TOMIGRAINE Tablet ٹومیگرین ٹیبلیٹ

(Topiramate)

COMPOSITION

Each film coated tablet contains:

Topiramate....25mg

Topiramate....50mg

Topiramate....100mg

Topiramate....200mg

THERAPEUTIC INDICATIONS

Epilepsy
TOMIGRAINE (Topiramate) is indicated as monotherapy in adults and children aged 6 years and above with newly diagnosed epilepsy who have generalised tonic-clonic seizures or partial seizures with or without secondarily generalised seizures.
TOMIGRAINE is indicated as adjunctive therapy for adults and children over 2 years of age who are inadequately controlled on conventional first line antiepileptic drugs for: partial seizures with or without secondarily generalised seizures; seizures associated with Lennox Gastaut Syndrome and primary generalised tonic-clonic seizures.

Migraine
TOMIGRAINE is indicated in adults for the prophylaxis of migraine headache. Initiation of treatment with TOMIGRAINE should be restricted to specialist care and treatment should be managed under specialist supervision or shared care arrangements.
Prophylactic treatment of migraine may be considered in situations such as: Adults experiencing three or more migraine attacks per month; frequent migraine attacks that significantly interfere with the patient's daily routine.
Continuing therapy should be reviewed every six months.
The usefulness of TOMIGRAINE in the acute treatment of migraine has not been studied.

DOSAGE AND METHOD OF ADMINISTRATION

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. TOMIGRAINE can be taken without regard to meals. The dosing recommendations apply to children and to all adults, including the elderly, in the absence of underlying renal disease.
Since TOMIGRAINE is removed from plasma by haemodialysis, a supplemental dose of TOMIGRAINE equal to approximately one-half 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.

Epilepsy

a) Monotherapy
Adults and children over 16 years
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 TOMIGRAINE monotherapy in adults with newly diagnosed epilepsy is 100 mg/day and the maximum recommended daily dose is 400 mg. These dosing recommendations apply to all adults including the elderly in the absence of underlying renal disease.

Children aged 6-16 years
Treatment of children aged 6 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 TOMIGRAINE monotherapy in children with newly diagnosed epilepsy aged 6 years and above is 3 to 6 mg/kg/day. Higher doses have been tolerated and rarely doses up to 16 mg/kg/day have been given.
The tablet formulations are not appropriate for children requiring doses of less than 25 mg/day.

b) Adjunctive Therapy
Adults and children over 16 years
The minimal effective dose as adjunctive therapy is 200 mg per day. The usual total daily dose is 200 mg to 400 mg in two divided doses. Some patients may require doses up to 800 mg per day, which is the maximum recommended dose. It is recommended that therapy be initiated at a low dose, followed by titration to an effective dose.
Titration should begin at 25 mg daily for one week. The total daily dose should then be increased by 25-50 mg increments at one to two weekly intervals and should be taken in two divided doses. If the patient is unable to tolerate the titration regimen then lower increments or longer intervals between increments may be used. Dose titration should be guided by clinical outcome.

Children aged 2 - 16 years
The recommended total daily dose of TOMIGRAINE as adjunctive therapy is approximately 5 to 9 mg/kg/day in two divided doses. Titration should begin at 25 mg 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.

Migraine
Adults and children over 16 years
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.
The recommended total daily dose of TOMIGRAINE as treatment for the prophylaxis of migraine headache is 100 mg/day administered in two divided doses. Some patients may experience a benefit at a total daily dose of 50 mg/day. No extra benefit has been demonstrated from the administration of doses higher than 100 mg/day. Dose and titration rate should be guided by clinical outcome.

Children
TOMIGRAINE in migraine prophylaxis has not been studied in children under 16 years.

CONTRAINDICATIONS
Hypersensitivity to any component of this product.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In patients with or without a history of seizures or epilepsy, antiepileptic drugs, including TOMIGRAINE, should be gradually withdrawn to minimise the potential for seizures or increased seizure frequency. In clinical trials of children, TOMIGRAINE was gradually withdrawn over a 2-8 week period. In situations where rapid withdrawal of TOMIGRAINE is medically required, appropriate monitoring is recommended.

