



## New Zealand Data Sheet

### APO-TOPIRAMATE

#### Topiramate 25mg, 50mg, 100mg and 200mg Tablets

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#### Presentation

25 mg, white to off – white, round unscored film-coated tablets, Engraved "APO" on one side and "TP" over "25" on the other side

50 mg, light-yellow, round unscored film-coated tablets, Engraved "APO" on one side and "TP" over "50" on the other side

100 mg, mustard yellow, round unscored film-coated tablets, Engraved "APO" on one side and "TP" over "100" on the other side

200 mg, reddish-brown, round unscored film-coated tablets, Engraved "APO" on one side and "TP" over "200" on the other side

#### Uses

#### 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<sub>A</sub> 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<sub>A</sub> receptors.

Because the antiepileptic profile of topiramate differs markedly from that of the benzodiazepines, it may modulate a benzodiazepine-insensitive subtype of GABA<sub>A</sub> receptor. Topiramate antagonised the ability of kainate to activate the kainate/AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) subtype of excitatory amino acid (glutamate) receptor, but had no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype. These effects of topiramate were concentration-dependent over a range of 1 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<sub>A</sub> receptor antagonist, pentylenetetrazole.

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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.

### Pharmacokinetics

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  $^{14}C$ -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

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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.

### **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.

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 the 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 is 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.

## **Indications**

### **EPILEPSY**

APO-TOPIRAMATE is indicated in adults and children, 2 years and over:

- as monotherapy in patients with newly diagnosed epilepsy
- for conversion to monotherapy in patients with epilepsy
- as add-on therapy in partial onset seizures, generalised tonic-clonic seizures or seizures associated with Lennox-Gastaut syndrome.
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### **MIGRAINE**

APO-TOPIRAMATE is indicated in adults for the prophylaxis of migraine headache.

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### Dosage and Administration

APO-TOPIRAMATE tablets should be swallowed whole.

APO-TOPIRAMATE can be taken without regard to meals.

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 APO-TOPIRAMATE in adults and children with epilepsy are summarised in Table 1.

### Epilepsy - Monotherapy

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

In patients who are being converted to APO-TOPIRAMATE 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. When enzyme inducing medicines are withdrawn, topiramate levels will increase. A decrease in APO-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 (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 400 mg/day. The daily dosage should be given as two divided doses.

### Epilepsy - Add-on therapy

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

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

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**Table 1: Recommended dosages in adults and children**

		Monotherapy	Add-on therapy
Adults	<b>Starting dose</b>	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).
	<b>Escalation dose</b>	Increase by 25 to 50 mg/day at weekly or longer intervals.	Increase by 25 to 100 mg/day at weekly or longer intervals.
	<b>Target dose</b>	100 mg/day	200 to 400 mg/day
	<b>Maximum dose</b>	Up to 500 mg/day <sup>1</sup>	Up to 1000 mg/day
Children 2 years & over	<b>Starting dose</b>	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.
	<b>Escalation dose</b>	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.
	<b>Target dose</b>	3 to 6 mg/kg/day	5 to 9 mg/kg/day
	<b>Maximum dose</b>	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. <sup>1</sup> Some patients with refractory epilepsy have tolerated doses of 1000 mg/day.)			

It is not necessary to monitor topiramate plasma concentrations to optimise APO-TOPIRAMATE therapy. For patients receiving concomitant phenytoin and carbamazepine, dosage adjustment for APO-TOPIRAMATE may be required (see **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 APO-TOPIRAMATE as treatment for prophylaxis of migraine headache is 100 mg/day administered in two divided doses. Some patients may experience a benefit at a total daily dose of 50 mg/day. Patients have received a total daily dose up to 200 mg/day. Dose and titration should be guided by clinical outcome.

## 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 **Warnings and Precautions**).

## Use in patients undergoing haemodialysis

Topiramate is cleared by haemodialysis. To avoid rapid reduction in topiramate plasma concentration during haemodialysis, a supplemental dose of APO-TOPIRAMATE should be added to the patient's normal daily dose as follows:

## Patients on Concomitant Enzyme Inducers

(phenytoin, carbamazepine, phenobarbitone and other barbiturates)

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

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of the supplemental dose at the start of haemodialysis. The remaining 3/4 of the supplemental dose should be administered at the completion of the haemodialysis.

#### **Patients Not on Concomitant Enzyme Inducers**

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

#### **Drug withdrawal and Dosage reduction**

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

#### **Contraindications**

Hypersensitivity to any component of this product.

