Epilepsy indication
It is recommended to consider alternative therapeutic options in women of childbearing potential. If Topiramate is used in women of childbearing potential, it is recommended that highly effective contraception be used, and that the woman is fully informed of the known risks of uncontrolled epilepsy to the pregnancy and the potential risks of the medicinal product to the fetus. If a woman plans a pregnancy, a preconceptional visit is recommended in order to reassess the treatment, and to consider other therapeutic options. In case of administration during the first trimester, careful prenatal monitoring should be performed.

Migraine prophylaxis indication
Topiramate is contraindicated in pregnancy and in women of childbearing potential if a highly effective method of contraception is not used.

Risk related to epilepsy and AEDs in general
Specialist advice should be given to women who are of childbearing potential. The need for treatment with AEDs should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, sudden discontinuation of AED therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child. Monotherapy should be preferred whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated antiepileptics. Topiramate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In treating and counseling women of childbearing potential, the prescribing physician should weigh the benefits of therapy against the risks and consider alternative therapeutic options. 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.

Breastfeeding
The excretion of Topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggest an extensive excretion of Topiramate into breast milk. Diarrhea and somnolence have been reported in breastfed infants whose mothers receive Topiramate treatment. Therefore, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the benefit of breast-feeding for the child and the benefit of the drug to the mother.

♦ SIDE EFFECT:
Adverse reactions are adverse events that were considered to be reasonably associated with the use of Topiramate based on the comprehensive assessment of the available adverse event information. A causal relationship with Topiramate cannot be reliably established in individual cases.

Tabulated list of adverse reactions in Adult patients

System Organ Class	Adverse Reactions
Blood and Lymphatic System Disorders	Leukopenia, lymphadenopathy, thrombocytopenia
Immune System Disorders	Hypersensitivity
Metabolism and Nutrition Disorders	Acidosis hyperchloremic, hypokalemia, increased appetite, metabolic acidosis, polydipsia
Psychiatric Disorders	Abnormal behavior, anorgasmia, apathy, crying, distractibility, disturbance in sexual arousal, dysphemia, early morning awakening, elevated mood, euphoric mood, flat affect, hallucination, hallucination-auditory, hallucination-visual, hypomania, initial insomnia, lack of spontaneous speech, libido decreased, listless, loss of libido, mania, middle insomnia, orgasmic sensation decreased, panic attack, panic disorder, panic reaction, paranoia, perseveration, reading disorder, restlessness, sleep disorder, suicidal ideation, suicide attempt, tearfulness, thinking abnormal
Nervous System Disorders	Ageusia, akinesia, anosmia, aphasia, apraxia, aura, burning sensation, cerebellar syndrome, circadian rhythm sleep disorder, clumsiness, complex partial seizure convulsion, depressed level of consciousness, dizziness postural, drooling, dysesthesia, dysgraphia, dyskinesia, dysphasia, dystonia, essential tremor, formication, grand mal convulsion, hyperesthesia, hypersomnia, hypogeusia, hypokinesia, hyposmia, neuropathy peripheral, parosmia, poor quality sleep, presyncope, repetitive speech, sensory disturbance, sensory loss, stupor, syncope, unresponsive to stimuli
Eye Disorders	Accommodation disorder, altered visual depth perception, amblyopia, blepharospasm, blindness transient, blindness unilateral, glaucoma, lacrimation increased, mydriasis, night blindness, photopsia, presbyopia, scintillating scotoma, scotoma, visual acuity reduced
Ear and Labyrinth Disorders	Deafness, deafness neurosensory, deafness unilateral, ear discomfort, hearing impaired
Cardiac Disorders	Bradycardia, sinus bradycardia, palpitations
Vascular Disorders	Flushing, hot flush, orthostatic hypotension, Raynaud's phenomenon
Respiratory, Thoracic, and Mediastinal Disorders	Dysphonia, dyspnea exertional, nasal congestion, paranasal sinus hypersecretion
Gastrointestinal Disorders	Abdominal discomfort, abdominal pain lower, abdominal tenderness, breath odor, epigastric discomfort, flatulence, glossodynia, hypoesthesia oral, oral pain, pancreatitis, salivary hypersecretion
Skin and Subcutaneous Tissue Disorders	Anhidrosis, dermatitis allergic, erythema, rash macular, skin discoloration, skin odor abnormal, swelling face, urticaria, urticaria localized
Musculoskeletal and Connective Tissue Disorders	Flank pain, muscle fatigue, muscular weakness, musculoskeletal stiffness
Renal and Urinary Disorders	Calculus ureteric, calculus urinary, hematuria, incontinence, micturition urgency, renal colic, renal pain, urinary incontinence Very rare: Nephrocalcinosis
Reproductive System and Breast Disorders	Sexual dysfunction
General Disorders	Face edema, feeling abnormal, feeling drunk, feeling jittery, malaise, peripheral coldness, sluggishness
Investigations	Blood bicarbonate decreased, crystal urine present, tandem gait test abnormal, white blood cell count decreased

