
TOPAMAX[®]

Tablets and Sprinkle Capsules

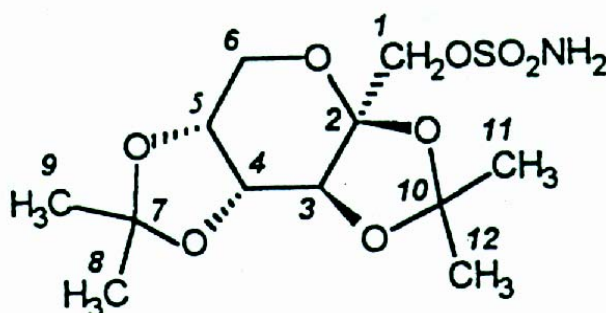
PRODUCT INFORMATION

NAME OF THE MEDICINE

Topiramate

DESCRIPTION

Topiramate [2,3:4,5-bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate] 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.



C₁₂H₂₁NO₈S

CAS-97240-79-4

MW: 339.36

TOPAMAX tablets contain topiramate, and the inactive ingredients lactose, pregelatinised maize starch, carnauba wax, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and the OPADRY[®] coating and colouring for each tablet comprising titanium dioxide, hypromellose, laurmacrogol 400 and polysorbate 80. Additionally, in the coating, the 50 mg and 100 mg tablets contain iron oxide yellow, and the 200 mg and 300 mg tablets contain iron oxide red.

TOPAMAX Sprinkle capsules consist of sugar spheres enclosed in a gelatin capsule. The sugar spheres contain topiramate, povidone, cellulose acetate and sucrose. The capsule shells contain gelatin and titanium dioxide, and are imprinted with black ink.

PHARMACOLOGY

Pharmacodynamics

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

- Topiramate reduces the frequency at which action potentials are generated when neurons are subjected to a sustained depolarisation, which is indicative of a state-dependent blockade of voltage-sensitive sodium channels.
- Topiramate markedly enhances the activity of GABA at some types of GABA_A receptors. This effect was not blocked by flumazenil, a benzodiazepine antagonist, nor did topiramate increase the duration of the channel open time, differentiating topiramate from barbiturates that modulate GABA_A receptors. Because the antiepileptic profile of topiramate differs markedly from that of the benzodiazepines, it may modulate a benzodiazepine-insensitive subtype of GABA_A receptor.
- Topiramate antagonises the ability of kainate to activate the kainate/AMPA subtype of excitatory amino acid (glutamate) receptors but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype.

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

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

Pharmacokinetics

The tablet and capsule formulations of TOPAMAX are bioequivalent at equivalent doses.

The pharmacokinetic profile of topiramate compared to other antiepileptic drugs shows a long plasma elimination half-life, linear pharmacokinetics, predominantly renal clearance, absence of significant protein binding and lack of clinically relevant active metabolites. Topiramate is not a potent inducer of drug metabolising enzymes. It can be administered without regard to meals and routine monitoring of plasma topiramate concentrations is not necessary. In clinical studies, there was no consistent relationship between plasma concentrations and efficacy or adverse events.

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

Absorption: Based on recovery of radioactivity from urine in humans, the mean extent of absorption of a 100 mg dose of ¹⁴C-topiramate was at least 81%. Following oral administration of 100 mg topiramate to healthy subjects, a mean peak plasma concentration (C_{max}) of approximately 2 micrograms/mL was achieved within 2 or 3 hours (T_{max}). The bioavailability of topiramate is not significantly affected by food.

Distribution: Generally 13-17% of topiramate is bound to plasma proteins. A low capacity binding site for topiramate in/on erythrocytes that is saturated at steady-state has been observed. Following single dose administration, the volume of distribution varies inversely with dose. The mean apparent volume of distribution has been measured as 0.8 - 0.55 L/kg for a single dose range of 100 mg to 1200 mg. There is an effect of gender on the volume of distribution. Values for females are about 50% lower than those for males. This is attributed to the higher percent body fat in females and is of no clinical consequence.

Metabolism: Topiramate is not extensively metabolised (~20%) in healthy volunteers. It is metabolised up to 50% in patients receiving concomitant antiepileptic therapy with known inducers of drug-metabolising enzymes. Six metabolites formed through hydroxylation, hydrolysis and glucuronidation, have been isolated, characterised and identified from plasma, urine and faeces of humans. Each metabolite represents less than 3% of the total radioactivity

excreted following administration of ¹⁴C-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 ¹⁴C-topiramate was excreted unchanged in the urine within four days. Following twice a day dosing with 50 mg and 100 mg of topiramate, the mean renal clearance was approximately 18 mL/min and 17 mL/min, respectively. There is evidence of renal tubular reabsorption of topiramate. This is supported by studies in rats where topiramate was co-administered with probenecid and a significant increase in renal clearance of topiramate was observed. Overall, plasma clearance is approximately 20 to 30 mL/min in humans following oral administration. Concomitant multiple-dose administration of topiramate, 100 to 400 mg twice a day, with phenytoin or carbamazepine shows dose proportional increases in plasma concentrations of topiramate.

Topiramate exhibits low intersubject variability in plasma concentrations and, therefore, has predictable pharmacokinetics. The pharmacokinetics of topiramate are linear at steady state with plasma clearance remaining constant and area under the plasma concentration curve increasing in a dose-proportional manner over a 200 to 800 mg daily oral dose range. 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.

