**Approved Professional Information for TOPIRAMATE 25 / 50 / 100 UNICORN**

## SCHEDULING STATUS

S3

## 1. NAME OF THE MEDICINE

**TOPIRAMATE 25 UNICORN film-coated tablets**

**TOPIRAMATE 50 UNICORN film-coated tablets**

**TOPIRAMATE 100 UNICORN film-coated tablets**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each TOPIRAMATE 25 UNICORN tablet contains 25 mg topiramate.

Each TOPIRAMATE 50 UNICORN tablet contains 50 mg topiramate.

Each TOPIRAMATE 100 UNICORN tablet contains 100 mg topiramate.

*Excipient with known effect:*

Contains sugar:

TOPIRAMATE 25 UNICORN: Contains 27,5 mg lactose per tablet.

TOPIRAMATE 50 UNICORN: Contains 55,0 mg lactose per tablet.

TOPIRAMATE 100 UNICORN: Contains 110,0 mg lactose per tablet.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablets.

TOPIRAMATE 25 UNICORN: White coloured, round shaped, biconvex, bevelled edge, film-coated

tablets debossed with “ZD 16” on one side and plain on the other side.

TOPIRAMATE 50 UNICORN: White coloured, round shaped, biconvex, bevelled edge, film-coated tablets debossed with “ZD 15” on one side and plain on the other side.

TOPIRAMATE 100 UNICORN: White coloured, round shaped, biconvex, bevelled edge, film-coated tablets debossed with “ZD 14” on one side and plain on the other side.

The tablets should be free of all physical defects.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

**Epilepsy**

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

TOPIRAMATE UNICORN is indicated as adjunctive therapy for adults and children over 4 years old who are inadequately controlled on conventional first line anti-epileptic medicines for:

- Partial onset seizures with or without secondarily generalised seizures.
- Seizures associated with Lennox-Gastaut syndrome.
- Primary generalised tonic clonic seizures.

### 4.2 Posology and method of administration

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.

It is recommended that film-coated tablets not be broken.

TOPIRAMATE UNICORN can be taken with or without meals.

**Monotherapy**

When concomitant anti-epileptic medicines are withdrawn to achieve monotherapy with TOPIRAMATE UNICORN, consideration should be given to the effects this may have on seizure

control. Unless safety concerns require an abrupt withdrawal of the concomitant anti-epileptic medicine, a gradual discontinuation at the rate of approximately one-third of the concomitant anti-epileptic medicine dose every 2 weeks is recommended. When enzyme inducing medicines are withdrawn, TOPIRAMATE UNICORN levels will increase. A decrease in TOPIRAMATE UNICORN 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 100 – 400 mg/day. Children with recently diagnosed partial onset seizures have received doses of up to 500 mg/day.

**Adjunctive therapy**

*Adults:*

Therapy should begin at 25 – 50 mg at night for one week. Subsequently, the dose should be increased at weekly intervals 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 effective dose is usually within the range of 200 mg (minimum dose) to 400 mg daily taken in two divided doses; some patients may require up to 800 mg (maximum dose) daily. It is recommended that therapy be initiated at a low dose, followed by titration to an effective dose. These dosing recommendations apply to all adults, including the elderly, in the absence of underlying renal disease.

*Children 4 years and older:*

The recommended total daily dose of TOPIRAMATE UNICORN 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.

**Special populations:**

*Renal impairment:*

Patients with moderate and severe renal impairment may require a dose reduction. Half of the usual starting and maintenance dose is recommended (see section 5.2).

*Haemodialysis:*

Since TOPIRAMATE UNICORN is removed from plasma by haemodialysis, a supplemental dose of TOPIRAMATE UNICORN 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 (see section 5.2).

*Hepatic impairment:*

TOPIRAMATE UNICORN should be administered with caution and at reduced dosages in patients with hepatic impairment (see section 5.2).

## 4.3 Contraindications

- Hypersensitivity to topiramate or to any of the inactive ingredients of TOPIRAMATE UNICORN (see section 6.1).
- Children under 2 years (as safety and efficacy of TOPIRAMATE UNICORN have not yet been established).
- Pregnancy and lactation, as topiramate is teratogenic in animals (see section 4.6).

