# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

Topiramate Actavis 25, film-coated tablets 25 mg
Topiramate Actavis 50, film-coated tablets, 50 mg
Topiramate Actavis 100, film-coated tablets, 100 mg
Topiramate Actavis 200, film-coated tablets, 200 mg

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 25 mg, 50 mg, 100 mg or 200 mg topiramate.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

25 mg – White, round, biconvex, film coated tablet marked with 'V1'.

50 mg – Light yellow, round biconvex, film coated tablet marked with 'V3'.

100 mg – Yellow, round biconvex film, coated tablet marked with 'V4'.

200 mg – Salmon, oval biconvex, film coated tablet marked with 'V5'.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

**Epilepsy**

Topiramate Actavis 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.

** Topiramate Actavis tablet range cannot deliver lower doses required for younger paediatric patients (See section 4.2 **Dose and method of administration**).

**Migraine**

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

### 4.2 Dose and method of administration

Topiramate Actavis Tablets should be swallowed whole. Topiramate Actavis Tablets can be taken with or without food.

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 Actavis in adults and children with epilepsy are listed as follows and summarised in Table 1.

**Epilepsy - Monotherapy**

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

In patients who are being converted to Topiramate Actavis 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 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. 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**
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 400 mg/day. The daily dosage should be given as two divided doses.

** Topiramate Actavis tablet range cannot deliver lower doses required for younger paediatric patients (See section 4.2 **Dose and method of administration**).

**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**
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.

** Topiramate Actavis tablet range cannot deliver lower doses required for younger paediatric patients (see section 4.2 **Dose and method of administration**).

**Table 1 Recommended dosages of Topiramate Actavis 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 **** | | |
| **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.

** Topiramate Actavis tablet range cannot deliver lower doses required for younger paediatric patients (See section 4.2 **Dose and method of administration**).

It is not necessary to monitor topiramate plasma concentrations to optimise topiramate therapy. For patients receiving concomitant phenytoin and carbamazepine, dosage adjustment for Topiramate Actavis 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 Actavis 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 **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 equal to approximately one-half the daily dose should be administered on hemodialysis days. The supplemental dose should be administered in divided doses at the beginning and completion of the hemodialysis procedure. The supplemental dose may differ based on the characteristics of the dialysis equipment being used (see section 5.2 **Pharmacokinetic properties).**

**Drug withdrawal and dosage reduction**
In patients with or without a history of seizures or epilepsy, antiepileptic drugs, including Topiramate Actavis, should be gradually withdrawn to minimize the potential for seizures or of increased seizure frequency (see section 4.4 **Special warnings and precautions for use**). In situations where rapid withdrawal of Topiramate Actavis is medically required, appropriate monitoring is recommended.

## 4.3 Contraindications
Hypersensitivity to topiramate and the excipients listed under section 6.1.

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
**Drug withdrawal**
In patients with or without a history of seizures or epilepsy, antiepileptic agents, including Topiramate Actavis, 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 to 100 mg in adults with epilepsy and by 25 to 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- to 8-week period. In situations where rapid withdrawal of topiramate 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 Topiramate Actavis 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 topiramate (see section 4.8 **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 Actavis 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.

Healthcare 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 topiramate**
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 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 Actavis 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**
A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving topiramate. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include some or all of the following: myopia, mydriasis, anterior chamber shallowing, ocular hyperaemia (redness), choroidal detachments, retinal pigment epithelial detachments, macular striae and increased intraocular pressure. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating topiramate therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in paediatric patients as well as adults. Treatment includes discontinuation of topiramate, as rapidly as possible in the judgement of the treating physician, and appropriate measures to reduce intraocular pressure. These measures generally result in a decrease in intraocular pressure.

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

**Visual field defects**
Visual field defects have been reported in patients receiving topiramate independent of elevated intraocular pressure. In clinical trials, most of these events were reversible after topiramate discontinuation. If visual problems occur at any time during topiramate treatment, consideration should be given to discontinuing the drug.

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

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

Chronic metabolic acidosis in paediatric patients can reduce growth rates. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated in 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 Topiramate Actavis therapy. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing Topiramate Actavis (using dose tapering).

**Hyperammonemia and encephalopathy**
Hyperammonemia with or without encephalopathy has been reported with topiramate treatment (see section 4.8 **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 and depression**
An increased incidence of mood disturbances and depression has been observed during topiramate treatment. Psychiatric or 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 on topiramate (13 events/3999 patient years) versus 0 on placebo (0 events/1430 patient years). One completed suicide was reported in a bipolar disorder trial in a patient on topiramate.