Tabulated list of adverse reactions in Pediatric patients

System Organ Class	Adverse Reactions
Blood and Lymphatic System Disorders	Eosinophilia, leucopenia, lymphadenopathy, thrombocytopenia
Immune System Disorders	Hypersensitivity
Metabolism and Nutrition Disorders	Acidosis hyperchloremic, hypokalemia, increased appetite
Psychiatric Disorders	Anger, apathy, crying, distractibility, expressive language disorder, initial insomnia, insomnia, middle insomnia, mood swings, perseveration, sleep disorder, suicidal ideation, suicide attempt
Nervous System Disorders	Circadian rhythm sleep disorder, convulsion, dysarthria, dysgeusia, grand mal convulsion, hypoesthesia, mental impairment, nystagmus, parosmia, poor quality sleep, psychomotor hyperactivity, psychomotor skills impaired, syncope, tremor
Eye Disorders	Diplopia, lacrimation increased, vision blurred
Ear and Labyrinth Disorders	Ear pain
Cardiac Disorders	Palpitations, sinus bradycardia
Vascular Disorders	Orthostatic hypotension
Respiratory, Thoracic, and Mediastinal Disorders	Nasal congestion, paranasal sinus hypersecretion, rhinorrhea
Gastrointestinal Disorders	Abdominal discomfort, abdominal pain, dry mouth, flatulence, gastritis, gastroesophageal reflux disease, gingival bleeding, glossodynia, pancreatitis, paresthesia oral, stomach discomfort
Musculoskeletal and Connective Tissue Disorders	Arthralgia, musculoskeletal stiffness, myalgia
Renal and Urinary Disorders	Incontinence, micturition urgency, pollakiuria
General Disorders	Feeling abnormal, hyperthermia, malaise, sluggishness

Post-marketing data
Adverse events first identified as adverse reactions during post-marketing experience with Topiramate tablet are included in table below. In each table, the frequencies are provided according to the following convention:
Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1000 to <1/100
Rare ≥1/10000 to <1/1000
Very rare <1/10000, including isolated reports

Adverse Reactions Identified During Post-marketing Experience with Topiramate tablet by Frequency Category Estimated from Spontaneous Reporting Rates

Infections and Infestations	
Very rare	Nasopharyngitis
Blood and Lymphatic System Disorders	
Very rare	Neutropenia
Immune System Disorders	
Very rare	Allergic edema
Metabolism and Nutrition Disorder	
Very rare	Hyperammonemia
Very rare	Hyperammonemic encephalopathy
Psychiatric Disorders	
Very Rare	Feeling of despair
Eye Disorders	
Very rare	Abnormal sensation in eye
Very rare	Angle closure glaucoma
Very rare	Conjunctival edema
Very rare	Eye movement disorder
Very rare	Eyelid edema
Very rare	Maculopathy
Very rare	Myopia
Not known	Uveitis
Respiratory, Thoracic and Mediastinal Disorders	
Very rare	Cough
Skin and Subcutaneous Tissue Disorders	
Very rare	Erythema multiforme
Very rare	Periorbital edema
Very rare	Stevens-Johnson syndrome
Very rare	Toxic epidermal necrolysis
Musculoskeletal and Connective Tissue Disorders	
Very rare	Joint swelling
Very rare	Limb discomfort
Renal and Urinary Disorders	
Very rare	Renal tubular acidosis
Very rare	Nephrocalcinosis
General Disorders and Administration Site Reactions	
Very rare	General edema
Very rare	Influenza like illness
Investigations	
Very rare	Weight increased

♦ EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
Topiramate acts on the central nervous system and may produce drowsiness, dizziness or other related symptoms. It may also cause visual disturbances and/or blurred vision. These adverse events could potentially be dangerous in patients driving a vehicle or operating machinery, particularly until such time as the individual patient's experience with the drug is established.

