Professional Prescribing Information

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

TOPLEP 25 Tablets

TOPLEP 50 Tablets

TOPLEP 100 Tablets

TOPLEP 200 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TOPLEP 25

Each tablet contains topiramate 25 mg.

Contains sugar: lactose monohydrate 5 mg per tablet

TOPLEP 50

Each tablet contains topiramate 50 mg.

Contains sugar: lactose monohydrate 10 mg per tablet

TOPLEP 100

Each tablet contains topiramate 100 mg.

Contains sugar: lactose monohydrate 20 mg per tablet

TOPLEP 200

Each tablet contains topiramate 200 mg

Contains sugar: lactose monohydrate 40 mg per tablet

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets

TOPLEP 25

White, film coated, circular tablets debossed with ‘TP1’ on one side and plain on the other side.

TOPLEP 50

Yellow coloured, film coated, circular tablets debossed with ‘TP2’ on one side and plain on the other side.

TOPLEP 100

Yellow coloured, film coated, circular tablets debossed with ‘TP3’ on one side and plain on the other side.

TOPLEP 200

Peach coloured, film coated, circular tablets debossed with ‘TP4’ on one side and plain on the other side

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Epilepsy

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

TOPLEP tablets are indicated as adjunctive therapy for adults and children over 4 years old 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 generalized tonic clonic seizures
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4.2 Posology and Method of Administration

ADJUNCTIVE THERAPY

Adults

Therapy should begin at 25-50 mg nightly 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.

Since **TOPLEP** is removed from plasma by haemodialysis, an additional dosage equal to approximately one-half of the daily dose should be administered on haemodialysis days. The additional dose should be administered in divided doses at the beginning and completion of the haemodialysis procedure. The additional doses may vary based on the dialysis equipment being used. No dosage adjustment is necessary in elderly patients. For patients with underlying renal disease (see **Section 4.4**).

Children 4 years and over

The initial dose for children is 25 mg for the first week. Titration should begin at 25 mg, based on a range of 1 – 3 mg/kg/day nightly for the first week. The dose is then increased at 1 or 2 week intervals by increments of 1 – 3 mg/kg/day administered in two doses, to achieve optimal clinical response. The recommended dose thereafter is about 5 – 9 mg/kg/day in two divided doses. Dose titration should be guided by clinical outcome.

The recommended initial target dose range of **TOPLEP** monotherapy in children aged four 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

MONOTHERAPY

When concomitant antiepileptic medicines (AEMs) are withdrawn to achieve monotherapy with **TOPLEP** 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 **TOPLEP** levels will increase. A reduction in **TOPLEP** 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 at 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 **TOPLEP** monotherapy in adults is 100 mg/day and the maximum dose is 500 mg. Some patients with refractory forms of epilepsy have tolerated doses of topiramate monotherapy at doses of 1 g per day. These dosing recommendations apply to adults including the elderly in the absence of underlying renal disease.

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 **TOPLEP** is removed from plasma by haemodialysis, a supplemental dose of **TOPLEP** 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

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

Method of administration

For optimal seizure control, in both adults and children, it is recommended that therapy be initiated at a low dose, followed by titration to an effective dose.

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

TOPLEP can be taken without meals

4.3 Contraindications:

TOPLEP tablets are contra-indicated in the following conditions:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- The safety and efficacy of TOPLEP 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.

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 **TOPLEP**. 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 **TOPLEP** 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 **TOPLEP**, 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 TOPLEP independent of elevated intraocular pressure. In clinical trials, most of these events were reversible after **TOPLEP** discontinuation. If visual problems occur at any time during **TOPLEP** 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 redispose 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

TOPLEP 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 TOPLEP

In patients with or without a history of seizures or epilepsy, antiepileptic medicines, including TOPLEP, 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, TOPLEP was gradually withdrawn over a 2 – 8 week period. In situations where rapid withdrawal of TOPLEP 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 **TOPLEP**. Decreased sweating and hyperthermia (rise in body temperature) may occur especially in young children exposed to high ambient temperatures.

