PACKAGE INSERT TEMPLATE FOR TOPIRAMATE TABLET

Brand or Product Name
[Product name] Tablet 25mg
[Product name] Tablet 50mg
[Product name] Tablet 100mg

Name and Strength of Active Substance(s)

Topiramate …mg

Product Description
[Visual description of the appearance of the product (eg colour, markings etc)
eg White, circular flat beveled edge film-coated tablets marked '100' on one side

Pharmacodynamics
Topiramate is a sulfamate-substituted monosaccharide. The exact mechanism of action is unknown, but four properties that may contribute to topiramate's antiepileptic and antimigraine efficacy include a blockage of voltage-dependent sodium channels, an augmentation of gamma-aminobutyrate acid activity at some subtypes of the GABA- A receptors, antagonism of AMPA/kainate subtype of the glutamate receptor, and inhibition of the carbonic anhydrase enzyme, particularly isozymes II and IV

Pharmacokinetics
The pharmacokinetics of topiramate may be affected when used with other antiepileptics

Absorption
Absorption of topiramate is rapid. Topiramate is readily absorbed after oral doses, with peak plasma concentrations occurring after about 2 hours. The relative bioavailability of the tablet is about 80% compared to solution. Bioavailability is not affected by the presence of food.

Distribution
Topiramate is only minimally bound to plasma proteins (9% to 17%); however, the drug exhibits significant binding to erythrocytes.
Volume of Distribution: 0.6 to 0.8 L/kg. The volume of distribution in women is about half that in men. Topiramate crosses the placental barrier and is distributed into breast milk.

Metabolism

Topiramate is not extensively metabolized in the liver, and undergoes hydroxylation, hydrolysis and glucuronidation

Elimination
It is eliminated chiefly in urine, as unchanged drug and metabolites; mean plasma elimination half-life is about 21 hours. Steady-state concentrations occur after about 4 to 8 days in patients with normal renal function. Clearance is decreased in patients with impaired renal or hepatic function, and steady-state plasma concentrations may not occur for 10 to 15 days in the former. Children exhibit a higher clearance and shorter elimination half-life than adults.

Indication
Epilepsy
As monotherapy in patients with newly diagnosed epilepsy or for conversion to monotherapy in patients with epilepsy.
As adjunctive therapy for adults and children 2 years and above with partial onset seizures or generalized tonic-clonic seizures.
Indicated in adults and children as adjunctive therapy for the treatment of seizures associated with Lennox Gastaut syndrome.

Migraine
Indicated in adults for the prophylaxis of migraine headache.

Recommended Dosage
It is recommended that therapy be initiated at a low dose followed by titration to an effective dose.

Adults
Therapy should begin at 25 - 50mg nightly for one week. Use of lower initial doses has been reported, but has not been studied systematically. Subsequently, at weekly or bi-weekly intervals, the dose should be increased by 25 – 50 to 100 mg/day and taken in two divided doses.
Dose titration should be guided by clinical outcome. Some patients may achieve efficacy with once-a-day dosing.

As adjunctive therapy, the usual daily dose is 200-400 mg in two divided doses. Individual patients have received doses as high as 1600 mg/day.

Since topiramate is removed from plasma by hemodialysis, a supplemental dose of equal to approximately one-half the daily dose should be administered on hemodialysis days. The supplemental dose should be administered in divided doses at the beginning and completion of

the hemodialysis procedure. The supplemental dose may differ based on the characteristics of the dialysis equipment being used.
These dosing recommendations apply to all adults, including elderly, in the absence of underlying renal disease.

Children aged 2 and above
The recommended total daily dose of topiramate as adjunctive therapy 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 3mg/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. Daily doses up to 30 mg/kg/day have been studied and were generally well tolerated.

Monotherapy

Epilepsy
General
When concomitant antiepileptic drug(AED)s are withdrawn to achieve monotherapy with topiramate, consideration should be given to the effects this may have on seizure control. Unless safety concerns require an abrupt withdrawal of the concomitant AED, a gradual discontinuation at the rate of approximately one-third of the concomitant AED dose every 2 weeks is recommended.
When enzyme inducing drugs are withdrawn, topiramate levels will increase.
A decrease in topiramate dosage may be required if clinically indicated.

Adults
Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased at 1- or 2- week intervals by increments of 25 or 50 mg/day, administered in two divided doses. If the patient is unable to tolerate the titration regimen, smaller increments or longer intervals between increments can be used.
Dose and titration rate should be guided by clinical outcome.
The recommended initial target dose for topiramate monotherapy in adults is 100 mg/day and the maximum recommended daily dose is 500 mg. Some patients with refractory forms of epilepsy have tolerated topiramate monotherapy at doses of 1,000 mg/day. These dosing recommendations apply to all adults including the elderly in the absence of underlying renal disease.

Children

Treatment of children aged 2 years and above should begin at 0.5 to 1 mg/kg nightly for the first week. The dosage should then be increased at 1- or 2- week intervals by increments of 0.5 to 1 mg/kg/day, administered in two divided doses. If the child is unable to tolerate the titration regimen, smaller increments or longer intervals between dose increments can be used. Dose and dose titration rate should be guided by clinical outcome.
The recommended initial target dose range for topiramate monotherapy in children aged two years and above is 3 to 6 mg/kg/day. Children with recently diagnosed partial onset seizures have received doses of up to 500 mg/day.