#### **Warnings and Precautions**

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

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

#### **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 antiepileptic drugs had approximately twice the risk of suicidal behavior or ideation (0.43%) compared to patients receiving placebo (0.24%). The increased risk of suicidal behavior 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

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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 behavior that could indicate the emergence or worsening of suicidal thoughts or behavior 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 APO-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), 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 APO-TOPIRAMATE is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity.

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

#### **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 myopia, anterior chamber shallowing, ocular hyperaemia (redness) and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating topiramate therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in paediatric patients as well as adults. Treatment includes discontinuation of topiramate, as rapidly as possible in the judgement of the treating physician,

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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.

#### **Metabolic Acidosis**

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

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

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

#### **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.

#### **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.

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#### Use in Pregnancy and Lactation

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

There are no studies using APO-TOPIRAMATE in pregnant women.

Topiramate can cause foetal harm when administered to a pregnant women. Data from pregnancy registries indicate that infants exposed to Topiramate in utero have an increased risk of congenital malformations (e.g., craniofacial defects, such as cleft lip/palate, hypospadias and anomalies involving various body systems). This has been reported with Topiramate monotherapy and Topiramate as part of a polytherapy regimen.

Data from the North American AED (NAAED) Pregnancy Registry indicates 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 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 = CL 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%.

Compared with reference group not taking antiepileptic drugs, registry data for Topiramate monotherapy showed a higher prevalence of low birth weight (<2500 grams). A casual relationship has not been established.

In addition, data from these registries and other studies suggest that, compared with monotherapy, there may be an increased risk of teratogenic effects associated with the use of anti-epileptic drugs in combination therapy.

Topiramate should be used during pregnancy only if the potential benefits justifies the potential risk to the foetus. In treating and counselling 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 foetus.

The risk of having an abnormal child as a result of antiepileptic medication is far outweighed by the danger to the mother and foetus 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 continued for twelve weeks after conception;
- Specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered

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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. Since many medicines are excreted in human milk, a decision should be made whether to discontinue breastfeeding or to discontinue the medicine, taking into account the importance of the medicine to the mother.

#### **Teratogenicity / 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, centrolobular 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.

#### **Effects on ability to drive and use machines**

APO-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.

### **Adverse Effects**

#### **Clinical Trial Data**

The safety of Topiramate was evaluated from a clinical trial database consisting of 4111 patients (3182 on Topiramate and 929 on placebo) who participated in 20 double-blind trials and 2847 patients who participated in 34 open-label trials, respectively, for the treatment of primary generalized tonic-clonic seizures, partial onset seizures, seizures associated with Lennox-Gastaut syndrome, newly or recently diagnosed epilepsy or migraine. The information presented in this section was derived from pooled data.

The majority of all adverse reactions were mild to moderate in severity.

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

Adverse Drug Reactions (ADRs) reported in  $\geq 1\%$  of TOPIRAMATE- treated adult patients in double-blind, placebo-controlled adjunctive epilepsy trials are shown in Table 2. 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.

<b>Table 2: Adverse Drug Reactions Reported by <math>\geq 1\%</math> of TOPIRAMATE-Treated Adult Patients in Double-Blind, Placebo-Controlled, Adjunctive Epilepsy Trials</b>			
<b>System/Organ Class Adverse Reaction</b>	<b>TOPIRAMATE 200-400 mg/day (N=354) %</b>	<b>TOPIRAMATE 600-1000 mg/day (N=437) %</b>	<b>PLACEBO (N=382) %</b>
<b>Metabolism and Nutrition Disorders</b>			
Anorexia	5.4	6.2	1.8
Decreased appetite	5.1	8.7	3.7
<b>Psychiatric Disorders</b>			
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
<b>Nervous System Disorders</b>			
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

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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
<b>Eye Disorders</b>			
Diplopia	7.3	12.1	5.0
Vision blurred	5.4	8.9	2.4
Visual disturbance	2.0	1.4	0.3
<b>Gastrointestinal Disorders</b>			
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
<b>Musculoskeletal and Connective Tissue Disorders</b>			
Myalgia	2.0	2.5	1.3
Muscle spasms	1.7	2.1	0.8
Musculoskeletal chest pain	1.1	1.8	0.3

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### Topiramate 25mg, 50mg, 100mg and 200mg Tablets

<b>General Disorders and Administration Site Conditions</b>			
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
<b>Investigations</b>			
Weight decreased	9.0	11.9	4.2

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

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

ADRs reported in >2% of TOPIRAMATE-treated pediatric patients (2 to 16 years of age) in double-blind, placebo-controlled adjunctive epilepsy trials are shown in Table 3. 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.