Adequate hydration while using **TOPLEP** 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 TOPLEP, 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

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 TOPLEP 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 TOPLEP 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 TOPLEP

TOPLEP may be more sedating than other antiepileptic medicines

Lactose

Patients with rare heriditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsoption should not take this medicine

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per the maximum recommended dose, that is to say essentially 'sodium-free'

4.5 Interaction with other medicines and other forms of Interaction

***Effects of TOPLEP on Other Antiepileptic Medic*ines**

The addition of TOPLEP 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 TOPLEP 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 **TOPLE**P to lamotrigine had no effect on steady state plasma concentration of lamotrigine at TOPLEP doses of 100 to 400 mg/day. In addition, there was no change in steady state plasma concentration of TOPLEP 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 anti-epileptic medicines on TOPLEP

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

The above interactions are summarised in the following table:

AEM Coadministered	AEM Coadministered	**TOPLEP** 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 **TOPLEP** 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), **TOPLEP** 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, **TOPLEP** (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 inpatients taking combination oral contraceptive products with TOPLEP. 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 **TOPLEP** at doses of 200 mg/day; however, there was an observed increase in systemic exposure (26 % for AUC) following **TOPLEP** doses of up to 600 mg/day. Lithium levels should be monitored when co-administered with **TOPLEP**.

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 **TOPLEP** 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 **TOPLEP**, 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 **TOPLEP** (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that **TOPLEP** Cmax increased by 27 % and AUC increased by 29 % when HCTZ was added to **TOPLEP**. The clinical significance of this change is unknown. The addition of HCTZ to **TOPLEP** therapy may require an adjustment of the **TOPLEP** dose. The steady-state pharmacokinetics of HCTZ

were not significantly influenced by the concomitant administration of **TOPLEP**. Clinical laboratory results indicated decreases in serum potassium after **TOPLEP** or HCTZ administration, which were greater when HCTZ and **TOPLEP** were administered in combination.

Metformin:

An interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin and **TOPLEP** in plasma when metformin was given alone and when metformin and **TOPLEP** 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 coadministered with **TOPLEP**. **TOPLEP** did not affect metformin t_{max}. The clinical significance of the effect of **TOPLEP** on metformin pharmacokinetics is unclear. Oral plasma clearance of T**OPLEP** 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 **TOPLEP** pharmacokinetics is unclear. When **TOPLEP** 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 TOPLEP and pioglitazone when administered alone and concomitantly. A 15 % decrease in the AUC□,ss of pioglitazone with no alteration in Cmax,ss was observed. This finding was not statistically significant. In addition, a 13 % and 16 % decrease in Cmax,ss and AUC□,ss respectively, of the active hydroxy-metabolite was noted as well as a 60 % decrease in Cmax,ss and AUC□,ss of the active keto-metabolite.

The clinical significance of these findings is not known. When **TOPLEP** is added to pioglitazone therapy or pioglitazone is added to **TOPLEP** 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 steadystate pharmacokinetics of glyburide (5 mg/day) alone and concomitantly with **TOPLEP** (150 mg/day). There was a 25 % reduction in glyburide AUC24 during **TOPLEP** 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 **TOPLEP** were unaffected by concomitant administration of glyburide. When **TOPLEP** *is added to glyburide therapy or glyburide is added to* **TOPLEP** 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 **TOPLEP** with alcohol or other central nervous system (CNS) depressant medicines should be avoided.

Other forms of interactions:

Agents predisposing to nephrolithiasis

TOPLEP, when used concomitantly with other agents predisposing to nephrolithiasis, may increase the risk of nephrolithiasis. While using **TOPLEP**, 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 **TOPLEP** 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 WARNINGS AND SPECIAL PRECAUTIONS) 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 **TOPLEP** and valproic acid (VPA) both in conjunction with hyperammonemia and in the absence of hyperammonemia. This adverse event in patients using concomitant **TOPLEP** and valproate can occur after starting **TOPLEP** treatment or after increasing the daily dose of **TOPLEP**.