## 4.4 Special warnings and precautions for use

*Suicide/suicidal ideation:*

Suicide related events (suicidal ideation, suicide attempts and suicide) have been reported in patients treated with TOPIRAMATE UNICORN.

Patients should therefore be monitored for signs of suicidal ideation and behaviour 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 behaviour emerge.

*Serious skin reactions:*

Serious skin reactions (Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) have been reported in patients receiving TOPIRAMATE UNICORN (see section 4.8). 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 UNICORN should be discontinued.

*Acute myopia and secondary angle closure glaucoma:*

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients using TOPIRAMATE UNICORN. Symptoms include acute 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 occur. 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 one month of initiating TOPIRAMATE UNICORN therapy. Secondary angle closure glaucoma associated with TOPIRAMATE UNICORN has been reported in paediatric as well as adult patients. Treatment includes discontinuation of TOPIRAMATE UNICORN as rapidly as possible and appropriate measures to reduce intraocular pressure.

*Visual field defects:*

Visual field defects have been reported in patients receiving TOPIRAMATE UNICORN, independent of elevated intraocular pressure. These events may be reversible after topiramate discontinuation. If visual problems occur at any time during TOPIRAMATE UNICORN treatment, consideration should be given to discontinuing treatment.

*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 topiramate 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, however patients have experienced decreases to values below 10 mmol/L. Conditions or therapies that predispose acidosis (such as renal disease and 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 TOPIRAMATE UNICORN therapy. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing TOPIRAMATE UNICORN (using dose tapering).

*Hyperammonaemia and encephalopathy:*
Hyperammonaemia with or without encephalopathy has been reported with TOPIRAMATE UNICORN treatment (see section 4.8). The risk of hyperammonaemia with TOPIRAMATE UNICORN appears to be dose-related. Hyperammonaemia has been reported more frequently when TOPIRAMATE UNICORN is used concomitantly with valproic acid (see section 4.5).

Clinical symptoms of hyperammonaemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy. In most cases, hyperammonaemic 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 hyperammonaemic encephalopathy and measuring ammonia levels.

*Women of childbearing potential:*

TOPIRAMATE UNICORN may cause fetal harm when administered to a pregnant woman (see section 4.3). There is an increased risk of pre-term labour and premature delivery associated with the use of anti-epileptic medicines including topiramate.

*Withdrawal:*

In patients with or without a history of seizures or epilepsy, anti-epileptic medicines such as TOPIRAMATE UNICORN, should be withdrawn gradually to minimise the potential of increased seizure frequency. In clinical trials, dosages were decreased in weekly intervals by 50 – 100 mg in adults with epilepsy. In clinical trials of children, TOPIRAMATE UNICORN was gradually withdrawn over a 2 – 8 week period. In situations where rapid withdrawal of TOPIRAMATE UNICORN is medically required, appropriate monitoring is recommended.

*Hydration:*

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

Adequate hydration while taking TOPIRAMATE UNICORN is very important. Hydration can reduce the risk of nephrolithiasis (see “Nephrolithiasis” below). Proper hydration prior to and during activities such as exercise or exposure to warm temperatures may reduce the risk of heat-related adverse reactions (see section 4.8).

*Mood disturbances/depression:*

An increased incidence of mood disturbances and depression has been observed during treatment with TOPIRAMATE UNICORN.

*Renal impairment:*

TOPIRAMATE UNICORN should be used with caution in patients with renal impairment. 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.

The titration schedule should be guided by clinical outcome (i.e. seizure control and 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.

*Hepatic impairment:*

In patients with hepatic impairment, TOPIRAMATE UNICORN should be administered with caution, as the clearance of TOPIRAMATE UNICORN may be decreased.

Reports of hepatotoxicity and less commonly liver failure have been received in patients taking TOPIRAMATE UNICORN, with or without other medicines. Isolated reports have been received of hepatitis and hepatic failure in patients taking multiple medicines while being treated with TOPIRAMATE UNICORN.

*Nephrolithiasis:*

Some patients, especially those with a predisposition to nephrolithiasis, may be at risk for renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain. Concomitant use of TOPIRAMATE UNICORN with medicines predisposing to nephrolithiasis (renal stone formation) should be avoided.

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 UNICORN treatment. In addition, patients taking other medicines associated with nephrolithiasis

may be at increased risk (see section 4.5).

