PROFESSIONAL INFORMATION

SCHEDULING STATUS

Schedule 3

1. NAME OF THE MEDICINE

TOPALEX® 25 mg tablets

TOPALEX® 50 mg tablets

TOPALEX® 100 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each TOPALEX® 25 mg tablet contains 25 mg topiramate

Each TOPALEX® 50 mg tablet contains 50 mg topiramate

Each TOPALEX® 100 mg tablet contains 100 mg topiramate

TOPALEX® Tablets contains sugar (lactose monohydrate)

Each TOPALEX 25 mg tablet contains 30,85 mg lactose monohydrate

Each TOPALEX 50 mg tablet contains 61,70 mg lactose monohydrate

Each TOPALEX 100 mg tablet contains 123,40 mg lactose monohydrate

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

TOPALEX is available as embossed, round, coated tablets in the following strengths and colours: 25 mg white, 50 mg light yellow and 100 mg yellow.

The tablets are imprinted as follows:

TOPALEX 25 mg:	"TOP" on one side, "25" on the other.
TOPALEX 50 mg:	"TOP" on one side, "50" on the other.
TOPALEX 100 mg:	"TOP" on one side, "100" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Epilepsy

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

TOPALEX 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 generalized seizures.
- seizures associated with Lennox-Gastaut syndrome.
- primary generalized 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.

TOPALEX is available in tablets. It is recommended that tablets not be broken.

TOPALEX can be taken without regard to meals.

Posology

MONOTHERAPY

When concomitant AEMs are withdrawn to achieve monotherapy with topiramate, consideration should be given to the effects this may have on seizure control.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 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 When enzyme inducing medicines are withdrawn, topiramate levels will increase. A decrease in TOPALEX 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 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.

In clinical trials, 200 mg was effective and was the lowest dosage studied. This is therefore considered the minimal effective dose. 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.

These dosing recommendations apply to all adults, including the elderly, in the absence of underlying renal disease. (see section 4.4 – Renal impairment).

Children 4 years and over:

The recommended total daily dose of TOPALEX 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.

4.3 Contraindications

Hypersensitivity to any component of this product.

The safety and efficacy of TOPALEX in children under 2 years has not yet been established.

Pregnancy and lactation, as topiramate is teratogenic in animals, whilst there are no adequate data in humans. (see section 4.6)

4.4 Special warnings and precautions for use

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 TOPALEX. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (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 TOPALEX 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 TOPALEX, 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.

Oral contraceptives

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

Visual field defects

Visual field defects have been reported in patients receiving TOPALEX independent of elevated intraocular pressure. In clinical trials, most of these events were reversible after TOPALEX discontinuation. If visual problems occur at any time during TOPALEX treatment, consideration should be given to discontinuing the medicine.

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 (average decrease of 4 mmol/L at doses of 100 mg/day or above in adults and at approximately 6 mg/kg/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, untreated metabolic acidosis may increase the risk of nephrolithiasis or nephrocalcinosis (see section 4.4 - Nephrolithiasis).

Chronic metabolic acidosis in paediatric patients can reduce growth rates. Chronic metabolic acidosis can lead to nephrolithiasis and increased risk for fractures.

Evaluation of 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 (See section 4.8). The risk for hyperammonemia with topiramate appears dose-related. Hyperammonemia has been reported more frequently when topiramate is used concomitantly with valproic acid (See section 4.5).

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

TOPALEX may cause foetal harm when administered to a pregnant woman. There is an increased risk of pre-term labour and premature delivery associated with the use of Antiepileptic Medicines (AEMs) including topiramate.

Withdrawal of TOPALEX

In patients with or without a history of seizures or epilepsy, antiepileptic medicines, including TOPALEX, should be gradually withdrawn to minimise the potential for seizures or increased seizure frequency. In clinical trials, daily dosages were decreased in weekly intervals by 50 – 100 mg in adults with epilepsy. In clinical trials of children, TOPALEX was gradually withdrawn over

a 2 – 8 week period. In situations where rapid withdrawal of TOPALEX is medically required, appropriate monitoring is recommended.

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.

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 TOPALEX. Decreased sweating and hyperthermia (rise in body temperature) may occur especially in young children exposed to high ambient temperatures.

