For the Use Only of a Registered Medical Practitioner

ROPIMATE TABLETS
(Topiramate Tablets 50 mg / 100 mg)

COMPOSITION

ROPIMATE 50 mg
Each film-coated tablet contains:
Topiramate……50 mg

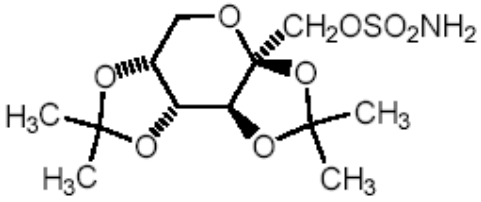
ROPIMATE 100 mg
Each film-coated tablet contains:
Topiramate…….100 mg

PRODUCT DESCRIPTION:

ROPIMATE 50 mg
Yellow coloured, film-coated, circular tablet debossed with 'TP2' on one side and plain on the other side.

ROPIMATE 100 mg
Yellow coloured, film-coated, circular tablet debossed with 'TP3' on one side and plain on the other side.

DESCRIPTION
ROPIMATE TABLETS contains topiramate, which is an antiepileptic. Topiramate is chemically described as 2,3:4,5-Di-O-isopropylidene-β-Dfructopyranose sulfamate. Its empirical formula is $C_{12}H_{21}NO_8S$, molecular weight is 339.37 and its structural formula is as follows:



TOPIRAMATE

PHARMACOLOGY

- **Mechanism of action**

Topiramate is classified as a sulphamate-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 neurones are subjected to a sustained depolarisation indicative of a state-dependent blockade of voltage-sensitive sodium channels. Topiramate markedly enhances the activity of GABA at some types of GABA receptors but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype. Topiramate weakly antagonises the excitatory activity of kainate/AMPA subtype of glutamate receptor.

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.

- **Pharmacokinetics**

The pharmacokinetic profile of topiramate compared to other antiepileptic drugs 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.

Topiramate is rapidly and well absorbed. Following oral administration of 100 mg topiramate to healthy subjects, a mean plasma concentration (C_{max}) of 1.5 mcg/mL was achieved within 2-3 hrs (T_{max}). Based on the recovery of radioactivity from the urine, the mean extent of absorption of a 100-mg oral dose of 14C-topiramate was at least 81%. There was no clinically significant effect of food on the bioavailability of topiramate. Generally, 13-17% of topiramate is bound to plasma protein. A low capacity binding site for topiramate in/on erythrocytes that is satiable above plasma concentrations of 4 mcg/mL has been observed. The volume of distribution varied inversely with the dose. The mean apparent volume of distribution was 0.8-0.55 L/kg for a single dose range of 100-1200 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. Topiramate is not extensively metabolized (~20%) in healthy 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 <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.

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

Topiramate exhibits low intersubject variability in plasma concentrations and, therefore, has predictable pharmacokinetics. The pharmacokinetics of topiramate are linear with plasma clearance remaining constant and area under the plasma concentration curve increasing in a dose-proportional manner over a 100-400 mg single oral dose range in healthy subjects. Patients with normal renal function may take 4-8 days to reach steady-state plasma concentrations. The mean Cmax following multiple, twice-a-day oral doses of 100 mg to healthy subjects was 6.76 mcg/mL. Following administration of multiple doses of 50 and 100 mg of topiramate twice a day, the mean plasma elimination half-life was approximately 21 hrs.

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

Topiramate modestly reduces the bioavailability of risperidone, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance.

Topiramate modestly reduces the bioavailability of diltiazem and one of its active metabolites. This is unlikely to be of clinical significance.

Pharmacokinetics in Special Populations

Renal Impairment*:* The plasma and renal clearance of topiramate are decreased in patients with impaired renal function (CLCR ≤60 mL/min), and the plasma clearance is decreased in patients with end-stage renal disease. As a result, higher steady-state topiramate plasma concentrations are expected for a given dose in renally-impaired patients as compared to those with normal renal function. Topiramate is effectively removed from plasma by haemodialysis.

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

Hepatic Impairment: Plasma clearance of topiramate is decreased in patients with moderate to severe hepatic impairment.

