TRITOP
25mg & 50mg
Tablets

(Topiramate)

ٹرائی ٹوپ ۲۵-۵۰ ملی گرام ٹیبلٹس
(ٹوپائیرامیٹ)

DESCRIPTION:
Topiramate is a sulfamate-substituted monosaccharide TRITOP Tablets are available as 25mg & 50mg, Tablets for oral administration.

CLINICAL PHARMACOLOGY:

Mechanism of Action:
The precise mechanism by which topiramate exerts its anti convulsant and migraine prophylaxis effects are unknown: however, preclinical studies have revealed four properties that may contribute to topiramate efficacy for epilepsy and migraine prophylaxis Electrophysiological and biochemical evidence suggests that topiramate, at pharmacologically relevant concentrations, blocks voltage dependent sodium channels, augments the activity of the neurotransmitter gamma aminobutyrate at some subtypes of the GABA-A receptor antagonizes the kainite subtype of the glutamate receptor and inhibits the carbonic anhydrase enzyme, particulary isozymes II and IV.

Pharmacodynamics:
Topiramate has anticonvulsant activity in rat and mouse maximal electro shock 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 epileptic rat (SER) and tonic and clonic seizures induced, in rats by kinding of the amygdata or by global ischemia.

Pharmacokinetics:
Absorption of topiramate is rapid, with peak plasma concentrations occurring at approximately 2 hours following a 400mg oral dose. The relative bioavailability of topiramate from the tablet formulation is not 80% compared to a solution. The bioavailability of topiramate is not affected by food. The pharmacokinetics of topiramate are liner with dose proportional increases in plasma concentration over the dose range studied (200 to 800mg/day). The mean plasma elimination half-life is 21 hours after single or multiple dose. Steady state is thus reached in about 4 days in patients with normal renal function. Topiramte is 13-17% bound to human plasma proteins over the blood concentration range of 1-250 ug/ml. The fraction bound decreased as blood concentration increased. Carbamazepine and phenytoin do not alter the binding of topiramate. Sodium valproate, at 500 ug/ml (a concentration 5-10 times higher than considered therapeutic for valproate) decreased the protein binding of topiramate from 23% to 13%. Topiarmate does not influence the binding of sodium valproate.

Metabolism and Excretion:
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 if renal tubular reabsorption of topiramate. In rats, given probenecid to inhibit tubular reabsorption, along with 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 imparied (creatinine clearance 30-69 mL/min/1.73m) and by 54% in severely renally impaired subjects (creatnine clearance <30 ml/min/1.73m2) compared to normal renal function subjects (creatinine clearance >70 mL/min/1.73m2). Since topiramte 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 starting and maintenance dose is recommended in patients with moderate or severe renal impairment.

Hemodialysis:
Topiramate is clerared by hemodialysis. Using high efficiency, counter flow, single pass dialysate hemodialysis procedure, topiramate dialysis clearance was 120ml/min with blood flow through the dialyzer at 400mL/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 sublets, the clearance of topiramate may be decreased; the mechanism underlying the decrease is not well understood.

Age, Gender, and Race:
The pharmacokinetics of topiramate in elderly subjects (65-85 years of age, ISM 6) were evaluated in a controlled clinical study. The elderly subject population had reduced renal function [creatinine clearance(-20%)] compared to young adults. Following a single oral 100mg dose, maximum plasma concentration for elderly and young adults was achieved at approximately 1-2 hours. Reflecting the primary renal elimination of topiramate, topiramate plasma and renal clearance were reduced 21% and 19% respectively, in elderly subjects, compared to young adults. Similarly, topiramate half-life was longer (13%) in the elderly. Reduced topiramate clearance resulted in slightly higher maximum plasma concentration (23%) and AUC (25%) in elderly subjects than observed in young adults. Topiramate clearance is decreased in th elderly only to the extent that renal function is reduced. As recommended for all patients, dosage adjustment may be indigated in the elderly patient when impaired renal function (creatinine clearance rate < 70 mL/min1.73m2) is evident. It may be useful to monitor renal function in the elderly patient. Clearance of topiramate in adults was not affected by gender or race.

Pediatric Pharmacokinetics:
Pharmacokinetics of topiramate was evaluated in patients ages 4 to 17 years receiving one or two other antiepileptic drugs. Pharmacokinetics profiles were obtained after one week at doses of 1,3 and 9mg/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:

Epilepsy:
TRITOP Tablets are 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.

Migraine:
TRITOP Tablets are indicated for adults for the prophylaxis of migraine headache. The usefulness of TRITOP in the acute treatment of migraine headache has not been Studied.

CONTRAINDICATIONS:
TRITOP is contraindicated in patients with a history of hyper sensitivity to any component of this product.

WARNINGS:

Metabolic Acidosis:
Hyperchloremic, non-anion gap, metabolic acidosis (i.e, decreased serumbicarbonate below the normal refence range in the absence of chronic respiratory alkalosis) is associated with topiramate treatment. This metabolic acid is caused by renal bicarbonate loss due to the inhibitory effect of topiramate on carbonic anhydrase. Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering). If the decision is made to continue patients on topiramate in the face of persistant acidosis, alkali treatment should be considered.