Patients with renal impairment: **The plasma and renal clearance of topiramate decreased in patients with moderate and severe impaired renal function (CL_{CR} < 70 mL/min). As a result, higher steady-state plasma concentrations are expected for a given dose in renal-impaired patients as compared to those with normal renal function. *In addition, patients with renal impairment will require a longer time to reach steady-state at each dose.*

**Topiramate is effectively removed from plasma by haemodialysis. A prolonged period of hemodialysis may cause topiramate concentration to fall below levels that are required to maintain an anti-seizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis, a supplemental dose of topiramate may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialysed.*

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

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

Paediatric up to 12 years of age: The pharmacokinetics of topiramate in children receiving the drug as add-on therapy are linear. The clearance is independent of dose and steady-state plasma concentrations increase in proportion to dose. Hepatic enzyme-inducing antiepileptic drugs decrease the steady state plasma concentrations. In comparison to adults, however, children have a higher clearance, and shorter elimination half-life when TOPAMAX is used as adjunctive therapy to both enzyme-inducing and non-enzyme-inducing antiepileptic drugs. Consequently, the plasma concentrations of topiramate for the same mg/kg dose may be lower in children compared to adults.

CLINICAL TRIALS

Monotherapy Epilepsy: Three double-blind, randomised, parallel-group clinical trials were conducted to evaluate the efficacy and safety of TOPAMAX given as monotherapy. Study YI

and EPMN-104 evaluated the safety and efficacy of TOPAMAX monotherapy using a dose-response design by comparing the low dose regimen with the high dose regimen. Study EPMN-105 compared TOPAMAX monotherapy to carbamazepine or valproate in patients with newly diagnosed epilepsy.

In study YI, adults with refractory partial onset seizures (n=48) were converted from their existing treatment to TOPAMAX 100 mg/day or 1000 mg/day as monotherapy. The high dose group was statistically superior to the low dose group for efficacy variables. 54% of high dose patients achieved monotherapy compared with 17% in the low dose group with the difference between the doses being statistically significant (p=0.005). The mean time to exit was significantly greater in the high dose group (p=0.002). The investigator and subject global evaluations of clinical response statistically favoured the high dose group (≤ 0.002). In study EPMN-104, adult and paediatric patients with recently diagnosed epilepsy (n=252) were randomised into the low dose (25 or 50 mg/day) or the high dose group (200 or 500 mg/day) based on their body weight. Overall, 54% of high dose patients and 39% of low dose patients were reported to be seizure free during the double-blind phase (p=0.022). The high dose group was also superior to the low dose group with respect to seizure frequency distribution (p=0.008) and the difference in time to first seizure across three plasma topiramate concentration strata (p=0.015).

In study EPMN-105, patients with newly diagnosed epilepsy (n=613) were randomised to receive either 100 or 200 mg/day of TOPAMAX or standard anti-epileptic treatment (carbamazepine or valproate). TOPAMAX was at least as efficacious as carbamazepine or valproate in reducing seizures in these patients; -the 95% confidence intervals for the difference between the two treatment groups were narrow and included zero, indicating that there were no statistically significant between-group difference. The two treatment groups were also comparable with respect to all clinical utility and efficacy endpoints including time to exit, proportion of seizure-free subjects and time to first seizure.

Patients (n=207; 32 were aged ≤ 16 years) who completed the double-blind phase of study YI and EPMN-104 were enrolled in long term extension studies with the majority of patients receiving TOPAMAX for 2 to 5 years. In these studies, sustained efficacy was demonstrated with long term administration of TOPAMAX as monotherapy. There was no significant change in dosage during the extension period and no indication that effectiveness of TOPAMAX monotherapy diminished with continued exposure.

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

Add-on therapy *Epilepsy*: Over 2000 patients worldwide were involved in the clinical trials of TOPAMAX as an add-on treatment in adults and children with the following type of epilepsy: partial onset seizures with or without secondary generalised seizures, primary generalised tonic-clonic seizures and seizures associated with Lennox-Gastaut syndrome. These trials were randomised, placebo-controlled, double-blind, multi-centre, parallel group studies in which patients were given TOPAMAX or placebo as add-on treatment while they were receiving phenytoin, carbamazepine, primidone, phenobarbitone or valproic acid, as concomitant therapy.

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

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

There is limited clinical experience with TOPAMAX at or above a daily dose of 1000 mg. Comparative data or data on the safety and efficacy of using TOPAMAX with lamotrigine,

vigabatrin or gabapentin are not available. Geriatric patients and patients with known or suspected coronary artery disease did not participate in these studies.

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

The pooled results of the two pivotal trials, evaluating TOPAMAX doses of 50 (N=233), 100 (N=244), and 200 mg/day (N=228), found a median percent reduction in average monthly migraine period rate of 35%, 51% and 49% respectively, compared to 21% for the pooled placebo group (N=229). Notably 27% of patients administered TOPAMAX 100 mg/day achieved at least a 75% reduction in migraine frequency, whilst 52% achieved at least a 50% reduction.

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

Results from each trial are summarised in Table 1.

Table 1: Responder Rates (at least a 50% reduction in average monthly migraine period compared to baseline - ITT)

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

* Nominal p values for comparison of TOPAMAX with placebo.

^a difference - treatment responder rate of TOPAMAX minus placebo.

^b 95% Confidence interval - pairwise difference of TPM minus placebo.

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

INDICATIONS

EPILEPSY

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

- as monotherapy in patients with newly diagnosed epilepsy

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

MIGRAINE

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

CONTRAINDICATIONS

Hypersensitivity to any component of this product.

PRECAUTIONS

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

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

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

Suicidal Behaviour and Ideation

Antiepileptic drugs (AEDs), including TOPAMAX[®], increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behaviour compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behaviour for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behaviour with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analysed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any

indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analysed.