Pediatric Pharmacokinetics: Children up to 12 years- 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 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 enzymes inducing antiepileptic drugs decrease the steady-state plasma concentrations.

INDICATIONS

Epilepsy

ROPIMATE TABLETS are indicated as monotherapy in patients with newly diagnosed epilepsy or for conversion to monotherapy in patients with epilepsy.

ROPIMATE TABLETS are indicated as adjunctive therapy for adults and children 2 years and above with partial onset seizures or generalized tonic-clonic seizures**.**

ROPIMATE TABLETS are also indicated in adults and children as adjunctive therapy for the treatment of seizures associated with Lennox Gastaut syndrome.

Migraine

ROPIMATE TABLETS are indicated in adults for the prophylaxis of migraine headache. Topiramate is not useful in the acute treatment of migraine**.**

DOSAGE AND ADMINISTRATION

ROPIMATE TABLETS is available as 50 mg and 100 mg strengths only. **ROPIMATE TABLETS** may not be suitable for all dosages and therefore, other suitable available strengths and/or dosage forms of topiramate should be considered as necessary.

Adjunctive therapy epilepsy
Adult

Initially 25-50 mg every night for 1 week. Subsequently at weekly or bi-weekly intervals, increase dose to 25-50 (to 100) mg/day in 2 divided doses.

Children ≥2 yr
Approximately 5-9 mg/kg/day in 2 divided doses.
Titrate at ≤25 mg (based on a range of 1-3 mg/kg/day) nightly for the 1st week. Subsequently at 1 or 2 weekly intervals, with increments of 1-3 mg/kg/day in 2 divided doses.

Monotherapy epilepsy
Adult
Titrate at 25 mg nightly for 1 week. Subsequently at 1 or 2 weekly intervals, increase dose by increments of 25 or 50 mg/day in 2 divided doses. Initial target dose: 100 mg/day. Max: 500 mg.

Children ≥2 yr
Initially at 0.5-1 mg/kg/day every night for the 1st week. Subsequently at 1 or 2 weekly intervals, increase dose by increments of 0.5-1 mg/kg/day in 2 divided doses. Initial target dose: 3-6 mg/kg/day.

Prophylaxis of migraine
Initially 25 mg nightly for 1 week then increased at 25 mg/day increments at 1-week intervals. Recommended total daily dose: 100 mg in 2 divided doses.

General

For optimal seizure control in both adults and children, it is recommended that therapy be initiated at a low dose followed by titration to an effective dose.

Tablet should not be broken. Topiramate can be taken without regard to meals.

It is not necessary to monitor topiramate plasma concentrations to optimise Topiramate therapy. The dosing recommendations apply to children and to all adults, including the elderly, in the absence of underlying renal disease.

Since Topiramate is removed from plasma by haemodialysis, a supplemental dose of Topiramate equal to approximately one-half the daily dose should be administered on haemodialysis days. The supplemental dose should be administered in divided doses at the beginning and completion of the haemodialysis procedure. The supplemental dose may differ based on the characteristics of the dialysis equipment being used.

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 topiramate adjunctive therapy may require adjustments of the dose of topiramate.

Adults: It is recommended that therapy be initiated at a low dose, followed by titration to effective dose. Titration should begin at 25-50 mg nightly for 1 week. Subsequently, at weekly or bi-weekly intervals, the dose should be increased by 25-50 (to 100) mg/day and taken in 2 divided doses. Dose titration should be guided by clinical outcome. Some patients may achieve efficacy with once-a-day dosing.

The usual daily dose is 200-400 mg in 2 divided doses. Individual patients have received as high as 1600 mg/day.

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

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

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

Route of administration: Oral

CONTRAINDICATIONS

ROPIMATE TABLETS (topiramate) are contraindicated in patients with a history of hypersensitivity to any component of this product.
Migraine prophylaxis: in pregnancy and in women of childbearing potential if not using a highly effective method of contraception.

WARNINGS AND PRECAUTIONS

- **General**

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

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

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

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. Adequate hydration whilst using topiramate is very important as it can reduce the risk of developing renal stones. In addition, it may reduce the risk of heat-related adverse events during exercise and exposure to particularly warm environments.