♦ CONTRAINDICATION:
Hypersensitivity to any component of this product.
Migraine prophylaxis: in pregnancy and in women of childbearing potential if not using a highly effective method of contraception.

♦ DRUG INTERACTION:
Interactions
(For purposes of this section, a no effect dose is defined as a ≤ 15% change.)

Effects of other AEDs 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.

The results of these interactions are summarized below:

AED Co-administered	AED Concentrations	Topiramate Concentration
Phenytoin	↔**	↓ (48%)
Carbamazepine (CBZ)	↔	↓ (40%)
Valproic acid	↔	↔
Lamotrigine	↔	↔
Phenobarbital	↔	NS
Primidone	↔	NS

↔ = No effect on plasma concentration (≤ 15% change)
** = Plasma concentrations increase in individual patients
↓ = Plasma concentrations decrease
NS = Not studied
AED = Antiepileptic drug

Effects of Topiramate on other AEDs
The addition of Topiramate to other AEDs (Phenytoin, Carbamazepine, Valproic acid, Phenobarbital, Primidone) has no effect on their steady-state plasma concentrations, except in the occasional patient, 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 (CYP2C19). Consequently, any patient on Phenytoin showing clinical signs or symptoms of toxicity should have Phenytoin levels monitored.
A pharmacokinetic interaction of patients with epilepsy indicated the addition of Topiramate to Lamotrigine had no effect on steady state plasma concentration of Lamotrigine at Topiramate doses of 100 to 400 mg/day. In addition, there was no change in steady state plasma concentration of Topiramate during or after removal of Lamotrigine treatment (mean dose of 327 mg/day).

Other drug interactions
Digoxin
When Topiramate is added or withdrawn in patients on Digoxin therapy, careful attention should be given to the routine monitoring of serum Digoxin.
Central Nervous System (CNS) depressants
It is recommended that Topiramate not be used concomitantly with alcohol or other CNS depressant drugs.
Oral contraceptives
The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with Topiramate. Patients taking Estrogen-containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding.
Lithium
Lithium levels should be monitored when co-administered with Topiramate.
Risperidone
There were no clinically significant changes in the systemic exposure of the Risperidone total active moiety or of Topiramate, therefore this interaction is not likely to be of clinical significance.
Hydrochlorothiazide (HCTZ)
The addition of HCTZ to Topiramate therapy may require an adjustment of the Topiramate dose. The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of Topiramate. Clinical laboratory results indicated decreases in serum potassium after Topiramate or HCTZ administration, which were greater when HCTZ and Topiramate were administered in combination.
Metformin
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. The extent of change in the clearance is unknown. The clinical significance of the effect of Metformin on Topiramate pharmacokinetics is unclear. When Topiramate is added or withdrawn in patients on Metformin therapy, careful attention should be given to the routine monitoring for adequate control of their diabetic disease state.
Pioglitazone
When Topiramate is added to Pioglitazone therapy or Pioglitazone is added to Topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.
Glyburide
The steady-state pharmacokinetics of Topiramate were unaffected by concomitant administration of Glyburide. When Topiramate is added to Glyburide therapy or Glyburide is added to Topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Other forms of interactions
Agents predisposing to nephrolithiasis
Topiramate when used concomitantly with other agents 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.
Valproic acid
Concomitant administration of Topiramate and Valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. In most cases, symptoms and signs abated with discontinuation of either drug.
This adverse reaction is not due to a pharmacokinetic interaction.
Hypothermia, defined as an unintentional drop in body core temperature to <35°C, has been reported in association with concomitant use of Topiramate and Valproic acid (VPA) both in conjunction with hyperammonemia and in the absence of hyperammonemia. This adverse event in patients using concomitant Topiramate and Valproate can occur after starting Topiramate treatment or after increasing the daily dose of Topiramate.
Vitamin K-antagonist anticoagulant medications
Decreased Prothrombin Time/International Normalized Ratio (PT/INR) responses have been reported following concomitant administration of Topiramate with Vitamin K-antagonist anticoagulant medications. Closely monitor INR during concomitant administration of Topiramate therapy with Vitamin K-antagonist anticoagulant medications.

