For the use of Registered Medical Practitioner or a Hospital or a Laboratory Only 8042239-5253

EPIMATE

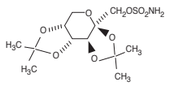
(Topiramate Tablets, 50/100 mg)

COMPOSITION

Each tablet contains:
Topiramate 50/100 mg

DESCRIPTION

Topiramate is a sulfamate-substituted monosaccharide that is intended for use as an antiepileptic drug.
Topiramate is a white crystalline powder with a bitter taste. Topiramate is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and having a pH of 9 to 10. It is freely soluble in acetone, chloroform, dimethylsulfoxide, and ethanol. The solubility in water is 9.8 mg/mL. Its saturated solution has a pH of 6.3. Topiramate has the molecular formula $C_{12}H_{21}NO_8S$ and a molecular weight of 339.37. Topiramate is designated chemically as 2,3:4,5-Di-O-isopropylidene-β-D-fructopyranose sulfamate and has the following structural formula:



CLINICAL PHARMACOLOGY

Mechanism of action

The precise mechanism by which topiramate exerts its antiseizure effect is unknown; however, electrophysiological and biochemical studies of the effects of topiramate on cultured neurons have revealed three properties that may contribute to topiramate's antiepileptic efficacy. First, action potentials elicited repetitively by a sustained depolarization of the neurons are blocked by topiramate in a time-dependent manner, suggestive of a state-dependent sodium channel blocking action. Second, topiramate increases the frequency at which γ-aminobutyrate (GABA) activates $GABA_A$ receptors, and enhances the ability of GABA to induce a flux of chloride ions into neurons, suggesting that topiramate potentiates the activity of this inhibitory neurotransmitter. This effect was not blocked by flumazenil, a benzodiazepine antagonist, nor did topiramate increase the duration of the channel open time, differentiating topiramate from barbiturates that modulate $GABA_A$ receptors. Third, topiramate antagonizes the ability of kainate to activate the kainate/AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; non-NMDA) subtype of excitatory amino acid (glutamate) receptor, but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype. These effects of topiramate are concentration-dependent within the range of 1 μM to 200 μM.
Topiramate also inhibits some isoenzymes of carbonic anhydrase (CA-II and CA-IV). This pharmacologic effect is generally weaker than that of acetazolamide, a known carbonic anhydrase inhibitor, and is not thought to be a major contributing factor to topiramate's antiepileptic activity.

Pharmacodynamics

Topiramate has anticonvulsant activity in rat and mouse maximal electroshock seizure (MES) tests. Topiramate is only weakly effective in blocking clonic seizures induced by the $GABA_A$ receptor antagonist, pentylenetetrazole. Topiramate is also effective in rodent models of epilepsy, which include tonic and absence-like seizures in the spontaneous epileptic rat (SER) and tonic and clonic seizures induced in rats by kindling of the amygdala or by global ischemia.

Pharmacokinetics

Absorption and Distribution

Absorption of topiramate is rapid, with peak plasma concentrations occurring at approximately 2 hours following a 400 mg oral dose. The relative bioavailability of topiramate from the tablet formulation is about 80% compared to a solution. The bioavailability of topiramate is not affected by food.
The pharmacokinetics of topiramate is linear with dose proportional increases in plasma concentration over the dose range studied (200 to 800 mg/day). The mean plasma elimination half-life is 21 hours after single or multiple doses. Steady state is thus reached in about 4 days in patients with normal renal function. Topiramate is 13-17% bound to human plasma proteins over the concentration range of 1-250 μ g/mL.

Metabolism and Elimination

Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine (approximately 70% of an administered dose). Six metabolites have been identified
in humans, none of which constitutes more than 5% of an administered dose. The metabolites are formed via hydroxylation, hydrolysis, and glucuronidation. There is evidence of renal tubular reabsorption of topiramate. In rats, given probenecid to inhibit tubular reabsorption, along with topiramate, a significant increase in renal clearance of topiramate was observed. This interaction has not been evaluated in humans. Overall, oral plasma clearance (CL/F) is approximately 20 to 30 mL/min in humans following oral administration.

Special populations

Renal impairment

The clearance of topiramate was reduced by 42% in moderately renally impaired (creatinine clearance 30-69mL/min/1.73m^2) and by 54% in severely renally impaired subjects (creatinine clearance <30 mL/min/1.73m^2) compared to normal renal function subjects (creatinine clearance >70 mL/min/1.73m^2). Since topiramate is presumed to undergo significant tubular reabsorption, it is uncertain whether this experience can be generalized to all situations of renal impairment. It is conceivable that some forms of renal disease could differentially affect glomerular filtration rate and tubular reabsorption resulting in a clearance of topiramate not predicted by creatinine clearance. In general, however, use of one-half the usual dose is recommended in patients with moderate or severe renal impairment.