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

In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased.

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

In reported 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 (43 out of 7,999 patients treated) and at a 3 fold higher incidence than in those treated with placebo (0.15%; 5 out of 3,150 patients treated).

Patients should be monitored for signs of depression and referred for appropriate treatment if necessary. Patients (and caregivers of patients) should be advised to seek medical advice immediately should suicidal thoughts emerge.

In accordance with good clinical practice, patients with a history of depression and/or suicidal behaviour, adolescents and young adults may be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Acute myopia with secondary angle-closure glaucoma has been reported rarely in both children and adults receiving topiramate. Symptoms typically occur within 1 month of the start of treatment and include decreased visual acuity and/or ocular pain. Ophthalmological findings include bilateral myopia, anterior chamber shallowing, hyperaemia and increased intra-ocular pressure with or without mydriasis. There may be supraciliary effusion resulting in anterior displacement of the lens and iris. Treatment includes discontinuation of topiramate as rapidly as is clinically feasible and appropriate measures to reduce intraocular pressure. These measures generally result in a decrease in intraocular pressure. If increased intraocular pressure is suspected, immediate specialist advice should be sought.

Visual field defects
Visual field defects have been reported in patients receiving topiramate independent of elevated intraocular pressure. In clinical trials, most of these events were reversible following topiramate discontinuation, however some cases were not. In a large proportion of postmarketing case reports reversibility was unknown, but in cases where an outcome was reported, the majority was reversible. If visual problems occur at any time during topiramate treatment, consideration should be given to discontinuing the drug.

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

Chronic, untreated metabolic acidosis may increase the risk of nephrocalcinosis.

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

Depending on underlying conditions, appropriate evaluation including serum bicarbonate levels is recommended with topiramate therapy. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering). A dietary supplement or increased food intake may be considered if the patient is losing weight or has inadequate weight gain while on this medication. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.

Women of childbearing potential

ROPIMATE may cause fetal harm when administered to a pregnant woman. Before the initiation of treatment with topiramate in a woman of childbearing potential, pregnancy testing should be performed and a highly effective contraceptive method used. The patient should be fully informed of the risks related to the use of topiramate during pregnancy. ROPIMATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Migraine Prophylaxis

In migraine prophylaxis, before discontinuation of treatment, dosage should be gradually reduced over at least 2 weeks to minimize the possibility of rebound migraine headaches.

Weight loss

In the reported double-blind treatment with topiramate 100 mg/day, the mean change from baseline to the final visit in body weight was 2.5 kg, compared to 0.1 kg in the placebo group. Overall, 68% of patients treated with topiramate 100 mg/day lost weight during the trials, compared to 33% of patients receiving placebo. Weight decrease was reported as an adverse event in 1% of all placebo treated patients and in 9% of all patients receiving topiramate 100 mg/day.

Significant weight loss may occur during long-term topiramate treatment for migraine prophylaxis. In clinical studies of topiramate 100 mg in migraine prophylaxis, a continuing weight decrease was observed with a mean weight decrease of 5.5 kg over 20 months. Twenty-five per cent of patients treated with topiramate for migraine prophylaxis had a weight loss of≥ 10% of their body weight. It is recommended that patients on long term topiramate for migraine prophylaxis should be regularly weighed and monitored for continuing weight loss.

- **Pregnancy and Lactation:**

Topiramate should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. ROPIMATE 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) and neurodevelopmental disorders (e.g., autism spectrum disorders and intellectual disability). This has been reported with topiramate monotherapy and topiramate as part of a polytherapy regimen.

In addition, data from other studies indicate that, compared with monotherapy, there is an increased risk of teratogenic effects associated with the use of antiepileptic drugs in combination therapy. The risk has been observed in all doses and effects were reported to be dose-dependent. In women treated with topiramate who have had a child with a congenital malformation, there appears to be an increased risk of malformations in subsequent pregnancies when exposed to topiramate.