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]	↔

$_{A0/0}$ 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

TOPLEP 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 **TOPLEP** 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 **TOPLEP** 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.
TOPLEP 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.

Lactation

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

Toplep 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.

Toplep may be more sedating than other antiepileptic medicines**.**

4.8 Undesirable effects

System Organ Class	Frequent	Less Frequent	Frequency Unknown
Infections and infestations	Nasopharyngitis, infections, viral infection, moniliasis, otitis media, genital moniliasis, pneumonia, upper respiratory tract infection, urinary tract infection.		

Blood and lymphatic system disorders	Anaemia	Leucopenia, thrombocytopenia lymphadenopathy eosinophilia	Neutropenia,hyperammonaemia
Immune system disorders	Hypersensitivity, allergy (allergic reaction).		Allergic oedema, conjunctival oedema, angioedema.
Endocrine disorders			Hyperthyroidism
Metabolism and nutritional disorders	Anorexia/decreased appetite, decrease in weight, hypoglycaemia.	Metabolic acidosis, hypokalaemia, increased appetite, polydipsia, acidosis hyperchloraemic, hypocalcaemia, hyperlipidaemia, hyperglycaemia, xerophthalmia, diabetes mellitus, hypernatraemia, hypocholesterolaemia.	Hyperammonaemia
Psychiatric disorders	Nervousness, psychomotor slowing, difficulty with memory not otherwise specified, confusion (confusional state), difficulty with concentration/attention, depression, aggravated depression, mood	Affect lability, apathy, psychosis/psychotic symptoms, hallucinations (auditory & visual), suicidal ideas / behaviour or attempts, lack of spontaneous speech, sleep disorder, decreased libido/loss of libido or increased libido, restlessness, crying, dysphemia,	

	problems (mood altered, agitation, mood swings, depressed mood, anger), personality changes/disorder, insomnia, bradyphrenia, expressive language disorder, anxiety, disorientation, aggression, abnormal behaviour, cognitive problems, emotional lability, impotence, depersonalisation, neurosis	euphoric mood, paranoia, perseveration, panic attack, tearfulness, reading disorder, initial insomnia, flat affect, abnormal thinking, listless, middle insomnia, distractibility, early morning awakening, panic reaction/panic disorder, elevated mood, mania, feeling of despair, hypomania, euphoria, paranoid reaction, delusion, delirium, abnormal dreaming, manic reaction.	
Nervous system disorders	Paraesthesia, ataxia, dizziness, speech disorders/related speech problems, language problems, tremor, hyperkinesias, co-ordination problems (abnormal co-ordination), somnolence, attention disturbances , memory impairment, amnesia, cognitive disorder, mental impairment, impaired psychomotor	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, postural dizziness, poor quality sleep, burning sensation, sensory loss, parosmia, cerebellar syndrome,	

	skills, convulsion, lethargy, hypoaesthesia, nystagmus, dysgeusia, balance disorder, dysarthria, intention tremor, sedation, hypertonia, leg cramps, hyporeflexia, aggravated migraine	dysaesthesia, hypogeusia, stupor, clumsiness, aura, ageusia, dysgraphia, dysphasia, peripheral neuropathy, presyncope, dystonia, formication, ptosis, abnormal EEG, upper motor neuron lesion, tongue paralysis, apraxia, circadian rhythm sleep disorder, hyperaesthesia, hyposmia, anosmia, essential tremor, akinesia, unresponsive to stimuli.	
Eye disorders	Abnormal vision, blurred vision, diplopia, nystagmus, secondary angle closure glaucoma, visual disturbance, "abnormal" lacrimation, conjunctivitis, eye abnormality, eye pain	Reduced visual acuity, scotoma, acute myopia, abnormal sensation in eye, dry eye, photophobia, blepharospasm, increased lacrimation, photopsia, mydriasis, presbyopia, unilateral blindness, transient blindness, glaucoma, abnormal accommodation disorder**,** altered visual depth perception, scintillating eyelid oedema, night blindness, amblyopia, strabismus, iritis.	Angle closure glaucoma, maculopathy, eye movement disorder,conjuctival oedema,eyelid oedema,maculopathy,myopia
Ear and labyrinth disorders	Vertigo, tinnitus, ear pain, decreased hearing	Deafness, unilateral deafness, neurosensory deafness, ear discomfort, impaired hearing	