*Impairment of cognitive function:*

Cognitive impairment in epilepsy is multifactorial and may be due to the underlying aetiology, due to the epilepsy or due to the anti-epileptic treatment. There have been reports in the literature of impairment of cognitive function in adults on topiramate therapy which required reduction in dosage or discontinuation of treatment. However, studies regarding cognitive outcomes in children treated with topiramate are insufficient and its effect in this regard still needs to be elucidated.

*Oral contraceptives:*

Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding (see section 4.5).

*Nutritional supplementation:*

Some patients may experience weight loss whilst on treatment with TOPIRAMATE UNICORN and should be monitored for weight loss. A dietary supplement or increased food intake should be considered for patients losing weight while on treatment with TOPIRAMATE UNICORN.

*Lactose:*

TOPIRAMATE UNICORN contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take TOPIRAMATE UNICORN.

## 4.5 Interaction with other medicines and other forms of interaction

**Effects of TOPIRAMATE UNICORN on other anti-epileptic medicines**

If TOPIRAMATE UNICORN is taken concomitantly with other anti-epileptic medicines (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone), there is no effect on their steady-state

plasma concentrations, except in very rare cases where the addition of TOPIRAMATE UNICORN to phenytoin may result in an increase of plasma concentrations of phenytoin. Consequently, any patient on phenytoin, taking TOPIRAMATE UNICORN, in addition, should have phenytoin levels monitored.

**Effects of other anti-epileptic medicines on TOPIRAMATE UNICORN**

Phenytoin and carbamazepine decrease the plasma concentration of TOPIRAMATE UNICORN. The addition or withdrawal of phenytoin or carbamazepine to TOPIRAMATE UNICORN therapy may require an adjustment in dosage of TOPIRAMATE UNICORN. This should be done by titrating to clinical effect. The withdrawal or addition of valproic acid does not produce clinically significant changes in plasma concentration of TOPIRAMATE UNICORN and therefore, dosage adjustment of TOPIRAMATE UNICORN is not necessary.

**Other medicine interactions**

*Digoxin:*

Serum digoxin levels have decreased with concomitant administration of TOPIRAMATE UNICORN. When TOPIRAMATE UNICORN is added or withdrawn in patients on digoxin therapy, careful attention should be given to the routine monitoring of serum digoxin.

*Central nervous system depressants:*

Concomitant administration of TOPIRAMATE UNICORN and alcohol or other central nervous system (CNS) depressant medicines has not been evaluated. It is recommended that TOPIRAMATE UNICORN not be used concomitantly with alcohol or other CNS depressant medicines.

*St John's wort:*

A risk of decreased plasma concentrations resulting in a loss of efficacy could be observed with co-administration of TOPIRAMATE UNICORN and St John's wort *(Hypericum perforatum).*

*Oral contraceptives:*

Efficacy of oral contraceptives may be compromised when used concurrently with TOPIRAMATE UNICORN. Bearing in mind the potential risk of teratogenicity, patients should receive a preparation containing not less than 50 micrograms of oestrogen or use some alternative non-hormonal method of contraception, as TOPIRAMATE UNICORN increases plasma clearance of the estrogenic component significantly. Patients on oral contraceptives are advised to report any change in their bleeding patterns.

*Lithium:*

In patients with bipolar disorder, the pharmacokinetics of lithium were unaffected during treatment with topiramate at doses of 200 mg/day; however, there was an observed increase in systemic exposure (26 % for AUC) following topiramate doses of up to 600 mg/day. Lithium levels should be monitored when co-administered with TOPIRAMATE UNICORN.

*Risperidone:*

Concomitant use of risperidone with TOPIRAMATE UNICORN at escalating doses of 100, 250 and 400 mg/day may reduce risperidone (administered at doses ranging from 1 to 6 mg/day) systemic exposure. There were no clinically significant changes in the systemic exposure of the risperidone total active moiety or of TOPIRAMATE UNICORN, therefore this interaction is not likely to be of clinical significance.

*Hydrochlorothiazide (HCTZ):*

The addition of HCTZ to TOPIRAMATE UNICORN treatment may require an adjustment of the TOPIRAMATE UNICORN dose. Clinical laboratory results indicated decreases in serum potassium after TOPIRAMATE UNICORN or HCTZ administration, which were greater when HCTZ and TOPIRAMATE UNICORN were administered in combination.