**Women of childbearing potential**
Topiramate may cause foetal 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 and a highly effective contraceptive method used. The patient should be fully informed of the risks related to the use of topiramate during pregnancy (see **section 4.6 Fertility, pregnancy and lactation**).

For migraine prophylaxis, topiramate is contraindicated in pregnancy and in women of childbearing potential if a highly effective method of contraception is not used (see **section 4.3 Contraindications** and **section 4.5 Interactions with other medicines and other forms of interaction**).

Topiramate should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus (see section **4.3 Contraindications** and 4.6 **Fertility, pregnancy and lactation**).

**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 Interaction with other medicines and other forms of interaction

**Effects of topiramate on other antiepileptic agents**
The addition of topiramate 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 topiramate to phenytoin may result in an increase of plasma concentrations of phenytoin. This is possibly due to inhibition of a specific enzyme polymorphic isoform (CYP2C19). Consequently , any patient on phenytoin showing clinical signs or symptoms of toxicity should have phenytoin levels monitored.

**Effects of other antiepileptic agents on topiramate**
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 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 as below:

**Table 2: Interactions between antiepileptic agents (AEA) and topiramate**

| AEA co-administered | AEA plasma concentration | Topiramate plasma concentration |
|---|---|---|
| Phenytoin | ↔ * | Decrease (48%) |
| Carbamazepine | ↔ | Decrease (40%) |
| Valproic Acid | ↔ | ↔ |
| Phenobarbitone | ↔ | Not studied |
| Primidone | ↔ | Not studied |
| Lamotrigine | ↔ | ↔ |

↔ = No effect on plasma concentration (< 15% change)
* Plasma concentrations increase occasionally in some patients.

No data are available on the use of topiramate 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 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 medicines has not been evaluated in clinical studies. It is recommended that topiramate 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 plus 35

microgram ethinyl oestradiol, topiramate given in the absence of other medications at doses of 50 to 200 mg/day was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive.

In another study, exposure to ethinyl oestradiol 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 norethindrone. Although there was a dose dependent decrease in ethinyl oestradiol exposure for doses between 200 to 800 mg/day, there was no significant dose dependent change in ethinyl oestradiol exposure for doses of 50 to 200 mg/day. The clinical significance of the changes observed is not known. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking contraceptive products with topiramate. Patients taking oestrogen containing or progestin only contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding.

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

**Risperidone:** Drug-drug interaction studies conducted under single and multiple dose conditions in healthy volunteers and patients with bipolar disorder yielded similar results. When administered concomitantly with topiramate at escalating doses of 100, 250 and 400 mg/day, there was a reduction in risperidone (administered at doses ranging from 1 to 6 mg/day) with 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 24-hourly) and topiramate (96 mg 12-hourly) 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. The steady-state pharmacokinetics of HCTZ was not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicated decreases in serum potassium after topiramate or HCTZ administration, which were greater when HCTZ and topiramate were administered in combination.

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

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

**Pioglitazone:** A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of topiramate and pioglitazone when administered alone and concomitantly. A 15% decrease in the $AUC_{t,ss}$ of pioglitazone with no alteration in $C_{max,ss}$ was observed. This finding was not statistically significant. In addition, a 13% and 16% decrease in $C_{max,ss}$ and $AUC_{t,ss}$ respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in $C_{max,ss}$ and $AUC_{t,ss}$ of the active keto-metabolite. The clinical significance of these findings is not known. When topiramate is added to pioglitazone therapy or pioglitazone is added to topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

**Glibenclamide:** A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glibenclamide (5 mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 25% reduction in glibenclamide $AUC_{24}$ during topiramate administration. Systemic exposure of the active metabolites, 4-*trans*-hydroxy-glibenclamide and 3-*cis*-hydroxyglibenclamide, 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:** When topiramate is used concomitantly with other agents predisposing to nephrolithiasis, the risk of nephrolithiasis may be increased. Thus, while on topiramate therapy, agents like these should be avoided, as 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 **Special warnings and precautions for use** and 4.8 **Undesirable effects**). 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 the 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 summarized 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 co-administration of a drug listed in the first column modifies the concentration of topiramate.

