For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

NEXTOP

1. Generic Name

Topiramate Tablets I.P.

2. Qualitative and quantitative composition

NEXTOP 25

Each film coated tablet contains:

Topiramat I.P. ……25 mg

Colour: Titanium dioxide I.P.

The excipients used are Lactose, Microcrystalline Cellulose, Pregelatinized Starch, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Talc, Magnesium Stearate, Hydroxypropyl Methyl Cellulose, Polyethylene Glycol, Titanium Dioxide.

NEXTOP 50

Each film coated tablet contains:

Topiramate I.P. ……50 mg

Excipients……...q.s.

Colours: Yellow Oxide of Iron and Titanium Dioxide I.P.

The excipients used are Lactose, Microcrystalline Cellulose, Pregelatinized Starch, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Talc, Magnesium Stearate, Hydroxypropyl Methyl Cellulose, Polyethylene Glycol, Titanium Dioxide and Yellow Oxide of Iron.

NEXTOP 100

Each film coated tablet contains:

Topiramate I.P. ……100 mg

Excipients……...q.s.

Colours: Yellow Oxide of Iron and Titanium Dioxide I.P.

The excipients used are Lactose, Microcrystalline Cellulose, Pregelatinized Starch, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Talc, Magnesium Stearate, Hydroxypropyl Methyl Cellulose, Polyethylene Glycol, Titanium Dioxide and Yellow Oxide of Iron

3. Dosage form and strength

Dosage form: Film Coated Tablets

Strength: 25, 50, 100 mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for the treatment of partial and generalized tonic clonic seizures.

4.2 Posology and method of administration

Posology

It is recommended that therapy be initiated at a low dose followed by titration to an effective dose. Dose and titration rate should be guided by clinical response.

It is not necessary to monitor topiramate plasma concentrations to optimize therapy with NEXTOP. On rare occasions, the addition of topiramate to phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcome. Addition or withdrawal of phenytoin and carbamazepine to adjunctive therapy with NEXTOP may require adjustment of the dose of NEXTOP.

In patients with or without a history of seizures or epilepsy, antiepileptic drugs (AEDs) including topiramate should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency.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 and by 25-50 mg in adults receiving topiramate at doses up to 100 mg/day for migraine prophylaxis. In paediatric clinical trials, topiramate was gradually withdrawn over a 2-8 week period.

Monotherapy epilepsy

General
When concomitant AEDs are withdrawn to achieve monotherapy with topiramate, consideration should be given to the effects this may have on seizure control. Unless safety concerns require an abrupt withdrawal of the concomitant AED, a gradual discontinuation at the rate of approximately one-third of the concomitant AED dose every 2 weeks is recommended.

When enzyme inducing medicinal products are withdrawn, topiramate levels will increase. A decrease in NEXTOP (topiramate) dosage may be required if clinically indicated.

Adults
Dose and titration should be guided by clinical response. 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.

The recommended initial target dose for topiramate monotherapy in adults is 100 mg/day to 200 mg/day in 2 divided doses. The maximum recommended daily dose is 500 mg/day in 2 divided doses. 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.

Paediatric population (children over 6 years of age)
Dose and titration rate in children should be guided by clinical outcome. Treatment of children over 6 years of age 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.

The recommended initial target dose range for topiramate monotherapy in children over 6 years of age is 100 mg/day depending on clinical response, (this is about 2.0mg/kg/day in children 6-16 years).

Adjunctive therapy epilepsy (partial onset seizures with or without secondary generalization, primary generalized tonic-clonic seizures, or seizures associated with
Lennox-Gastaut syndrome)
Adults
Therapy should begin at 25-50 mg nightly for one week. Use of lower initial doses has been reported, but has not been studied systematically. Subsequently, at weekly or biweekly intervals, the dose should be increased by 25-50 mg/day and taken in two divided doses. Some patients may achieve efficacy with once-a-day dosing.