The major route of elimination of unchanged TOMIGRAINE and its metabolites is via the kidney. Renal elimination is dependent on renal function and is independent of age. Patients with moderate or severe renal impairment may take 10 to 15 days to reach steady-state plasma concentrations as compared to 4 to 8 days in patients with normal renal function.
Some patients, especially those with a predisposition to nephrolithiasis, may be at increased risk for renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain. Adequate hydration whilst using TOMIGRAINE is very important as it can reduce the risk of developing renal stones. In hepatically impaired patients, TOMIGRAINE should be administered with caution as the clearance of TOMIGRAINE may be decreased.
Depression and mood alterations have been reported in patients treated with TOMIGRAINE. Patients should be monitored for signs of depression and referred for appropriate treatment if necessary. Patients (and caregivers of patients) should be advised to seek medical advice immediately should suicidal thoughts emerge.
In accordance with good clinical practice, patients with a history of depression and/or suicidal behaviour, adolescents and young adults may be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.
Acute myopia with secondary angle-closure glaucoma has been reported rarely in both children and adults receiving TOMIGRAINE. Symptoms typically occur within 1 month of the start of treatment and include decreased visual acuity and/or ocular pain. Ophthalmological findings include bilateral myopia, anterior chamber shallowing, hyperaemia and increased intra-ocular pressure with or without mydriasis. There may be supraciliary effusion resulting in anterior displacement of the lens and iris. Treatment includes discontinuation of TOMIGRAINE as rapidly as is clinically feasible and appropriate measures to reduce intraocular pressure.

Metabolic Acidosis: Hyperchloraemic, non-anion gap, metabolic acidosis i.e. decreased serum bicarbonate below the normal reference range in the absence of respiratory alkalosis) is associated with TOMIGRAINE treatment. Chronic metabolic acidosis in paediatric patients can reduce growth rates. Depending on underlying conditions, appropriate evaluation including serum bicarbonate levels is recommended with TOMIGRAINE therapy. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing TOMIGRAINE (using dose tapering).
A dietary supplement or increased food intake may be considered if the patient is losing weight or has inadequate weight gain while on this medication.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Migraine Prophylaxis
In migraine prophylaxis, before discontinuation of treatment, dosage should be gradually reduced over at least 2 weeks to minimise the possibility of rebound migraine headaches.

Weight loss
During the double-blind treatment with TOMIGRAINE 100 mg/day, the mean change from baseline to the final visit in body weight was -2.5 kg, compared to -0.1 kg in the placebo group. Overall, 68% of patients treated with TOMIGRAINE 100 mg/day lost weight during the trials, compared to 33% of patients receiving placebo. It is recommended that patients on long term TOMIGRAINE for migraine prophylaxis should be regularly weighed and monitored for continuing weight loss.

DRUG INTERACTIONS

Effects of TOMIGRAINE on Other Antiepileptic Drugs.
The addition of TOMIGRAINE to other antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no clinically significant effect on their steady-state plasma concentrations, except in some patients where the addition of TOMIGRAINE to phenytoin may result in an increase of plasma concentrations of phenytoin.
A pharmacokinetic interaction study of patients with epilepsy indicated the addition of TOMIGRAINE to lamotrigine had no effect on steady state plasma concentration of lamotrigine at TOMIGRAINE doses of 100 to 400 mg/day.
Phenytoin and carbamazepine decrease the plasma concentration of TOMIGRAINE. The addition or withdrawal of phenytoin or carbamazepine to TOMIGRAINE therapy may require an adjustment in dosage of the latter.
The addition or withdrawal of valproic acid does not produce clinically significant changes in plasma concentrations of TOMIGRAINE and, therefore, does not warrant dosage adjustment of TOMIGRAINE.

OTHER DRUG INTERACTIONS
When TOMIGRAINE is added or withdrawn in patients on digoxin therapy, careful attention should be given to the routine monitoring of serum digoxin.

CNS Depressants:
Concomitant administration of TOMIGRAINE and alcohol or other CNS depressant drugs has not been evaluated in clinical studies.

Oral Contraceptives:
TOMIGRAINE increases plasma clearance of the oestrogenic component significantly. Consequently, and bearing in mind the potential risk of teratogenicity, patients should receive a preparation containing not less than 50 µg of oestrogen or use some alternative non-hormonal method of contraception.

