

**TOPIRAMATE****EPI TOP™**

25 mg Film-Coated Tablet

50 mg Film-Coated Tablet

100 mg Film-Coated Tablet

ANTICONVULSANT / ANTI EPILEPTIC

PRODUCT NAME: Epitop

DOSAGE FORM AND STRENGTH: Topiramate tablets 25/50/100mg

PHARMACOLOGIC CATEGORY: Antiepileptics, other antiepileptics, Antimigraine preparations

## PRODUCT DESCRIPTION:

25 mg : White Circular, biconvex film coated tablets.

50 mg : Light yellow colored, circular, film coated tablets with a breakline on one surface.

100 mg: Yellow coloured, circular, biconvex film coated tablets with a breakline on one surface.

## FORMULATION/COMPOSITION:

Each film-coated Tablet contains:

Topiramate USP 25 mg/50 mg/100 mg

## PHARMACODYNAMICS/PHARMACOKINETICS:

## Pharmacodynamics:

Topiramate is classified as a sulfamate-substituted monosaccharide. The precise mechanism by which topiramate exerts its antiseizure and migraine prophylaxis effects are unknown. Electrophysiological and biochemical studies on cultured neurons have identified three properties that may contribute to the antiepileptic efficacy of topiramate.

Action potentials elicited respectively by a sustained depolarization 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 antagonized the ability of kainate to activate the kainate/AMPA ( $\alpha$ -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  $\mu$ M to 200  $\mu$ M, with minimum activity observed at 1  $\mu$ M to 10  $\mu$ M.

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 antiepileptic activity.

## Pharmacokinetics:

The pharmacokinetic profile of topiramate compared to other AEDs 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 metabolizing enzymes, 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  $\mu$ g/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  $^{14}\text{C}$ -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  $\mu$ g/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. An effect of gender on the volume of distribution was detected, with values for females circa 50% of those for males. This was attributed to the higher percent body fat in female patients and is of no clinical consequence.

**Biotransformation:** Topiramate is not extensively metabolized (~20%) in healthy volunteers. It is metabolized up to 50% in patients receiving concomitant antiepileptic therapy with known inducers of drug metabolizing enzymes. Six metabolites, formed through hydroxylation, hydrolysis and glucuronidation, have been isolated, characterized and identified from plasma, urine and faeces of humans. Each metabolite represents less than 3% of the total radioactivity excreted following administration of  $^{14}\text{C}$ -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  $^{14}\text{C}$ -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 Probencid, 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.

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

Use with other AEDs

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.

**Renal impairment:** The plasma and renal clearance of topiramate are decreased in patients with moderate and severe impaired renal function ( $\text{CL}_{CR} \leq 70 \text{ mL/min}$ ). As a result, higher steady-state topiramate plasma concentrations are expected for a given dose in renal-impaired patients as compared to those with normal renal function. In addition, patients with renal impairment will require a longer time to reach steady-state at each dose. In patients with moderate and severe renal impairment, half of the usual starting and maintenance dose is recommended.

Topiramate is effectively removed from plasma by hemodialysis. 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 dialyzed.

**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 population:** Plasma clearance of topiramate is unchanged in elderly subjects in the absence of underlying renal disease.

**Paediatric population (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 AEDs decrease the steady-state plasma concentrations.

## INDICATIONS:

Monotherapy in adults, adolescents and children over 6 years of age with partial seizures with or without secondary generalized seizures, and primary generalized tonic-clonic seizures.

Adjunctive therapy in children aged 2 years and above, adolescents and adults with partial onset seizures with or without secondary generalization or primary generalized tonic-clonic seizures and for the treatment of seizures associated with Lennox-Gastaut syndrome.

Topiramate is indicated in adults for the prophylaxis of migraine headache after careful evaluation of possible alternative treatment options.

Topiramate is not intended for acute treatment.

## DOSAGE AND MODE/ROUTE OF ADMINISTRATION:

## Posology

It is recommended that therapy be initiated at a low dose followed by titration to an effective dose. Dose and titration rate should be guided by clinical response.