*Metformin:*

Oral plasma clearance of TOPIRAMATE UNICORN appears to be reduced when administered with metformin. When TOPIRAMATE UNICORN is added or withdrawn in patients on metformin treatment, careful attention should be given to the routine monitoring for adequate control of their diabetic disease state.

*Pioglitazone:*

When TOPIRAMATE UNICORN is added to pioglitazone treatment or pioglitazone is added to TOPIRAMATE UNICORN treatment, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

*Glyburide:*

When TOPIRAMATE UNICORN is added to glyburide treatment or glyburide is added to TOPIRAMATE UNICORN treatment, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

**Other forms of interactions**

*Medicines predisposing to nephrolithiasis:*

Concomitant use of TOPIRAMATE UNICORN with medicines predisposing to nephrolithiasis (renal stone formation) should be avoided.

*Valproic acid:*

Concomitant administration of TOPIRAMATE UNICORN and valproic acid has been associated with hyperammonaemia with or without encephalopathy in patients who have tolerated either medicine alone. In most cases, signs and symptoms subsided with discontinuation of either TOPIRAMATE UNICORN or valproic acid. 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 UNICORN and valproic acid, both in conjunction with hyperammonaemia and in the absence of hyperammonaemia. This adverse event in patients using concomitant TOPIRAMATE UNICORN and valproate can occur after starting TOPIRAMATE UNICORN treatment or after increasing the daily dose of TOPIRAMATE UNICORN.

*Vitamin K-antagonist anticoagulant medicines:*
Decreased prothrombin time/international normalised ratio (PT/INR) has been reported in patients treated with topiramate in combination with vitamin K-antagonist anticoagulant medicines. Therefore, INR should be carefully monitored in patients concomitantly treated with TOPIRAMATE UNICORN and vitamin K-antagonist anticoagulant medicines.

**Additional pharmacokinetic medicine interaction studies**
Clinical studies have been conducted to assess the potential pharmacokinetic medicine interaction between topiramate and other medicines. The changes in $C_{max}$ or AUC as a result of the interactions are summarised below. The second column (concomitant medicine concentration) describes what happens to the concentration of the concomitant medicine listed in the first column when topiramate is added. The third column (topiramate concentration) describes how the co-administration of a medicine listed in the first column modifies the concentration of topiramate.

Summary of results from additional clinical pharmacokinetic medicine interaction studies:

| **Concomitant medicine** | **Concomitant medicine concentration [a]** | **Topiramate concentration [a]** |
|---|---|---|
| Amitriptyline | ↔ | NS |

| | | |
|---|---|---|
| | 20 % increase in $C_{max}$ and AUC of nortriptyline metabolite | |
| Dihydroergotamine (oral and subcutaneous) | ↔ | ↔ |
| Haloperidol | ↔<br>31 % increase in AUC of the reduced metabolite | NS |
| Propranolol | ↔<br>17 % increase in $C_{max}$ for 4-OH propranolol (TPM 50 mg q12h) | 9 % and 16 % increase in Cmax, 9 % and 17 % increase in AUC (40 mg and 80 mg propranolol q 12h, respectively) |
| Sumatriptan (oral and subcutaneous) | ↔ | NS |
| Pizotifen | ↔ | ↔ |
| Diltiazem | 25 % decrease in AUC of diltiazem and 18 % decrease in DEA, and ↔ for DEM* | 20 % increase in AUC |
| Venlafaxine | ↔ | ↔ |
| Flunarizine | 16 % increase in AUC (TPM 50 mg q12h) [b] | ↔ |

[a] % values and 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.

*DEA = des acetyl diltiazem, DEM = N-demethyl diltiazem.

[b] Flunarizine AUC increased 14 % in subjects taking flunarizine alone. Increase in exposure may be attributed to accumulation during achievement of steady state.

## 4.6 Fertility, pregnancy and lactation

**Pregnancy**

TOPIRAMATE UNICORN is contraindicated during pregnancy (see section 4.3)

Studies in animals and humans have shown reproductive toxicity. In humans, topiramate crosses the placenta and similar concentrations have been reported in the umbilical cord and maternal blood. There are no adequate and well-controlled studies using topiramate in pregnant women.

TOPIRAMATE UNICORN 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). 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 anti-epileptic medicines 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 congenital malformation, there appears to be an increased risk of malformations in subsequent pregnancies when exposed to topiramate.

