SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM
EPIMATE 25 (tablets)
EPIMATE 50 (tablets)
EPIMATE 100 (tablets)
EPIMATE 200 (tablets)

COMPOSITION
EPIMATE 25: Each film-coated tablet contains 25 mg topiramate
EPIMATE 50: Each film-coated tablet contains 50 mg topiramate
EPIMATE 100: Each film-coated tablet contains 100 mg topiramate
EPIMATE 200: Each film-coated tablet contains 200 mg topiramate

Each tablet also contains the following inactive ingredients:
Lactose monohydrate, microcrystalline cellulose, pregelatinised starch, purified water, sodium starch glycolate, colloidal silicon dioxide, talc, magnesium stearate, hypromellose 2910, polyethylene glycol 400 and titanium dioxide.

PHARMACOLOCIAL CLASSIFICATION
A.2.5 Anticonvulsants, including antiepileptics.

PHARMACOLOGICAL ACTION
Pharmacodynamics:
Topiramate is an antiepileptic agent classified as a sulfamate-substituted monosaccharide. The pharmacological properties identified that may contribute to the anticonvulsant activity of topiramate are as follows:
- It reduces the frequency at which action potentials are generated when neurons are subjected to a sustained depolarisation indicative of a state-dependent blockade of voltage-sensitive sodium channels.
- It markedly enhances the activity of gamma-amino butyric acid (GABA) at some types of GABA receptors.
- It weakly antagonises the excitatory activity of kainate/alpha-amino-3-hydroxy-5-methyl-4 isoxazole propionic acid (AMPA) subtype of glutamate receptor but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype.
- Additionally it inhibits some isoenzymes of carbonic anhydrase, which is not considered to be a primary component contributing to antiepileptic activity.

Pharmacokinetics:
Topiramate is well-absorbed after oral administration with peak plasma concentrations achieved within 2 to 3 hours. Bioavailability is not significantly affected by food. Protein binding is 9 to 17 %. The mean apparent volume of distribution is 0,80 to 0,55 l/kg. Gender affects the volume of distribution, which is 50 % lower in women compared to that in men. Topiramate is not extensively metabolised (about 20 %), but up to 50 % of the dose may undergo hepatic metabolism in patients receiving enzyme-inducing medication.
The major route of elimination of unchanged topiramate and its metabolites is via the kidney (at least 81 % of the dose). Mean plasma elimination half-life is about 21 hours. Steady-state concentrations are achieved after about 4 to 8 days in patients with normal renal function. Children exhibit a higher clearance and shorter elimination half-life than adults. Pharmacokinetics may be affected by concomitant use of other antiepileptics.

INDICATIONS
EPIMATE is indicated as monotherapy in patients with newly diagnosed epilepsy or for conversion to monotherapy in patients with epilepsy.
EPIMATE is indicated as adjunctive therapy for adults and children older than 4 years of age who are inadequately controlled on conventional first-line antiepileptic medicines for:
- Partial onset seizures with or without secondarily generalised seizures.
- Seizures associated with Lennox-Gastaut syndrome.
- Primary generalised tonic clonic seizures.

CONTRAINDICATIONS
Hypersensitivity to any component in **EPIMATE**.
The safety and efficacy of **EPIMATE** in children under 4 years has not been established.
Pregnancy and lactation (See **"PREGNANCY AND LACTATION"**).

WARNINGS AND SPECIAL PRECAUTIONS
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 **EPIMATE**. Symptoms include onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperaemia (redness) and increased intraocular pressure. Mydriasis may or may not be present. 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 **EPIMATE** 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 paediatric patients as well as adults. Treatment includes discontinuation of **EPIMATE**, as rapidly as possible in the judgement of the treating doctor and appropriate measures to reduce intraocular pressure. These measures generally result in a decrease in intraocular pressure.
Visual Field Defects
Visual field defects have been reported in patients receiving **EPIMATE** independent of elevated intraocular pressure. In clinical trials, most of these events were reversible after **EPIMATE** discontinuation. If visual problems occur at any time during **EPIMATE** treatment, consideration should be given to discontinuing the medicine.

Oral contraceptives
Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding, see "**INTERACTIONS**".

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 **EPIMATE** treatment. This decrease in serum bicarbonate is due to the inhibitory effect of topiramate on renal carbonic anhydrase and consequent renal bicarbonate wasting. 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/day in paediatric patients. However, 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, diarrhoea, surgery, ketogenic diet, or certain medicines) may be additive to the bicarbonate lowering effects of topiramate.
Chronic metabolic acidosis in paediatric patients can reduce growth rates. Chronic metabolic acidosis can lead to nephrolithiasis and increased risk for fractures.
Evaluation of bicarbonate levels is recommended with **EPIMATE** therapy. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing **EPIMATE** (using dose tapering).

Special Precautions
EPIMATE should be withdrawn gradually to minimise the potential of increased seizure frequency at a recommended rate of 100 mg daily at weekly intervals.
Use with caution in patients with renal or hepatic impairment. Adequate hydration while using **EPIMATE** is recommended to reduce the risk of developing renal calculi especially in predisposed patients.
EPIMATE contains lactose. Patients with rare hereditary problems of galactose intolerance, the lapp lactose deficiency or glucose-galactose malabsorption should not take **EPIMATE.**

Effects on driving ability and use of machinery:
EPIMATE may produce central nervous system related events such as: drowsiness, dizziness or other related symptoms. Caution is advised when driving or operating machinery.