In clinical trials as adjunctive therapy, 200 mg was the lowest effective dose. The usual daily dose is 200-400 mg in two divided doses.

These dosing recommendations apply to all adults, including the elderly, in the absence of underlying renal disease.

Paediatric population (children aged 2 years and above)
The recommended total daily dose of NEXTOP (topiramate) as adjunctive therapy is approximately 5 to 9 mg/kg/day in two divided doses. Titration should begin at 25 mg (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses), to achieve optimal clinical response.

Daily doses up to 30 mg/kg/day have been studied and were generally well tolerated.

<u>Migraine</u>
Adults
The recommended total daily dose of topiramate for prophylaxis of migraine headache is 100 mg/day administered in two divided doses. Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased in increments of 25 mg/day administered at 1-week intervals. If the patient is unable to tolerate the titration regimen, longer intervals between dose adjustments can be used.

Some patients may experience a benefit at a total daily dose of 50 mg/day. Patients have received a total daily dose up to 200 mg/day. This dose may be benefit in some patients, nevertheless, caution is advised due to an increase incidence of side effects.

Paediatric population
NEXTOP (topiramate) is not recommended for treatment or prevention of migraine in children due to insufficient data on safety and efficacy.

<u>General dosing recommendations for NEXTOP in special patient populations</u>

Renal impairment
In patients with impaired renal function (CLCR ≤ 70 mL/min) topiramate should be administered with caution as the plasma and renal clearance of topiramate are decreased. Subjects with known renal impairment may require a longer time to reach steady-state at each dose. Half of the usual starting and maintenance dose is recommended.

In patients with end-stage renal failure, since topiramate is removed from plasma by haemodialysis, a supplemental dose of NEXTOP 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.

Hepatic impairment
In patients with moderate to severe hepatic impairment topiramate should be administered with caution as the clearance of topiramate is decreased.

Elderly
No dose adjustment is required in the elderly population providing renal function is intact.

Method of administration
NEXTOP is available in film-coated tablets and a hard capsule formulation, for oral administration. It is recommended that film-coated tablets not be broken. The hard capsule formulation is provided for those patients who cannot swallow tablets, e.g. paediatric and the elderly.

NEXTOP can be taken without regard to meals.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in List of excipients.
- Migraine prophylaxis in pregnancy and in women of childbearing potential if not using a highly effective method of contraception

4.4 Special warnings and precautions for use

In situations where rapid withdrawal of topiramate is medically required, appropriate monitoring is recommended.

As with other AEDs, some patients may experience an increase in seizure frequency or the onset of new types of seizures with topiramate. These phenomena may be the consequence of an overdose, a decrease in plasma concentrations of concomitantly used AEDs, progress of the disease, or a paradoxical effect.

Adequate hydration while using topiramate 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 reactions.

Women of childbearing potential

Topiramate may cause fetal harm and fetal growth restriction (small for gestational age and low birth weight) when administered to a pregnant woman. The North American Antiepileptic Drug pregnancy registry data for topiramate monotherapy showed an approximate 3-fold higher prevalence of major congenital malformations (4.3%), compared with a reference group not taking AEDs (1.4%). In addition, data from other studies indicate that, compared with monotherapy, there is an increased risk of teratogenic effects associated with the use of AEDs in combination therapy.

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

Oligohydrosis

Oligohydrosis (decreased sweating) has been reported in association with the use of topiramate. Decreased sweating and hyperthermia (rise in body temperature) may occur especially in young children exposed to high ambient temperature.

Mood disturbances/depression

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

Suicide/suicide ideation

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of AEDs has shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for topiramate.

In double blind clinical trials, suicide related events (SREs) (suicidal ideation, suicide attempts and suicide) occurred at a frequency of 0.5% in topiramate treated patients (46 out of 8,652 patients treated) and at a nearly 3-fold higher incidence than those treated with placebo (0.2%; 8 out of 4,045 patients treated).