Cardiac disorderrs		Bradycardia, sinus bradycardia, palpitations, angina pectoris, AV block	
Vascular disorders	Hypertension	Hypotension, orthostatic/postural hypotension, flushing, hot flush, Raynaud's phenomenon, vasodilation, deep vein thrombosis, phlebitis, vasospasm	
Respiratory, thoracic and mediastinal disorders	Dyspnoea, epistaxis, nasal congestion, rhinorrhoea, pharyngitis, rhinitis, bronchitis, sinusitis, asthma	Exertional dyspnoea, paranasal sinus hypersecretion, dysphonia, pulmonary embolism.	Cough
Gastro-intestinal disorders	Nausea, diarrhoea, vomiting, constipation, upper abdominal pain, dyspepsia, abdominal pain, dry mouth, stomach discomfort, oral paraesthesia, gastritis, abdominal discomfort, gastroenteritis, GI disorder, faecal incontinence,	Pancreatitis, flatulence, gastro esophageal reflux disease, lower abdominal pain, oral hypoaesthesia, gingival bleeding, abdominal distension, epigastric discomfort, abdominal tenderness, salivary hypersecretion (increased saliva production), oral pain, breath odour, glossodynia, haemorrhoids, stomatitis,	

	dysphagia, glossitis, gum hyperplasia, pharynx oedema.	melaena, oesophagitis, tongue oedema, enlarged abdomen	
Hepato-biliary disorders	Increased Gamma-GT	Hepatic failure, hepatitis, and hepatotoxicity.	
Skin and subcutaneous tissue disorders	Alopecia, rash, pruritus, gingivitis, increased sweating, acne, skin disorder, rash erythematous, pallor, hypertrichosis, eczema, seborrhoea	Anhidrosis, facial hypoaesthesia, urticaria, erythema, macular rash, skin discolouration, allergic dermatitis, swelling face, abnormal skin odour, periorbital oedema, photosensitivity reaction, abnormal hair texture, chloasma	Bullous skin and mucosal reactions, including pemphigus, and toxic epidermal necrolysis, erythema multiforme, periorbital oedema, Steven-Johnson syndrome, toxic epidermal necrosis
Musculoskeletal and subcutaneous tissue disorders	Arthralgia, muscle spasms, myalgia, muscle twitching, muscular weakness, musculoskeletal chest pain, muscle weakness, skeletal pain	musculoskeletal stiffness, flank pain, muscle fatigue, arthrosis	Joint swelling, limb discomfort
Renal and urinary disorders	Nephrolithiasis (kidney stones), pollakiuria, dysuria, cystitis, frequent micturition, prostatic disorder, abnormal urine, nocturia	Incontinence, urinary calculus (ureteric calculus), urinary retention, haematuria, micturition urgency, renal colic, renal pain, albuminuria, polyuria, oliguria.	Renal failure. renal tubular acidosis,nephrocalcinosis
Reproductive system and	Intermenstrual bleeding, vaginal heamorrhage, dysmenorrhoea, breast	Erectile dysfunction, sexual dysfunction, ejaculation disorder, breast discharge.	