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

Topiramate can produce central nervous system related adverse events and may be more sedative than other antiepileptic drugs. Drowsiness is likelihood. In addition, there have been reports of visual disturbances/blurred vision. Patients should be warned of these and advised that if affected, they should not drive, operate machinery and/or take part in activities where such reactions could put themselves or others at risk.

- **Drug Interactions**

Effects of Topiramate on Other Antiepileptic Drugs: The addition of topiramate to other antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no clinically significant effect on their steady-state plasma concentrations, except in the occasional patients, where the addition of topiramate to phenytoin may result in an increase of plasma concentrations of phenytoin. This is possibly due to inhibition of a specific enzyme polymorphic isoform (CPY2Cmeph). Consequently, any patient on phenytoin showing clinical signs or symptoms of toxicity should have phenytoin levels monitored.

Effects of Other Antiepileptic Drugs on topiramate: Phenytoin and carbamazepine decrease the plasma concentration of topiramate. The addition or withdrawal of phenytoin or carbamazepine to topiramate therapy may require an adjustment in dosage of the latter. This should be done by titrating to clinical effect. The addition or withdrawal of valproic acid does not produce clinically significant changes in plasma concentrations of topiramate and, therefore, does not warrant dosage adjustment of topiramate.

The results of these interactions are summarized in the following table:

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

↔ = No effect on plasma concentration
** = Plasma concentrations increase in individual patients
↓ = Plasma concentrations decrease
NS = Not studied
AED = antiepileptic drug

Other Drug 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.

CNS Depressants: Concomitant administration of topiramate and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, topiramate should be used with caution if used in combination with alcohol and other CNS depressants.

Oral Contraceptives: In an interaction study with a combined oral contraceptive, topiramate increased plasma clearance of the oestrogenic component significantly. Consequently, and bearing in mind the potential risk of teratogenicity, patients should receive a preparation containing not less than 50 µg of oestrogen or use some alternative non-hormonal method of contraception. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns.

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.

Hydrochlorothiazide (HCTZ): A drug-drug interaction study in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg q24h) and topiramate (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that topiramate C_{max} increased by 27% and AUC increased by 29% when HCTZ was added to topiramate. The clinical significance of this change is unknown. The addition of HCTZ to 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 in healthy volunteers evaluated the steady-state pharmacokinetics of metformin 500mg bd and topiramate 100mg bd in plasma when metformin was given alone and when metformin and topiramate were given simultaneously indicated that metformin mean C_{max} and mean $AUC_{0\text{-}12h}$ increased by 18% and 25%, respectively, while mean CL/F decreased 20% when metformin was co-administered with topiramate. Topiramate did not affect metformin t_{max}. The clinical significance of the effect of topiramate on metformin pharmacokinetics is unclear. Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The extent of change in the clearance is unknown. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear. When 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 in healthy volunteers evaluated the steady-state pharmacokinetics of topiramate and pioglitazone when administered alone and concomitantly reported a 15% decrease in the $AUC_{\tau,ss}$ 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 $AUC_{\tau,ss}$ respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in $C_{max,ss}$ and $AUC_{\tau,ss}$ of the active keto-metabolite. The clinical significance of these findings is not known. When topiramate is added to pioglitazone therapy or pioglitazone is added to topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Glibenclamide: A drug-drug interaction study in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glibenclamide (5mg/day) alone and concomitantly with topiramate (150 mg/day) reported a 25% reduction in glibenclamide AUC_{24} during topiramate administration. Systemic exposure of the active metabolites, 4-*trans*-hydroxy-glibenclamide (M1) and 3-*cis*-hydroxyglibenclamide (M2), were also reduced by 13% and 15%, respectively. The steady-state pharmacokinetics of topiramate were unaffected by concomitant administration of glibenclamide. When topiramate is added to glibenclamide therapy or glibenclamide is added to topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Other forms of interactions

Agents predisposing to nephrolithiasis
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. The interaction with benzodiazepines has not been studied.

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 topiramate monotherapy or concomitant treatment with other anti-epileptics has not been established.

Additional Pharmacokinetic Drug Interaction Studies
Clinical studies have been reported which 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. 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.