Patients therefore should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek 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. It is recommended that patients be informed about the signs of serious skin reactions. If SJS or TEN are suspected, use of Topamax should be discontinued.

Nephrolithiasis

Some patients, especially those with a predisposition to nephrolithiasis, may be at increased risk for renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain.

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

Decreased renal function

In patients with impaired renal function ($CL_{CR} \leq 70$ mL/min) topiramate should be administered with caution as the plasma and renal clearance of topiramate are decreased. For specific posology recommendations in patients with decreased renal function.

Decreased hepatic function

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

Acute myopia and secondary angle closure glaucoma

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving topiramate. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperaemia (redness) and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating topiramate therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in paediatric patients as well as adults. Treatment includes discontinuation of topiramate, as rapidly as possible in the judgment of the treating physician, and appropriate measures to reduce intraocular pressure. These measures generally result in a decrease in intraocular pressure.

Elevated intraocular pressure of any aetiology, if left untreated, can lead to serious sequelae including permanent vision loss.

A determination should be made whether patients with history of eye disorders should be treated with topiramate.

Visual field defects

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

Metabolic acidosis

Hyperchloremic, non-anion gap, metabolic acidosis (i.e. decreased serum bicarbonate below the normal reference range in the absence of respiratory alkalosis) is associated with

topiramate treatment. This decrease in serum bicarbonate is due to the inhibitory effect of topiramate on renal carbonic anhydrase. Generally, the decrease in bicarbonate occurs early in treatment although it can occur at any time during treatment. These decreases are usually mild to moderate (average decrease of 4 mmol/l at doses of 100 mg/day or above in adults and at approximately 6 mg/kg/day in paediatric patients). Rarely, patients have experienced decreases to values below 10 mmol/l. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhoea, surgery, ketogenic diet, or certain medicinal products) may be additive to the bicarbonate lowering effects of topiramate.

Chronic metabolic acidosis increases the risk of renal stone formation and may potentially lead to osteopenia.

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

Depending on underlying conditions, appropriate evaluation including serum bicarbonate levels is recommended with topiramate therapy. If signs or symptoms are present (e.g. Kussmaul's deep breathing, dyspnoea, anorexia, nausea, vomiting, excessive tiredness, tachycardia or arrhythmia), indicative of metabolic acidosis, measurement of serum bicarbonate is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering).

Topiramate should be used with caution in patients with conditions or treatments that represent a risk factor for the appearance of metabolic acidosis.

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.

Hyperammonemia and encephalopathy

Hyperammonemia with or without encephalopathy has been reported with topiramate treatment. The risk for hyperammonemia with topiramate appears doserelated. Hyperammonemia has been reported more frequently when topiramate is used concomitantly with valproic acid.

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.

Nutritional supplementation

Some patients may experience weight loss whilst on treatment with topiramate. It is recommended that patients on topiramate treatment should be monitored for weight loss. A dietary supplement or increased food intake may be considered if the patient is losing weight while on topiramate.

Lactose intolerance
NEXTOP tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medication.

Sodium
Each tablet contains less than 1 mmol sodium (23 mg), and is essentially 'sodium free'.

4.5 Drugs interactions

Effects of NEXTOP on other antiepileptic medicinal products

The addition of NEXTOP to other AEDs (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no effect on their steady-state plasma concentrations, except in the occasional patient, where the addition of NEXTOP to phenytoin may result in an increase of plasma concentrations of phenytoin. This is possibly due to inhibition of a specific enzyme polymorphic isoform (CYP2C19). Consequently, any patient on phenytoin showing clinical signs or symptoms of toxicity should have phenytoin levels monitored.

A reported pharmacokinetic interaction study of patients with epilepsy indicated the addition of topiramate to lamotrigine had no effect on steady state plasma concentration of lamotrigine at topiramate doses of 100 to 400 mg/day. In addition, there was no change in steady state plasma concentration of topiramate during or after removal of lamotrigine treatment (mean dose of 327 mg/day).