Lithium:
Lithium levels should be monitored when co-administered with TOMIGRAINE.

Hydrochlorothiazide (HCTZ):
Clinical laboratory results indicated decreases in serum potassium after TOMIGRAINE or HCTZ administration, which were greater when HCTZ and TOMIGRAINE were administered in combination.

Metformin:
Careful attention should be given to the routine monitoring for adequate control of the diabetic disease state.

Pioglitazone:
Careful attention should be given to the routine monitoring for adequate control of the diabetic disease state.

Glibenclamide:
Careful attention should be given to the routine monitoring for adequate control of the diabetic disease state.

Others:
TOMIGRAINE, when used concomitantly with other agents predisposing to nephrolithiasis, may increase the risk of nephrolithiasis. While using TOMIGRAINE, agents like these should be avoided since they may create a physiological environment that increases the risk of renal stone formation.

Valproic Acid:
Concomitant administration of TOMIGRAINE and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone.

PREGNANCY AND LACTATION

TOMIGRAINE was teratogenic in mice, rats and rabbits. In rats, TOMIGRAINE crosses the placental barrier. There are no studies using TOMIGRAINE in pregnant women. However, TOMIGRAINE should not be used during pregnancy unless, in the opinion of the physician, the potential benefit outweighs the potential risk to the foetus.

Before starting TOMIGRAINE, women of childbearing potential should be fully informed of the possible effects of TOMIGRAINE on the unborn foetus and the risks should be discussed with the patient in relation to the benefits of TOMIGRAINE treatment in migraine prophylaxis.

It is recommended that women of child bearing potential use adequate contraception.

TOMIGRAINE should not be used during breast feeding.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

TOMIGRAINE can produce central nervous system related adverse events and may be more sedative than other antiepileptic drugs. Drowsiness is a likelihood. In addition, there have been reports of visual disturbances/blurred vision. Patients should be warned of these and advised that if affected, they should not drive, operate machinery and/or take part in activities where such reactions could put themselves or others at risk.

SIDE EFFECTS

Reported adverse events were classified using a modified WHO-ART dictionary. The majority of the most common adverse events in clinical trials were mild-moderate in severity and dose-related.

Epilepsy
a) Monotherapy
The types of adverse events observed in monotherapy trials were similar to those observed during adjunctive therapy trials. With the exception of paraesthesia and fatigue in adults, these adverse events were reported at similar or lower incidence rates in monotherapy trials.

Adults:
The most common adverse events, i.e., those occurring in 10% or more of the TOMIGRAINE-treated adult patients were paraesthesia, headache, fatigue, dizziness, somnolence, weight decrease, nausea and anorexia.
Adverse events occurring at 5% or more but less than 10% included: insomnia, difficulty with memory, depression, difficulty with concentration/attention, abdominal pain, nervousness, hypoaesthesia, mood problems and anxiety.

Children:
The most common adverse events, i.e., those occurring in 10% or more of the TOMIGRAINE-treated children were headache, anorexia and somnolence.
Adverse events occurring at 5% or more but less than 10% included: difficulty with concentration/attention, fatigue, weight decrease, dizziness, paraesthesia, insomnia and nervousness.

b) Adjunctive Therapy
Adults:
Since TOMIGRAINE has most frequently been co-administered with other antiepileptic agents, it is not possible to determine which agents, if any, are associated with adverse effects. Adverse events which occurred with a frequency greater than or equal to 5% included: abdominal pain, ataxia, anorexia, asthenia, confusion, difficulty with concentration/attention, difficulty with memory, diplopia, dizziness, fatigue, language problems, nausea, nystagmus, paraesthesia, psychomotor slowing, somnolence, speech disorders/related speech problems, abnormal vision and weight decrease. TOMIGRAINE may cause agitation and emotional lability (which may manifest mood problems and nervousness) and depression. Other less common adverse effects include, gait abnormal, aggressive reaction, apathy, cognitive problems, co-ordination problems, leucopenia, psychotic symptoms (such as hallucinations) and taste perversion.
Isolated cases of venous thromboembolic events have been reported. A causal association with the drug has not been established.
Reports of increases in liver enzymes in patients taking TOMIGRAINE with and without other medications have been received. Isolated reports have been received of hepatitis and hepatic failure occurring in patients taking multiple medications while being treated with TOMIGRAINE.

