

Use in lactating women:

Excretion of topiramate in human milk has not been studied.

Effects on driving ability and use of machinery:

Topiramate may cause drowsiness, dizziness or other related symptoms. Hence caution is advised when driving or operating machinery.

OVERDOSAGE

If overdosage with topiramate is acute i.e. recent, stomach should be immediately emptied through gastric lavage or emesis. Appropriate supportive measures should be undertaken as required. The drug can be effectively removed from the body through haemodialysis if dose exceeds 20 g.

DRUG INTERACTIONS:

Co-administration of topiramate with other antiepileptic drugs:

In general topiramate combined with other anti-epileptic drugs like phenytoin, carbamazepine, valproic acid, Phenobarbital and primidone causes no effect on their steady-state plasma concentrations. Occasionally, there may be an increase in plasma concentration of phenytoin possibly due to inhibition of specific-enzyme polymorphic isoform (CYP2Cmeph). Hence, phenytoin serum concentrations monitoring should be done in patients on phenytoin plus topiramate.

Co-administration of other antiepileptic drugs with topiramate:

There is a decrease in plasma concentration of topiramate when phenytoin or carbamazepine are co-administered with it. Hence, in case of addition or discontinuation of phenytoin or carbamazepine in patients already on topiramate therapy, the patient may need readjustment in dose of topiramate to the point of optimal seizure control. Co-administration of valproic acid does not cause any clinically significant change in plasma concentration of topiramate. Hence there is no need to adjust the dose of topiramate when co-administered with valproic acid.

USE WITH ORAL CONTRACEPTIVES

Concomitant use of topiramate causes a significant increase in plasma clearance of oestrogenic component. Hence, the patient should use a preparation containing no less than 50 micrograms of oestrogen or some other alternative including non-hormonal method of contraception. If patients taking oral contraceptives notice any change in their bleeding pattern, they should be advised to report it to the physician.

USE WITH DIGOXIN

Simultaneous administration of topiramate with digoxin causes a decrease in serum concentration of digoxin. Hence serum concentration of digoxin should be carefully monitored in such patients.

OTHERS

Concomitant use of topiramate with agents known to cause nephrolithiasis should be avoided.

Concomitant use of topiramate with alcohol or CNS depressant drugs should be avoided.

STORAGE INSTRUCTIONS

Store below 30°C in a dry place, protect from light.

To be dispensed on the prescription of registered medical practitioner only.

Keep out of the reach of children.

PRESENTATION:

Topiramate 25 mg tablets are available in Alu Alu pack of 20's.

Topiramate 50 mg tablets are available in Alu Alu pack of 20's.

Topiramate 100 mg tablets are available in Alu Alu pack of 10's.

خوراک: 10 تا 20 گولی در روز، صبح و شام، کھانا کے ساتھ۔

نوٹ: 20 گولی کی بوتلی میں گولی کے ساتھ درجہ حرارت پر خشک جگہ پر رکھیں۔

دستی سے بچا جائے۔ صرف رجسٹرڈ ڈاکٹر کے نسخے پر فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

Note: Product contains lactose.

نوٹ: ہر پوکٹ میں لکٹوز شامل ہے۔

Manufactured by:

Platinum
Pharmaceuticals (Pvt.) Ltd.

A-20, North Western Industrial Zone,
Bin Qasim, Karachi-75020, Pakistan.

Mfg. Lic No. 000415

QAR No.AW/23-1114

Topirama

(Topiramate)

Tablets 25, 50
& 100 mg

ٹوپیراما
(ٹوپیرامیٹ)

COMPOSITION

Topiramate Tablet 25 mg

Each film coated tablet contains:

Topiramate 25 mg,

Product Complies U.S.P. Specs.

Topiramate Tablet 50 mg

Each film coated tablet contains:

Topiramate 50 mg,

Product Complies U.S.P. Specs.

Topiramate Tablet 100 mg

Each film coated tablet contains:

Topiramate 100 mg,

Product Complies U.S.P. Specs.