Topiramate inhibits the enzyme CYP 2C19 and may interfere with other substances metabolized via this enzyme (e.g., diazepam, imipramin, moclobemide, proguanil, omeprazol).

Effects of other antiepileptic medicinal products on NEXTOP

Phenytoin and carbamazepine decrease the plasma concentration of topiramate. The addition or withdrawal of phenytoin or carbamazepine to NEXTOP 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 NEXTOP and, therefore, does not warrant dosage adjustment of NEXTOP. The results of these interactions are summarized below:

AED Coadministered	**AED Concentration**	**NEXTOP Concentration**
Phenytoin	↔**	↓
Carbamazepine (CBZ)	↔	↓
Valproic acid	↔	↔

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

Other medicinal product interactions

Digoxin

In a reported single-dose study, serum digoxin area under plasma concentration curve (AUC) decreased 12% due to concomitant administration of NEXTOP. The clinical relevance of this observation has not been established. When NEXTOP 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 NEXTOP and alcohol or other central nervous system (CNS) depressant medicinal products has not been evaluated in clinical studies. It is recommended that NEXTOP not be used concomitantly with alcohol or other CNS depressant medicinal products.

St John's Wort (Hypericum perforatum)

A risk of decreased plasma concentrations resulting in a loss of efficacy could be observed with co-administration of topiramate and St John's Wort. There have been no clinical studies evaluating this potential interaction.

Oral contraceptives

In a reported pharmacokinetic interaction study in healthy volunteers with a concomitantly administered combination oral contraceptive product containing 1 mg norethindrone (NET) plus 35 µg ethinyl estradiol (EE), NEXTOP 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 reported 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 epilepsy patients taking valproic acid. In both studies, NEXTOP (50-200 mg/day in healthy volunteers and 200-800 mg/day in epilepsy patients) did not significantly affect exposure to NET. Although there was a dose dependent decrease in EE exposure for doses between 200-800 mg/day (in epilepsy patients), there was no significant dose dependent change in EE exposure for doses of 50-200 mg/day (in healthy volunteers). The clinical significance of the changes observed is not known. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered

Patients taking combination oral contraceptive products with NEXTOP. 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 healthy volunteers, there was an observed reduction (18% for AUC) in systemic exposure for lithium during concomitant administration with topiramate 200 mg/day. 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.

Risperidone

Drug-drug interaction studies conducted under single dose conditions in healthy volunteers and multiple dose conditions in patients with bipolar disorder, yielded similar results. When administered concomitantly with topiramate 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). However, differences in AUC for the total active moiety between treatment with risperidone alone and combination treatment with topiramate were not statistically significant. Minimal alterations in the pharmacokinetics of the total active moiety (risperidone plus 9hydroxyrisperidone) and no alterations for 9-hydroxyrisperidone were observed. There were no significant changes in the systemic exposure of the risperidone total active moiety or of topiramate. When topiramate was added to existing risperidone (1-6 mg/day) treatment, adverse events were reported more frequently than prior to topiramate (250-400 mg/day) introduction (90% and 54% respectively). The most frequently reported AE's when topiramate was added to risperidone treatment were: somnolence (27% and 12%), paraesthesia (22% and 0%) and nausea (18% and 9% respectively).

Hydrochlorothiazide (HCTZ)

A reported drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg every 24 h) and topiramate (96 mg every 12 h) when administered alone and concomitantly. The results of this reported study indicate that topiramate C_{max} increased by 27% and AUC increased by 29% when HCTZ was added to topiramate. The clinical significance of this change is unknown. The addition of HCTZ to topiramate therapy may require an adjustment of the topiramate dose. The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicated decreases in serum potassium after topiramate or HCTZ administration, which were greater when HCTZ and topiramate were administered in combination.

