear (natural) capsule cap and a white capsule body.

15 mg: imprinted with “TOP” on cap and “15 mg” on body

25 mg: imprinted with “TOP” on cap and “25 mg” on body

50mg: imprinted with “TOP” on cap and “50mg” on body (not marketed).

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

EPILEPSY

TOPAMAX 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, generalised tonic-clonic seizures or seizures associated with Lennox-Gastaut syndrome.

MIGRAINE

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

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 TOPAMAX in adults and children with epilepsy are summarised in **Table 1**.

Epilepsy - Monotherapy

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

In patients who are being converted to TOPAMAX monotherapy, consideration should be given to the effects of seizure control when withdrawing concomitant antiepileptic agents (AEAs). Unless safety concerns require an abrupt withdrawal of the concomitant AEA, a gradual discontinuation at the rate of approximately one-third of the concomitant AEA dose every 2 weeks is recommended (see **Drug withdrawal and dosage reduction** and see **section 4.4**). When enzyme inducing medicines are withdrawn, topiramate levels will increase. A decrease in TOPAMAX 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. 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 100 to 400mg/ 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 TOPAMAX therapy. For patients receiving concomitant phenytoin and carbamazepine, dosage adjustment for TOPAMAX may be required (see **section 4.5**).

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 TOPAMAX 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.

Special populations

Use in patients with hepatic and/or renal impairment

Caution is advised during titration in the elderly and in patients with renal disease and/or hepatic impairment (see **section 4.4**). 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**).

Use in patients undergoing haemodialysis

Topiramate is cleared by haemodialysis. To avoid rapid reduction in topiramate plasma concentration during haemodialysis, a supplemental dose of TOPAMAX 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**).

Drug withdrawal and Dosage reduction

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

Method of administration

TOPAMAX tablets should be swallowed whole.

TOPAMAX Sprinkle capsules can be swallowed whole. However, for patients who cannot swallow the capsules (e.g. young children and the elderly), the content of the capsules should be sprinkled on a small amount of soft food and swallowed immediately without chewing. This mixture should not be stored for future use.

TOPAMAX can be taken without regard to meals.

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 TOPAMAX

In patients with or without a history of seizures or epilepsy, antiepileptic agents (AEDs), including TOPAMAX, 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 TOPAMAX at doses up to 100 mg/day for migraine prophylaxis. In clinical trials of children, TOPAMAX was gradually withdrawn over a 2-8 week period. In situations where rapid withdrawal of TOPAMAX is medically required, appropriate monitoring is recommended.

Nephrolithiasis

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

Risk factors for nephrolithiasis include prior stone formation, a family history or nephrolithiasis and hypercalciuria (see **section 4.4, Metabolic acidosis and sequelae**). 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.

Hydration

Adequate hydration while using TOPAMAX 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.

Serious skin reactions

Serious skin reactions (Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)) have been reported in patients receiving TOPAMAX (see 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 TOPAMAX should be discontinued.

Suicidality (suicidal behaviour and ideation)

An analysis of reports of suicidality (suicidal behaviour or ideation) from placebo controlled clinical studies of eleven medicines used to treat epilepsy as well as psychiatric disorders, and other conditions revealed that patients receiving anti-epileptic drugs had approximately twice the risk of suicidal behaviour or ideation (0.43%) compared to patients receiving placebo (0.24%). The increased risk of suicidal behaviour and suicidal ideation was observed as early as one week after starting the anti-epileptic medicine and continued through 24 weeks. The results were generally consistent among the eleven medicines. As 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.

Patients who were treated for epilepsy, psychiatric disorders, and other conditions were all at increased risk for suicidality when compared to placebo, and there did not appear to be a specific demographic subgroup of patients to which the increased risk could be attributed. The relative risk for suicidality was higher in the patients with epilepsy compared to patients who were given one of the medicines in the class for psychiatric or other conditions.

In double-blind clinical trials, 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.

All patients who are currently taking or starting on any anti-epileptic drug should be closely monitored for notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behaviour or depression.