Adequate hydration while using TOPALEX is very important. Hydration can reduce the risk of nephrolithiasis (see below). Proper hydration prior to and during activities such as exercise or exposure to warm temperatures may reduce the risk of heat-related adverse events (see section 4.8). Patients should be warned about this.

Mood Disturbances/Depression

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

Suicide / Suicidal Ideation

In double-blind clinical trials with TOPALEX suicide related events (suicidal ideation, suicide attempts and suicide) occurred at a frequency of 0,5 % in topiramate treated patients (46 out of 8 652 patients treated) compared to 0,2 % treated with placebo (8 out of 4 045 patients treated). One completed suicide was reported in a bipolar disorder double-blind trial in a patient on topiramate.

Patients therefore should 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 TOPALEX (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 TOPALEX should be discontinued.

Nephrolithiasis

Some patients, especially those with a predisposition to nephrolithiasis, are 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 stone formation, a family history of nephrolithiasis and hypercalciuria (see section 4.4 – Metabolic Acidosis). 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.

Concomitant use of TOPALEX with agents predisposing to nephrolithiasis (renal stone formation) should be avoided.

Hepatic impairment

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

Reports of hepatotoxicity and less commonly liver failure in patients taking TOPALEX with and without other medications have been received. Isolated reports have been received of hepatitis and hepatic failure occurring in patients taking multiple medications while being treated with TOPALEX.

Lactose intolerance and lactase deficiency

TOPALEX tablets contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

TOPALEX tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take TOPALEX tablets.

4.5 Interaction with other medicines and other forms of interaction

For purposes of this section, a no effect dose is defined as a ≤ 15 % change.

Effects of TOPALEX on Other Antiepileptic Medicines

The addition of TOPALEX to other antiepileptic medicines (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no effect on their steady-state plasma concentrations, except in the occasional patient, where the addition of TOPALEX 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 should have phenytoin levels monitored.

A pharmacokinetic interaction study of patients with epilepsy indicated the addition of TOPALEX to lamotrigine had no effect on steady state plasma concentration of lamotrigine at TOPALEX doses of 100 to 400 mg/day. In addition, there was no change in steady state plasma concentration of TOPALEX during or after removal of lamotrigine

treatment (mean dose of 327 mg/day). However, the incidence of adverse effects was meaningfully increased on the combination

Effects of Other Antiepileptic Medicines on TOPALEX

Phenytoin and carbamazepine decrease the plasma concentration of TOPALEX. The addition or withdrawal of phenytoin or carbamazepine to TOPALEX 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 TOPALEX and, therefore, does not warrant dosage adjustment of TOPALEX

The above interactions are summarised in the following table:

AEM Coadministered	AEM Concentration	[TOPALEX] 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

AEM = Antiepileptic medicine

Other Medicine Interactions

Digoxin:

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

Oral Contraceptives:

In a pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 mcg ethinyl estradiol (EE), TOPALEX given in the absence of other medications at doses of 50 to 200 mg/day was not associated with statistically significant changes in mean exposure (AUC) to either component of the oral contraceptive. In another study, exposure to EE was statistically significantly decreased at doses of 200, 400 and 800 mg/day (18 %, 21 %, and 30 %, respectively) when given as adjunctive therapy in patients taking valproic acid. In both studies, TOPALEX (50 mg/day to 800 mg/day) did not significantly effect exposure to NET. Although there was a dose dependent decrease in EE exposure for doses between 200-800 mg/day, there was no significant dose dependent change in EE exposure for doses of 50-200 mg/day. The clinical significance of the changes observed is not known. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with TOPALEX. 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:

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

Risperidone:

Interaction studies conducted under single and multiple dose conditions in healthy volunteers and patients with bipolar disorder yielded similar results. When administered concomitantly with TOPALEX at escalating doses of 100, 250 and 400 mg/day there was a reduction in risperidone (administered at doses ranging from 1 to 6 mg/day) systemic exposure (16 % and 33 % for steady-state AUC at the 250 and 400 mg/day doses, respectively). Minimal alterations in the pharmacokinetics of the total active moiety (risperidone plus 9-hydroxyrisperidone) and no alterations for 9-hydroxyrisperidone were observed. There were no clinically significant changes in the systemic exposure of the risperidone total active moiety or of TOPALEX, therefore this interaction is not likely to be of clinical significance.