Acute Myopia and Secondary Angle Closure Glaucoma: A syndrome consisting if 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. Opthalmologic findings can include myopia, anterior chamber shallowing ocular hyperemia (redness) and increased intraocular pressure. The primay treatment to reverse symptoms is discontinuation of Topiramate as rapidly as possible according to the judgment of the treating physician. Other measures, in conjunction with discontinuation of Topiramate, may be helpful. Elevated intraocular pressure of any etiology, if left untreated, can lead to serious sequelae including permanent vision loss.

Oligo-hidrosis and Hyperthermia:
Patients, especially pediatric patients treated with TRITOP should be monitored closely for evidence of decreased sweating and increased body temperature. Especially in not weather Caution should be used when TRITOP is prescribed with other drugs that predispose patients to heat-related disorders: these drugs includes but are not limited to other carbonic anhydrate inhibitors and drug with anticholinergic activity.

Withdrawal of AEDs:
Antiepileptic drugs, including TRITOP, should be withdrawn gradually to minimize the potential of increased seizure frequencey.

PRECAUTIONS:
Hyperammonemia and Encephalopathy Associated with Concomitant Valporic Acid Use Concomitant administration to Topiramate and Valporic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. Patient with inborn errors of metabolisms are reduced hepatic mitochondria activity may be at an increased risk for hyperammonemia with or without encephalopathy. Although not studied an interaction Topiramate and Valporic acid may exacetate existing defects are unmask deficiencies in susceptible persons. In patients who developed unexplained Hyperammonemia encephalopathu should be considered.

Kidney Stones:
The Concomitant use of TRITOP with other carbonic anhydrate inhibitors or potentially in patients on a ketogenic diet may create a physiological environment that increases the risk of kidney stone formation, and should there fore 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.

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 in patients with reduce renal function.

Decreased Hepatic Function:
In hepatically impaired patients, Topiramate should be administered with caution as the clearance of topiramate may be decreased.

Pregnancy: Pregnancy Catgory C.
There are no studies using Topiramate in pregnant women, Topiramate TRITOP Should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Labor and Delivery:
The effect of TRITOP on labor and delivery in humans is unknown.

Nursing Mother:
Limited observation in patients suggest an extensive secretion of topiramate into breast milk. Since many drugs are excreted in human milk, and because the potential for serious advers reactions in nursing infants to Topiramate is unknown, the potential benefit to the mother should be weighed against the potential risk to the infant when considering recommendation regarding nursing.

Pediatric Use:
Safety and effectiveness in patients below the age of 2 years have not been established for the adjunctive therapy treatment of partial onset seizures, primary generalized tonic-clonic seizures or seizures associated with Lennox-Gastaut syndrome Topiramate is associated with metabolic acidosis Chronic untreated metabolic acidosis in pediatric patients may cause ostemalacia/rickets and may reduce growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequence has not been systematically investigated. Safety and effectiveness in pediatric patients have not been established for the prophylaxis treatment of migraine headache.

Geriatric Use:
In clinical trials, 3% of patients were over 60. No age related difference in effectiveness or adverse effects were evident. However, clinical studies of topiramate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Dosage adjustment may be necessary for elderly with impaired renal function (creatinine clearance rate<70mL/min/1.73 m2) due to reduced clearance of topiramate.

Race and Gender Effects:
Evaluation of effectiveness and safety in clinical trials has shown no race or gender related effects.

ADVERSE EVENTS:
The most commonly observed adverse events associated with the use of Topiramate are ataxia, difficulty in concentration confusion. dizziness, fatigue, paraesthesia, somnolence, emotional liability, depression, CMS disturbances. Rarely, renal stones weight loss.

DRUG ABUSE AND DEPENDENCE:
The abuse and dependence potential of TRITOP has not been evaluated in humans seiduts.

OVER DOSAGE:
Overdoses of Topiramate have been reported. Signs and symptoms included convulsions drowsiness speech disturbance, blurred vision diplopia, mentation impaired lethargy, abnormal coordination, stupor, hypotension abdominal pain agitation, dizziness and depression. The clinical consequences were not sever in most cases, but deaths have been reported after poly-drug ovedoses involving. Topiramate overdose has resulted in severe metabolic acidosis. A patient who ingested a dose between 96 and 110g topiramate was admitted to hospital with coma lasting 20-24 hours followed, by full recovery after 3 to 4 days. In acute Topiramate ovedose, 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.

DOSAGE AND ADMINISTRATION:

Epilepsy:

Adults:
Initially dose of topiramate in adult is 25 mg once daily by mouth for 1 week increased thereafter by increments of 25 to 50 mg at interval of 1 to 2 weeks until the effective dose is reached. Daily doses of more than 25 mg should be taken in 2 divided doses.

Children:
Under 2 years: initially 25mg at night increasing at 1-2 weeks intervals by 1-3mg/kg/day increments to effective dose. Usually, 5-9mg/kg daily in 2 divided doses.

Migraine:
The recommended total daily dose of TRITOP as treatment for prophylaxis of migraine headache is 100 mg/day administered in two divided doses. The recommended titration rate for topiramate for migraine prophylaxis is 100 mg/day: Dose and titration rate should be guided by clinical outcome. If required, longer interval between dose adjustments can be used:

PRESENTATION:
TRITOP tablets 25mg are available in blisters of 2x10's
TRITOP tablets 50mg are available in blisters of 2x10's

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ٹھنڈی جگہ پر رکھیں۔
صرف رجسٹرڈ میڈیکل پریکٹشنر کے نسخے پر فروخت کریں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

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