<b>Table 3: Adverse Drug Reactions Reported by ≥2% of TOPIRAMATE-Treated Pediatric Patients in Double-Blind, Placebo-Controlled, Adjunctive Epilepsy Trials</b>		
<b>System/Organ Class Adverse Reaction</b>	<b>TOPIRAMATE (N=104) %</b>	<b>PLACEBO (N=102) %</b>
<b>Metabolism and Nutrition Disorders</b>		
Decreased appetite	19.2	12.7
Anorexia	5.8	1.0
<b>Psychiatric Disorders</b>		
Aggression	8.7	6.9
Abnormal behaviour	5.8	3.9
Confusional state	2.9	2.0
Mood altered	2.9	2.0
<b>Nervous System Disorders</b>		
Somnolence	15.4	6.9
Lethargy	13.5	8.8
Disturbance in attention	10.6	2.0

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### Topiramate 25mg, 50mg, 100mg and 200mg Tablets

Balance disorder	5.8	2.0
Dizziness	4.8	2.9
Memory impairment	3.8	1.0
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Epistaxis	4.8	1.0
<b>Gastrointestinal Disorders</b>		
Constipation	5.8	4.9
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash	6.7	5.9
<b>General Disorders and Administration Site Conditions</b>		
Fatigue	16.3	4.9
Irritability	11.5	8.8
Gait disturbance	4.8	2.0
<b>Investigations</b>		
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, Placebo-Controlled Data, Monotherapy Epilepsy Trials - Adult Patients**

ADRs reported in  $\geq 1\%$  of TOPIRAMATE treated adult patients in double-blind, placebo-controlled monotherapy epilepsy trials are shown in Table 4 below. 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.

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Topiramate 25mg, 50mg, 100mg and 200mg Tablets

**Table 4: Adverse Drug Reactions Reported by  $\geq 1\%$  of TOPIRAMATE-Treated Adult Patients in Double-Blind, Controlled Monotherapy Epilepsy Trials**

<b>System/Organ Class Adverse Reaction</b>	<b>TOPIRAMATE 50 mg/day (N=257) %</b>	<b>TOPIRAMATE 400 mg/day (N=153) %</b>
<b>Blood and Lymphatic System Disorders</b>		
Anaemia	0.8	2.0
<b>Metabolism and Nutrition Disorders</b>		
Anorexia	3.5	12.4
Decreased appetite	2.3	2.6
<b>Psychiatric Disorders</b>		
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
<b>Nervous System Disorders</b>		
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
<b>Eye Disorder</b>		

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Dry eye	0	1.3
<b>Ear and Labyrinth Disorders</b>		
Ear pain	0	1.3
Tinnitus	1.6	1.3
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Dyspnoea	1.2	1.3
Rhinorrhoea	0	1.3
<b>Gastrointestinal Disorders</b>		
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
<b>Skin and Subcutaneous Tissue Disorders</b>		
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
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Muscle spasms	2.7	3.3
Arthralgia	1.9	2.0
Muscle twitching	0.4	1.3
<b>Renal and Urinary Disorders</b>		
Nephrolithiasis	0	2.6
Dysuria	0.8	2.0

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Pollakiuria	0.8	2.0
<b>Reproductive System and Breast Disorders</b>		
Erectile dysfunction	0.8	1.3
<b>General Disorders and Administration Site Conditions</b>		
Fatigue	15.2	14.4
Asthenia	3.5	5.9
Irritability	3.1	3.3
<b>Investigations</b>		
Weight decreased	7.0	17.0

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

#### Double-Blind, Placebo-Controlled Data, Monotherapy Epilepsy Trials - Pediatric Patients

ADRs reported in  $\geq 2\%$  of TOPIRAMATE treated pediatric patients (10 to 16 years of age) in double-blind, placebo-controlled monotherapy epilepsy trials are shown in Table 5. 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.