Summary of Results from Additional Clinical Pharmacokinetic Drug Interaction Studies

Concomitant Drug	Concomitant Drug Concentration[a]	Topiramate Concentration[a]
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 50 mg q12h)	16% increase in C_{max} , 17% increase in AUC (80 mg propranolol q12h)
Sumatriptan (Oral and Subcutaneous)	↔	NS
Pizotifen	↔	↔

[a] % values are the changes in treatment mean C_{max} or AUC with respect to monotherapy
↔ = No effect on Cmax and AUC (15% change) of the parent compound
NS = Not studied

Interaction studies showed that Topiramate did not significantly alter the serum levels of amitriptyline, propranolol or dihydroergotamine mesylate. The combination of Topiramate with each of these drugs was well tolerated and no dose adjustments were necessary.

ADVERSE REACTIONS

Reported adverse events were classified using a modified WHO-ART dictionary. The majority of the most common adverse events in clinical trials were mild-moderate in severity and dose-related. These dose-related adverse events typically began in the titration phase and often persisted into the maintenance phase but infrequently began in the maintenance phase. Rapid titration rate and higher initial dose were associated with higher incidences of adverse events leading to discontinuation.

Epilepsy

a) Monotherapy

Qualitatively, the types of adverse events observed in reported monotherapy trials were generally similar to those observed during adjunctive therapy trials (see below). With the exception of paraesthesia and fatigue in adults, these adverse events were reported at similar or lower incidence rates in monotherapy trials.

Adults:
In reported double-blind monotherapy clinical trials, the most common adverse events, i.e., those occurring in 10% or more of the topiramate-treated adult patients were paraesthesia, headache, fatigue, dizziness, somnolence, weight decrease, nausea and anorexia. Adverse events occurring at 5% or more but less than 10% included: insomnia, difficulty with memory, depression, difficulty with concentration/attention, abdominal pain, nervousness, hypoaesthesia, mood problems and anxiety.

Children:
In reported double-blind monotherapy clinical trials, the most common adverse events, i.e., those occurring in 10% or more of the topiramate-treated children were headache, anorexia and somnolence. Adverse events occurring at 5% or more but less than 10% included: difficulty with concentration/attention, fatigue, weight decrease, dizziness, paraesthesia, insomnia and nervousness.

b) Adjunctive Therapy

Adults:
Since Topiramate has most frequently been co-administered with other antiepileptic agents, it is not possible to determine which agents, if any, are associated with adverse effects. In reported double blind clinical trials, some of which included a rapid titration period, adverse events which occurred with a frequency greater than or equal to 5% and with a higher incidence in the topiramate-treated adult patients than in placebo included: abdominal pain, ataxia, anorexia, asthenia, confusion, difficulty with concentration/attention, difficulty with memory, diplopia, dizziness, fatigue, language problems, nausea, nystagmus, paraesthesia, psychomotor slowing, somnolence, speech disorders/related speech problems, abnormal vision and weight decrease. Topiramate may cause agitation and emotional lability (which may manifest mood problems and nervousness) and depression. Other less common adverse effects include, gait abnormal, aggressive reaction, apathy, cognitive problems, co-ordination problems, leucopenia, psychotic symptoms (such as hallucinations) and taste perversion.

Isolated cases of venous thromboembolic events have been reported. A causal association with the drug has not been established. Reports of increases in liver enzymes in patients taking Topiramate with and without other medications have been received. Isolated reports have been received of hepatitis and hepatic failure occurring in patients taking multiple medications while being treated with Topiramate

Children:
In reported double blind clinical trials, some of which included a rapid titration period, adverse events which occurred with a frequency greater than or equal to 5% and with a higher incidence in the topiramate-treated children than in placebo included: somnolence, anorexia, fatigue, insomnia, nervousness, personality disorder (behaviour problems), difficulty with concentration/attention, aggressive reaction, weight decrease, gait abnormal, mood problems, ataxia, saliva increased, nausea, difficulty with memory, hyperkinesia, dizziness, speech disorders/related speech problems and paraesthesia.