**Table 3: Pharmacokinetic drug interaction studies**

| Concomitant drug | Concomitant drug concentration | Topiramate concentration |
|---|---|---|
| Amitriptyline | ↔<br>20% increase in $C_{max}$ and AUC of nortriptyline metabolite | Not studied |
| Dihydroergotamine (oral and subcutaneous) | ↔ | ↔ |
| Haloperidol | ↔<br>31% increase in AUC of the reduced metabolite | Not studied |
| Propranolol | ↔<br>17% Increase in $C_{max}$ for 4-OH propranolol (topiramate 50 mg 12-hourly) | 9% and 16% Increase in $C_{max}$, 9% and 17% increase in AUC (40 mg and 80 mg propranolol 12-hourly respectively) |
| Sumatriptan (oral and subcutaneous) | ↔ | Not studied |
| 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 (topiramate 50 mg 12-hourly)[b] | ↔ |

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

Topiramate 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 topiramate 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 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 (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 topiramate in pregnant women.

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

*Congenital malformations*
Data from pregnancy registries indicate that infants exposed to topiramate *in utero* have an increased risk of congenital malformations (e.g., craniofacial defects, such as cleft lip/palate, hypospadias, and anomalies involving various body systems) and neurodevelopmental disorders (e.g., autism spectrum disorders and intellectual disability).

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. 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 Maori (2.37 per 1000 live births) compared with 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 antiepileptic drugs, registry data for topiramate monotherapy showed a higher prevalence of low birth weight (<2500 grams). One pregnancy registry reported an increased frequency of infants who were small for gestational age (SGA: defined as birth weight below the 10$^{th}$ 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 4.5 **Interactions with other medicines and other forms of interactions**), and that the woman is fully informed of the known risks of uncontrolled epilepsy to the pregnancy and the potential risks of the medicinal product to the foetus. 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** and section 4.5 **Interactions with other medicines and other forms of interactions**).

**Lactation**
Topiramate is excreted in the milk of lactating rats. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observation in patients suggests an extensive excretion of topiramate into breast milk. Diarrhoea 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 breastfeeding for the child and the benefit of the medicine to the mother.

### 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 Undesirable effects

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 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 topiramate-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, nystgamus, lethargy, anorexia, dysarthria, vision blurred, decreased appetite, memory impairment and diarrhoea.

**Table 4: Adverse Drug Reactions Reported by ≥1% of Topiramate-treated Adult Patients in Double-Blind, Placebo-Controlled, Adjunctive Epilepsy Trials**

| System/Organ Class<br>Adverse Reaction | Topiramate 200-400 mg/day (N=354)<br>% | Topiramate 600-1000 mg/day (N=437)<br>% | Placebo<br>(N=382)<br>% |
|---|---|---|---|
| **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 |
| 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 topiramate-treated paediatric 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 Topiramate-treated Paediatric Patients in Double-Blind, Placebo-Controlled, Adjunctive Epilepsy Trials**

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

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

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

ADRs reported in ≥1% of topiramate-treated adult patients in 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 Topiramate-treated Adult Patients in Double-Blind, Controlled Monotherapy Epilepsy Trials**

| **System/Organ Class**<br>**Adverse Reaction** | **Topiramate 50 mg/day (N=257) %** | **Topiramate 400 mg/day (N=153) %** |
|---|---|---|
| **Blood and Lymphatic System Disorders** | | |
| Anaemia | 0.8 | 2.0 |
| **Metabolism and Nutrition Disorders** | | |
| Anorexia | 3.5 | 12.4 |
| Decreased appetite | 2.3 | 2.6 |
| **Psychiatric Disorders** | | |
| Depression | 4.3 | 8.5 |
| Anxiety | 3.9 | 6.5 |
| Bradyphrenia | 2.3 | 4.6 |
| Expressive language disorder | 3.5 | 4.6 |
| Depressed mood | 0.8 | 2.6 |
| Mood altered | 0.4 | 2.0 |
| Mood swings | 1.6 | 2.0 |
| **Nervous System Disorders** | | |
| Paraesthesia | 18.7 | 40.5 |
| Memory impairment | 1.2 | 7.2 |
| Dysgeusia | 2.3 | 5.9 |
| Hypoaesthesia | 4.3 | 5.2 |
| Balance disorder | 1.6 | 3.3 |
| Dysarthria | 1.6 | 2.6 |
| Cognitive disorder | 0.4 | 2.0 |
| Lethargy | 1.2 | 2.0 |
| Mental impairment | 0.8 | 2.0 |
| Psychomotor skills impaired | 0 | 2.0 |
| Sedation | 0 | 1.3 |
| Visual field defect | 0.4 | 1.3 |