Health Care professionals should inform patients, their families, and caregivers of the potential for an increase in the risk of suicidality. Prescribers should advise patients to seek medical advice immediately if they develop any symptoms suggestive of suicidality.

Rapid dose reduction, discontinuation or substitution of TOPAMAX

In patients who are seizure-free or whose seizures are well controlled, the need for dosage reduction, discontinuation or substitution should be assessed by a healthcare professional and any changes should be implemented gradually.

Oligohydrosis and Hyperthermia

Oligohydrosis (decreased sweating) and anhidrosis, infrequently resulting in hospitalization, has been reported in association with TOPAMAX use. Decreased sweating and an elevation in body temperature above normal characterised 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 TOPAMAX should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather. Caution should be used when TOPAMAX 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.

Decreased hepatic function

In patients with hepatic impairment, 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 TOPAMAX. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include some or all of the following: myopia, mydriasis, anterior chamber shallowing, ocular 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 TOPAMAX 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 TOPAMAX, 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. 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 TOPAMAX treatment. This decrease in serum bicarbonate is due to the inhibitory effect of TOPAMAX on renal carbonic anhydrase. Generally, the decrease in bicarbonate occurs early in treatment although it can occur at any time during treatment. These decreases are usually mild to moderate (average decrease of 4 mmol/L at doses of 100 mg/day or above in adults and at approximately 6 mg/kg/day in paediatric patients). Rarely, patients have experienced decreases to values below 10 mmol/L. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhoea, surgery, ketogenic diet, or certain drugs) may be additive to the bicarbonate lowering effects of TOPAMAX.

Chronic, untreated metabolic acidosis may increase the risk of nephrolithiasis or nephrocalcinosis (see **section 4.4, Nephrolithiasis**).

Chronic metabolic acidosis in paediatric patients can reduce growth rates. The effect of TOPAMAX on growth and bone-related sequelae has not been systematically investigated in adult populations. A one year, open-label study in pediatric 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 TOPAMAX therapy. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing TOPAMAX (using dose tapering).

Hyperammonemia and encephalopathy

Hyperammonemia with or without encephalopathy has been reported with topiramate treatment (see **section 4.8**). 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**).

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 majority of affected patients were dose related for both the add-on epilepsy and migraine populations.

Suicide Attempt

In the double-blind phases of clinical trials with topiramate in approved and investigational indications, suicide attempts occurred at a rate of 0.003 (13 events/3999 patient years) on topiramate versus 0 (0 events/1430 patient years) on placebo. One completed suicide was reported in a bipolar disorder trial in a patient on topiramate.

Women of childbearing potential

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

Before the initiation of treatment with topiramate in a woman of childbearing potential, pregnancy testing should be performed. A highly effective contraceptive method should be used during treatment and for at least 4 weeks after stopping treatment with topiramate. 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, TOPAMAX 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**). If a woman being treated with topiramate as migraine prophylaxis becomes pregnant, treatment should be stopped immediately. The woman should be referred to a specialist for careful antenatal monitoring and counselling.

TOPAMAX 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**).

The need for topiramate treatment in women of childbearing potential should be reassessed at least annually.

Nutritional supplementation

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

Decreased renal function

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

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects Of TOPAMAX On Other Antiepileptic Agents

The addition of TOPAMAX to other antiepileptic agents (phenytoin, carbamazepine, valproic acid, phenobarbitone, primidone) has no effect on their steady-state plasma concentrations, except in the occasional patient, where the addition of TOPAMAX 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 Agents On TOPAMAX

Topiramate is metabolised up to 50% in patients receiving concomitant antiepileptic therapy with known inducers of enzymes, which metabolise medicines.

Phenytoin and carbamazepine decrease the plasma concentration of topiramate. The addition or withdrawal of phenytoin or carbamazepine to TOPAMAX 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 TOPAMAX.