PHARMACOLOGY

Topiramate (topiramate), a sulfamate substituted monosaccharide, is an anti-epileptic drug.

Topiramate produces its anticonvulsant activity through the following:

- Blocks non-NMDA subtype (AMPA/kainate) of glutamate receptor
- Enhanced effect of GABA
- Blocks Na⁺ channels
- Activates K⁺ conductance
- Blocks Ca²⁺ channels
- Carbonic anhydrase inhibition

PHARMACOKINETICS

Absorption of topiramate is rapid and extensive. Mean maximum plasma concentration (C_{max}) of 1.5 micrograms/ml is achieved in 2-3 hours (T_{max}) after oral administration of 100 mg topiramate. A 100 mg oral dose of ¹⁴C topiramate is absorbed >80% as deduced from its traces in urine. Presence of food has no clinically significant impact on bioavailability of topiramate. On average, 15% of topiramate is bound to plasma proteins. It has been seen that erythrocytes saturable above plasma concentrations of 4 micrograms/ml have low capacity binding sites for topiramate. Topiramate achieves volume of distribution (V_d) in inverse proportion to the dose (average V_d is 0.80 to 0.55 l/kg for a single dose ranging from 100-1200 mg. V_d for females circa 50% of those of males. This is because of higher percent of body fat in females and has no clinical significance. Metabolism of topiramate is not extensive. In patients receiving concomitant anti-epileptic therapy with known inducers of drug metabolizing enzymes, topiramate is metabolized upto 50%. At least 81% of the dose of topiramate is eliminated as unchanged drug and its metabolism via the kidney at the rate of 25 ml/min (average) after oral administration. Topiramate has predictable pharmacokinetics because of low variability in its plasma concentrations. Topiramate has linear pharmacokinetics following a single oral dose ranging from 100-400 mg. Topiramate takes 4-8 days to reach steady-state plasma concentrations with normal kidney function. After multiple dose-administration of 50 mg and 100 mg twice a day, the mean plasma elimination half-life of topiramate is approx 21 hours. Co-administration of multi-dose topiramate, 100-400 mg twice a day, with carbamazepine or phenytoin results in dose related increase in plasma concentrations of topiramate. In renal dysfunction, plasma and renal clearance of topiramate are reduced, and in end stage renal diseases its plasma clearance is decreased. Topiramate is haemodialysable. Plasma clearance is decreased in patients with moderate to severe hepatic impairment. Topiramate pharmacokinetics is linear in children (4-6 years) with dose-independent clearance and dose dependent steady-state plasma concentrations with higher clearance and shorter elimination half-life. Hence, the plasma concentrations of topiramate on mg/kg dose may be lower in children as compared to adults. In children as well, hepatic enzyme inducing anti-epileptic drugs decrease the steady state plasma concentration.

INDICATIONS AND USAGE

Monotherapy Epilepsy:

Topirama (topiramate) Tablets are indicated as initial monotherapy in patients 6 years of age and older with partial onset or primary generalized tonic-clonic seizures.

Adjunctive Therapy Epilepsy:

Topirama (topiramate) 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:

Topirama (topiramate) Tablets are indicated in adults for the prophylaxis of migraine headache. The usefulness of topiramate in the acute treatment of migraine has not been studied.

CONTRAINDICATION

Hypersensitivity to any ingredient of the product.

DOSAGE AND ADMINISTRATION

Epilepsy

Monotherapy:

Adults and Children (Age 6 years and older)

The recommended initial target dose of topiramate monotherapy in adults and children 6 years of age and older is 100 mg/day and the maximum recommended dose is 400 mg/day, administered in two divided doses, as needed and tolerated. The recommended titration rate for topiramate monotherapy to 100 mg/day is:

Duration	Morning Dose	Evening Dose
Week 1	None	25 mg
Week 2-3	25 mg	25 mg
Week 3-4	50 mg	50 mg

If doses above 100 mg/day are required, the dose may be increased at weekly intervals in increments of 50 mg/day to a maximum of 400 mg/day. Dose and titration rate should be guided by clinical outcome. Some patients may benefit from a slower titration schedule. Daily doses above 400 mg have not been adequately studied.