There is an increased risk of pre-term labour and premature delivery associated with the use of anti-epileptic medicines, including topiramate.

Compared with a reference group not taking anti-epileptic medicines, registry data for topiramate as monotherapy showed a higher prevalence of low birth weight (< 2 500 grams).

One pregnancy registry reported an increased frequency of infants who were small for gestational age (SGA; defined as birth weight below the 10th percentile corrected for their gestational age, stratified by sex) among those exposed to topiramate monotherapy *in utero.*

Specialist advice should be given to women who are of childbearing potential. The need for treatment with anti-epileptic medicines should be reviewed when a woman is planning to become pregnant. In women being treated for epilepsy, sudden discontinuation of anti-epileptic therapy should be avoided as this may lead to breakthrough seizures that could have serious consequences for the woman and the unborn child.

It is recommended to consider alternative therapeutic options in women of child-bearing potential. If TOPIRAMATE UNICORN is used in women of childbearing potential, it is recommended that highly effective contraception be used (see section 4.5), and that the woman is fully informed of the known risks of uncontrolled epilepsy to the pregnancy and the potential risks of topiramate to the fetus. If a woman plans a pregnancy, a pre-conceptional visit is recommended in order to reassess the treatment, and to consider other therapeutic options.

**Lactation**

TOPIRAMATE UNICORN is contraindicated during breastfeeding (see section 4.3).

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. Diarrhoea

and somnolence have been reported in breastfed infants whose mothers receive topiramate treatment.

**Fertility**

Animal studies did not reveal impairment of fertility by topiramate. The effect of topiramate on human fertility has not been established.

## 4.7 Effects on ability to drive and use machines

TOPIRAMATE UNICORN may produce central nervous system related events such as: drowsiness, dizziness or other related symptoms. Caution is advised when driving or operating machinery.

TOPIRAMATE UNICORN may be more sedating than other anti-epileptic medicines.

## 4.8 Undesirable effects

**Tabulated list of adverse reactions**

| System organ class | Frequent | Less frequent |
|---|---|---|
| *Blood and lymphatic system disorders* | Anaemia. | Leucopenia, thrombocytopenia, lymphadenopathy, eosinophilia. |
| *Immune system disorders* | Hypersensitivity. | |
| *Metabolism and nutrition disorders* | Anorexia, decreased appetite. | Metabolic acidosis, hypokalaemia, increased appetite, polydipsia, acidosis hyperchloraemic. |
| *Psychiatric disorders* | Depression, bradyphrenia, insomnia, expressive language disorder, anxiety, confusional | Suicidal ideation, suicidal attempt, hallucination, psychotic disorder, hallucination auditory, |

| | | |
|---|---|---|
| | state, disorientation, aggression, mood altered, agitation, mood swings, depressed mood, anger, abnormal behaviour. | hallucination visual, apathy, lack of spontaneous speech, sleep disorder, affect lability, libido decreased, restlessness, crying, dysphemia, euphoric mood, paranoia, perseveration, panic attach, tearfulness, reading disorder, initial insomnia, flat affect, thinking abnormal, loss of libido, listless, middle insomnia, distractibility, early morning awakening, panic reaction, elevated mood, mania, panic disorder, hypomania. |
| *Nervous system disorders* | Paraesthesia, somnolence, dizziness, disturbance in attention, memory impairment, amnesia, cognitive disorder, mental impairment, psychomotor skills impaired, convulsion, coordination abnormal, lethargy, hypoesthesia, nystagmus, dysgeusia, balance disorder, dysarthria, intension tremor, sedation. | Depressed level of consciousness, grand mal convulsion, visual field defect, complex partial seizures, speech disorder, psychomotor hyperactivity, syncope, sensory disturbance, drooling, hypersomnia, aphasia, repetitive speech, hypokinesia, dyskinesia, dizziness postural, poor quality sleep, burning sensation, sensory loss, parosmia, cerebellar syndrome, dysaesthesia, |