INTERACTIONS
Effects of EPIMATE on other antiepileptic medicines
The addition of **EPIMATE** to other antiepileptic medicines such as phenytoin, carbamazepine, valproic acid, phenobarbital and primidone, has no effect on their steady-state plasma concentrations, except in the occasional patient where the addition of **EPIMATE** to phenytoin may result in an increase of plasma concentrations of phenytoin. This is possibly due to inhibition of a specific enzyme polymorphic isoform ($CYP2C_{meph}$). Consequently, any patient on phenytoin should have phenytoin levels monitored.
The addition of topiramate to lamotrigine has no effect of steady state plasma concentration on lamotrigine at topiramate doses of 100 to 400 mg/day. However, the incidence of adverse effects was meaningfully increased on the combination.

Effects of other antiepileptic medicines on EPIMATE
Phenytoin and carbamazepine decrease the plasma concentration of **EPIMATE**. The addition or withdrawal of phenytoin or carbamazepine to **EPIMATE** 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 significant changes in plasma concentrations of topiramate and, therefore, does not warrant dosage adjustment of **EPIMATE.**

Other medicine interactions
Digoxin
Concomitant administration has shown a decrease in serum digoxin. When **EPIMATE** is added or withdrawn in patients on digoxin therapy, careful attention should be given to the routine monitoring of serum digoxin.

Oral contraceptives
The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with **EPIMATE**. Patients taking oestrogen-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.

Hydrochlorothiazide (HCTZ)
The addition of HCTZ to **EPIMATE** therapy may require adjustment of the **EPIMATE** dose as C_{max} and AUC of **EPIMATE** are increased. The steady-state pharmacokinetics of HCTZ are not significantly influenced by the concomitant administration of **EPIMATE**.
Clinical laboratory results indicated decreases in serum potassium after **EPIMATE** or HCTZ administration, which were greater when HCTZ and **EPIMATE** were administered in combination.

Metformin
When metformin and **EPIMATE** are given simultaneously, the metformin C_{max} and AUC is increased. The clinical significance of this effect is unknown.
When **EPIMATE** 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 **EPIMATE** is added to pioglitazone therapy or pioglitazone is added to **EPIMATE** therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

CNS depressants
Concomitant use of **EPIMATE** with alcohol or other central nervous system (CNS) depressant medicines should be avoided.

Additional pharmacokinetic interaction studies
Clinical studies have been conducted to assess the potential pharmacokinetic interaction between topiramate and other agents.

Summary of results from additional clinical pharmacokinetic drug interaction studies

Concomitant Medicine	Concomitant Medicine Concentration	Topiramate Concentration
Amitriptyline	↔ 20 % increase in C_{max} and AUC of nortriptyline metabolite	NS
Dihydroergotamine (Oral and Subcutaneous)	↔	↔
Haloperidol	↔ 31 % increase in AUC of the reduced metabolite	NS
Propranolol	↔ 17 % increase in C_{max} for 4-OH propranolol (TPM 50 mg 12 hourly)	16 % increase in C_{max} 17 % increase in AUC (80 mg propranolol /12 hourly)
Sumatrip (Oral and Subcutaneous)	↔	↔
Pizotifen	↔	↔

↑ a % values are the changes in treatment mean C_{max} or AUC with respect to monotherapy
↔ = No effect on C_{max} and AUC (± 15 % change) of the parent compound
NS = Not studied

Laboratory tests
EPIMATE has been associated with an average decrease of 4 mmol/l in the serum bicarbonate level. Refer to "**Special precautions**".

PREGNANCY AND LACTATION
EPIMATE is contraindicated for use during pregnancy. (See **"CONTRAINDICATIONS"**).
EPIMATE crosses the placenta and is teratogenic in animals. There is no adequate data in humans. It is recommended that women of child-bearing potential use adequate contraception. (See **"INTERACTIONS"**).
The safety of **EPIMATE** during lactation has not been established. There is extensive excretion of **EPIMATE** into breast milk. Patients using **EPIMATE** should not breastfeed.

DOSAGE AND DIRECTIONS FOR USE
For optimal control in both adults and children, it is recommended that therapy be initiated at a low dose, followed by titration to an effective dose. **EPIMATE** can be taken without regard to meals.
Monotherapy
When concomitant antiepileptic medicines (AEMs) are withdrawn to achieve monotherapy with **EPIMATE**, consideration should be given to the effects this may have on seizure control. Unless safety concerns require an abrupt withdrawal of the concomitant AEM, a gradual discontinuation at the rate of approximately one-third of the concomitant AEM dose every 2 weeks is recommended. When enzyme-inducing medicines are withdrawn, **EPIMATE** levels will increase. A decrease in **EPIMATE** 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, small 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 **EPIMATE** monotherapy in adults is 100 mg/day and the maximum recommended daily dose is 500 mg. These dosing recommendations apply to all adults, including the elderly, in the absence of underlying renal disease.
Children
Treatment of children aged 4 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 **EPIMATE** monotherapy in children aged 4 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.
Note: Children aged 2 years requires a dosage regimen and dosage form, which cannot be achieved with the lowest dosage strength (and form) of this range.