♦ OVERDOSE AND TREATMENT:
Signs and symptoms
Overdoses of Topiramate have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbances, blurred vision, diplopia, mentation impaired, lethargy, 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 polydrug overdoses involving topiramate.
Topiramate overdose can result in severe metabolic acidosis.
The highest Topiramate overdose reported was calculated to be between 96 and 110 g and resulted in coma lasting 20 to 24 hours followed by full recovery after 3 to 4 days.

Treatment
In the event of overdose, Topiramate should be discontinued and general supportive treatment given until clinical toxicity has been diminished or resolved. Hemodialysis has been shown to be an effective means of removing Topiramate from the body. The patient should be well hydrated.
It is advisable to contact a poison control center to obtain the latest recommendations for the management of an overdose.

♦ STORAGE:
Store at temperature of not more than 30ºC. Protected from moisture.

♦ DOSAGE FORM AND PACKAGING AVAILABLE:
25 mg Tablet, Blister 6x10's
50 mg Tablet, Blister 6x10's
100 mg Tablet, Blister 6x10's

♦ DATE OF REVISION:
October 16, 2023

Manufactured by:
UNISON LABORATORIES CO., LTD.
39 Moo 4, Klong Udomcholjorn, Muang Chachoengsao,
Chachoengsao 24000 Thailand

C-MY/241023-00 (AR)

IPMY 0090

28 cm.
Back
20 cm.
Thickness: 60 g (0.08 mm.)
Packaging Type: Wood Free Paper
Dimension: W 20 x L 28 cm.
Code No.: IPMY 0090
Product: PRADOX 25, 50, 100
PM Specification
Print : Fit to Page
PRADOX 25, 50, 100_Insert_IPMY 0090
by...Ann 13/11/2023

PRADOX 25 mg Film Coated Tablet
PRADOX 50 mg Film Coated Tablet
PRADOX 100 mg Film Coated Tablet

Each film coated tablet contains:
Topiramate 25 mg
Topiramate 50 mg
Topiramate 100 mg

♦ PRODUCT DESCRIPTION:

25 mg: White, round, biconvex, film coated tablet with engraved T on one side and 25 on the other (6.0 mm)
50 mg: Pale yellow, round, biconvex, film coated tablet with engraved T on one side and 50 on the other (7.1 mm)
100 mg: Yellow, round, biconvex, film coated tablet with engraved T on one side and 100 on the other (9.3 mm)

♦ MECHANISM OF ACTION:

Pharmacology

Topiramate is classified as a sulfamate-substituted monosaccharide. The precise mechanism by which Topiramate exerts its antiseizure and migraine prophylaxis effects are unknown. Electrophysiological and biochemical studies on cultured neurons have identified three properties that may contribute to the antiepileptic efficacy of Topiramate.

Action potentials elicited repetitively by a sustained depolarization of the neurons were blocked by Topiramate in a time-dependent manner, suggestive of a state-dependent sodium channel blocking action. Topiramate increased the frequency at which γ-aminobutyrate (GABA) activated GABAA receptors, and enhanced 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.

Because the antiepileptic profile of Topiramate differs markedly from that of the benzodiazepines, it may modulate a benzodiazepine-insensitive subtype of GABAA receptor. Topiramate antagonized the ability of kainate to activate the kainate/AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) subtype of excitatory amino acid (Glutamate) receptor, but had no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype. These effects of Topiramate were concentration-dependent over a range of 1 µM to 200 µM, with minimum activity observed at 1 µM to 10 µM.

In addition, Topiramate 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 Topiramate's antiepileptic activity.

Pharmacokinetics

The pharmacokinetic profile of Topiramate compared to other AEDs shows a long plasma half-life, linear pharmacokinetics, predominantly renal clearance, absence of significant protein binding, and lack of clinically relevant active metabolites. Topiramate is not a potent inducer of drug metabolizing enzymes, can be administered without regard to meals, and routine monitoring of plasma Topiramate concentrations is not necessary.

<u>Absorption</u>

Topiramate is rapidly and well absorbed. Following oral administration of 100 mg Topiramate to healthy individuals, a mean peak plasma concentration (C_{max}) of 1.5 µg/mL was achieved within 2 to 3 hours (T_{max}). Based on the recovery of radioactivity from the urine the mean extent of absorption of a 100 mg oral dose of ^{14}C-topiramate was at least 81%. There was no clinically significant effect of food on the bioavailability of Topiramate.