Hydrochlorothiazide (HCTZ):

An interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg q24h) and TOPALEX (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that TOPALEX Cmax increased by 27 % and AUC increased by 29 % when HCTZ was added to TOPALEX. The clinical significance of this change is unknown. The addition of HCTZ to TOPALEX

therapy may require an adjustment of the TOPALEX dose. The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of TOPALEX. Clinical laboratory results indicated decreases in serum potassium after TOPALEX or HCTZ administration, which were greater when HCTZ and TOPALEX were administered in combination.

Metformin:

An interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin and TOPALEX in plasma when metformin was given alone and when metformin and TOPALEX were given simultaneously. The results of this study indicated that metformin mean C_{max} and mean AUC_{0-12h} increased by 18 % and 25 %, respectively, while mean CL/F decreased 20 % when metformin was co-administered with TOPALEX. TOPALEX did not affect metformin $t_{max.}$ The clinical significance of the effect of TOPALEX on metformin pharmacokinetics is unclear. Oral plasma clearance of TOPALEX 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 TOPALEX pharmacokinetics is unclear. When TOPALEX 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:

An interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of TOPALEX and pioglitazone when administered alone and concomitantly. A 15 % decrease in the $AUC\tau_{,ss}$ of pioglitazone with no alteration in $C_{max,ss}$ was observed. This finding was not statistically significant. In addition, a 13 % and 16 % decrease in $C_{max,ss}$ and $AUC\tau_{,ss}$ respectively, of the active hydroxy-metabolite was noted as well as a 60 % decrease in $C_{max,ss}$ and $AUC\tau_{,ss}$ of the active keto-metabolite. The

clinical significance of these findings is not known. When TOPALEX is added to pioglitazone therapy or pioglitazone is added to TOPALEX therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Glyburide:

An interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glyburide (5 mg/day) alone and concomitantly with TOPALEX (150 mg/day). There was a 25 % reduction in glyburide AUC_{24} during TOPALEX administration. Systemic exposure of the active metabolites, 4-*trans*-hydroxy-glyburide (M1) and 3-*cis*-hydroxyglyburide (M2), were also reduced by 13 % and 15 %, respectively. The steady-state pharmacokinetics of TOPALEX were unaffected by concomitant administration of glyburide. When TOPALEX is added to glyburide therapy or glyburide is added to TOPALEX 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 TOPALEX with alcohol or other central nervous system (CNS) depressant medicines should be avoided.

Other forms of interactions:

Agents predisposing to nephrolithiasis

TOPALEX, when used concomitantly with other agents predisposing to nephrolithiasis, may increase the risk of nephrolithiasis. While using TOPALEX, 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 TOPALEX and valproic acid has been associated with hyperammonaemia with or without encephalopathy in patients who have tolerated either medicine alone. In most cases, symptoms and signs abated with discontinuation of either medicine. (See section 4.4) 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 TOPALEX and valproic acid (VPA) both in conjunction with hyperammonemia and in the absence of hyperammonemia. This adverse event in patients using concomitant TOPALEX and valproate can occur after starting TOPALEX treatment or after increasing the daily dose of TOPALEX.

Vitamin K-antagonist anticoagulant medications

Decreased Prothrombin Time/International Normalised 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 K-antagonist anticoagulant medications.

***Additional Pharmacokinetic Medicine Interaction Studies*:**

Clinical studies have been conducted to assess the potential pharmacokinetic medicine interaction between topiramate and other agents. 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	↔ 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 50mg q12h)	9 % and 16 % increase in C_{max}, 9 % and 17 % increase in AUC (40 mg

		and 80 mg propranolol q12h, 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 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

*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

Studies in animals and humans have shown reproductive toxicity. In rats, topiramate crosses the placental barrier. 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 TOPALEX in pregnant women.

TOPALEX 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 of AEMs (Anti-epileptic medications) 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 AEMs, including topiramate.