<b>Table 5: Adverse Drug Reactions Reported by <math>\geq 2\%</math> of TOPIRAMATE-Treated Pediatric Patients in Double-Blind, Controlled Monotherapy Epilepsy Trials</b>		
<b>System/Organ Class Adverse Reaction</b>	<b>TOPIRAMATE 50 mg/day (N=77) %</b>	<b>TOPIRAMATE 400 mg/day (N=63) %</b>
<b>Metabolism and Nutrition Disorders</b>		
Decreased appetite	1.3	4.8
<b>Psychiatric Disorders</b>		
Bradyphrenia	0	4.8
Mood altered	1.3	4.8
Depression	0	3.2

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<b>Nervous System Disorders</b>		
Paraesthesia	3.9	15.9
Disturbance in attention	3.9	7.9
<b>Ear and Labyrinth Disorders</b>		
Vertigo	0	3.2
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Epistaxis	0	3.2
<b>Gastrointestinal Disorders</b>		
Diarrhoea	3.9	9.5
Vomiting	3.9	4.8
<b>Skin and Subcutaneous Tissue Disorders</b>		
Alopecia	0	6.3
<b>General Disorders and Administration Site Conditions</b>		
Pyrexia	0	6.3
Asthenia	0	4.8
<b>Investigations</b>		
Weight decreased	7.8	20.6
<b>Social Circumstances</b>		
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  $\geq 1\%$  of TOPIRAMATE-treated adult patients in double-blind, placebo-controlled migraine prophylaxis trials are shown in Table 6. 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,

## APO-TOPIRAMATE

### Topiramate 25mg, 50mg, 100mg and 200mg Tablets

insomnia, hypoesthesia, disturbance in attention, anxiety, somnolence, and expressive language disorder.

**Table 6: Adverse Drug Reactions Reported by  $\geq 1\%$  of TOPIRAMATE-Treated Adult Patients in Double-Blind, Placebo-Controlled Migraine Prophylaxis Trials**

<b>System/Organ Class Adverse Reaction</b>	<b>TOPIRAMATE 50 mg/day (N=227) %</b>	<b>TOPIRAMATE 100 mg/day (N=374) %</b>	<b>TOPIRAMATE 200 mg/day (N=501) %</b>	<b>PLACEBO (N=436) %</b>
<b>Metabolism and Nutrition Disorders</b>				
Anorexia	3.5	7.5	7.2	3.0
Decreased appetite	5.7	7.0	6.8	3.0
<b>Psychiatric Disorders</b>				
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
<b>Nervous System Disorders</b>				
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

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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
<b>Eye Disorders</b>				
Vision blurred	4.0	2.4	4.4	2.5
<b>Ear and Labyrinth Disorders</b>				
Tinnitus	0.4	1.3	1.6	0.7
<b>Respiratory, Thoracic and Mediastinal Disorders</b>				
Dyspnoea	1.3	2.7	1.6	1.4
Epistaxis	0.4	1.1	0.6	0.5
<b>Gastrointestinal Disorders</b>				
Nausea	9.3	13.6	14.6	8.3
Diarrhoea	9.3	11.2	10.0	4.4
Dry mouth	1.8	3.2	5.0	2.5
Paraesthesia oral	1.3	2.9	1.6	0.5
Constipation	1.8	2.1	1.8	1.4
Abdominal distension	0	1.3	0.2	0.2
Stomach discomfort	2.2	1.3	1.0	0.2
Gastroesophageal reflux disease	0.4	1.1	1.2	0.5
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Muscle twitching	1.8	1.3	1.8	0.7
<b>General Disorders and Administration</b>				

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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 clinical trial in <1% of Topiramate-treated adult patients or at any rate in open-label trials of Topiramate-treated adult patients are shown in Table 7

<b>Table 7: Adverse Drug Reactions Reported in Double-Blind Controlled Clinical Trials in &lt;1% of Topiramate-Treated Adult Patients or at Any Rate in Open-Label Clinical Trials of Topiramate-Treated Adult Patients</b>
<b>Blood and Lymphatic System Disorders</b>
Leukopenia, lymphadenopathy, thrombocytopenia
<b>Immune System Disorders</b>
Hypersensitivity
<b>Metabolism and Nutrition Disorders</b>
Acidosis hyperchloraemic, hypokalaemia, increased appetite, metabolic acidosis, polydipsia
<b>Psychiatric Disorders</b>
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
<b>Nervous System Disorders</b>
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
<b>Eye Disorders</b>
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
<b>Ear and Labyrinth Disorders</b>