It is not necessary to monitor topiramate plasma concentrations to optimize therapy with Topiramate. On rare occasions, the addition of topiramate to phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcome. Addition or withdrawal of phenytoin and carbamazepine to adjunctive therapy with Topiramate may require adjustment of the dose of Topiramate.

In patients with or without a history of seizures or epilepsy, antiepileptic drugs (AEDs) including topiramate should be gradually withdrawn to minimize 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 paediatric clinical trials, topiramate was gradually withdrawn over a 2-8 week period.

## Monotherapy epilepsy

**General**

When concomitant AEDs are withdrawn to achieve monotherapy with topiramate, consideration should be given to the effects this may have on seizure control. 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 medicinal products are withdrawn, topiramate levels will increase. A decrease in Topiramate (topiramate) dosage may be required if clinically indicated.

## Adults

Dose and titration should be guided by clinical response. Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased at 1- or 2-week intervals by increments of 25 or 50 mg/day, administered in two divided doses. If the patient is unable to tolerate the titration regimen, smaller increments or longer intervals between increments can be used.

The recommended initial target dose for topiramate monotherapy in adults is 100 mg/day to 200 mg/day in 2 divided doses. The maximum recommended daily dose is 500 mg/day in 2 divided doses. Some patients with refractory forms of epilepsy have tolerated topiramate monotherapy at doses of 1,000 mg/day. These dosing recommendations apply to all adults including the elderly in the absence of underlying renal disease.

## Paediatric population (children over 6 years of age)

Dose and titration rate in children should be guided by clinical outcome. Treatment of children over 6 years of age should begin at 0.5 to 1 mg/kg nightly for the first week. The dosage should then be increased at 1 or 2 week intervals by increments of 0.5 to 1 mg/kg/day, administered in two divided doses. If the child is unable to tolerate the titration regimen, smaller increments or longer intervals between dose increments can be used.

The recommended initial target dose range for topiramate monotherapy in children over 6 years of age is 100 mg/day depending on clinical response, (this is about 2.0mg/kg/day in children 6-16 years).

Adjunctive therapy epilepsy (partial onset seizures with or without secondary generalization, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome)

## Adults

Therapy should begin at 25-50 mg nightly for one week. Use of lower initial doses has been reported, but has not been studied systematically. Subsequently, at weekly or bi-weekly intervals, the dose should be increased by 25-50 mg/day and taken in two divided doses. Some patients may achieve efficacy with once-a-day dosing.

In clinical trials as adjunctive therapy, 200 mg was the lowest effective dose. The usual daily dose is 200-400 mg in two divided doses.

These dosing recommendations apply to all adults, including the elderly, in the absence of underlying renal disease.

## Paediatric population (children aged 2 years and above)

The recommended total daily dose of Topiramate (topiramate) as adjunctive therapy is approximately 5 to 9 mg/kg/day in two divided doses. Titration should begin at 25 mg (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses), to achieve optimal clinical response.

Daily doses up to 30 mg/kg/day have been studied and were generally well tolerated.

## Front

Size: 280 (L) x 420 (H) mm

Folding size: 35 x 105 mm

Carton size: 46 x 28 x 106 mm

## Migraine

## Adults

The recommended total daily dose of topiramate for prophylaxis of migraine headache is 100 mg/day administered in two divided doses. Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased in increments of 25 mg/day administered at 1-week intervals. If the patient is unable to tolerate the titration regimen, longer intervals between dose adjustments can be used.

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. This dose may be benefit in some patients; nevertheless, caution is advised due to an increase incidence of side effects.

**Paediatric population:** Topiramate (topiramate) is not recommended for treatment or prevention of migraine in children due to insufficient data on safety and efficacy.

## General dosing recommendations for Topiramate in special patient populations

**Renal impairment:** In patients with impaired renal function ( $\text{CL}_{CR} \leq 70 \text{ mL/min}$ ) topiramate should be administered with caution as the plasma and renal clearance of topiramate are decreased. Subjects with known renal impairment may require a longer time to reach steady-state at each dose. Half of the usual starting and maintenance dose is recommended.