Children
Adverse events which occurred with a frequency greater than or equal to 5% included: somnolence, anorexia, fatigue, insomnia, nervousness, personality disorder (behaviour problems), difficulty with concentration/attention, aggressive reaction, weight decrease, gait abnormal, mood problems, ataxia, saliva increased, nausea, difficulty with memory, hyperkinesia, dizziness, speech disorders/related speech problems and paraesthesia.
Adverse events that occurred less frequently but were considered potentially medically relevant included: emotional lability, agitation, apathy, cognitive problems, psychomotor slowing, confusion, hallucination, depression and leucopenia.

Migraine prophylaxis
Adverse events which occurred at a frequency of 5% or more included: fatigue, paraesthesia, dizziness, hypoaesthesia, language problems, nausea, diarrhoea, dyspepsia, dry mouth, weight decrease, anorexia, somnolence, difficulty with memory, difficulty with concentration/attention, insomnia, anxiety, mood problems, depression, taste perversion, abnormal vision. Fifty per cent of patients experienced paraesthesia.

Children
The effect of TOMIGRAINE in children less than 16 years old with migraine has not been studied.

OVERDOSE

Signs and Symptoms
Signs and symptoms included convulsions, drowsiness, speech disturbances, blurred vision, diplopia, mentation impaired, lethargy, abnormal co-ordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. TOMIGRAINE overdose can result in severe metabolic acidosis.

Treatment
In acute TOMIGRAINE 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 TOMIGRAINE in vitro. Treatment should be appropriately supportive. Haemodialysis has been shown to be an effective means of removing TOMIGRAINE from the body. The patient should be well hydrated.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
TOMIGRAINE is classified as a sulphamate-substituted monosaccharide. Three pharmacological properties of TOMIGRAINE have been identified that may contribute to its anticonvulsant activity: TOMIGRAINE reduces the frequency at which action potentials are generated when neurones are subjected to a sustained depolarisation indicative of a state-dependent blockade of voltage-sensitive sodium channels. TOMIGRAINE markedly enhances the activity of GABA at some types of GABA receptors but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype. TOMIGRAINE weakly antagonises the excitatory activity of kainate/AMPA subtype of glutamate receptor. In addition, TOMIGRAINE inhibits some isoenzymes of carbonic anhydrase. This pharmacologic effect is much weaker than that of acetazolamide, a known carbonic anhydrase inhibitor, and is not thought to be a major component of TOMIGRAINE's antiepileptic activity.

Pharmacokinetic properties
TOMIGRAINE is rapidly and well absorbed. There is no clinically significant effect of food on TOMIGRAINE.
Generally 13-17% of TOMIGRAINE is bound to plasma proteins.
TOMIGRAINE is not extensively metabolised. The major route of elimination of unchanged TOMIGRAINE and its metabolites is via the kidney.
Following administration of multiple doses of 50 mg and 100 mg of TOMIGRAINE twice a day, the mean plasma elimination half-life was approximately 21 hours.
The plasma and renal clearance of TOMIGRAINE are decreased in patients with impaired renal function (CLCR < 60 mL/min), and the plasma clearance is decreased in patients with end-stage renal disease. Plasma clearance of TOMIGRAINE is unchanged in elderly subjects in the absence of underlying renal disease.
Plasma clearance of TOMIGRAINE is decreased in patients with moderate to severe hepatic impairment.

PRESENTATION

TOMIGRAINE tablets are available as:
25mg in the blister pack of 6 X 10's tablets
50mg in the blister pack of 6 X 10's tablets
100mg in the blister pack of 3 X 10's tablets
200mg in the blister pack of 3 X 10's tablets

INSTRUCTIONS

To be sold on the prescription of a registered medical practitioner only.
Avoid exposure to heat and light.
Store below 30 ^{o}C.
Keep out of the reach of children.

خوراک:
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔
دوا کو دھوپ اور گرمی سے بچائیں۔
۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
بچوں کی پہنچ سے دور رکھیں۔

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