Metformin

A reported drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin and topiramate in plasma when metformin was given alone and when metformin and topiramate 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 topiramate. Topiramate did not affect metformin t_{max}. The clinical significance of the

effect of topiramate on metformin pharmacokinetics is unclear. Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The extent of change in the clearance is unknown. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear.
When NEXTOP 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

A reported drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of topiramate 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 NEXTOP is added to pioglitazone therapy or pioglitazone is added to NEXTOP therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Glibenclamide

A reported drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steadystate pharmacokinetics of glibenclamide (5 mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 25% reduction in glibenclamide AUC_{24} during topiramate 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 topiramate were unaffected by concomitant administration of glibenclamide.

When topiramate is added to glibenclamide therapy or glibenclamide is added to topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state. Other forms of interactions

Agents predisposing to nephrolithiasis

NEXTOP, when used concomitantly with other agents predisposing to nephrolithiasis, may increase the risk of nephrolithiasis. While using NEXTOP, agents like these should be avoided since they may create a physiological environment that increases the risk of renal stone formation. *Valproic acid*

Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either medicinal product alone. In most cases, symptoms and signs abated with discontinuation of either medicinal product. This adverse reaction is not due to a pharmacokinetic interaction.

Hypothermia, defined as an unintentional drop in body core temperature to <35°C, has been reported in association with concomitant use of topiramate and valproic acid (VPA) both in conjunction with hyperammonemia and in the absence of hyperammonemia. This adverse event in patients using concomitant topiramate and valproate can occur after starting topiramate treatment or after increasing the daily dose of topiramate.

Warfarin
Decreased Prothrombin Time/International Normalized Ratio (PT/INR) has been reported in patients treated with topiramate in combination with warfarin. Therefore, INR should be carefully monitored in patients concomitantly treated with topiramate and warfarin.

Additional pharmacokinetic drug interaction studies

Clinical studies have been conducted to assess the potential pharmacokinetic drug interaction between topiramate and other agents. The changes in C_{max} or AUC as a result of the interactions are summarized below. The second column (concomitant drug concentration) describes what happens to the concentration of the concomitant drug listed in the first column when topiramate is added. The third column (topiramate concentration) describes how the coadministration of a drug listed in the first column modifies the concentration of topiramate.

Summary of Results from Additional Clinical Pharmacokinetic Drug Interaction Studies		
Concomitant Drug	**Concomitant Drug Concentration[a]**	**Topiramate Concentration[a]**
Amitriptyline	↔ 20% increase in Cmax and AUC of nortriptyline metabolite	NS
Dihydroergotamine (Oral and Subcutaneous)	↔	↔
Haloperidol	↔ 31% increase in AUC of the reduced metabolite	NS
Propranolol	↔ 17% increase in Cmax for 4-OH propranolol (TPM 50 mg q12h)	9% and 16% increase in C_{max}, 9% and17% increase in AUC (40 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 Cmax 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 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Risk related to epilepsy and AEDs in general

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

Monotherapy should be preferred whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated antiepileptics.

Risk related to topiramate

Topiramate was teratogenic in mice, rats and rabbits. 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.

Clinical data from pregnancy registries indicate that infants exposed to topiramate monotherapy have:

An increased risk of congenital malformations (particularly cleft lip/palate, hypospadias, and anomalies involving various body systems) following exposure during the first trimester. The North American Antiepileptic Drug pregnancy registry data for topiramate monotherapy showed an approximate 3-fold higher prevalence of major congenital malformations (4.3%), compared with a reference group not taking AEDs (1.4%). In addition, data from other studies indicate that, compared with monotherapy, there is an increased risk of teratogenic effects associated with the use of AEDs in combination therapy. The risk has been reported to be dose dependent; effects were observed in all doses. In women treated with topiramate who have had a child with a congenital malformation, there appears to be an increased risk of malformations in subsequent pregnancies when exposed to topiramate.

- A higher prevalence of low birth weight (<2500 grams) compared with a reference group.