In patients with end-stage renal failure, since topiramate is removed from plasma by hemodialysis, a supplemental dose of Topiramate equal to approximately one-half the daily dose should be administered on hemodialysis days. The supplemental dose should be administered in divided doses at the beginning and completion of the hemodialysis procedure. The supplemental dose may differ based on the characteristics of the dialysis equipment being used.

**Hepatic impairment:** In patients with moderate to severe hepatic impairment topiramate should be administered with caution as the clearance of topiramate is decreased.

**Elderly:** No dose adjustment is required in the elderly population providing renal function is intact.

## Method of administration

Topiramate is available in film-coated tablets and a hard capsule formulation, for oral administration. It is recommended that film-coated tablets not be broken. The hard capsule formulation is provided for those patients who cannot swallow tablets, e.g. paediatric and the elderly. Topiramate can be taken without regard to meals.

## CONTRAINDICATIONS &amp; PRECAUTION(S), WARNING(S):

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Migraine prophylaxis in pregnancy and in women of childbearing potential if not using a highly effective method of contraception.

## PRECAUTIONS &amp; WARNINGS:

In situations where rapid withdrawal of topiramate is medically required, appropriate monitoring is recommended.

As with other AEDs, some patients may experience an increase in seizure frequency or the onset of new types of seizures with topiramate. These phenomena may be the consequence of an overdose, a decrease in plasma concentrations of concomitantly used AEDs, progress of the disease, or a paradoxical effect.

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

## Oligohydrosis

Oligohydrosis (decreased sweating) has been reported in association with the use of topiramate. Decreased sweating and hyperthermia (rise in body temperature) may occur especially in young children exposed to high ambient temperature.

## Mood disturbances/depression

An increased incidence of mood disturbances and depression has been observed during topiramate treatment.

## Suicide/suicide ideation

Suicidal ideation and behavior have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of AEDs has shown a small increased risk of suicidal ideation and behavior. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for topiramate.

In double blind clinical trials, suicide related events (SREs) (suicidal ideation, suicide attempts and suicide) occurred at a frequency of 0.5% in topiramate treated patients (46 out of 8,652 patients treated) and at a nearly 3-fold higher incidence than those treated with placebo (0.2%; 8 out of 4,045 patients treated).

Patients therefore should be monitored for signs of suicidal ideation and behavior and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behavior emerge.

## Nephrolithiasis

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

Risk factors for nephrolithiasis include prior stone formation, a family history of nephrolithiasis and hypercalcaemia. None of these risk factors can reliably predict stone formation during topiramate treatment. In addition, patients taking other medicinal products associated with nephrolithiasis may be at increased risk.

## Decreased renal function

In patients with impaired renal function ( $\text{CL}_{CR} \leq 70 \text{ mL/min}$ ) topiramate should be administered with caution as the plasma and renal clearance of topiramate are decreased. For specific posology recommendations in patients with decreased renal function.

## Decreased hepatic function

In hepatically-impaired patients, topiramate should be administered with caution as the clearance of topiram

AED Coadministered	AED Concentration	Topiramate Concentration
Phenytoin	↔*	↓
Carbamazepine (CBZ)	↔	↓
Valproic acid	↔	↔
Lamotrigine	↔	↔
Phenobarbital	↔	NS
Primidone	↔	NS

↔ = No effect on plasma concentration ( $\leq 15\%$  change)

\* = Plasma concentrations increase in individual patients

↓ = Plasma concentrations decrease

NS = Not studied

AED = antiepileptic drug

*Other medicinal product interactions*

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

*Central nervous system depressants:* Concomitant administration of Topiramate and alcohol or other central nervous system (CNS) depressant medicinal products has not been evaluated in clinical studies. It is recommended that Topiramate not be used concomitantly with alcohol or other CNS depressant medicinal products.