| | | |
|---|---|---|
| **Eye Disorders** | | |
| Dry Eye | 0 | 1.3 |
| **Ear and Labyrinth Disorders** | | |
| Ear pain | 0 | 1.3 |
| Tinnitus | 1.6 | 1.3 |
| **Respiratory, Thoracic and Mediastinal Disorders** | | |
| Dyspnoea | 1.2 | 2.0 |
| Rhinorrhoea | 0 | 1.3 |
| **Gastrointestinal Disorders** | | |
| Diarrhoea | 5.4 | 6.5 |
| Paraesthesia oral | 1.2 | 3.3 |
| Dry mouth | 0.4 | 2.6 |
| Gastritis | 0.8 | 2.6 |
| Abdominal pain | 1.2 | 2.0 |
| Gastrooesophageal 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 – Paediatric Patients

ADRs reported in ≥2% of topiramate-treated paediatric patients (10 to 16 years of age) in double-blind, controlled monotherapy epilepsy trials are shown in Table 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 Topiramate-treated Paediatric Patients in Double-Blind, Controlled Monotherapy Epilepsy Trials**

| **System/Organ Class<br>Adverse Reaction** | **Topiramate 50 mg/day (N=77) %** | **Topiramate 400 mg/day (N=63) %** |
|---|---|---|
| **Metabolism and Nutrition Disorders** | | |
| Decreased appetite | 1.3 | 4.8 |
| **Psychiatric Disorders** | | |
| Bradyphrenia | 0 | 4.8 |
| Mood altered | 1.3 | 4.8 |
| Depression | 0 | 3.2 |
| **Nervous System Disorders** | | |
| Paraesthesia | 3.9 | 15.9 |
| Disturbance in attention | 3.9 | 7.9 |
| **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.

**Migraine Prophylaxis**

**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 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 Topiramate-treated Adult Patients in Double-Blind, Placebo-Controlled Migraine Prophylaxis Trials**

| **System/Organ Class Adverse Reaction** | **Topiramate 50 mg/day (N=227) %** | **Topiramate 100 mg/day (N=374) %** | **Topiramate 200 mg/day (N=501) %** | **Placebo (N=436) %** |
|---|---|---|---|---|
| **Metabolism and Nutrition Disorders** | | | | |
| Anorexia | 3.5 | 7.5 | 7.2 | 3.0 |
| Decreased appetite | 5.7 | 7.0 | 6.8 | 3.0 |
| **Psychiatric Disorders** | | | | |
| Insomnia | 4.8 | 7.0 | 5.6 | 3.9 |
| Anxiety | 4.0 | 5.3 | 5.0 | 1.8 |
| Expressive language disorder | 6.6 | 5.1 | 5.2 | 1.4 |
| Depression | 3.5 | 4.8 | 7.4 | 4.1 |
| Depressed mood | 0.4 | 2.9 | 2.0 | 0.9 |
| Confusional state | 0.4 | 1.6 | 2.0 | 1.1 |
| Mood swings | 1.8 | 1.3 | 1.0 | 0.2 |
| Affect lability | 0.4 | 1.1 | 0.2 | 0.2 |
| Bradyphrenia | 1.8 | 1.1 | 3.4 | 1.4 |
| **Nervous System Disorders** | | | | |
| Paraesthesia | 35.7 | 50.0 | 48.5 | 5.0 |
| Dysgeusia | 15.4 | 8.0 | 12.6 | 0.9 |
| Hypoaesthesia | 5.3 | 6.7 | 7.4 | 1.4 |
| Disturbance in attention | 2.6 | 6.4 | 9.2 | 2.3 |
| Somnolence | 6.2 | 5.1 | 6.8 | 3.0 |
| Memory impairment | 4.0 | 4.5 | 6.2 | 1.6 |
| Amnesia | 3.5 | 2.9 | 5.2 | 0.5 |
| Tremor | 1.3 | 1.9 | 2.4 | 1.4 |
| Balance disorder | 0.4 | 1.3 | 0.4 | 0 |

| | | | | |
|---|---|---|---|---|
| Mental impairment | 0.4 | 1.1 | 1.8 | 0.9 |
| **Eye Disorders** | | | | |
| Vision blurred | 4.0 | 2.4 | 4.4 | 2.5 |
| **Ear and Labyrinth Disorders** | | | | |
| Tinnitus | 0.4 | 1.3 | 1.6 | 0.7 |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | | |
| Dyspnoea | 1.3 | 2.7 | 1.6 | 1.4 |
| Epistaxis | 0.4 | 1.1 | 0.6 | 0.5 |
| **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 |