Adjunctive therapy
Adults
Therapy should begin at 25 – 50 mg nightly for one week. Subsequently, at weekly intervals, the dose should be increased by 25 – 50 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.
The minimal effective dose is considered to be 200 mg. 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 dose. It is recommended that therapy be initiated at a low dose, followed by titration to an effective dose.
Since **EPIMATE** is removed from plasma by haemodialysis, a supplemental dosage of **EPIMATE** 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.
These dosing recommendations apply to all adults, including the elderly, in the absence of underlying renal disease. Refer to "**Special precautions**" under heading **"WARNINGS AND SPECIAL PRECAUTIONS**".

Children 4 years and over
The recommended total daily dose of **EPIMATE** 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 doses), to achieve optimal clinical response. Dose titration should be guided by clinical outcome.

SIDE EFFECTS
Blood and lymphatic system disorders:
- Frequent: Anaemia, purpura.
- Less Frequent: Leucopenia, thrombocytopenia, hyperammonaemia.
- Frequency not known: Thromboembolic events.

Metabolic and nutritional disorders:
- Frequent: Weight loss, anorexia.
- Less Frequent: Metabolic acidosis.

Psychiatric disorders:
- Frequent: Depression, somnolence, nervousness, difficulty with memory, confusion, difficulty with concentration/ attention, anorexia, emotional liability, insomnia, psychomotor slowing, mood changes, personality changes, aggressive reaction.
- Less frequent: Agitation, cognitive problems NOS, psychomotor slowing, confusion, emotional liability with mood disorders, apathy, psychosis/ psychotic symptoms, hallucination, aggressive reaction/ behavior, suicidal ideation or attempts, anxiety.

Nervous system disorders:
- Frequent: Paraesthesia, ataxia, dizziness, drowsiness, speech problems, hyperkinesia, tremor, language problems, abnormal gait.
- Less Frequent: Hyperthermia, hemiparesis, hypoaesthesia, oligohidrosis.

Eye disorders:
- Frequent: Abnormal vision, nystagmus, diplopia.
- Less frequent: Acute myopia with secondary angle closure glaucoma.

Cardiac disorders:
- Frequency not known: Hypotension, postural hypotension.

Respiratory, thoracic and mediastinal disorders:
- Frequent: Rhinitis, pharyngitis, pneumonia.

Gastrointestinal disorders:
- Frequent: Nausea, abdominal pain, dyspepsia, constipation, increased saliva, taste perversion.

Hepato-biliary disorders:
- Frequency not known: Hepatotoxicity, hepatic failure, pancreatitis.

Skin and subcutaneous tissue disorders:
- Less Frequent: Erythema multiforme, pemphigus, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Renal and urinary disorders:
- Less Frequent: Nephrolithiasis.
- Frequency not known: Renal failure.

General disorders and administration site conditions:
- Frequent: Fatigue, asthenia.
- Less Frequent: Viral infection.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
Signs and symptoms
Signs and symptoms include: convulsions, drowsiness, speech disturbances and blurred vision. Diplopia, mentation impaired, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. Deaths may occur after multiple medicine overdoses involving **EPIMATE**.
EPIMATE overdose can result in severe metabolic acidosis. Refer to **"WARNINGS AND SPECIAL PRECAUTIONS"**.
Treatment
In acute **EPIMATE** 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 topiramate in vitro. Treatment should be appropriately supportive. Haemodialysis has been shown to be an effective means of removing topiramate from the body. The patient should be well hydrated.

IDENTIFICATION
EPIMATE 25: White to off-white, round, biconvex film-coated tablets debossed with '1' mark separating 10 & 31 on one side and '25' on other side.
EPIMATE 50: Yellow coloured, round, biconvex film-coated tablets debossed with breakline on both sides, 10 & 32 on one side and '50' on other side.
EPIMATE 100: Light yellow coloured, round, biconvex film-coated tablets debossed with breakline on both sides, 10 & 33 on one side and '100' on other side.
EPIMATE 200: Peach coloured, round, biconvex film-coated tablets debossed with breakline on both sides, 10 & 34 on one side and '200' on other side.

PRESENTATION
6 blister strips (OPA/Alu/PVC sealed with Alu foil) containing 10 tablets each per carton box.

STORAGE INSTRUCTIONS
Store at or below 25 °C. Protect from moisture and light.
Keep blisters in the carton box until required for use.
KEEP OUT OF REACH AND SIGHT OF CHILDREN.

REGISTRATION NUMBER
EPIMATE 25: 43/2.5/0823
EPIMATE 50: 43/2.5/0824
EPIMATE 100: 43/2.5/0825
EPIMATE 200: 43/2.5/0826

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
3 Gwen Lane, 4th Floor,
Sandton, 2031.
Contact No.: +27 (0)10 594 5610
PV Email Address: pv@trinitypharma.co.za

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