*St John's Wort (Hypericum perforatum)*

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

*Oral contraceptives:* In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 µg ethinyl estradiol (EE), 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 EE was statistically significantly decreased at doses of 200, 400, and 800 mg/day (18%, 21%, and 30%, respectively) when given as adjunctive therapy in epilepsy patients taking valproic acid. In both studies, Topiramate (50-200 mg/day in healthy volunteers and 200-800 mg/day in epilepsy patients) did not significantly affect exposure to NET. Although there was a dose dependent decrease in EE exposure for doses between 200-800 mg/day (in epilepsy patients), there was no significant dose dependent change in EE exposure for doses of 50-200 mg/day (in healthy volunteers). The clinical significance of the changes observed is not known. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with Topiramate. Patients taking estrogen 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 dose conditions in healthy volunteers and multiple dose conditions in 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). However, differences in AUC for the total active moiety between treatment with risperidone alone and combination treatment with topiramate were not statistically significant. Minimal alterations in the pharmacokinetics of the total active moiety (risperidone plus 9-hydroxyrisperidone) and no alterations for 9-hydroxyrisperidone were observed. There were no significant changes in the systemic exposure of the risperidone total active moiety or of topiramate. When topiramate was added to existing risperidone (1-6 mg/day) treatment, adverse events were reported more frequently than prior to topiramate (250-400 mg/day) introduction (90% and 54% respectively). The most frequently reported AE's when topiramate was added to risperidone treatment were: somnolence (27% and 12%), paraesthesia (22% and 0%) and nausea (18% and 9% respectively).

*Hydrochlorothiazide (HCTZ):* A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg every 24 h) and topiramate (96 mg every 12 h) when administered alone and concomitantly. The results of this study indicate that topiramate  $C_{max}$  increased by 27% and AUC increased by 29% when HCTZ was added to topiramate. The clinical significance of this change is unknown. The addition of HCTZ to topiramate therapy may require an adjustment of the topiramate dose. 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 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  $AUC_{T_{max}}$  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  $AUC_{T_{max}}$ , respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in  $C_{max,ss}$  and  $AUC_{T_{max}}$  of the active keto-metabolite. The clinical significance of these findings is not known. When Topiramate is added to pioglitazone therapy or pioglitazone is added to Topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

*Glyburide:* A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glyburide (5 mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 25% reduction in glyburide  $AUC_{0-t}$  during topiramate administration. Systemic exposure of the active metabolites, 4-trans-hydroxy-glyburide (M1) and 3-cis-hydroxyglyburide (M2), were also reduced by 13% and 15%, respectively. The steady-state pharmacokinetics of topiramate were unaffected by concomitant administration of glyburide.

When topiramate is added to glyburide therapy or glyburide is added to topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

*Other forms of interactions*

*Agents predisposing to nephrolithiasis*

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

*Valproic acid:* Concomitant administration of topiramate and valproic acid has been associated with Hyperammonemia with or without encephalopathy in patients who have tolerated either medicinal product alone. In most cases, symptoms and signs abated with discontinuation of either medicinal product. This adverse reaction is not due to a pharmacokinetic interaction. An association of Hyperammonemia with topiramate monotherapy or concomitant treatment with other AEDs has not been established.

*Hypothermia:* defined as an unintentional drop in body core temperature to  $<35^{\circ}\text{C}$ , has been reported in association with concomitant use of topiramate and valproic acid (VPA) both in conjunction with Hyperammonemia and in the absence of Hyperammonemia. This adverse event in patients using concomitant topiramate and valproate can occur after starting topiramate treatment or after increasing the daily dose of topiramate.

**ADVERSE DRUG REACTIONS:**

The safety of topiramate was evaluated from a clinical trial database consisting of 4,111 patients (3,182 on topiramate and 929 on placebo) who participated in 20 double-blind trials and 2,847 patients who participated in 34 open-label trials, respectively, for topiramate as adjunctive treatment of primary generalized tonic-clonic seizures, partial onset seizures, seizures associated with Lennox-Gastaut syndrome, monotherapy for newly or recently diagnosed epilepsy or migraine prophylaxis. The majority of adverse reactions were mild to moderate in severity. Adverse reactions identified in clinical trials, and during post-marketing experience (as indicated by \*) are listed by their incidence in clinical trials in Table 1. Assigned frequencies are as follows:

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
Not known	cannot be estimated from the available data

The most common adverse reactions (those with an incidence of  $>5\%$  and greater than that observed in placebo in at least 1 indication in double-blind controlled studies with topiramate) include: anorexia, decreased appetite, bradypnea, depression, expressive language disorder, insomnia, coordination abnormal, disturbance in attention, dizziness, dysarthria, dysgeusia, hypoesthesia, lethargy, memory impairment, nystagmus, paresthesia, somnolence, tremor, diplopia, vision blurred, diarrhea, nausea, fatigue, irritability, and weight decreased.