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

Table 2: Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events per 1000 Patients	Drug Patients with Events per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/ Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

In double-blind clinical trials with TOPAMAX[®] in approved and investigational indications, suicide related events (suicidal ideation, suicide attempts, and suicide) occurred at a frequency of 0.5% in TOPAMAX[®] treated patients (46 out of 8,652 patients treated) compared to 0.2% treated with placebo (8 out of 4,045 patients treated). One completed suicide was reported in a bipolar disorder double-blind trial in a patient on topiramate.

Anyone considering prescribing TOPAMAX[®] or any other AED must balance the risk of suicidal thoughts or behaviour with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

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

Nephrolithiasis

Patients, especially those with a predisposition to nephrolithiasis, may be at increased risk for renal stone formation (none of 216 placebo patients versus 1.6% of 1446 patients who had received topiramate were reported to have nephrolithiasis) and associated signs and symptoms such as renal colic, renal pain or flank pain.

Risk factors for nephrolithiasis include prior stone formation, a family history of nephrolithiasis and hypercalciuria, and gender (male). None of these risk factors can reliably predict stone formation during topiramate treatment. In addition, patients taking other medication associated with nephrolithiasis may be at increased risk

Oligohydrosis and Hyperthermia

Oligohydrosis (decreased sweating), infrequently resulting in hospitalization, has been reported in association with TOPAMAX 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 TOPAMAX should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather. Caution should be used when TOPAMAX is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity.

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

Use in patients with renal impairment

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

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

Use in patients with hepatic impairment

In hepatically-impaired patients, TOPAMAX 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 TOPAMAX. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmological findings can include myopia, anterior chamber shallowing, ocular hyperaemia (redness) and increased intraocular pressure.

Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating TOPAMAX therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in paediatric patients as well as adults. Treatment includes discontinuation of TOPAMAX as rapidly as possible in the judgement of the treating physician and appropriate measures to reduce intraocular pressure. These measures generally result in a decrease in intraocular pressure.

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

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 TOPAMAX treatment. This decrease in serum bicarbonate is due to the inhibitory effect of TOPAMAX on renal carbonic anhydrase. Generally, the decrease in bicarbonate occurs early in treatment although it can occur at any time during treatment. These decreases are usually mild to moderate (average decrease of 4 mmol/L at doses of 100 mg/day or above in adults and at approximately 6 mg/kg/day in 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 TOPAMAX.

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

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

In pediatric patients (<16 years of age), the incidence of persistent treatment-emergent decreases in serum bicarbonate in placebo-controlled trials for adjunctive treatment of Lennox-Gastaut syndrome or refractory partial onset seizures was 67% for TOPAMAX (at approximately 6 mg/kg/day), and 10% for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mmol/L and >5 mmol/L decrease from pretreatment) in these trials was 11% for TOPAMAX and 0% for placebo. Cases of moderately severe metabolic acidosis have been reported in patients as young as 5 months old, especially at daily doses above 5 mg/kg/day.

Some manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fractures. Chronic metabolic acidosis in pediatric patients can reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of TOPAMAX 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 TOPAMAX therapy. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing TOPAMAX (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.

Effects on ability to drive or operate machinery

TOPAMAX acts on the central nervous system and may produce drowsiness, dizziness or other related symptoms. It may also cause visual disturbances and/ or blurred vision. These adverse events are potentially dangerous in patients driving a vehicle or operating machinery, particularly until the individual patient's experience with the drug is established.

Effects on fertility

There were no effects on fertility or reproductive parameters in rats following oral administration of topiramate at doses up to 100mg/kg/day, with estimated exposures (plasma AUC) less than

human exposure at the maximal recommended clinical dose. Oral administration of topiramate to juvenile rats did not affect subsequent reproductive development, mating or fertility (see **Growth and development**).

Carcinogenicity

No evidence of carcinogenicity was seen in rats following oral administration of topiramate for 2 years at doses of 120 mg/kg/day. An increased incidence of urinary bladder tumours of a proliferative nature was observed in mice following oral administration of topiramate for 22 months at doses of 300 mg/kg/day. These tumours probably resulted from chronic irritation and may lack clinical significance. The plasma concentration exposure obtained in the animal studies was less than the likely clinical exposure at the maximum recommended dose.

Genotoxicity

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

Use in pregnancy

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

In post-marketing experience, cases of hypospadias have been reported in male infants exposed in-utero to topiramate, with or without other anticonvulsants. A causal relationship with topiramate has not been established.

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

**Data from the North American AED (NAAED) Pregnancy Registry indicate an increased risk of oral clefts in infants exposed to topiramate monotherapy during the first trimester of pregnancy. The prevalence of oral clefts was 1.4% compared to a prevalence of 0.38% - 0.55% in infants exposed to other AEDs, and a prevalence of 0.07 % in infants of mothers without epilepsy or treatment with other AEDs. The relative risk of oral clefts in topiramate-exposed pregnancies in the NAAED Pregnancy Registry was 21.3 (95% Confidence Interval 7.9 – 57.1) as compared to the risk in a background population of untreated women. The UK Epilepsy and Pregnancy Register reported a similarly increased prevalence of oral clefts of 3.2% among infants exposed to topiramate monotherapy. The observed rate of oral clefts was 16 times higher than the background rate in the UK, which is approximately 0.2%.*

Compared with a reference group not taking antiepileptic drugs, registry data for TOPAMAX® monotherapy showed a higher prevalence of low birth weight (<2500 grams). **A causal relationship has not yet 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.