<u>Distribution</u>

Generally, 13 to 17% of Topiramate is bound to plasma protein. A low capacity binding site for Topiramate in/on erythrocytes that is saturable above plasma concentrations of 4 µg/mL has been observed. The volume of distribution varied inversely with the dose. The mean apparent volume of distribution was 0.80 to 0.55 L/Kg for a single dose range of 100 to 1200 mg. An effect of gender on the volume of distribution was detected, with values for females circa 50% of those for males. This was attributed to the higher percent body fat in female patients and is of no clinical consequence.

<u>Metabolism</u>

Topiramate is not extensively metabolized (~20%) in healthy individuals. It is metabolized up to 50% in patients receiving concomitant antiepileptic therapy with known inducers of drug metabolizing enzymes. Six metabolites, formed through hydroxylation, hydrolysis and glucuronidation, have been isolated, characterized and identified from plasma, urine and feces of humans. Each metabolite represents less than 3% of the total radioactivity excreted following administration of $1^{14}C$-topiramate. Two metabolites, which retained most of the structure of Topiramate, were tested and found to have little or no anticonvulsant activity.

<u>Elimination</u>

In humans, the major route of elimination of unchanged Topiramate and its metabolites is via the kidney (at least 81% of the dose). Approximately 66% of a dose of ^{14}C-topiramate was excreted unchanged in the urine within four days. Following twice a day dosing with 50 mg and 100 mg of Topiramate the mean renal clearance was approximately 18 mL/min and 17 mL/min, respectively. There is evidence of renal tubular reabsorption of Topiramate. Overall, plasma clearance is approximately 20 to 30 mL/min in humans following oral administration.

Topiramate exhibits low intersubject variability in plasma concentrations and, therefore, has predictable pharmacokinetics. The pharmacokinetics of Topiramate are linear with plasma clearance remaining constant and area under the plasma concentration curve increasing in a dose-proportional manner over a 100 to 400 mg single oral dose range in healthy subjects. Patients with normal renal function may take 4 to 8 days to reach steady-state plasma concentrations. The mean C_{max} following multiple, twice a day oral doses of 100 mg to healthy subjects was 6.76 µg/mL. Following administration of multiple doses of 50 mg and 100 mg of Topiramate twice a day, the mean plasma elimination half-life was approximately 21 hours.

<u>Use with other AEDs</u>

Concomitant multiple-dose administration of Topiramate, 100 to 400 mg twice a day, with Phenytoin or Carbamazepine shows dose proportional increases in plasma concentrations of Topiramate.

<u>Special Populations</u>

Pediatrics (up to 12 years of age)

The pharmacokinetics of Topiramate in children, as in adults receiving add-on therapy, are linear, with clearance independent of dose and steady-state plasma concentrations increasing in proportion to dose. Children, however, have a higher clearance and a shorter elimination half-life. Consequently, the plasma concentrations of Topiramate for the same mg/Kg dose may be lower in children compared to adults. As in adults, hepatic enzyme inducing AEDs decrease the steady-state plasma concentrations.

Elderly

Plasma clearance of Topiramate is unchanged in elderly subjects in the absence of underlying renal disease.

Renal impairment

The plasma and renal clearance of Topiramate are decreased in patients with moderate and severe impaired renal function (CL_{CR} < 70 mL/min). As a result, higher steady-state Topiramate plasma concentrations are expected for a given dose in renal-impaired patients as compared to those with normal renal function. In addition, patients with renal impairment will require a longer time to reach steady-state at each dose. In patients with moderate and severe renal impairment, half of the usual starting and maintenance doseis recommended.

Topiramate is effectively removed from plasma by hemodialysis. A prolonged period of hemodialysis may cause Topiramate concentration to fall below levels that are 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.

Hepatic impairment

Plasma clearance of Topiramate decreased a mean of 26% in patients with moderate to severe hepatic impairment. Therefore, Topiramate should be administered with caution in patients with hepatic impairment.

♦ INDICATION:

Epilepsy

It is indicated as monotherapy in patients with newly diagnosed epilepsy or for conversion to monotherapy in patients with epilepsy.

It is indicated as adjunctive therapy for adults and children aged 2 and above with partial onset seizures or generalized tonic-clonic seizures.

It is also indicated in adults and children as adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut syndrome.

Migraine

It is indicated in adults for the prophylaxis of migraine headache. The usefulness of Topiramate in the acute treatment of migraine headache has not been studied.