The results of these interactions are summarised in **Table 2**:

Table 2: Summary of AEA interactions with TOPAMAX

AEA Co-administered	AEA Concentration	Topiramate Concentration
Phenytoin	<-> **	↓ (48%)
Carbamazepine (CBZ)	<->	↓ (40%)
Valproic Acid	<->	<->
Phenobarbitone	<->	NS
Primidone	<->	NS
Lamotrigine	<->	<->

<-> = No effect on plasma concentration (< 15% change)
** = Plasma concentrations increase in occasional patients
↓ = Plasma concentrations decrease
NS = Not studied
AEA = antiepileptic agent

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

Other Interactions

Digoxin:

In a single dose study, the serum digoxin area under plasma concentration curve (AUC) decreased 12% due to concomitant administration of TOPAMAX. The clinical relevance of this observation has not been established. When TOPAMAX 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 TOPAMAX and alcohol or other CNS depressant medicines has not been evaluated in clinical studies. It is recommended that TOPAMAX not be used concomitantly with alcohol or other CNS depressant medicines.

Contraceptives:

In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 mcg ethinyl oestradiol (EO), TOPAMAX 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 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, TOPAMAX (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 200-800 mg/day, there was no significant dose dependent change in EO 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 TOPAMAX. 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. There were no clinically significant changes in the systemic exposure of the risperidone total active moiety or of topiramate, therefore this interaction is not likely to be of clinical significance.

Hydrochlorothiazide (HCTZ):

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg q24h) and TOPAMAX (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that TOPAMAX C_{max} increased by 27% and AUC increased by 29% when HCTZ was added to TOPAMAX. The clinical significance of this change is unknown. The addition of HCTZ to TOPAMAX therapy may require an adjustment of the TOPAMAX dose. The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of TOPAMAX. Clinical laboratory results indicated decreases in serum potassium after TOPAMAX or HCTZ administration, which were greater when HCTZ and TOPAMAX 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 $AUC_{0\text{-}12h}$ 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 TOPAMAX 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 TOPAMAX 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 TOPAMAX is added to pioglitazone therapy or pioglitazone is added to TOPAMAX 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 (5mg/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

TOPAMAX, when used concomitantly with other agents predisposing to nephrolithiasis, may increase the risk of nephrolithiasis. While using TOPAMAX, 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 **sections 4.4** and **4.8**). This adverse reaction 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 Normalised 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 summarised below in **Table 3**. 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 3: 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)	↔	↔

Concomitant Drug	Concomitant Drug Concentration	Topiramate Concentration
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 (40mg and 80mg 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

NS = Not studied

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

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

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.

TOPAMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see **section 4.3 Contraindications**). In treating and counseling women of childbearing potential, the prescribing physician should weigh the benefits of therapy against the risks, particularly when TOPAMAX is considered for a condition not usually associated with permanent injury or death. 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 (5mg) 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.

Risk related to topiramate

As with other antiepileptic medicines, topiramate was teratogenic in mice, rats and rabbits. In rats, topiramate crosses the placental barrier.

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

TOPAMAX 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 Antiepileptic Drugs (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 antiepileptic drugs (AEDs), and a prevalence of 0.07 % in infants of mothers without epilepsy or treatment with other AEDs. For comparison, the Centers for Disease Control and Prevention (CDC) reviewed available data on oral clefts in the United States and found a background rate of 0.17%. The relative risk of oral clefts in topiramate-exposed pregnancies in the NAAED Pregnancy Registry was 21.3 (95% Confidence Interval=CI 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%.

The background incidence rate of oral clefts is higher for Māori (2.37 per 1000 live births) compared to the overall New Zealand population (1.79 per 1000 live births).

In addition, data from other studies indicate that, compared with monotherapy, there is an increased risk of teratogenic effects associated with the use of AEDs 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 AEDs, registry data for TOPAMAX 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.

Indication epilepsy

It is recommended to consider alternative therapeutic options in women of child bearing potential. If topiramate is used in women of childbearing potential, it is recommended that highly effective contraception be used (see **section 4.4 Special warnings and precautions for use** and **4.5 Interactions with other medicines and other forms of interactions**) during treatment and for at least 4 weeks after stopping treatment with topiramate, 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.