breast disorders	pain, amenorrhoea, menorrhagia, leucorrhoea, premature ejaculation.		
General disorders and administration site conditions	Asthenia, fatigue, fever or pyrexia, irritability, gait disturbance/abnormal, feeling abnormal, malaise, , injury, leg pain, taste perversion, back pain, body odour, rigor, pain, neoplasm.	Hyperthermia, thirst, , sluggishness, peripheral coldness, feeling drunk, feeling jittery, face calcinosis, alcohol intolerance, dehydration, taste loss	Oligohydrosis, hypothermia with concomitant valproic acid, influenza like illness,generalised oedema
Investigations	Decreased weight, hyperammonaemia and encephalopathy without and with concomitant valproic acid.	Crystaluria, hypercalcuria, abnormal tandem gait test, decreased white blood cell count, increase in liver enzymes (AST, ALT), decreased blood bicarbonate	increased weight,
Social circumstances		Learning disability	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the **"6.04**

Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/

4.9 Overdose

Overdoses of **TOPLEP** have been reported. Signs and symptoms include headache, severe metabolic acidosis and hypokalaemia, convulsions, drowsiness, speech disturbance, blurred vision, diplopia, impaired mentation, 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 is symptomatic and supportive. An attempt should be made to remove undigested **TOPLEP** from the gastro-intestinal tract using induction of emesis or activated charcoal. Haemodialysis has been shown to be an effective means to remove **TOPLEP** from the body. The patient should be well hydrated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

A 2.5 Anticonvulsants, including anti-epileptics,

Pharmacotherapeutic group: antiepileptics, other antiepileptics, ATC code: N03AX11

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 the neurons 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, thereby enhancing GABA-induced influx of chloride into neurons.
- 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.

Topiramate also inhibits some isoenzymes of carbonic anhydrase, this pharmacological effect is generally weak and may not be a major contributing factor to the antiepileptic activity of topiramate.

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 (Cmax) of 1,5 µg/ml was achieved within 2 to 3 hours (Tmax). Based on the recovery of radioactivity from the urine the mean extent of absorption of a 100 mg oral dose of 14C-topiramate was at least 81 %.

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.

Distribution

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

Biotransformation

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.

Elimination

The mean elimination half-life ($t_{½}$) 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

Linearity/non linearity

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.

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

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

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

6.PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate (Pharmatose 200, microcrystalline cellulose (Avicel PH 101), pregelatinised starch (Starch 1500),sodium starch glycollate (Type A)

Coating material

Opadry 12B58956 White(25mg)

Hypromellose 5 cp (HPMC 2910), , macrogol PEG 400, polysorbate 80, titanium dioxide (CI No.77891),

Opadry 12B52749 Yellow (50 and 100 mg)

Hypromellose 5 cp (HPMC 2910), iron oxide yellow (CI No.77492), macrogol PEG 400, polysorbate 80 titanium dioxide

Opadry 12B56662 Brown (200 mg)

Hypromellose 5 cp (HPMC 2910), iron oxide red (CI No.77491) , macrogol PEG 400, polysorbate 80, titanium dioxide (CI No.77891

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

- Store at or below 25°C in the original package
- Protect from moisture.

6.5 Nature and contents of container

Cartons contain a white opaque HDPE bottle with a desiccant and absorbent cotton wool containing 60 tablets.

6.6 Special precautions for disposal

Return all unused or expired medicines to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewage systems (e.g. toilets)

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals {Pty) Ltd

14 Lautre Road,

Stormill Ext 1

Roodepoort,

1724

South Africa

8.REGISTRATION NUMBER(S)

TOPLEP 25: 40/2.5/0348

TOPLEP 50: 40/2.5/0349

TOPLEP 100: 40/2.5/0350

TOPLEP 200: 40/2.5/0351

NAMIBIA: NS2

TOPLEP 25: Reg.No.: 07/2.5/0168

TOPLEP 50: Reg.No.: 07/2.5/0169

TOPLEP 100: Reg.No.: 07/2.5/0170

TOPLEP 200: Reg.No.: 07/2.5/0171

9.DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 March 2007

10.DATE OF REVISON OF THE TEXT

16 May 2022