TOPAMAX should be used during pregnancy only if potential benefit justifies the potential risk to the fetus. In treating and counseling women of childbearing potential, the prescribing physician should weigh the benefits of therapy against the risks. If this drug is used during

pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

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

Use in lactation

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

Growth and development

In juvenile rats, oral administration of topiramate at doses up to 300 mg/kg/day during the period of development corresponding to infancy, childhood, and adolescence resulted in toxicities similar to those in adult animals (decreased food consumption with decreased body weight gain, 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. Exposure (plasma AUC) was up to 2-fold human exposure at the maximal recommended clinical dose.

Interactions with other medicines

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

Effects of TOPAMAX on other antiepileptic drugs

The addition of TOPAMAX to other antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbitone, primidone) has no effect on their steady-state plasma concentrations, except in the occasional patient, where the addition of TOPAMAX to phenytoin may result in an increase of plasma concentrations of phenytoin. This is possibly due to inhibition of a specific enzyme polymorphic isoform (CYP2C19). Consequently, any patient on phenytoin showing clinical signs or symptoms of toxicity should have phenytoin levels monitored.

Effects of other antiepileptic drugs on TOPAMAX

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

Phenytoin and carbamazepine decrease the plasma concentration of topiramate. The addition or withdrawal of phenytoin or carbamazepine to TOPAMAX therapy may require an adjustment in dosage of the latter. This should be done by titrating to clinical effect.

The addition or withdrawal of valproic acid does not produce clinically significant changes in plasma concentrations of topiramate and, therefore, does not warrant dosage adjustment of TOPAMAX.

The results of these interactions are summarised in Table 3.

Table 3: Summary of AED interactions with TOPAMAX

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

<-> = No effect on plasma concentration

* = Plasma concentrations increase in occasional patients

↓ = Decrease in plasma AUC_{0-12ss}

** = Approximately 35% decrease in plasma C_{maxss} and 57% decrease in plasma C_{minss} concentrations

N = Not studied

AED = antiepileptic drug

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

Other drug interactions

Digoxin: In a single-dose study, serum digoxin area under plasma concentration curve (AUC) decreased 12% due to concomitant administration of TOPAMAX. The clinical relevance of this observation has not been established. When TOPAMAX is added or withdrawn in patients on digoxin therapy, careful attention should be given to the routine monitoring of serum digoxin.

CNS Depressants: Concomitant administration of TOPAMAX and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. It is recommended that TOPAMAX not be used concomitantly with alcohol or other CNS depressant drugs.

Oral Contraceptives: In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethisterone (NET) plus 35 mcg ethinyl oestradiol (EO), TOPAMAX given in the absence of other medications at doses of 50 to 200 mg/day was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. In another study, exposure to EO was statistically significantly decreased at doses of 200, 400, and 800 mg/day (18%, 21%, and 30%, respectively) when given as adjunctive therapy in patients taking valproic acid. In both studies, TOPAMAX (50 mg/day to 800 mg/day) did not significantly effect 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 TOPAMAX. 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. The clinical relevance of the observed, apparently not statistically significant changes in the systemic exposure of the total active moiety (risperidone plus 9-hydroxyrisperidone) or of topiramate is not known.

Hydrochlorothiazide (HCTZ): A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg q24h) and TOPAMAX (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that TOPAMAX C_{max} increased by 27% and AUC increased by 29% when HCTZ was added to TOPAMAX. The clinical significance of this change is unknown. The addition of HCTZ to TOPAMAX therapy may require an adjustment of the TOPAMAX dose. Clinical laboratory results indicated decreases in serum potassium after TOPAMAX or HCTZ administration, which were greater when HCTZ and TOPAMAX were administered in combination.

Metformin: A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin and TOPAMAX in plasma when metformin was given alone and when metformin and TOPAMAX 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 TOPAMAX. TOPAMAX did not affect metformin t_{max}. The clinical significance of the effect of TOPAMAX on metformin pharmacokinetics is unclear. Oral plasma clearance of TOPAMAX 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 TOPAMAX pharmacokinetics is unclear. When TOPAMAX is added or withdrawn in patients on metformin therapy, careful attention should be given to the routine monitoring for adequate control of their diabetic disease state.

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

Glibenclamide: A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glibenclamide (5mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 25% reduction in glibenclamide AUC₂₄ during topiramate administration. Systemic exposure of the active metabolites, 4-*trans*-hydroxy-glibenclamide (M1) and 3-*cis*-hydroxyglibenclamide (M2), were also reduced by 13% and 15%, respectively. The steady-state pharmacokinetics of topiramate were unaffected by concomitant administration of glibenclamide. When topiramate is added to glibenclamide therapy or glibenclamide is added to topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Other forms of interactions:

Agents predisposing to nephrolithiasis

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

Valproic Acid

Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse event is not due to a pharmacokinetic interaction. An association of hyperammonemia with either topiramate or valproic acid monotherapy has not been established.

Additional Pharmacokinetic Drug Interaction Studies: Clinical studies have been conducted to assess the potential pharmacokinetic drug interaction between topiramate and other agents. The changes in C_{max} or AUC as a result of the interactions are summarized below in Table 4. The second column (concomitant drug concentration) describes what happens to the concentration of the concomitant drug listed in the first column when topiramate is added. The third column (topiramate concentration) describes how the coadministration of a drug listed in the first column modifies the concentration of topiramate.