Hemodialysis

Topiramate is cleared by hemodialysis. Using a high efficiency, counterflow, single pass-dialysate hemodialysis procedure, topiramate dialysis clearance was 120 mL/min with blood flow through the dialyzer at 400 mL/min. This high clearance (compared to 20-30 mL/min total oral clearance in healthy adults) will remove a clinically significant amount of topiramate from the patient over the hemodialysis treatment period. Therefore, a supplemental dose may be required.

Hepatic impairment

In hepatically impaired subjects, the clearance of topiramate may be decreased; the mechanism underlying the decrease is not well understood.

Age, Gender, and Race

Clearance of topiramate in adults was not affected by age (18-67 years), gender, or race.

Pediatrics

Pharmacokinetics of topiramate was evaluated in patients ages 4 to 17 years receiving one or two other antiepileptic drugs. Pharmacokinetic profiles were obtained after one week at doses of 1, 3, and 9 mg/kg/day. Clearance was independent of dose.
Pediatric patients have a 50% higher clearance and consequently shorter elimination half-life than adults. Consequently, the plasma concentration for the same mg/kg dose may be lower in pediatric patients compared to adults. As in adults, hepatic enzyme-inducing antiepileptic drugs decrease the steady state plasma concentrations of topiramate.

INDICATIONS AND USAGE

Topiramate tablets is indicated as adjunctive therapy for adults and pediatric patients ages 2-16 years with partial onset seizures, or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome.

CONTRAINDICATIONS

Topiramate is contraindicated in patients with a history of hypersensitivity to any component of this product.

WARNINGS

'Potential for an increase of suicidal thoughts or behaviours'

Acute Myopia and Secondary Angle Closure Glaucoma:-

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving topiramate. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness) and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating topiramate therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in pediatric patients as well as adults. The primary treatment to reverse symptoms is discontinuation of topiramate as rapidly as possible, according to the judgment of the treating physician. Elevated intraocular pressure of any etiology, if left untreated, can lead to serious sequelae including permanent vision loss.

Visual Field defects

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

Oligohidrosis and Hyperthermia:-

Oligohidrosis (decreased sweating), infrequently resulting in hospitalization, has been reported in association with topiramate use. Decreased sweating and an elevation in body temperature above normal characterized these cases. Some of the cases were reported after exposure to elevated environmental temperatures. The majority of the reports have been in children. Patients, especially pediatric patients, treated with topiramate should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather. Caution should be used when topiramate 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.

Withdrawal of AEDs:-

Antiepileptic drugs, including topiramate, should be withdrawn gradually to minimize the potential of increased seizure frequency.

Cognitive/Neuropsychiatric Adverse Events:-

Adults

Adverse events most often associated with the use of topiramate were central nervous system related. In adults, the most significant of these can be classified into two general categories: 1) psychomotor slowing, difficulty with concentration, and speech or language problems, in particular, word-finding difficulties and 2) somnolence or fatigue. Additional nonspecific CNS effects occasionally observed with topiramate as add-on therapy include dizziness or imbalance, confusion, memory problems, and exacerbation of mood disturbances (e.g., irritability and depression). Reports of psychomotor slowing, speech and language problems, and difficulty with concentration and attention were common in adults. Although in some cases these events were mild to moderate, they at times led to withdrawal from treatment. The incidence of psychomotor slowing is only marginally dose-related, but both language problems and difficulty with concentration or attention clearly increased in frequency with increasing dosage. Somnolence and fatigue were the most frequently reported adverse events during clinical trials with topiramate. These events were generally mild to moderate and occurred early in therapy. While the incidence of somnolence does not appear to be dose-related, that of fatigue increases at dosages above 400 mg/day.

Pediatric Patients

The incidences of cognitive/ neuropsychiatric adverse events in pediatric patients were generally lower than previously observed in adults. These events included psychomotor slowing, difficulty with concentration/ attention, speech disorders/related speech problems and language problems. The most frequently reported neuropsychiatric events in this population were somnolence and fatigue.

PRECAUTIONS

General

Kidney Stones

A total of 32/2,086 (1.5%) of adults exposed to topiramate during its development reported the occurrence of kidney stones, an incidence about 2-4 times than expected in a similar, untreated population. As in the general population, the incidence of stone formation among topiramate treated patients was higher in men. Kidney stones have also been reported in pediatric patients. An explanation for the association of topiramate and kidney stones may lie in the fact that topiramate is a weak carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. The concomitant use of topiramate with other carbonic anhydrase inhibitors or potentially in patients on a ketogenic diet may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided. Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Hydration is recommended to reduce new stone formation.