♦ DOSAGE AND ADMINISTRATION:

Oral

It is not necessary to monitor Topiramate plasma concentrations to optimize therapy with Topiramate. On rare occasions, 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 Carbamazepine to adjunctive therapy with Topiramate may require adjustment of the dose of Topiramate.

<u>Dosage</u>

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

<u>Epilepsy – adjunctive therapy</u>

Adults

Therapy should begin at 25 to 50 mg 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 to 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.

In clinical trials as adjunctive therapy, 200 mg was effective and was the lowest dosage studied. This is therefore considered the minimum effective dose. The usual daily dose is 200 to 400 mg in two divided doses. Individual patients have received doses as high as 1600 mg/day.

These dosing recommendations apply to all adults, including the 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 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 dose), 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.

<u>Epilepsy - monotherapy</u>

When concomitant antiepileptic drugs (AEDs) 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 1000 mg/day. These dosing recommendations apply to all adults including the elderly in the absence of underlying renal disease.

Children aged 2 and above

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 mg/Kg/day 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.

<u>Migraine</u>

Adults

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 interval. 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.

Special population

Renal impairment

Patients with moderate and severe renal impairment (CL_{CR} < 70 mL/min) may require a dose reduction. Half of the usual starting and maintenance dose is recommended.

Since Topiramate is removed from plasma by hemodialysis, a supplemental dose of Topiramate 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.

Hepatic impairment

Topiramate should be administered with caution in patients with hepatic impairment.

<u>Administration</u>

Pradox is available in tablets formulation, for oral administration. It is recommended that Topiramate tablets not be broken. Topiramate can be taken without regard to meals.

♦ WARNING AND PRECAUTION:

Withdrawal of Topiramate

In patients with or without a history of seizures or epilepsy, AEDs including Topiramate should be gradually withdrwn to minimize the potential for seizures or increased seizure frequency. Daily dosages were decreased in weekly intervals by 50 to 100 mg in adults with epilepsy and by 25 to 50 mg in adults receiving Topiramate at doses up to 100 mg/day for migraine prophylaxis. In children, Topiramate should be gradually withdrawn over a 2 to 8 week period. In situations where rapid withdrawal of Topiramate is medically required, appropriate monitoring is recommended.

Renal impairment

The major route of elimination of unchanged Topiramate 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. As with all patients, the titration schedule should be guided by clinical outcome (i.e., seizure control, avoidance of side effects) with the knowledge that subjects with known renal impairment may require a longer time to reach steady-state at each dose.

Hydration

Oligohidrosis (decreased sweating) and anhidrosis have been reported in association with the use of Topiramate. Decreased sweating and hyperthermia (rise in body temperature) may occur especially in young children exposed to high ambient temperatures.

Adequate hydration while using Topiramate is very important. Hydration can reduce the risk of nephrolithiasis. Proper hydration prior to and during activities such as exercise or exposure to warm temperatures may reduce the risk of heat-related adverse events.

Mood disturbances/depression

An increased incidence of mood disturbances and depression has been observed during Topiramate treatment.

Suicide/suicidal ideation

Potential for an increase in risk of suicidal thoughts or behaviors.

AEDs, including Topiramate, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. The mechanism of this risk is not known. Patients therefore should be monitored for signs of suicidal ideation and behavior and appropriate treatment should be considered. Patients (and, when appropriate, caregivers of patients) should be advised to seek immediate medical advice should signs of suicidal ideation or behavior emerge.

Serious skin reactions

Serious skin reactions (Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)) have been reported in patients receiving Topiramate. The majority of cases have occurred in patients concurrently taking other medications that are known to be associated with SJS and TEN. There have also been several cases in patients receiving monotherapy. It is recommended that patients be informed about the signs of serious skin reactions. If SJS or TEN are suspected, use of Topiramate should be discontinued.

Nephrolithiasis

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. Risk factors for nephrolithiasis include prior stone formation, a family history of nephrolithiasis and hypercalciuria. None of these risk factors can reliably predict stone formation during Topiramate treatment. In addition, patients taking other medication associated with nephrolithiasis may be at increased risk.

Hepatic impairment

In hepatically-impaired patients, Topiramate should be administered with caution as the clearance of Topiramate may be decreased.