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

Concomitant Drug	Concomitant Drug Concentration	Topiramate Concentration
Amitriptyline	↔ 20% increase in C _{max} and AUC of nortriptyline metabolite	NS
Dihydroergotamine (Oral and Subcutaneous)	↔	↔
Haloperidol	↔ 31% increase in AUC of the reduced metabolite	NS
Propranolol	↔ 17% Increase in C _{max} for 4-OH propranolol (TPM 50mg q12h)	9% and 16% Increase in C _{max} , 9% and 17% increase in AUC (40mg and 80mg propranolol q12h respectively)
Sumatriptan (Oral and Subcutaneous)	↔	NS
Pizotifen	↔	↔
Diltiazem	25% decrease in AUC of diltiazem and 18% decrease in DEA, and ↔ for DEM*	20% increase in AUC
Venlafaxine	↔	↔
Flunarizine	16% increase in AUC (TPM 50 mg q12h) ^b	↔

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

NS = Not studied

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

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

ADVERSE EFFECTS

Clinical Trial Data

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

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

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

Adverse Drug Reactions (ADRs) reported in ≥1% of TOPAMAX[®]-treated adult patients in double-blind, placebo-controlled adjunctive epilepsy trials are shown in Table 5. ADRs that had an incidence >5% in the recommended dose range (200 to 400 mg/day) in adults in double-blind, placebo-controlled adjunctive epilepsy studies in descending order of frequency included somnolence, dizziness, fatigue, irritability, weight decreased, bradypnea, paresthesias, diplopia, coordination abnormal, nausea, nystagmus, lethargy, anorexia, dysarthria, vision blurred, decreased appetite, memory impairment and diarrhoea.

Table 5: Adverse Drug Reactions Reported by ≥1% of TOPAMAX®-Treated Adult Patients in Double-Blind, Placebo-Controlled, Adjunctive Epilepsy Trials

System/Organ Class Adverse Reaction	TOPAMAX 200-400 mg/day (N=354) %	TOPAMAX 600-1000 mg/day (N=437) %	PLACEBO (N=382) %
Metabolism and Nutrition Disorders			
Anorexia	5.4	6.2	1.8
Decreased appetite	5.1	8.7	3.7
Psychiatric Disorders			
Bradyphrenia	8.2	19.5	3.1
Expressive language disorder	4.5	9.4	1.6
Confusional state	3.1	5.0	0.8
Depression	3.1	11.7	3.4
Insomnia	3.1	6.4	4.5
Aggression	2.8	3.2	1.8
Agitation	1.7	2.3	1.3
Anger	1.7	2.1	0.5
Anxiety	1.7	6.6	2.9
Disorientation	1.7	3.2	1.0
Mood altered	1.7	4.6	1.0
Nervous System Disorders			
Somnolence	17.8	17.4	8.4
Dizziness	16.4	34.1	13.6
Paraesthesia	8.2	17.2	3.7
Coordination abnormal	7.1	11.4	4.2
Nystagmus	6.2	11.7	6.8
Lethargy	5.6	8.0	2.1
Dysarthria	5.4	6.2	1.0
Memory impairment	5.1	10.8	1.8
Disturbance in attention	4.5	11.9	1.8
Tremor	4.0	9.4	5.0
Amnesia	3.4	5.3	1.0
Balance disorder	3.4	3.9	2.4
Hypoaesthesia	3.1	5.9	1.0
Intention tremor	3.1	4.8	2.9
Dysgeusia	1.4	4.3	0.8
Mental impairment	1.4	5.0	1.3
Speech disorder	1.1	2.7	0.5
Eye Disorders			
Diplopia	7.3	12.1	5.0
Vision blurred	5.4	8.9	2.4
Visual disturbance	2.0	1.4	0.3
Gastrointestinal Disorders			
Nausea	6.8	15.1	8.4
Diarrhoea	5.1	14.0	5.2
Abdominal pain upper	3.7	3.9	2.1
Constipation	3.7	3.2	1.8
Stomach discomfort	3.1	3.2	1.3
Dyspepsia	2.3	3.0	2.1
Dry mouth	1.7	3.7	0.3
Abdominal pain	1.1	2.7	0.8
Musculoskeletal and Connective Tissue Disorders			
Myalgia	2.0	2.5	1.3
Muscle spasms	1.7	2.1	0.8
Musculoskeletal chest pain	1.1	1.8	0.3
General Disorders and Administration Site Conditions			
Fatigue	13.0	30.7	11.8
Irritability	9.3	14.6	3.7
Asthenia	3.4	3.0	1.8
Gait disturbance	1.4	2.5	1.3
Investigations			
Weight decreased	9.0	11.9	4.2

Adverse drug reactions reported by <1% of TOPAMAX[®]-treated adult patients in double-blind, placebo-controlled, adjunctive epilepsy trials included increased appetite, abnormal behaviour, apathy, depressed mood, distractibility, disturbance in sexual arousal, dysphemia, euphoric mood, flat affect, lack of spontaneous speech, mood swings, panic disorder, paranoia, reading disorder, sleep disorder, suicidal ideation, thinking abnormal, aphasia, cerebellar syndrome, cognitive disorder, dysaesthesia, dysgraphia, dyskinesia, formication, parosmia, psychomotor skills impaired, repetitive speech, sensory disturbance, sensory loss, stupor, unresponsive to stimuli, lacrimation increased, presbyopia, visual acuity reduced, deafness, deafness unilateral, hearing impaired, tinnitus, sinus bradycardia, dyspnoea, dyspnoea exertional, paranasal sinus hypersecretion, abdominal discomfort, abdominal tenderness, breath odour, flatulence, hypoaesthesia oral, paraesthesia oral, erythema, hypoaesthesia facial, skin odour abnormal, swelling face, calculus urinary, dysuria, haematuria, incontinence, pollakiuria, renal colic, renal pain, urinary, incontinence, erectile dysfunction, sexual dysfunction, feeling abnormal, feeling drunk, tandem gait test abnormal, and white blood cell count decreased.