Table 1: Topiramate Adverse Reactions

System Organ Class	Very common	Common	Uncommon	Rare	Not known
Infections and infestations	Nasopharyngitis*				
Blood and lymphatic system disorders		Anaemia	Leucopenia, thrombocytopenia lymphadenopathy, eosinophilia	Neutropenia*	
Immune system disorders		Hypersensitivity			Allergic oedema*
Metabolism and nutrition disorders		Anorexia, decreased appetite	Metabolic acidosis, hypokalemia, increased appetite, polydipsia	Acidosis hyperchloremic	
Psychiatric disorders	Depression	Bradyphrenia, insomnia, expressive language disorder, anxiety, confusional state, disorientation, aggression, mood altered, agitation, mood swings, depressed mood, anger, abnormal behavior	Suicidal ideation, hallucination, psychotic disorder, hallucination auditory, hallucination visual, apathy, lack of spontaneous speech, sleep disorder, affect lability, libido decreased, restlessness, crying, dysphoria, euphoric mood, paranoia, perseveration, panic attack, tearfulness, reading disorder, initial insomnia, flat affect, thinking abnormal, loss of libido, listless, middle insomnia, distractibility, early morning awakening, panic reaction, elevated mood	Mania, panic disorder, feeling of despair*, hypomania	
Nervous system disorders	Paraesthesia, somnolence Dizziness	Disturbance in attention, memory impairment, amnesia, cognitive disorder, mental impairment, psychomotor skills impaired, convolution, coordination abnormal, tremor	Depressed level of consciousness, grand mal convolution, visual field defect, complex partial seizures, speech disorder, psychomotor hyperactivity, syncope, sensory disturbance, drooling, hypersomnia, aphasia, repetitive speech, hypokinesia,	Apraxia, circadian rhythm sleep disorder, hyperesthesia, hyposmia, anosmia, essential tremor, akinesia, unresponsive to stimuli	