Migraine
The recommended total daily dose of topiramate for prophylaxis of migraine headache is 100 mg/day administered in two divided doses. Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased in increments of 25 mg/day administered at 1-week intervals. If the patient is unable to tolerate the titration regimen, longer intervals between dose adjustments can be used.
Some patients may experience a benefit at a total daily dose of 50 mg/day. Patients have received a total daily dose up to 200 mg/day. Dose and titration rate should be guided by clinical outcome

Mode of Administration
Oral

Contraindications
Hypersensitivity to any component of this product

Warnings and Precautions
- Topiramate should be used with caution in patients with renal or hepatic impairment. Adequate hydration is recommended to reduce the risk of developing renal calculi, especially in predisposed patients. *In* moderate to severe renal impairment, there is risk of drug toxicity; dose reduction may be necessary
- Topiramate should be administered with caution in patients with hepatic impairment as the clearance of topiramate may be decreased
- Abrupt withdrawal may increase seizure frequency in patients with or without history of seizures/epilepsy; should be gradually withdrawn; if sudden discontinuation is required, monitoring is recommended
- Concomitant use of alcohol or other CNS depressants; use extreme caution
- Concomitant use of drugs that induce metabolic acidosis, including other carbonic anhydrase inhibitors (eg, zonisamide, or acetazolamide) should be avoided

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- Concomitant use of topiramate with valproic acid; associated with hyperammonemia with or without encephalopathy and hypothermia with or without hyperammonemia
- Metabolic acidosis has been reported; increased risk in patients with conditions or therapies that predispose to acidosis (eg, renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or drugs); monitoring recommended and dose reduction may be necessary
- Acute myopia and myopia associated with secondary angle closure glaucoma, has been reported; drug discontinuation recommended
- Oligohidrosis and hyperthermia have been reported; increased risk in pediatric patients; monitoring recommended
- An increased incidence of mood disturbances and depression has been observed during topiramate treatment
- Increase the risk of suicidal thoughts or behavior; monitoring recommended

Effects on the ability to drive and use machines

Driving by patients with epilepsy is generally regulated and restricted to those whose seizures are adequately controlled. Also, antiepileptic drugs may produce central nervous system(CNS)-related adverse effects, including dizziness and drowsiness that could impair a patient's ability to drive a vehicle or operate machinery, particularly during the initial stages of therapy.

Interactions with Other Medicaments

Effects of Topiramate on Other Antiepileptic Drugs:
The addition of topiramate to other antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no 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.

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

Oral Contraceptives
Topiramate increased plasma clearance of the oestrogenic component significantly. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns.

Concurrent use of anticonvulsants and the following drugs may result in reduced anticonvulsant effectiveness.

- naproxen
- ketorolac
- ginkgo
- evening primrose oil

Concurrent use of metformin and topiramate may result in additive risk of lactic acidosis.

Concurrent use of citalopram and topiramate may result in increased citalopram exposure and risk of QT interval prolongation.

Concurrent use of posaconazole and topiramate may result in elevated topiramate plasma concentrations and topiramate toxicity.

Concurrent use of pioglitazone and topiramate and may result in decreased pioglitazone exposure

Concurrent use of amitriptyline and topiramate may result in increased amitriptyline exposure.

Concurrent use of hydrochlorothiazide and topiramate may result in increased topiramate exposure.

Others: Topiramate when used concomitantly with other agents (e.g dorzolamide, acetazolamide) 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.

Statement on Usage During Pregnancy and Lactation

Pregnancy
There are no adequate and well-controlled studies using topiramate in pregnant women.
Topiramate should be used during pregnancy only if potential benefit justifies the potential risk to the fetus. The prescribing physician should weigh the benefits of therapy against the risks in treating and counseling women of childbearing potential,. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Lactation
Topiramate is excreted in the milk of lactating rats. It is not known if topiramate is excreted in human milk. Since many drugs are excreted in human milk, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into consideration the importance of the drug to the mother.

Adverse Effects / Undesirable Effects

Common

- **Dermatologic:** Flushing
- **Gastrointestinal:** Diarrhea , Loss of appetite, Nausea ,Taste sense altered ,Weight decreased
- **Neurologic:** Confusion , Dizziness , Impaired psychomotor performance , Memory impairment , Paresthesia , Reduced concentration span , Somnolence , Speech and language disorder
- **Ophthalmic:** Abnormal vision , Diplopia , Nystagmus
- **Psychiatric:** Feeling nervous
- **Reproductive:** Bleeding between periods
- **Respiratory:** Upper respiratory infection
- **Other:** Fatigue , Fever

Serious

- **Dermatologic:** Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis
- **Endocrine metabolic:** Hyperammonemia, with or without encephalopathy, Hypohidrosis, Increased body temperature, Metabolic acidosis
- **Hepatic:** Liver failure

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- **Ophthalmic:** Glaucoma, Myopia
- **Psychiatric:** Depression, Mood disorder , Suicidal thoughts
- **Renal:** Nephrolithiasis

Overdose and Treatment
Overdose is rare. In most cases, acute exposure produced only minimal to moderate effects. Fatalities have occurred, but were the result of polydrug exposure.

Symptoms
Convulsions, drowsiness, speech disturbances, blurred vision, diplopia, mentation impaired, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. Topiramate overdose can result in severe metabolic acidosis

Treatment
Treatment is symptomatic and supportive. In acute topiramate overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal may be considered in patients who are alert or in whom the airway is protected. Hemodialysis may be useful following a significant exposure because it is easily cleared by hemodialysis and minimally bound to plasma proteins

Storage Conditions
[eg Store below….°C]

Dosage Forms and Packaging Available
[Packaging type & pack size]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]

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