Paresthesia

Paresthesia, an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of topiramate.

Adjustment of Dose in Renal Failure

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Dosage adjustment may be required.

Decreased Hepatic Function

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

Drug Interactions

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy.

Antiepileptic Drugs

The effects of these interactions on mean plasma AUCs are summarized in the following table: In Table, the second column (AED concentration) describes what happens to the concentration of the AED listed in the first column when topiramate is added. The third column (topiramate concentration) describes how the co administration of a drug listed in the first column modifies the concentration of topiramate in experimental settings when topiramate was given alone.

Summary of AED Interactions with topiramate

AED co-administration	AED concentration	Topiramate concentration
Phenytoin	NC or 25% increase [a]	48% decrease
Carbamazepine (CBZ)	NC	40% decrease
CBZ epoxide [b]	NC	NE
Valproic acid	11% decrease	14% decrease
Phenobarbital	NC	NE
Primidone	NC	NE

a = Plasma concentration increased 25% in some patients, generally those on a b.i.d. dosing regimen of phenytoin.
b = Is not administered but is an active metabolite of carbamazepine.
NC = Less than 10% change in plasma concentration.
AED = Antiepileptic drug.
NE = Not Evaluated.

Other drug interactions

Digoxin

Serum digoxin AUC was decreased by 12% with concomitant topiramate administration. The clinical relevance of this observation has not been established.

CNS depressants

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 extreme caution if used in combination with alcohol and other CNS depressants.

Oral Contraceptives

Topiramate increased plasma clearance of the oestrogenic component significantly.

Metformin

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.

Hydrochlorothiazide (HCTZ)

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.

Pioglitazone

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.

Lithium

Multiple dosing of topiramate 100 mg every 12 hrs decreased the AUC and C_{max} of Lithium (300 mg every 8 hrs) by 20%.

Risperidone

Patients receiving risperidone in combination with topiramate should be closely monitored for clinical response.

Glyburide

Glyburide did not affect the pharmacokinetics of topiramate.

Others

Concomitant use of topiramate, a weak carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, may create a physiological environment that increases the risk of renal stone formation, and should therefore be avoided.

Pregnancy: Category C

Topiramate should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Lactation

Topiramate should not be used during breast feeding.

Pediatrics

Safety and effectiveness in patients below the age of 2 years have not been established.

ADVERSE REACTIONS

The most commonly observed adverse events associated with the use of topiramate at dosages of 200 to 400 mg/day in controlled trials in adults with partial onset seizures, primary generalized tonic-clonic seizures, or Lennox-Gastaut syndrome, that were seen at greater frequency in topiramate treated patients and did not appear to be dose-related were: somnolence, dizziness, ataxia, speech disorders and related speech problems, psychomotor slowing, abnormal vision, difficulty with memory, paresthesia and diplopia. The most common dose-related adverse events at dosages of 200 to 1,000 mg/day were: fatigue, nervousness, difficulty with concentration or attention, confusion, depression, anorexia, language problems, anxiety, mood problems, and weight decrease.
Adverse events associated with the use of topiramate at dosages of 5 to 9 mg/kg/day in controlled trials in pediatric patients with partial onset seizures, primary generalized tonic clonic seizures, or Lennox-Gastaut syndrome, that were seen at greater frequency in topiramate-treated patients were: fatigue, somnolence, anorexia, nervousness, difficulty with concentration/attention, difficulty with memory, aggressive reaction, and weight decrease.

Incidence of adverse events by body system reported in at least 1% of patients in the placebo-controlled, add on trials in adults