Indication migraine prophylaxis

Topiramate is contraindicated in pregnancy and in women of childbearing potential if a highly effective method of contraception is not used (see **sections 4.3 Contraindications, section 4.4 Special warnings and precautions for use** and **4.5 Interactions with other medicines and other forms of interactions**). A highly effective contraceptive method should be used during treatment and for at least 4 weeks after stopping treatment with topiramate. If a woman being treated with topiramate becomes pregnant, treatment should be stopped immediately. The woman should be referred to a specialist for careful antenatal monitoring and counselling.

Breastfeeding

Topiramate is excreted in the milk of lactating rats. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observation in patients suggests an extensive excretion of topiramate into breast milk. Diarrhea and somnolence have been reported in breastfed infants whose mothers receive topiramate treatment. Therefore, a decision should be made whether to discontinue breastfeeding or to discontinue the medicine, taking into account the benefit of breast-feeding for the child and the benefit of the medicine to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

TOPAMAX 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 UNDESIRABLE EFFECTS

Clinical Trial Data

The safety of TOPAMAX was evaluated from a clinical trial database consisting of 4111 patients (3182 on TOPAMAX 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.

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

Adverse Drug Reactions (ADRs) reported in ≥1% of TOPAMAX-treated adult patients in double-blind, placebo-controlled adjunctive epilepsy trials are shown in **Table 4**. 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 4: Adverse Drug Reactions Reported by ≥1% of TOPAMAX-Treated Adult Patients in Double-Blind, Placebo-Controlled, Adjunctive Epilepsy Trials

System/Organ Class Adverse Reaction	TOPAMAX 200-400 mg/day (N=354) %	TOPAMAX 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
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

System/Organ Class Adverse Reaction	TOPAMAX 200-400 mg/day (N=354) %	TOPAMAX 600-1000 mg/day (N=437) %	PLACEBO (N=382) %
Stomach discomfort	3.1	3.2	1.3
Dyspepsia	2.3	3.0	2.1
Dry mouth	1.7	3.7	0.3
Abdominal pain	1.1	2.7	0.8
Musculoskeletal and Connective Tissue Disorders			
Myalgia	2.0	2.5	1.3
Muscle spasms	1.7	2.1	0.8
Musculoskeletal chest pain	1.1	1.8	0.3
General Disorders and Administration Site Conditions			
Fatigue	13.0	30.7	11.8
Irritability	9.3	14.6	3.7
Asthenia	3.4	3.0	1.8
Gait disturbance	1.4	2.5	1.3
Investigations			
Weight decreased	9.0	11.9	4.2

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

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

ADRs reported in >2% of TOPAMAX-treated pediatric patients (2 to 16 years of age) in double-blind, placebo-controlled adjunctive epilepsy trials are shown in **Table 5**. 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 5: Adverse Drug Reactions Reported by ≥2% of TOPAMAX-Treated Paediatric Patients in Double-Blind, Placebo-Controlled, Adjunctive Epilepsy Trials

System/Organ Class Adverse Reaction	TOPAMAX (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
Gastrointestinal Disorders		

System/Organ Class Adverse Reaction	TOPAMAX (N=104) %	PLACEBO (N=102) %
Constipation	5.8	4.9
Skin and Subcutaneous Tissue Disorders		
Rash	6.7	5.9
General Disorders and Administration Site Conditions		
Fatigue	16.3	4.9
Irritability	11.5	8.8
Gait disturbance	4.8	2.0
Investigations		
Weight decreased	9.6	1.0

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

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

ADRs reported in ≥1% of TOPAMAX-treated adult patients in double-blind, controlled monotherapy epilepsy trials are shown in **Table 6**. ADRs that had an incidence >5% at the recommended dose (400 mg/day) in descending order of frequency included paraesthesia, weight decreased, fatigue, anorexia, depression, memory impairment, anxiety, diarrhoea, asthenia, dysguesia, and hypoesthesia.