Adjunctive Therapy

Adults (Age 17 years and older)

It is recommended that Topirama (Topiramate) as adjunctive therapy be initiated at 50 mg/day, followed by titration as needed and tolerated to an effective dose. At weekly intervals, the dose may be increased by 50 mg/day and taken in two divided doses. Some patients may benefit from lower initial doses, e.g. 25 mg and/or a slower titration schedule. Some patients may achieve efficacy with once-a-day dosing.

The recommended total daily maintenance dose is 200-400 mg/day in two divided doses. Doses above 400 mg/day have not been shown to improve responses and have been associated with greater incidence of adverse events. The maximum recommended dose is 800 mg/day. Daily doses above 1,600 mg have not been studied.

Children (Ages 2-16 years)

It is recommended that Topirama (Topiramate) as adjunctive therapy be initiated at 25 mg (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week followed by titration at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses). Some patients may benefit from lower initial doses and /or a slower titration schedule.

The recommended total daily maintenance dose is approximately 5 to 9 mg/kg/day in two divided doses.

Migraine

Adults

The recommended total daily dose of Topirama (topiramate) 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 to 100 mg/day is:

Duration	Morning Dose	Evening Dose
Week 1	None	25 mg
Week 2	25 mg	25 mg
Week 3	25 mg	50 mg
Week 4	50 mg	50 mg

Dose and titration rate should be guided by clinical outcome. If required, longer intervals between dose adjustments can be used.

SIDE- EFFECTS

Most common side effects in adults with topiramate are somnolence, fatigue, nervousness, psychomotor slowing, paresthesia, ataxia, dizziness, taste perversion, difficulty with memory, confusion, speech disorders/related speech problems, difficulty with concentration/attention, weight decrease, anorexia, nausea, abnormal vision. Nystagmus, depression, diplopia, language problems, tremor, mood problems, abdominal pain, dyspepsia, rhinitis, asthesia and pharyngitis.

Less frequently reported side effects are agitation, cognitive problems, emotional lability, coordination problems, abnormal gait, apathy, psychosis/psychotic symptoms, psychomotor slowing, confusion, hallucination, depression, aggressive reaction/behavior, leucopenia and nephrolithiasis.

Most common side effects in children are somnolence, anorexia, fatigue, nervousness, injury, personality changes, difficulty with concentration/attention, aggressive reaction, weight decrease, insomnia, abnormal gait, purpura, mood problems, viral infection, ataxia, increased salivation, nausea, pneumonia, hyperkinesias, constipation, dizziness, speech disorders/related speech psychomotor slowing and paraesthesia. Few cases of thromboembolic events have been seen through their causal relationship with topiramate is not proven.

PRECAUTIONS

*Topiramate, like other antiepileptic drugs, should be slowly withdrawn to minimize the seizure frequency. In some clinical trials on adult patients, topiramate was withdrawn at the rate of 100 mg/day every week. In some patients, withdrawal can be done at a faster rate without any complications.

* Patients with moderate or severe renal impairment may take 10-15 days to reach steady-state plasma concentrations as compared to 4 to 8 days in patients with normal renal function.

* Topiramate should be titrated with the objective of achieving optimal seizure control and side effect avoidance.

*There might be increased risk of renal stone formation, especially in those who have a tendency towards nephrolithiasis or who are exposed to risk factors like family history of nephrolithiasis, hypercalciuria and intake of medication associated with nephrolithiasis. However these risk factors can not reliably predict stone formation during topiramate treatment.

* In hepatic dysfunction, Topirama should be administered with caution since in this condition clearance of topiramate may be reduced.

Use in pregnancy:

Studies have not been conducted on topiramate use in pregnant women. Hence, safety in pregnancy has not been established. Some cases of hypospadias have been reported in male infants who were exposed to topiramate in utero, alone or combined with other anticonvulsants. However, a causal relationship of this complication with topiramate is not proven.