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

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

ADRs reported in >2% of TOPAMAX[®]-treated pediatric patients (2 to 16 years of age) in double-blind, placebo-controlled adjunctive epilepsy trials are shown in Table 6. ADRs that had an incidence >5% in the recommended dose range (5 to 9 mg/kg/day) in descending order of frequency included decreased appetite, fatigue, somnolence, lethargy irritability, disturbance in attention, weight decreased, aggression, rash, abnormal behaviour, anorexia, balance disorder, and constipation.

Table 6: Adverse Drug Reactions Reported by $\geq 2\%$ of TOPAMAX[®]-Treated Pediatric Patients in Double-Blind, Placebo-Controlled, Adjunctive Epilepsy Trials

System/Organ Class Adverse Reaction	TOPAMAX (N=104) %	PLACEBO (N=102) %
Metabolism and Nutrition Disorders		
Decreased appetite	19.2	12.7
Anorexia	5.8	1.0
Psychiatric Disorders		
Aggression	8.7	6.9
Abnormal behaviour	5.8	3.9
Confusional state	2.9	2.0
Mood altered	2.9	2.0
Nervous System Disorders		
Somnolence	15.4	6.9
Lethargy	13.5	8.8
Disturbance in attention	10.6	2.0
Balance disorder	5.8	2.0
Dizziness	4.8	2.9
Memory impairment	3.8	1.0
Respiratory, Thoracic and Mediastinal Disorders		
Epistaxis	4.8	1.0
Gastrointestinal Disorders		
Constipation	5.8	4.9
Skin and Subcutaneous Tissue Disorders		
Rash	6.7	5.9
General Disorders and Administration Site Conditions		
Fatigue	16.3	4.9
Irritability	11.5	8.8
Gait disturbance	4.8	2.0
Investigations		
Weight decreased	9.6	1.0

Adverse drug reactions reported by $<2\%$ of TOPAMAX[®]-treated pediatric patients in double-blind, placebo-controlled, adjunctive epilepsy trials included leukopenia, lymphadenopathy, thrombocytopenia, increased appetite, anger, middle insomnia, perseveration, dysarthria, dysgeusia, paraesthesia, poor quality sleep, syncope, tremor, diplopia, lacrimation increased, vision blurred, sinus bradycardia, paranasal sinus hypersecretion, abdominal pain, flatulence, gastroesophageal reflux disease, glossodynia, alopecia, skin discolouration, musculoskeletal stiffness, incontinence, pollakiuria, asthenia, feeling abnormal, malaise, and thirst.

Nausea and headache were not considered ADRs based on case review which indicated that these events could be attributed to other causes, including concomitant use of other medications or an intervening illness

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

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

ADRs reported in $\geq 1\%$ of TOPAMAX[®]-treated adult patients in double-blind, controlled monotherapy epilepsy trials are shown in Table 7. ADRs that had an incidence $>5\%$ at the recommended dose (400 mg/day) in descending order of frequency included paraesthesia, weight decreased, fatigue, anorexia, depression, memory impairment, anxiety, diarrhoea, asthenia, dysgeusia, and hypoesthesia.

Table 7: Adverse Drug Reactions Reported by ≥1% of TOPAMAX®-Treated Adult Patients in Double-Blind, Controlled Monotherapy Epilepsy Trials

	TOPAMAX 50 mg/day (N=257)	TOPAMAX 400 mg/day (N=153)
System/Organ Class		
Adverse Reaction	%	%
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
Gastroesophageal reflux disease	0.4	2.0
Gingival bleeding	0	1.3
Skin and Subcutaneous Tissue Disorders		
Rash	0.4	3.9
Alopecia	1.6	3.3
Pruritus	0.4	3.3
Hypoaesthesia facial	0.4	2.0
Pruritus generalised	0	1.3
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	2.7	3.3
Arthralgia	1.9	2.0
Muscle twitching	0.4	1.3

Table 7: Adverse Drug Reactions Reported by $\geq 1\%$ of TOPAMAX[®]-Treated Adult Patients in Double-Blind, Controlled Monotherapy Epilepsy Trials		
	TOPAMAX 50 mg/day	TOPAMAX 400 mg/day
Renal and Urinary Disorders		
Nephrolithiasis	0	2.6
Dysuria	0.8	2.0
Pollakiuria	0.8	2.0
Reproductive System and Breast Disorders		
Erectile dysfunction	0.8	1.3
General Disorders and Administration Site Conditions		
Fatigue	15.2	14.4
Asthenia	3.5	5.9
Irritability	3.1	3.3
Investigations		
Weight decreased	7.0	17.0
Adverse drug reactions reported by $<1\%$ of TOPAMAX [®] -treated adult patients in double-blind, controlled monotherapy epilepsy trials included lymphadenopathy, increased appetite, polydipsia, agitation, anger, dysphemia, euphoric mood, initial insomnia, suicidal ideation, drooling, hypogeusia, poor quality sleep, sensory disturbance, accommodation disorder, amblyopia, diplopia, palpitations, abdominal discomfort, breath odour, glossodynia, stomach discomfort, anhidrosis, urticaria localised, muscular weakness, and thirst.		
The recommended dose for monotherapy therapy in adults is 400 mg/day.		

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

ADRs reported in $\geq 2\%$ of TOPAMAX[®]-treated pediatric patients (10 to 16 years of age) in double-blind, controlled monotherapy epilepsy trials are shown in Table 8. ADRs that had an incidence $>5\%$ at the recommended dose (400 mg/day) in descending order of frequency included weight decreased, paraesthesia, diarrhoea, disturbance in attention, pyrexia, and alopecia.