| | | |
|---|---|---|
| | | hypogeusia, stupor, clumsiness, aura, ageusia, dysgraphia, dysphasia, neuropathy peripheral, presyncope, dystonia, formication, apraxia, circadian rhythm sleep disorder, hyperaesthesia, hyposmia, anosmia, essential tremor, akinesia, unresponsive to stimuli. |
| *Eye disorders* | Vision blurred, diplopia, visual disturbance. | Visual acuity reduced, scotoma, dry eye, photophobia, blepharospasm, lacrimation increased, photopsia, mydriasis, presbyopia, blindness, unilateral blindness, transient glaucoma, accommodation disorder, altered visual depth, perception, scintillating scotoma, night blindness, amblyopia. |
| *Ear and labyrinth disorders* | Vertigo, tinnitus, ear pain. | Deafness, deafness unilateral, deafness neurosensory, ear discomfort, hearing impaired. |
| *Cardiac disorders* | | Bradycardia, sinus bradycardia, palpitations. |

| | | |
|---|---|---|
| *Vascular disorders* | | Hypotension, orthostatic hypotension, flushing, hot flush, Raynaud's phenomenon. |
| *Respiratory, thoracic and mediastinal disorders* | Dyspnoea, epistaxis, nasal congestion, rhinorrhoea. | Dyspnoea exertional, paranasal sinus hypersecretion, dysphonia. |
| *Gastrointestinal disorders* | Nausea, diarrhoea, vomiting, constipation, abdominal pain upper, dyspepsia, abdominal pain, dry mouth, stomach discomfort, paraesthesia oral, gastritis, abdominal discomfort. | pancreatitis, flatulence, gastroesophageal reflux disease, abdominal pain lower, hypoaesthesia oral, gingival bleeding, abdominal distension, epigastric discomfort, abdominal tenderness, salivary hypersecretion, oral pain, breath odour, glossodynia. |

| | | |
|---|---|---|
| *Hepatobiliary disorders* | | Hepatitis, hepatic failure. |
| *Skin and subcutaneous disorders* | Alopecia, rash, pruritus. | Anhidrosis, hypoaesthesia facial, urticaria, erythema, rash macular, skin discolouration, dermatitis allergic, swelling face, skin odour abnormal, urticaria localised. |
| *Musculoskeletal and connective tissue disorders* | Arthralgia, muscle spasms, myalgia, muscle twitching, muscular weakness, musculoskeletal chest pain. | Musculoskeletal stiffness, flank pain, muscle fatigue. |
| *Renal and urinary disorders* | Nephrolithiasis, pollakiuria, dysuria. | Calculus urinary, urinary incontinence, haematuria, incontinence, micturition urgency, renal colic, renal pain, calculus ureteric. |
| *Reproductive and breast* | | Erectile dysfunction, |

| | | |
|---|---|---|
| *disorders* | | sexual dysfunction. |
| *General disorders and administration site conditions* | Fatigue, pyrexia, asthenia, irritability, gait disturbance, feeling abnormal, malaise. | Hyperthermia, thirst, sluggishness, peripheral coldness, feeling drunk, feeling jittery, face oedema. |
| *Investigations* | Weight decreased. | Crystal urine present, tandem gait test abnormal, white blood cell count decreased, Increase in liver enzymes, blood bicarbonate decreased. |
| *Social circumstances* | | Learning disability. |

**Post-marketing data**

*Infections and infestations:*

*Frequent:* Nasopharyngitis.

*Blood and lymphatic system disorders:*

*Less frequent:* Neutropenia.

*Immune system disorders:*

*Frequency unknown:* Allergic oedema.

*Metabolism and nutrition disorders:*

*Less frequent:* Hyperammonaemia, hyperammonaemia encephalopathy.

*Psychiatric disorders:*

*Less frequent:* Feeling of despair.

*Eye disorders:*

*Less frequent:* Myopia, abnormal sensation in eye, eyelid oedema.

*Frequency unknown:* Angle closure glaucoma, maculopathy, eye movement disorder, conjunctival oedema.

*Respiratory, thoracic and mediastinal disorders:*

*Frequent:* Cough.

*Skin and subcutaneous disorders:*

*Less frequent:* Stevens-Johnson syndrome, erythema multiforme, periorbital oedema.

*Frequency unknown:* Toxic epidermal necrolysis.

*Musculoskeletal and connective tissue disorders:*

*Less frequent:* Joint swelling, limb discomfort.

*Renal and urinary disorders:*

*Frequent:* Nephrocalcinosis.

*Less frequent:* Renal tubular acidosis.