Table 6: Adverse Drug Reactions Reported by ≥1% of TOPAMAX-Treated Adult Patients in Double-Blind, Controlled Monotherapy Epilepsy Trials

System/Organ Class Adverse Reaction	TOPAMAX 50 mg/day (N=257) %	TOPAMAX 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
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

System/Organ Class Adverse Reaction	TOPAMAX 50 mg/day (N=257) %	TOPAMAX 400 mg/day (N=153) %
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

The recommended dose for monotherapy therapy in adults is 400 mg/day.

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

ADRs reported in ≥2% of TOPAMAX-treated paediatric patients (10 to 16 years of age) 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 weight decreased, paraesthesia, diarrhoea, disturbance in attention, pyrexia, and alopecia.

Table 7: Adverse Drug Reactions Reported by ≥2% of TOPAMAX-Treated Paediatric Patients in Double-Blind, Controlled Monotherapy Epilepsy Trials

System/Organ Class Adverse Reaction	TOPAMAX 50 mg/day (N=77) %	TOPAMAX 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
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

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 TOPAMAX-treated adult patients in double-blind, placebo-controlled migraine prophylaxis trials are shown in **Table 8**. 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, dysguesia, anorexia, decreased appetite, insomnia, hypoesthesia, disturbance in attention, anxiety, somnolence, and expressive language disorder.

Table 8: Adverse Drug Reactions Reported by ≥1% of TOPAMAX-Treated Adult Patients in Double-Blind, Placebo-Controlled Migraine Prophylaxis Trials

System/Organ Class Adverse Reaction	TOPAMAX 50 mg/day (N=227) %	TOPAMAX 100 mg/day (N=374) %	TOPAMAX 200 mg/day (N=501) %	PLACEBO (N=436) %
Metabolism and Nutrition Disorders				
Anorexia	3.5	7.5	7.2	3.0

System/Organ Class Adverse Reaction	TOPAMAX 50 mg/day (N=227) %	TOPAMAX 100 mg/day (N=374) %	TOPAMAX 200 mg/day (N=501) %	PLACEBO (N=436) %
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
Gastrooesophageal 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

System/Organ Class Adverse Reaction	TOPAMAX 50 mg/day (N=227) %	TOPAMAX 100 mg/day (N=374) %	TOPAMAX 200 mg/day (N=501) %	PLACEBO (N=436) %

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

Other Clinical Trial Data

ADRs reported in double-blind controlled clinical trials in <1% of TOPAMAX-treated adult patients or at any rate in open-label clinical trials of TOPAMAX-treated adult patients are shown in **Table 9**.

Table 9: Adverse Drug Reactions Reported in Double-Blind Controlled Clinical Trials in <1% of TOPAMAX-Treated Adult Patients or at Any Rate in Open-Label Clinical Trials of TOPAMAX-Treated Adult Patients

Blood and Lymphatic System Disorders
Leukopenia, lymphadenopathy, thrombocytopenia

Immune System Disorders
Hypersensitivity

Metabolism and Nutrition Disorders
Acidosis hyperchloraemic, hypokalaemia, increased appetite, metabolic acidosis, polydipsia

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

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

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

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

Cardiac Disorders
Bradycardia, sinus bradycardia, palpitations

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

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

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

Skin and Subcutaneous Tissue Disorders
Anhidrosis, dermatitis allergic, erythema, rash macular, skin discolouration, skin odour abnormal, swelling face, urticaria, urticaria localised

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

Renal and Urinary Disorders

Calculus ureteric, calculus urinary, haematuria, incontinence, micturition urgency, renal colic, renal pain, urinary incontinence

Reproductive System and Breast Disorders
Sexual dysfunction

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

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

ADRs reported in double-blind controlled clinical trials in <2% of TOPAMAX-treated paediatric patients or at any rate in open-label clinical trials of TOPAMAX-treated paediatric patients are shown in **Table 10**.

