For the use of Registered Medical Practitioner or a Hospital or a Laboratory Only xxxxxxxx-8883

EPIMATE

(Topiramate Tablets, 25/50/100/200 mg)

COMPOSITION

Epimate 25
Each film coated tablet contains :
Topiramate..... 25mg

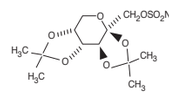
Epimate 50
Each film coated tablet contains :
Topiramate..... 50mg

Epimate 100
Each film coated tablet contains :
Topiramate..... 100mg

Epimate 200
Each film coated tablet contains :
Topiramate..... 200mg

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 C12H21NO8S 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

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 GABAA 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 GABAA 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 GABAA 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 μg/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

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.

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 in the five double-blind trials. 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

In double-blind clinical studies, 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. No patients discontinued treatment due to adverse events in double-blind trials.

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.

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 dosage (mg/day) 200-400 (N=183)	Topiramate dosage (mg/day) 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, pernphigus, and renal tubular acidosis

DOSAGE AND ADMINISTRATION

Topiramate has been shown to be effective in 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. In the controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations of topiramate and clinical efficacy. No evidence of tolerance has been demonstrated in humans. Doses above 400 mg/day (600, 800, or 1000 mg/day) have not been shown to improve responses in dose-response studies in adults with partial onset seizures.
On occasion, 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/or carbamazepine during adjunctive therapy with topiramate may require adjustment of the dose of topiramate. Because of the bitter taste, tablets should not be broken. Topiramate can be taken without regard to meals.

Adults (17 Years of Age and Over)

The recommended total daily dose of topiramate as adjunctive therapy is 400 mg/day in two divided doses. In studies of adults with partial onset seizures, a daily dose of 200 mg/day has inconsistent effects and is less effective than 400 mg/day, It is recommended that therapy be initiated at 25 - 50 mg/day followed by titration to an effective dose in increments of 25 - 50 mg/week. Titrating in increments of 25 mg/week may delay the time to reach an effective dose. Daily doses above 1,600 mg have not been studied. In the study of primary generalized tonic-clonic seizures the initial titration rate was slower than in previous studies; the assigned dose was reached at the end of 8 weeks.

Pediatric Patients (Ages 2-16 Years) - Partial Seizures, Primary Generalized Tonic-Clonic Seizures, or Lennox- Gastaut Syndrome

The recommended total daily dose of topiramate as adjunctive therapy for patients with partial seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut Syndrome 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. Dose titration should be guided by clinical outcome. In the study of primary generalized tonic-clonic seizures the initial titration rate was slower than in previous studies; the assigned dose of 6 mg/kg/day was reached at the end of 8 weeks.

Patients with Renal Impairment

In renally impaired subjects (creatinine clearance less than 70 mL/min/1.73m^2), one half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.

Patients Undergoing Hemodialysis

Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than a normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that 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.

Patients with Hepatic Disease

In hepatically impaired patients topiramate plasma concentrations may be increased. The mechanism is not well understood.

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:

Epimate 25: Store below 30°C.
Epimate 50/100: Store below 25°C.

PRESENTATION:

Epimate 25: White to off white, round, biconvex, film coated tablets debossed with 'I' mark separating '10 and 31' on one side and '25' on other side.
Epimate 50: Yellow colored, round, biconvex, film coated tablets debossed with breakline on both sides separating '10 and 32' on one side and '50' on other side.
Epimate 100: Light yellow colored, round, biconvex, film coated tablets debossed with breakline on both sides separating '10 and 33' on one side and '100' on other side.
Epimate 200: Peach coloured, round, biconvex film coated tablets debossed with breakline on both sides separating '10' & '34' on one side and '200' on the other side.
PACK STYLE: EPIMATE tablets are available in Alu/Alu blisters of 10 tablets.

torrent PHARMA
Manufactured by:
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