Table 8: Adverse Drug Reactions Reported by $\geq 2\%$ of TOPAMAX[®]-Treated Pediatric Patients in Double-Blind, Controlled Monotherapy Epilepsy Trials

System/Organ Class Adverse Reaction	TOPAMAX 50 mg/day (N=77) %	TOPAMAX 400 mg/day (N=63) %
Metabolism and Nutrition Disorders		
Decreased appetite	1.3	4.8
Psychiatric Disorders		
Bradyphrenia	0	4.8
Mood altered	1.3	4.8
Depression	0	3.2
Nervous System Disorders		
Paraesthesia	3.9	15.9
Disturbance in attention	3.9	7.9
Ear and Labyrinth Disorders		
Vertigo	0	3.2
Respiratory, Thoracic and Mediastinal Disorders		
Epistaxis	0	3.2
Gastrointestinal Disorders		
Diarrhoea	3.9	9.5
Vomiting	3.9	4.8
Skin and Subcutaneous Tissue Disorders		
Alopecia	0	6.3
General Disorders and Administration Site Conditions		
Pyrexia	0	6.3
Asthenia	0	4.8
Investigations		
Weight decreased	7.8	20.6
Social Circumstances		
Learning disability	0	3.2

Adverse drug reactions reported by $< 2\%$ of TOPAMAX[®]-treated pediatric patients in double-blind, controlled monotherapy epilepsy trials included eosinophilia, hypersensitivity, increased appetite, abnormal behaviour, apathy, confusional state, crying, distractibility, expressive language disorder, insomnia, mood swings, lethargy, mental impairment, poor quality sleep, diplopia, nasal congestion, rhinorrhoea, abdominal discomfort, gastritis, pruritus, rash, skin discolouration, urticaria, arthralgia, micturition urgency, pollakiuria, feeling abnormal, and hyperthermia.

The recommended dose for monotherapy therapy in children 10 years and older is 400 mg/day.

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

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

Table 9: Adverse Drug Reactions Reported by ≥1% of TOPAMAX®-Treated Adult Patients in Double-Blind, Placebo-Controlled Migraine Prophylaxis Trials

System/Organ Class Adverse Reaction	TOPAMAX 50 mg/day (N=227) %	TOPAMAX 100 mg/day (N=374) %	TOPAMAX 200 mg/day (N=501) %	PLACEBO (N=436) %
Metabolism and Nutrition Disorders				
Anorexia	3.5	7.5	7.2	3.0
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				
Paresthesia	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
Paresthesia oral	1.3	2.9	1.6	0.5
Constipation	1.8	2.1	1.8	1.4
Abdominal distension	0	1.3	0.2	0.2
Stomach discomfort	2.2	1.3	1.0	0.2
Gastroesophageal reflux disease	0.4	1.1	1.2	0.5
Musculoskeletal and Connective Tissue Disorders				
Muscle twitching	1.8	1.3	1.8	0.7
General Disorders and Administration Site Conditions				
Fatigue	15.0	15.2	19.2	11.2
Asthenia	0.9	2.1	2.6	0.5
Irritability	3.1	1.9	2.4	0.9
Thirst	1.3	1.6	1.0	0.5
Investigations				
Weight decreased	5.3	9.1	10.8	1.4

Adverse drug reactions reported by <1% of TOPAMAX®-treated adult patients in double-blind, placebo-controlled migraine prophylaxis trials included hypersensitivity, polydipsia, aggression, agitation, anger, crying, disorientation, euphoric mood, hallucination, lack of spontaneous speech, libido decreased, listless, loss of libido, mood altered, panic attack, panic disorder, restlessness, tearfulness, aphasia, burning sensation, clumsiness, cognitive disorder, coordination abnormal, dizziness postural, dyskinesia, dysphasia, hypogeusia, hypokinesia, poor quality sleep, presyncope,

psychomotor skills impaired, speech disorder, visual field defect, blepharospasm, diplopia, dry eye, night blindness, visual disturbance, ear discomfort, ear pain, palpitations, flushing, hot flush, dysphonia, nasal congestion, paranasal sinus hypersecretion, epigastric discomfort, gastritis, gingival bleeding, glossodynia, hypoaesthesia oral, alopecia, hypoaesthesia facial, pruritus generalised, urticaria, flank pain, muscular weakness, calculus urinary, micturition urgency, nephrolithiasis, renal pain, sexual dysfunction, feeling abnormal, gait disturbance, malaise, and peripheral coldness. The recommended dose for migraine prophylaxis is 100 mg/day.

Other Clinical Trial Data

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

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

ADRs reported, rate unspecified, in open-label clinical trials of TOPAMAX[®]-treated pediatric patients are shown in Table 11.