*General disorders and administration site conditions:*

*Less frequent:* Generalised oedema, influenza like illness.

*Investigations:*

*Frequent:* Weight increased.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of TOPIRAMATE UNICORN is important. It allows continued monitoring of the benefit/risk balance of TOPIRAMATE UNICORN. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

## 4.9 Overdose

**Signs and symptoms**

Overdosage 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 (see section 4.4). 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 UNICORN should be discontinued and general supportive treatment given until clinical toxicity has been diminished or resolved. Haemodialysis 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 centre to obtain the latest recommendations for the management of an overdose.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Category and class: A 2.5 Anticonvulsants, including anti-epileptics.

Pharmacotherapeutic group: Antiepileptics, other antiepileptics.

ATC code: N03AX11.

Topiramate is an anti-epileptic medicine classified as a sulfamate-substituted monosaccharide. Three pharmacological properties of topiramate that may contribute to its anticonvulsant activity are as follows:

- Topiramate reduces the frequency at which action potentials are generated when the neurons are subjected to sustained depolarisation indicative of a state-dependent blockade of voltage-sensitive sodium channels.
- Topiramate markedly enhances the activity of GABA at some types of GABA receptors, thereby enhancing GABA-induced influx of chloride into neurons.
- Topiramate weakly antagonises the ability of kainate to activate the kainate/AMPA subtype of excitatory glutamate receptor, but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype.

Topiramate also inhibits some isoenzymes of carbonic anhydrase. This pharmacological effect is generally weak and may not be a major contributing factor to the anti-epileptic activity of topiramate.

### 5.2 Pharmacokinetic properties

Topiramate is well absorbed after oral administration. The relative bioavailability is about 80 %. Food does not affect the bioavailability of topiramate. Protein binding is low, 13 to 17 %. The time to peak concentration ($T_{max}$) is approximately 2 hours following administration of a 400 mg oral dose. The volume of distribution is 0,6 – 0,8 L/kg with values for women circa 50 % of those for males.

In patients with normal renal function, steady state is reached in about 4 days. The pharmacokinetics of topiramate is linear, with dose-proportional increases in the plasma concentration over the range of 200 to 800 mg a day. The mean elimination half-life (t½) is 21 hours, following single or multiple dosing.

Approximately 70 % of an administered dose is excreted unchanged in the urine and the remainder undergoes metabolism by hydroxylation, hydrolysis and glucuronidation with no one metabolite accounting for more than 5 % of an oral dose.

Topiramate clearance is reduced by 42 % in patients with moderate renal function impairment and by 54 % in patients with severe renal impairment, as compared with the clearance in subjects with normal renal function.

Topiramate is effectively removed from plasma by haemodialysis. A prolonged period of haemodialysis 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 haemodialysis, a supplemental dose of topiramate may be required.

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

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.

Children exhibit a higher clearance and shorter elimination half-life than adults. Consequently, the plasma concentration of topiramate for the same mg/kg dose may be lower in children compared to adults.

The clearance of topiramate may be decreased in patients with impaired hepatic function.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Colloidal silicon dioxide

Lactose anhydrous

Magnesium stearate

Microcrystalline cellulose

Sodium starch glycolate

Opadry White (containing hypromellose, titanium dioxide, macrogol, talc).

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

TOPIRAMATE 25 UNICORN: 24 months

TOPIRAMATE 50 UNICORN and TOPIRAMATE 100 UNICORN: 36 months

### 6.4 Special precautions for storage

Store at or below 25 °C.

Keep the container tightly closed.

Protect from moisture.

### 6.5 Nature and contents of container

White polypropylene canister containing silica gel packed in a white HDPE container with a white child-resistant polypropylene cap.

Or

White HDPE container with a white polypropylene screw cap.

Pack size: 60 tablets.

### 6.6 Special precautions for disposal and other handling

Not applicable.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building B, Ground Floor

22 Karee Street

Centurion, Pretoria

0157

## 8. REGISTRATION NUMBERS

**TOPIRAMATE 25 UNICORN:** 42/2.5/0277

**TOPIRAMATE 50 UNICORN:** 42/2.5/0278

**TOPIRAMATE 100 UNICORN:** 42/2.5/0279

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1 October 2010

## 10. DATE OF REVISION OF THE TEXT

8 September 2022