Body System	Placebo (N=291)	Topiramate (mg/day) dosage	
		200-400 (N=183)	600-1000 (N=414)
Body as a whole			
General disorder			
Fatigue	13	15	30
Asthenia	1	6	3
Back pain	4	5	3
Chest pain	3	4	2
Allergy	1	2	3
Edema	1	2	1
Hot flushes	1	2	1
Leg pain	2	2	4
Central & peripheral nervous system			
Dizziness	15	25	32
Ataxia	7	16	14
Speech disorders	2	13	11
Paresthesia	4	11	19
Nystagmus	7	10	11
Tremor	6	9	9
Language problem	1	6	10
Coordination abnormal	2	4	4
Gastrointestinal system			
Nausea	8	10	12
Dyspepsia	6	7	6
Abdominal pain	4	6	7
Constipation	2	4	3
Hearing & vestibular disorders			
Hearing decreased	1	2	1
Metabolic & nutritional disorders			
Weight decrease	3	9	13
Muscle skeleton system			
Myalgia	1	2	2
Psychiatric disorders			
Somnolence	12	29	28
Nervousness	6	16	19
Psychomotor slowing	2	13	21
Difficulty with memory	3	12	14
Anorexia	4	10	12
Confusion	5	11	14
Depression	5	5	13
Attention	2	6	14
Agitation	2	3	3
Mood problems	2	4	9
Respiratory system			
Pharyngitis	2	6	3
Rhinitis	6	7	6
Sinusitis	4	5	6
Urinary system			
UTI	1	2	3
Vision disorders			
Vision abnormal	2	13	10
Diplopia	5	10	10

Incidence of adverse events by body system reported in at least 1% of patients in the placebo-controlled, add on trials in pediatric patients ages 2-16 years

Body System	Placebo (N=101)	Topiramate (N=98)
Body as a whole - General disorder		
Fatigue	5	16
Injury	13	14
Allergic reaction	1	2
Central & Peripheral nervous system		
Dizziness	2	4
Gait abnormal	5	8
Ataxia	2	6
Hyperkinesia	4	5
Speech disorders	2	4
Gastrointestinal system		
Nausea	5	6
Saliva increased	4	6
Constipation	4	6
Gastroenteritis	2	3
Metabolic & nutritional disorders		
Weight decrease	1	9
Muscle skeleton system		
Myalgia	1	2
Platelet, bleeding & clotting disorders		
Purpura	4	8
Epistaxis	1	4
Psychiatric disorders		
Somnolence	16	26
Nervousness	7	14
Personality disorder	9	11
Difficulty with attention	2	10
Anorexia	15	24
Aggressive reaction	4	9
Insomnia	7	8
Resistance mechanism disorder		
Viral infection	3	7
Respiratory system		
Pneumonia	1	5
Skin and appendages disorders		
Skin disorder	2	3
Alopecia	1	2
Urinary system		
Urinary incontinence	2	4
Vision disorders		
Vision abnormal	1	2
Eye abnormality	1	2
Diplopia	0	1

Other adverse events reported

In addition to the adverse experiences reported during clinical testing of topiramate, the following adverse experiences have been reported worldwide in patients receiving topiramate post-approval. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: bullous skin reactions (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), hepatic failure (including fatalities), hepatitis, pancreatitis, pemphigus, and renal tubular acidosis.

DOSAGE AND ADMINISTRATION

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.
Tablets should not be broken. Topiramate Tablet can be taken without regard to meals.
It is not necessary to monitor topiramate plasma concentrations to optimize Topiramate Tablet therapy. On rare occasions, the addition of Topiramate Tablet 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 Tablet adjunctive therapy may require adjustments of the dose of Topiramate Tablet.
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.
In clinical trials, as adjunctive therapy, 200 mg was effective and was the lowest dosage studied. This is therefore considered the minimum effective dose. The usual daily dose is 200-400 mg in 2 divided doses. Individual patients have received as high as 1600 mg/day.
Since Topiramate Tablet is removed from plasma by haemodialysis, a supplemental dose of Topiramate Tablet equal to approximately ½ 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.
These dosing recommendations apply to adults, including the elderly, in the absence of underlying renal disease. (See Precautions.)
Children ≥2 years: The recommended total daily dose of Topiramate Tablet 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.
MODE OF ADMINISTRATION: Oral

OVERDOSE

Overdoses of topiramate have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbance, blurred vision, diplopia, mentation impaired, lethargy, metabolic acidosis, 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 poly-drug overdoses involving topiramate.
A patient who ingested a dose 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.
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. Hemodialysis is an effective means of removing topiramate from the body.

STORAGE:

Store below 25^{0}C.

EXPIRY DATE:

24 months from the date of manufacturing.

PRESENTATION:

Topiramate Tablets 50 mg: yellow colored, round, biconvex, film coated tablets debossed with breakline on bothsides separating '10 and 32' on one side and '50' on other side.
Topiramate Tablets 100 mg: Light yellow colored, round, biconvex, film coated tablets debossed with breakline on bothsides separating '10 and 33' on one side and '100' on other side.

PACK STYLE: 3 x 10 and 10 x 10 Alu/Alu blister pack.

Date of Revision:

07 January 2015

torrent PHARMA

Manufactured by:
TORRENT PHARMACEUTICALS LTD.
Indrad - 382 721, Dist. Mehsana, INDIA.