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

Postmarketing Data

Adverse events first identified as ADRs during postmarketing experience with TOPAMAX[®], presented by frequency category based on spontaneous reporting rates are included in Table 12. The frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000, including isolated reports

Table 12: Adverse Drug Reactions Identified During Postmarketing Experience with TOPAMAX® by Frequency Category Estimated from Spontaneous Reporting Rates

Infections and Infestations	
<i>Very rare</i>	Nasopharyngitis
Blood and Lymphatic System Disorders	
<i>Very rare</i>	Neutropenia
Immune System Disorders	
<i>Very rare</i>	Allergic oedema
<i>Very rare</i>	Conjunctival oedema
Psychiatric Disorders	
<i>Very rare</i>	Feeling of despair
Eye Disorders	
<i>Very rare</i>	Abnormal sensation in eye
<i>Very rare</i>	Angle closure glaucoma
<i>Very rare</i>	Eye movement disorder
<i>Very rare</i>	Eyelid oedema
<i>Very rare</i>	Maculopathy
<i>Very rare</i>	Myopia
Skin and Subcutaneous Tissue Disorders	
<i>Very rare</i>	Erythema multiforme
<i>Very rare</i>	Periorbital oedema
<i>Very rare</i>	Stevens-Johnson syndrome
<i>Very rare</i>	Toxic epidermal necrolysis
Musculoskeletal and Connective Tissue Disorders	
<i>Very rare</i>	Joint swelling
<i>Very rare</i>	Limb discomfort
Renal and Urinary Disorders	
<i>Very rare</i>	Renal tubular acidosis
General Disorders and Administration Site Reactions	
<i>Very rare</i>	Generalized oedema
<i>Very rare</i>	Influenza like illness
Investigations	
<i>Very rare</i>	Weight increased

DOSAGE AND ADMINISTRATION

TOPAMAX tablets should be swallowed whole.

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

TOPAMAX can be taken without regard to meals.

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

The recommended dosages of TOPAMAX in adults and children for epilepsy are summarised in Table 13.

Monotherapy *Epilepsy*

In newly diagnosed epileptic patients, TOPAMAX monotherapy should be initiated at a low dose (see Table 13).

In patients who are being converted to TOPAMAX monotherapy, consideration should be given to the effects of seizure control when withdrawing concomitant antiepileptic agents (AEDs). Unless safety concerns require an abrupt withdrawal of the concomitant AED, a gradual

discontinuation at the rate of approximately one-third of the concomitant AED dose every 2 weeks is recommended. When enzyme inducing drugs are withdrawn, topiramate levels will increase. A decrease in TOPAMAX dosage may be required if clinically indicated.

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

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

Add-on therapy *Epilepsy*

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

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

Table 13: Recommended dosages in adults and children

		Monotherapy	Add-on therapy
Adults	Starting dose	25 mg as a single (nightly) dose for one week (or longer).	25 to 50 mg as a single (nightly) or divided dose for one week (or longer).
	Escalation dose	Increase by 25 to 50 mg/day at weekly or longer intervals.	Increase by 25 to 100 mg/day at weekly or longer intervals.
	Target dose	100 mg/day	200 to 400 mg/day
	Maximum dose	Up to 500 mg/day ¹	Up to 1000 mg/day
Children 2 years & older	Starting dose	0.5 to 1 mg/kg as a single (nightly) dose for the first week.	1 to 3 mg/kg/day up to 25 mg/day as a single (nightly) dose for the first week.
	Escalation dose	Increase by 0.5 to 1 mg/kg/day at weekly or longer intervals.	Increase by 1 to 3 mg/kg/day at weekly or longer intervals.
	Target dose	3 to 6 mg/kg/day	5 to 9 mg/kg/day
	Maximum dose	Up to 500 mg/day	Up to 30 mg/kg/day
Note: Daily doses greater or equal to 50 mg should be taken as two divided doses. ¹ Some patients with refractory epilepsy have tolerated doses of 1000 mg/day.			

It is not necessary to monitor topiramate plasma concentrations to optimise TOPAMAX therapy. For patients receiving concomitant phenytoin and carbamazepine, dosage adjustment for TOPAMAX may be required (see **PRECAUTIONS – Interactions with other drugs**).

Migraine

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

The recommended total daily dose of TOPAMAX as treatment for prophylaxis of migraine headache is 100 mg/day administered in two divided doses. Some patients may experience a benefit at a total daily dose of 50 mg/day. Patients have received a total daily dose up to 200 mg/day. Dose and titration should be guided by clinical outcome.

Use in the elderly

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

Use in patients with hepatic and/or renal impairment

Caution is advised during titration in patients with renal disease and/or hepatic impairment (see **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 TOPAMAX should be added to the patient's normal daily dose as follows:

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

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

Patients Not on Concomitant Enzyme Inducers

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

Drug withdrawal and Dosage reduction

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

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, 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)

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

Treatment

General supportive measures are indicated and an attempt should be made to remove undigested drug from the gastro intestinal tract using activated charcoal. Treatment should be appropriately supportive. Hemodialysis has been shown to be an effective means of removing topiramate from the body. The patient should be well hydrated.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Tablets

TOPAMAX film-coated tablets are supplied in blisters or bottles with tamper evident closures (not marketed):

25 mg, round and white, marked "TOP" on one side and "25" on the other

50 mg, round and light-yellow, marked "TOP" on one side and "50" on the other

100 mg, round and yellow, marked "TOP" on one side and "100" on the other

200 mg, round and salmon, marked "TOP" on one side and "200" on the other

Capsules

TOPAMAX Sprinkle capsules contain small, white to off-white spheres and are supplied in bottles. Each capsule consists of a clear capsule cap and a white capsule body:

15 mg, imprinted "TOP" on cap and "15 mg" on body

25 mg, imprinted "TOP" on cap and "25 mg" on body

50 mg, imprinted "TOP" on cap and "50 mg" on body

Storage Conditions

TOPAMAX tablets and Sprinkle capsules should be stored in a dry place below 25°C. Protect TOPAMAX tablets from light and store in the original package.

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

SPONSOR

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Date of first inclusion on the ARTG: 30 January 1998

Date of most recent amendment: 28 November 2011

* **Please note changes (presented as *italicised text*) in Product Information.**

TOPAMAX® is a registered trademark of is the registered trademark of ORTHO-MCNEIL PHARMACEUTICAL for topiramate preparations.