Table 10: Adverse Drug Reactions Reported in Double-Blind Controlled Clinical Trials in <2% of TOPAMAX-Treated Paediatric Patients or at Any Rate in Open-Label Clinical Trials of TOPAMAX-Treated Paediatric Patients

Blood and Lymphatic System Disorders
Eosinophilia, leukopenia, lymphadenopathy, thrombocytopenia

Immune System Disorders
Hypersensitivity

Metabolism and Nutrition Disorders
Acidosis hyperchloraemic, hypokalaemia, increased appetite

Psychiatric Disorders
Anger, apathy, crying, distractibility, expressive language disorder, initial insomnia, insomnia, middle insomnia, mood swings, perseveration, sleep disorder, suicidal ideation, suicide attempt

Nervous System Disorders
Circadian rhythm sleep disorder, convulsion, dysarthria, dysgeusia, grand mal convulsion, hypoaesthesia, mental impairment, nystagmus, parosmia, poor quality sleep, psychomotor hyperactivity, psychomotor skills impaired, syncope, tremor

Eye Disorders
Diplopia, lacrimation increased, vision blurred

Ear and Labyrinth Disorders
Ear pain

Cardiac Disorders
Palpitations, sinus bradycardia

Vascular Disorders
Orthostatic hypotension

Respiratory, Thoracic, and Mediastinal Disorders
Nasal congestion, paranasal sinus hypersecretion, rhinorrhoea

Gastrointestinal Disorders
Abdominal discomfort, abdominal pain, dry mouth, flatulence, gastritis, gastroesophageal reflux disease, gingival bleeding, glossodynia, pancreatitis, paraesthesia oral, stomach discomfort

Musculoskeletal and Connective Tissue Disorders
Arthralgia, musculoskeletal stiffness, myalgia

Renal and Urinary Disorders
Incontinence, micturition urgency, pollakiuria

General Disorders
Feeling abnormal, hyperthermia, malaise, sluggishness

Postmarketing Data

Adverse events first identified as ADRs during postmarketing experience with TOPAMAX, presented by frequency category based on incidence in clinical trials, are included in **Table 11**. 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 11: Adverse Reactions Identified During Postmarketing Experience with TOPAMAX 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
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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

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 - Precautions: Metabolic Acidosis**).

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

Treatment

In 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 risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antiepileptics, other antiepileptics, antimigraine preparations

ATC code: N03AX11

Mechanism of actions

Topiramate is classified as a sulfamate-substituted monosaccharide.

The precise mechanism by which topiramate exerts its antiseizure effect is unknown. Electrophysiological and biochemical studies on cultured neurons have identified three properties that may contribute to the antiepileptic efficacy of topiramate.

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

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

Because the antiepileptic profile of topiramate differs markedly from that of the benzodiazepines, it may modulate a benzodiazepine-insensitive subtype of $GABA_A$ receptor. Topiramate antagonised the ability of kainate to activate the kainate/AMPA (a-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) subtype of excitatory amino acid (glutamate) receptor, but had no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype. These effects of

topiramate were concentration-dependent over a range of 1 micromol to 200 micromols, with minimum activity observed at 1 micromol to 10 micromols.

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

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

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

5.2 PHARMACOKINETIC PROPERTIES

The tablet and Sprinkle formulations are bioequivalent at equivalent doses.

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

Topiramate is not a potent inducer of drug 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.

Absorption:

Topiramate is rapidly and well absorbed. Following oral administration of 100 mg topiramate to healthy subjects, a mean peak plasma concentration (C_{max}) of 1.5 micrograms/mL was achieved within 2 to 3 hours (T_{max}). Based on the recovery of radioactivity from the urine the mean extent of absorption of a 100 mg oral dose of 14C-topiramate was at least 81%. There was no clinically significant effect of food on the bioavailability of topiramate.