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 some or all of the following: myopia, mydriasis, anterior chamber shallowing, ocular hyperemia (redness), choroidal detachments, retinal pigment epithelial detachments, macular striae, and increased intraocular pressure. 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. Treatment includes discontinuation of Topiramate, as rapidly as possible in the judgment of the treating physician, and appropriate measures to reduce intraocular pressure. These measures generally result in a decrease in intraocular pressure. Elevated intraocular pressure of any etiology, if left untreated, can lead to serious sequelae including permanent vision loss.

<u>Special Warnings and Precautions for Use:</u>

Visual field defects

Visual field defects have been reported in patients receiving Topiramate independent of elevated intraocular pressure. In clinical trials, most of these events were reversible following Topiramate discontinuation, however some cases were not. In a large proportion of post-marketing case reports reversibility was unknown, but in cases where an outcome was reported, the majority were reversible. If visual problems occur at any time during Topiramate treatment, consideration should be given to discontinuing the drug.

Metabolic acidosis and sequelae

Hyperchloremic, non-anion gap, metabolic acidosis (i.e. decreased serum bicarbonate below the normal reference range in the absence of respiratory alkalosis) is associated with Topiramate treatment. This decrease in serum bicarbonate is due to the inhibitory effect of Topiramate on renal carbonic anhydrase. Generally, the decrease in bicarbonate occurs early in treatment although it can occur at any time during treatment. These decreases are usually mild to moderate (average decrease of 4 mmol/L at doses of 100 mg/day or above in adults and at approximately 6 mg/Kg/day in pediatric patients). Rarely, patients have experienced decreases to values below 10 mmol/L. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or certain drugs) may be additive to the bicarbonate lowering effects of Topiramate.

Chronic, untreated metabolic acidosis may increase the risk of nephrocalcinosis.

Chronic metabolic acidosis in pediatric patients can reduce growth rates. The effect of Topiramate on growth and bone-related sequelae has not been systematically investigated in pediatric or adult populations.

Depending on underlying conditions, appropriate evaluation including serum bicarbonate levels is recommended with Topiramate therapy. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing Topiramate (using dose tapering).

Hyperammonemia and encephalopathy

Hyperammonemia with or without encephalopathy has been reported with Topiramate treatment. The risk for hyperammonemia with Topiramate appears dose-related. Hyperammonemia has been reported more frequently when Topiramate is used concomitantly with Valproic acid.

Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy. In most cases, hyperammonemic encephalopathy abated with discontinuation of treatment. In patients who develop unexplained lethargy, or changes in mental status associated with Topiramate monotherapy or adjunctive therapy, it is recommended to consider hyperammonemic encephalopathy and measuring ammonia levels.

Women of childbearing potential

PRADOX may cause fetal harm when administered to a pregnant woman.

Before the initiation of treatment with Topiramate in a woman of childbearing potential, pregnancy testing should be performed and a highly effective contraceptive method used. The patient should be fully informed of the risks related to the use of Topiramate during pregnancy.

PRADOX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nutritional supplementation

A dietary supplement or increased food intake may be considered if the patient is losing weight while on this medication.

♦ PREGNANCY AND LACTATION:

Pregnancy

PRADOX can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to Topiramate in utero have an increased risk of congenital malformations (e.g. craniofacial defects, such as cleft lip/palate, hypospadias, and anomalies involving various body systems) and neurodevelopmental disorders (e.g., autism spectrum disorders and intellectual disability). This has been reported with Topiramate monotherapy and Topiramate as part of a polytherapy regimen.

In addition, data from other studies indicate that, compared with monotherapy, there is an increased risk of teratogenic effects associated with the use of antiepileptic drugs in combination therapy. The risk has been observed in all doses and effects were reported to be dose-dependent. In women treated with Topiramate who have had a child with a congenital malformation, there appears to be an increased risk of malformations in subsequent pregnancies when exposed to Topiramate.

28 cm.
Front
20 cm.
PM Specification
Product: PRADOX 25, 50, 100
Code No.: IPMY 0090
Dimension: W 20 x L 28 cm.
Packaging Type: Wood Free Paper กระดาษปอนด์
Thickness: 60 g (0.08 mm.)
Designed by:
Checked by:
Approved by:
Approved by:
PLC:
LRA:
IRA:
QCC-PM:
CUSTOMER/SALES DEPT.:
Print : Fit to Page
PRADOX 25, 50, 100_Insert_IPMY 0090
by...Ann 13/11/2023