Compared with a reference group not taking antiepileptic medicines, registry data for TOPALEX 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 TOPALEX monotherapy *in utero.*

SGA has been observed in all doses and is dose-dependent. The prevalence of SGA is greater in women who received higher doses of topiramate during pregnancy. In addition, the prevalence of SGA for women who continued topiramate use later in pregnancy is higher compared to women who stopped its use before the third trimester

The long-term consequences of the SGA findings could not be determined. A causal relationship for low birth weight and SGA has not been established.

TOPALEX should be used during pregnancy only if potential benefit justifies the potential risk to the foetus. In treating and counselling women of childbearing potential, the prescribing physician should weigh the benefits of therapy against the risks and consider alternative therapeutic options. If this medicine is used during pregnancy or if the patient becomes pregnant while taking this medicine, the patient should be apprised of the potential hazard to the foetus.

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

4.7 Effects on ability to drive and use machines

TOPALEX may produce central nervous system related events such as: 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 medicine is established.

TOPALEX may be more sedating than other antiepileptic medicines.

4.8 Undesirable effects

Adverse events identified in clinical trials, are listed by their incidence in

Table 1.

Assigned frequencies are as follows:

Very common ≥1/10

Common ≥1/100 to <1/10

Uncommon ≥1/1 000 to <1/100

Rare ≥1/10,000 to <1/1 000

The most common adverse events (those with an incidence of > 5 % and greater than that observed in placebo in at least 1 indication in double-blind controlled studies with TOPALEX include: anorexia, decreased appetite, bradyphrenia, depression, expressive language disorder, insomnia, coordination abnormal, disturbance in attention, dizziness, dysarthria, dysgeusia, hypoesthesia, lethargy, memory impairment, nystagmus, paresthesia, somnolence, tremor, diplopia, vision blurred, diarrhoea, nausea, fatigue, irritability, and weight decreased.

<u>Paediatric population</u>

Adverse events reported more frequently (≥ 2-fold) in children than in adults in double-blind controlled studies include: decreased appetite, increased appetite, acidosis hyperchloraemic, hypokalaemia, abnormal behaviour, aggression, apathy, initial

insomnia, suicidal ideation, disturbance in attention, lethargy, circadian rhythm sleep disorder, poor quality sleep, lacrimation increased, sinus bradycardia, feeling abnormal, and gait disturbance.

Adverse events that were reported in children but not in adults in double-blind controlled studies include: eosinophilia, psychomotor hyperactivity, vertigo, vomiting, hyperthermia, pyrexia, and learning disability.

Table 1: TOPALEX Adverse Reactions

System Organ Class	Very Common	Common	Uncommon	Rare
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 state, disorientation, aggression, mood altered, agitation, mood swings, depressed mood, anger, abnormal behaviour	Suicidal ideation, suicide attempt, hallucination, psychotic disorder, hallucination auditory, hallucination visual, apathy, lack of spontaneous speech, sleep disorder,	Mania, panic disorder, hypomania,

			affect lability, libido decreased, restlessness, crying, dysphemia, euphoric mood, paranoia, perseveration, panic attack, tearfulness, reading disorder, initial insomnia, flat affect, thinking abnormal, loss of libido, listless, middle insomnia, distractibility, early morning awakening, panic reaction, elevated mood	
Nervous system disorders	Paraesthesia, somnolence, dizziness	Disturbance in attention, memory impairment,	Depressed level of consciousness, grand mal convulsion, visual	Apraxia, circadian rhythm sleep disorder, hyperaesthesia, hyposmia,

		amnesia, cognitive disorder, mental impairment, psychomotor skills impaired, convulsion, coordination abnormal, tremor, lethargy, hypoaesthesia, nystagmus, dysgeusia, balance disorder, dysarthria, intention tremor, sedation	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,	anosmia, essential tremor, akinesia, unresponsive to stimuli

			neuropathy peripheral, presyncope, dystonia, formication	
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, gastro-oesophageal 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 tissue disorders		Alopecia, rash, pruritus	Anhidrosis, hypoaesthesia facial, urticaria, erythema, pruritus generalised, 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,	Calculus ureteric

			haematuria, incontinence, micturition urgency, renal colic, renal pain	
Reproductive system and breast disorders			Erectile dysfunction, 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	

Postmarketing Data

Adverse events first identified as ADRs during postmarketing experience with TOPALEX are included below.