Distribution:

Generally, 13 to 17% of topiramate is bound to plasma protein. A low capacity binding site for topiramate in/on erythrocytes that is saturable above plasma concentrations of 4 micrograms/mL has been observed. The volume of distribution varied inversely with the dose. The mean apparent volume of distribution was 0.80 to 0.55 L/kg for a single dose range of 100 to 1200 mg. There is an effect of gender on the volume of distribution. Values for females are about 50% lower than those for males. This was attributed to the higher percentage body fat in female patients and is of no clinical consequence.

Metabolism:

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.

Elimination:

In humans, the major route of elimination of unchanged topiramate and its metabolites is *via* the kidney (at least 81% of the dose). Approximately 66% of a dose of ^{14}C-topiramate was excreted

unchanged in the urine within four days. Following twice a day dosing with 50 mg and 100 mg of topiramate the mean renal clearance was approximately 18 mL/min and 17 mL/min, respectively. There is evidence of renal tubular reabsorption of topiramate. This is supported by studies in rats where topiramate was co-administered with probenecid, and a significant increase in renal clearance of topiramate was observed. Overall, plasma clearance is approximately 20 to 30 mL/min in humans following oral administration.

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

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

Special populations

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 topiramate plasma concentrations are expected for a given dose in renal impaired patients as compared to those with normal renal function. In addition, patients with renal impairment will require a longer time to reach steady-state at each dose. In patients with moderate and severe renal impairment, half of the usual starting and maintenance dose is recommended (see **section 4.2**).

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.

Paediatric pharmacokinetics up to 12 years of age

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

5.3 PRECLINICAL SAFETY DATA

Teratogenicity / Embryotoxicity

As with other antiepileptic agents, topiramate was teratogenic in mice, rats and rabbits. Overall numbers of fetal malformations in mice were increased for all topiramate treated groups, but no significant differences or dose-response relationships were observed for overall or specific malformations, suggesting that other factors such as maternal toxicity may be involved.

The teratogenic effects seen in rats and rabbits were similar to those seen with carbonic anhydrase inhibitors, which have not been associated with malformations in humans.

Mutagenicity

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

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

TOPAMAX tablets

Tablet core

Lactose monohydrate

Pregelatinised maize starch

Purified water

Microcrystalline cellulose

Sodium starch glycollate

Magnesium stearate

OPADRY® coating and colouring

Titanium dioxide

Hypromellose

Carnauba wax

Lauromacrogol 400

Polysorbate 80

Iron oxide yellow (50 mg and 100 mg tablets)

Iron oxide red (200 mg tablets).

TOPAMAX Sprinkle capsules

Sugar spheres

Povidone

Cellulose acetate

Sucrose

Capsule shells

Gelatin

Titanium dioxide

Black imprinting ink.

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

Tablets in blister packs – 3 years

Sprinkle capsules – 2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Tablets – Store at or below 25°C in a dry place. Store in the original package.

Sprinkle capsules – Store at or below 25°C in a dry place.

For TOPAMAX Sprinkle capsules, do not store the drug/ food mixture.

6.5 NATURE AND CONTENTS OF CONTAINER

Tablets:

Opaque plastic bottle with tamper-evident closure containing 60 tablets. In each bottle, there is a desiccant canister which should not be swallowed.

Blister pack of an aluminium/aluminium foil in strips. Pack sizes of 20* or 60 tablets. (* 25 mg tablets only.)

Not all pack type or pack sizes may be marketed.

Sprinkle capsules:

Supplied in opaque bottles with tamper-evident closures. Each bottle contains 60 Sprinkle capsules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Janssen-Cilag (New Zealand) Ltd

Auckland, NEW ZEALAND

Telephone: 0800 800 806

Fax: (09) 588 1398

Email: **medinfo@janau.jnj.com**

9. DATE OF FIRST APPROVAL

Tablets: 11 November 1998

Sprinkles Capsules: 11 November 1999

10. DATE OF REVISION OF THE TEXT

3 March 2025

Summary table of changes

Section changed	Summary of new information
4.4	Additional advice for women of childbearing potential
4.6	Additional advice for women of childbearing potential
4.9	Added risk assessment wording