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

**Other Clinical Trial Data**

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

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

| |
|---|
| **Blood and Lymphatic System Disorders** |
| Leukopenia, lymphadenopathy, thrombocytopenia |
| **Immune System Disorders** |
| Hypersensitivity |
| **Metabolism and Nutrition Disorders** |
| Acidosis 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 topiramate-treated paediatric patients or at any rate in open-label clinical trials of topiramate-treated paediatric patients are shown in Table 10.

**Table 10: Adverse Drug Reactions Reported in Double-Blind Controlled Clinical Trials in <2% of Topiramate-treated Paediatric Patients or at Any Rate in Open-Label Clinical Trials of Topiramate-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, gastrooesophageal 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 topiramate, 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 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 |
| *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 Conditions** | |
| *Very rare* | Influenza like illness |

| | |
|---|---|
| *Very rare* | Generalised oedema |
| **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, 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 **Metabolic acidosis** under section 4.4 **Special warnings and precautions for use**).

The highest topiramate overdose reported was calculated to be between 96 and 110 g and resulted 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 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

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.

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 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 (Cmax) of 1.5 micrograms/mL was achieved within 2 to 3 hours (Tmax). Based on the recovery of radioactivity from the urine the mean extent of absorption of a 100 mg oral dose of $^{14}C$-topiramate was at least 81%. There was no clinically significant effect of food on the bioavailability of topiramate.

### Distribution

Generally, 13 to 17% of topiramate is bound to plasma protein. A low capacity binding site for topiramate in/on erythrocytes that is saturable above plasma concentrations of 4 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 intersubject variability in plasma concentrations and therefore has predictable pharmacokinetics. The pharmacokinetics of topiramate are linear with plasma clearance remaining constant and area under the plasma concentration curve increasing in a dose proportional manner over a 100 to 400 mg single oral dose range in healthy subjects. Patients with normal renal function may take 4 to 8 days to reach steady state plasma concentrations. The mean $C_{max}$ following multiple, twice a day oral doses of 100 mg to healthy subjects was 6.76 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 Dose and method of administration**).

Topiramate is effectively removed from plasma by haemodialysis. A prolonged period of hemodialysis may cause topiramate concentration to fall below levels that are required to maintain an anti-seizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis, a supplemental dose of topiramate may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being 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 and embryotoxicity**
As with other antiepileptic agents, topiramate was teratogenic in mice, rats and rabbits. Overall numbers of foetal 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
Topiramate Actavis Tablets contain the following excipients: mannitol, microcrystalline cellulose, pregelatinised maize starch, magnesium stearate, croscarmellose sodium, and the colouring Opadry II White 85F18422for 25 mg Tablets, Opadry II Yellow 85G32312 for 50 mg Tablets, Opadry II Yellow 85G32313 for 100 mg Tablets, and Opadry II Pink 85G34776 for 200 mg Tablets.

### 6.2 Incompatibilities
Not applicable.

### 6.3 Shelf life
3 years for both blister packs and bottles.

### 6.4 Special precautions for storage
Store at or below 25°C.

### 6.5 Nature and contents of container
Topiramate Actavis Tablets are available in opaque bottles and foil blister packs of 10, 60 and 200 tablets.

Topiramate Actavis 25 mg tablets are also available as a sample pack of 20 tablets in an opaque bottle.

**Not all pack types and sizes may be marketed.**

### 6.6 Special precautions for disposal

No special requirements for disposal.

## 7. MEDICINE SCHEDULE

Prescription medicine

## 8. SPONSOR

Teva Pharma (New Zealand) Limited
P O Box 128 244
Remuera
Auckland 1541
Telephone: 0800 800 097

## 9. DATE OF FIRST APPROVAL

03 April 2014

## 10. DATE OF REVISION OF THE TEXT

3 February 2025

## SUMMARY TABLE OF CHANGES

| Section changed | Summary of new information |
|---|---|
| 4.2, 4.4, 4.5, 4.6, 4.8 | Editorial changes |
| 4.4 | Addition of anhidrosis under heading "Oligohydrosis and Hyperthermia" |
| 4.6 | Addition of observational studies data on neurodevelopmental disorders and editorial update. |