Adverse Reactions Identified During Postmarketing Experience with TOPALEX

Infections and Infestations

Nasopharyngitis

Blood and Lymphatic System Disorders

Neutropenia, hyperammonaemia

Immune System Disorders

Allergic oedema

Metabolism and Nutrition Disorders

Hyperammonemia

Hyperammonemic encephalopathy

Psychiatric Disorders

Feeling of despair

Eye Disorders

Abnormal sensation in eye, angle closure glaucoma, conjunctival oedema, eye movement disorder, eyelid oedema, maculopathy, myopia

Respiratory,Thoracic and Mediastinal Disorders

Cough

Skin and Subcutaneous Tissue Disorders

Erythema multiforme, periorbital oedema, Steven-Johnson syndrome,

toxic epidermal necrolysis

Musculoskeletal and Connective Tissue Disorders

Joint swelling, limb discomfort

Renal and Urinary Disorders

Nephrocalcinosis

Renal tubular acidosis

General Disorders and Administration Site Reactions

Generalised oedema, influenza like illness

Investigations

Increased weight

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine product is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via “6.04 Adverse Drug Reaction Reporting Form” found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/index/8

Alternatively, suspected adverse reactions may be reported directly to Janssen Pharmaceutica (see section 7 for contact details or visit www.janssen.com).

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 should be discontinued and general supportive treatment given until clinical toxicity has been diminished or resolved. Heamodialysis 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 centre to obtain the latest recommendations for the management of an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.5 Anticonvulsants, including anti-epileptics.

Topiramate is an antiepileptic agent classified as a sulfamate-substituted monosaccharide.

Three pharmacological properties of topiramate have been identified that may contribute to its anticonvulsant activity:

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

In addition, topiramate inhibits some isoenzymes of carbonic anhydrase, however it is not thought to be a major component of topiramate's antiepileptic activity.

5.2 Pharmacokinetic properties

Absorption

Topiramate is rapidly and well absorbed. Following oral administration of 100 mg topiramate to healthy subjects, 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.

Distribution

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 1 200 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.

Metabolism

Topiramate is not extensively metabolised (~ 20 %) in healthy volunteers. It is metabolised up to 50 % in patients receiving concomitant antiepileptic therapy with known inducers of drug metabolising enzymes.

Elimination

The major route of elimination of unchanged topiramate and its metabolites is via the kidney (at least 81 % of the dose). 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. In healthy subjects, pharmacokinetics of topiramate are linear over

a single oral dose range of 100 to 400 mg. Patients with normal renal function may take 4 to 8 days to reach steady-state plasma concentrations. 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.

Concomitant multi-dose administration of topiramate, 100 to 400 mg twice a day, with phenytoin or carbamazepine shows dose proportional increases in plasma concentrations of topiramate.

The plasma and renal clearance of topiramate 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.

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.

The pharmacokinetics of topiramate in children (4 – 16 years), 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 consequently 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 anti-epileptic medicines decrease the steady state plasma concentration.

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 TOPALEX is removed from plasma by haemodialysis, a supplemental dose of TOPALEX 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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablets also contain carnauba wax, lactose, magnesium stearate, microcrystalline cellulose, pregelatinised starch, sodium starch glycolate and OPADRY white, yellow, pink.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 ^{o}C in a dry place. Protect from moisture.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

TOPALEX is available in HDPE opaque containers containing 60 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

JANSSEN PHARMACEUTICA (Pty.) Ltd.

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MARKETED BY:

ZENTIVA
A SANOFI COMPANY

8. REGISTRATION NUMBERS

TOPALEX 25 mg: 41/2.5/0622

TOPALEX 50 mg: 41/2.5/0623

TOPALEX 100 mg: 41/2.5/0624

9 DATE OF FIRST AUTHORISATION

Date of registration:

TOPALEX TABLETS: 04 December 2009

10 DATE OF REVISION OF THE TEXT

Date of the most recently revised Professional Information as approved by SAHPRA: 03 May 2022