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Deafness, deafness neurosensory, deafness unilateral, ear discomfort, hearing impaired
<b>Cardiac Disorders</b>
Bradycardia, sinus bradycardia, palpitations
<b>Vascular Disorders</b>
Flushing, hot flush, orthostatic hypotension, Raynaud's phenomenon
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>
Dysphonia, dyspnoea exertional, nasal congestion, paranasal sinus hypersecretion
<b>Gastrointestinal Disorders</b>
Abdominal discomfort, abdominal pain lower, abdominal tenderness, breath odour, epigastric discomfort, flatulence, glossodynia, hypoaesthesia oral, oral pain, pancreatitis, salivary hypersecretion
<b>Skin and Subcutaneous Tissue Disorders</b>
Anhidrosis, dermatitis allergic, erythema, rash macular, skin discolouration, skin odour abnormal, swelling face, urticaria, urticaria localised
<b>Musculoskeletal and Connective Tissue Disorders</b>
Flank pain, muscle fatigue, muscular weakness, musculoskeletal stiffness
<b>Renal and Urinary Disorders</b>
Calculus ureteric, calculus urinary, haematuria, incontinence, micturition urgency, renal colic, renal pain, urinary incontinence
<b>Reproductive System and Breast Disorders</b>
Sexual dysfunction
<b>General Disorders</b>
Calcinosis, face oedema, feeling abnormal, feeling drunk, feeling jittery, malaise, peripheral coldness, sluggishness
<b>Investigations</b>
Blood bicarbonate decreased, crystal urine present, tandem gait test abnormal, white blood cell count decreased

ADRs reported in double-blind controlled 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 8

<b>Table 8: Adverse Drug Reactions Reported in Double-Blind Controlled Clinical Trials in &lt;2% of Topiramate-Treated Pediatric Patients or at Any Rate in Open-Label Clinical Trials of Topiramate-Treated Pediatric Patients</b>
<b>Blood and Lymphatic System Disorders</b>
Eosinophilia, leukopenia, lymphadenopathy, thrombocytopenia
<b>Immune System Disorders</b>
Hypersensitivity

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<b>Metabolism and Nutrition Disorders</b>
Acidosis hyperchloraemic, hypokalaemia, increased appetite
<b>Psychiatric Disorders</b>
Anger, apathy, crying, distractibility, expressive language disorder, initial insomnia, insomnia, middle insomnia, mood swings, perseveration, sleep disorder, suicidal ideation, suicide attempt
<b>Nervous System Disorders</b>
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
<b>Eye Disorders</b>
Diplopia, lacrimation increased, vision blurred
<b>Ear and Labyrinth Disorders</b>
Ear pain
<b>Cardiac Disorders</b>
Palpitations, sinus bradycardia
<b>Vascular Disorders</b>
Orthostatic hypotension
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>
Nasal congestion, paranasal sinus hypersecretion, rhinorrhoea
<b>Gastrointestinal Disorders</b>
Abdominal discomfort, abdominal pain, dry mouth, flatulence, gastritis, gastrooesophageal reflux disease, gingival bleeding, glossodynia, pancreatitis, paraesthesia oral, stomach discomfort
<b>Musculoskeletal and Connective Tissue Disorders</b>
Arthralgia, musculoskeletal stiffness, myalgia
<b>Renal and Urinary Disorders</b>
Incontinence, micturition urgency, pollakiuria
<b>General Disorders</b>
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 9. The frequencies are provided according to the following convention:

- Very common  $\geq 1/10$
- Common  $\geq 1/100$  to  $< 1/10$
- Uncommon  $\geq 1/1,000$  to  $< 1/100$
- Rare  $\geq 1/10,000$  to  $< 1/1,000$
- Very rare  $< 1/10,000$ , including isolated reports

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<b>Table 9: Adverse Drug Reactions Identified During Postmarketing Experience with TOPIRAMATE by Frequency Category Estimated from Clinical Trials</b>	
<b>Infections and Infestations</b>	
<i>Very Common</i>	Nasopharyngitis*
<b>Blood and Lymphatic System Disorders</b>	
<i>Rare</i>	Neutropenia
<b>Immune System Disorders</b>	
<i>Unknown</i>	Allergic oedema
<i>Unknown</i>	Conjunctival oedema
<b>Psychiatric Disorders</b>	
<i>Rare</i>	Feeling of despair
<b>Eye Disorders</b>	
<i>Rare</i>	Abnormal sensation in eye
<i>Rare</i>	Eyelid oedema
<i>Rare</i>	Myopia
<i>Unknown</i>	Angle closure glaucoma
<i>Unknown</i>	Eye movement disorder
<i>Unknown</i>	Maculopathy
<b>Skin and Subcutaneous Tissue Disorders</b>	
<i>Rare</i>	Erythema multiforme
<i>Rare</i>	Periorbital oedema
<i>Rare</i>	Stevens-Johnson syndrome
<i>Unknown</i>	Toxic epidermal necrolysis
<b>Musculoskeletal and Connective Tissue Disorders</b>	
<i>Uncommon</i>	Joint swelling

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<i>Rare</i>	Limb discomfort
<b>Renal and Urinary Disorders</b>	
<i>Rare</i>	Renal tubular acidosis
<b>General Disorders and Administration Site Conditions</b>	
<i>Uncommon</i>	Influenza like illness
<i>Unknown</i>	Generalised oedema
<b>Investigations</b>	
<i>Common</i>	Weight increased

\*Nasopharyngitis in the clinical trial database was attributed to infectious or other causes, and was deemed a non-ADR.