		lethargy, hypoesthesia, nystagmus, dysgeusia, balance disorder, dysarthria, intention tremor, sedation,	dyskinesia, dizziness postural, poor quality sleep, burning sensation, sensory loss, parosmia, cerebellar syndrome, dysaesthesia, hypogesia, stupor, clumsiness, aura, ageusia, dysgraphia, dysphasia, neuropathy peripheral, presyncope, dystonia, formication		
	Eye disorders	Vision blurred, diplopia, visual disturbance	Visual acuity reduced, scotoma, myopia*, abnormal sensation in eye*, dry eye, photophobia, blepharospasm, lacrimation increased, photopsia, mydriasis, presbyopia	Blindness unilateral, blindness transient, glaucoma, accommodation disorder, altered visual depth perception, scintillating scotoma, eyelid oedema*, night blindness, amblyopia	Angle closure glaucoma*, Maculopathy*, eye movement disorder*, conjunctival oedema*
	Ear and labyrinth disorders	Vertigo, tinnitus, ear pain	Deafness, deafness unilateral, deafness neurosensory, ear discomfort, hearing impaired		
	Cardiac disorders		Bradycardia, sinus bradycardia, palpitations		
	Vascular disorders		Hypotension, orthostatic hypotension, flushing, hot flush		Raynaud's phenomenon
	Respiratory, thoracic and mediastinal disorders	dyspnea, epistaxis, nasal congestion, rhinorrhea, cough*	Dyspnea exertional, Para nasal sinus hyper secretion, dysphonia		
	Gastrointestinal disorders	Nausea, Diarrhoea	Vomiting, constipation, abdominal pain upper, dyspepsia, abdominal pain, dry mouth, stomach discomfort, paraesthesia oral, gastritis, abdominal discomfort	Pancreatitis, flatulence, gastroesophageal reflux disease, abdominal pain lower, hypoesthesia oral, gingival bleeding, abdominal distension, epigastric discomfort, abdominal tenderness, salivary hyper secretion, oral pain, breath odour, glossodynia	
	Hepatobiliary disorders				Hepatitis, Hepatic failure
	Skin and subcutaneous tissue disorders		Alopecia, rash, pruritus	Anhidrosis, hypoesthesia facial, urticaria, erythema multiforme*, skin odour abnormal, periorbital oedema*, urticaria localized	Toxic epidermal necrolysis*
	Musculoskeletal and connective tissue disorders		Arthralgia, muscle spasms, myalgia, muscle twitching, muscular weakness, musculoskeletal chest pain	Joint swelling*, musculoskeletal stiffness, flank pain, muscle fatigue	Limb discomfort*
	Renal and urinary disorders		Nephrolithiasis, pollakiuria, dysuria	Calculus urinary, urinary incontinence, hematuria, incontinence, micturition urgency, renal colic, renal pain	Calculus ureteric, renal tubular acidosis*
	Reproductive system and breast disorders			Erectile dysfunction, sexual dysfunction	
	General disorders and administration site conditions	Fatigue	Pyrexia, asthenia, irritability, gait disturbance, feeling abnormal, malaise	Hyperthermia, thirst, influenza like illness*, sluggishness, peripheral coldness, feeling drunk, feeling jittery	Face oedema, calcinosis
	Investigations	Weight decreased	Weight increased*	Crystal urine present, tandem gait test abnormal, white blood cell count decreased, Increase in liver enzymes	Blood bicarbonate decreased
	Social circumstances			Learning disability	

\* identified as an adverse reaction from post marketing spontaneous reports. Its frequency was calculated based on clinical trial data.

**Paediatric population**

Adverse reactions reported more frequently ( $\geq 2$ -fold) in children than in adults in double-blind controlled studies include: Decreased appetite; Increased appetite; Hyperchloraemic acidosis; Hypokalemia; Abnormal behavior; Aggression; Apathy; Initial insomnia; Suicidal ideation; Disturbance in attention; Lethargy; Circadian rhythm sleep disorder; Poor quality sleep; Lacrimation increased; Sinus bradycardia; Feeling abnormal; Gait disturbance.

Adverse reactions that were reported in children but not in adults in double-blind controlled studies include: Eosinophilia; Psychomotor hyperactivity; Vertigo; Vomiting; Hyperthermia; Pyrexia; Learning disability.

**OVERDOSAGE AND TREATMENT:**

**Symptoms and symptoms:** Overdoses of topiramate have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbances, blurred vision, diplopia, impaired mentation, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. The clinical consequences were not severe in most cases, but deaths have been reported after overdoses with multiple medicinal products including topiramate.

Topiramate overdose can result in severe metabolic acidosis.

**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 and the patient should be well hydrated. Hemodialysis has been shown to be an effective means of removing topiramate from the body.

**STORAGE CONDITION:**

STORE AT TEMPERATURES NOT EXCEEDING 30°C.

**DOSAGE FORMS AND PACKAGING AVAILABLE:**

25 mg /50 mg: Alu/Alu Blister Pack of 10's (Box of 50's)

100 mg: Alu/Alu Blister Pack of 10's (Box of 30's)

**INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL (IF APPLICABLE):**

MICRO LABS LIMITED, BANGALORE, INDIA						
1	Product Name	Epitop			Colours Used  ■ BLACK	
2	Strength	100 mg				
3	Component	Leaflet				
4	Category	Export - Philippines				
5	Dimension	280 x 420 mm				
6	Artwork Code	EXG-ML01I-				
7	Pharma Code	N/A				
8	Reason for Change	New Artwork				
Prepared by (DTP)		Checked by (PD)	Approved by			
Sign			Head CQA	Head Production/ Packing (Site)	Head QC (Site)	
Date		24-11-2021			Head QA (Site)	