Adverse events that occurred less frequently but were considered potentially medically relevant included: emotional lability, agitation, apathy, cognitive problems, psychomotor slowing, confusion, hallucination, depression and leucopenia.

Migraine prophylaxis

In reported double-blind clinical trials, clinically relevant adverse events which occurred at a frequency of 5% or more and seen at a higher incidence in topiramate-treated patients than placebo-treated patients included: fatigue, paraesthesia, dizziness, hypoaesthesia, language problems, nausea, diarrhoea, dyspepsia, dry mouth, weight decrease, anorexia, somnolence, difficulty with memory, difficulty with concentration/attention, insomnia, anxiety, mood problems, depression, taste perversion, abnormal vision. Fifty per cent of patients in these trials experienced paraesthesia.

During a reported 6-month double-blind treatment with topiramate 100 mg/day for migraine prophylaxis, weight decrease was reported as an adverse event in 1% of all placebo – treated patients and in 9% of all patients receiving topiramate 100 mg/day. Weight loss continued with long-term topiramate treatment.

Post-marketing and Other Experience
Adverse drug reactions from spontaneous reports during the worldwide post-marketing experience with topiramate are included in Table below. The adverse drug reactions are ranked by frequency, using the following convention (all calculated per patient-years of estimated exposure):

Very common ≥ 1/10
Common ≥ 1/100 and < 1/10
Uncommon ≥ 1/1,000 and < 1/100
Rare ≥ 1/10,000 and < 1/1000
Very rare <1/10,000

The frequencies provided below reflect reporting rates for adverse drug reactions from spontaneous reports, and do not represent more precise estimates that might be obtained in clinical or experimental studies.

Topiramate increases the risk of nephrolithiasis especially in those with a predisposition. In the initial clinical trials none of the calculi required open surgery and three-quarters were passed spontaneously. Most of the patients opted to continue treatment despite nephrolithiasis.

Reduced sweating has been rarely reported. The majority of cases have been in children and some have been associated with flushing and raised temperature.

Very rarely, reports have been received for bullous skin and mucosal reactions (including erythema multiforme, pemphigus, Stevens-Johnson syndrome and toxic epidermal necrolysis). The majority of these reports have occurred in patients taking other medications also associated with bullous skin and mucosal reactions.

Post marketing reports of adverse drug reactions	
Blood and Lymphatic System Disorders	Very rare: leucopenia and neutropenia, thrombocytopenia
Metabolism and Nutrition Disorders	Rare: anorexia Very rare: metabolic acidosis; decreased appetite, hyperammonemia
Psychiatric Disorders	Uncommon: suicidal ideation, attempts, and suicide Rare: depression; agitation; somnolence Very rare: insomnia, confusional state, psychotic disorder, aggression, hallucination, expressive language disorder
Nervous System Disorders	Rare: paresthesia, convulsion, headache Very rare: speech disorder, dysgeusia, amnesia, memory impairment, drug withdrawal convulsion
Eye Disorders	Rare: visual disturbance, vision blurred Very rare: myopia, angle closure glaucoma, eye pain Frequency “not known”: Uveitis
Gastrointestinal Disorders	Rare: nausea Very rare: diarrhoea, abdominal pain, vomiting
Skin and Subcutaneous Tissue Disorders	Rare: alopecia Very rare: rash
Renal and Urinary Disorders	Rare: nephrolithiasis Very rare: nephrocalcinosis
General Disorders and Administration Site Conditions	Rare: fatigue Very rare: pyrexia, feeling abnormal, asthenia
Investigations	Rare: weight decreased

OVERDOSAGE

Signs and Symptoms
Overdoses of topiramate have been reported. Signs and symptoms included: convulsions, drowsiness, speech disturbances, blurred vision, diplopia, mentation impaired, lethargy, abnormal co-ordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. 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.
A patient who ingested a dose calculated to be between 96 and 110 g topiramate was admitted to hospital with coma lasting 20-24 hours followed by full recovery after 3 to 4 days.

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

STORAGE
STORE BELOW 30°C, PROTECTED FROM MOISTURE

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

SUPPLY

Blister strips (cold form) of 10 x 10's

Manufactured By/Product Registration Holder:

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