## Interactions

### 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 APO-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 APO-TOPIRAMATE.

The results of these interactions are summarised in Table 10:

**Table 10: Summary of AEA interactions with APO-TOPIRAMATE**

AEA Co-administered	AEA Concentration	Topiramate Concentration
Phenytoin	↔ **	↓
Carbamazepine (CBZ)	↔	↓
Valproic Acid	↔	↔
Phenobarbitone	↔	NS

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Primidone	↔	NS
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↔ = 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 APO-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 APO-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 APO-TOPIRAMATE and alcohol or other CNS depressant medicines has not been evaluated in clinical studies. It is recommended that APO-TOPIRAMATE not be used concomitantly with alcohol or other CNS depressant medicines.

**Oral Contraceptives:** In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 mcg ethinyl oestradiol (EO), 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 EO was statistically significantly decreased at doses of 200, 400, and 800 mg/day (18%, 21%, and 30%, respectively) when given as adjunctive therapy in patients taking valproic acid. In both studies, topiramate (50 mg/day to 800 mg/day) did not significantly affect exposure to NET. Although there was a dose dependent decrease in EO exposure for doses between 200-800 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 combination oral contraceptive products with APO-TOPIRAMATE. Patients taking oestrogen containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding.

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

**Risperidone:** Drug-drug interaction studies conducted under single and multiple dose conditions in healthy volunteers and patients with bipolar disorder yielded similar results. When administered concomitantly with topiramate at escalating doses of 100, 250 and 400 mg/day there was a reduction in risperidone (administered at doses ranging from 1 to 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.

**Hydrochlorothiazide (HCTZ):** A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg q24h) and topiramate (96 mg

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### Topiramate 25mg, 50mg, 100mg and 200mg Tablets

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q12h) when administered alone and concomitantly. The results of this study indicate that topiramate  $C_{max}$  increased by 27% and AUC increased by 29% when HCTZ was added to topiramate. The clinical significance of this change is unknown. The addition of HCTZ to APO-TOPIRAMATE therapy may require an adjustment of the APO-TOPIRAMATE dose. The steady-state pharmacokinetics of HCTZ were 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. The extent of change in the clearance is unknown. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear. When APO-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 APO-TOPIRAMATE is added to pioglitazone therapy or pioglitazone is added to APO-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 (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

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

##### Valproic Acid

Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug

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alone. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse event is not due to a pharmacokinetic interaction.

**Additional Pharmacokinetic Drug Interaction Studies:** Clinical studies have been conducted to assess the potential pharmacokinetic drug interaction between topiramate and other agents. The changes in  $C_{max}$  or AUC as a result of the interactions are summarized below in Table 11. 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 11: Summary of Results from Additional Clinical Pharmacokinetic Drug Interaction Studies**

Concomitant Drug	Concomitant Drug Concentration	Topiramate Concentration
Amitriptyline	↔ 20% increase in $C_{max}$ and AUC of nortriptyline metabolite	NS
Dihydroergotamine (Oral and Subcutaneous)	↔	↔
Haloperidol	↔ 31% increase in AUC of the reduced metabolite	NS
Propranolol	↔ 17% Increase in $C_{max}$ for 4-OH propranolol (TPM 50mg q12h)	9% & 16% Increase in $C_{max}$ , 9% & 17% increase in AUC (40mg & 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) <sup>b</sup>	↔

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

NS = Not studied

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

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

## Overdosage

### 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,



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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 Precautions: Metabolic Acidosis).

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

### Treatment

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

### Pharmaceutical Precautions

Store at or below 25°C.

Protect from heat, light and moisture.

Blister packs - shelf life of 2 years from the date of manufacture.

Bottle packs – shelf life of 3 years from date of manufacture.

### Medicine Classification

Prescription Medicine

### Package Quantities

Bottle packs of 60 tablets.

Blister packs of 60 tablets.

### Further Information

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