- An increased prevalence of being small for gestational age (SGA; defined as birth weight below the 10th percentile corrected for their gestational age, stratified by sex). The long term consequences of the SGA findings could not be determined.

Indication epilepsy

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

Indication migraine prophylaxis

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

Breast-feeding

Animal studies have shown excretion of topiramate in milk. 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 human milk. Effects that have been observed in breastfed newborns/infants of treated mothers, include diarrhea, drowsiness, irritability and inadequate weight gain. Therefore, a decision must be made whether to suspend breast-feeding or to discontinue/ abstain from topiramate therapy taking into account the benefit of breast-feeding for the child and the benefit of topiramate therapy for the women.

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

NEXTOP has minor or moderate influence on the ability to drive and use machines. Topiramate acts on the central nervous system and may produce drowsiness, dizziness or other related symptoms. It may also cause visual disturbances and/or blurred vision. These adverse reactions could potentially be dangerous in patients driving a vehicle or operating machinery, particularly until such time as the individual patient's experience with the medicinal products established.

4.8 Undesirable effects

The safety of topiramate was evaluated from a clinical trial database consisting of 4,111 patients (3,182 on topiramate and 929 on placebo) who participated in 20 double-blind trials and 2,847 patients who participated in 34 open-label trials, respectively, for topiramate as adjunctive treatment of primary generalized tonic-clonic seizures, partial onset seizures, seizures associated with Lennox-Gastaut syndrome, monotherapy for newly or recently diagnosed epilepsy or migraine prophylaxis. The majority of adverse reactions were mild to moderate in severity. Adverse reactions identified in clinical trials, and during post-marketing experience (as indicated by "*") are listed by their incidence in clinical trials 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
Not known	cannot be estimated from the available data

The most common adverse reactions (those with an incidence of >5% and greater than that observed in placebo in at least 1 indication in double-blind controlled studies with topiramate) 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.

Topiramate Adverse Reactions					
System Organ Class	**Very common**	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations	nasopharyngitis*				
Blood and lymphatic system disorders		anaemia	leucopenia, thrombocytopenia lymphadenopathy, eosinophilia	neutropenia*	
Immune system disorders		hypersensitivity			allergic oedema*

Metabolism and nutrition disorders		anorexia, decreased appetite	metabolic acidosis, hypokalaemia, increased appetite, polydipsia	acidosis hyperchloraemic, hyperammonemia*, hyperammonemic encephalopathy*	
Psychiatric disorders	depression	bradyphrenia, insomnia, expressive language disorder, anxiety, confusional state, disorientation, aggression, mood altered, agitation, mood swings, depressed	suicidal ideation, suicide attempt, hallucination, psychotic disorder, hallucination auditory, hallucination visual, apathy, lack of spontaneous speech, sleep disorder, affect lability, libido	mania, panic disorder, feeling of despair*, hypomania	

		mood, anger, abnormal behaviour	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, amnesia, cognitive disorder, mental impairment, psychomotor skills impaired, convulsion, coordination abnormal, tremor, lethargy, hypoaesthesia, nystagmus, dysgeusia, balance disorder, dysarthria,	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,	apraxia, circadian	rhythm sleep disorder, hyperaesthesia, hyposmia, anosmia, essential tremor, akinesia, unresponsive to stimuli
		intention tremor, sedation ,	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		
Eye disorders		vision blurred, diplopia, visual disturbance	visual acuity reduced, scotoma, myopia*, abnormal sensation in eye*, dry eye, photophobia, blepharospasm, lacrimation increased, photopsia, mydriasis, presbyopia	blindness unilateral, blindness transient, glaucoma, accommodation disorder, altered visual depth perception,	scintillating scotoma, eyelid oedema*, 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 , cough*	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, gastrooesophageal 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	StevensJohnson syndrome* erythema multiforme*, skin odour abnormal,	periorbital oedema*, urticaria localised

Musculoskeletal and connective tissue disorders		arthralgia, muscle spasms, myalgia, muscle twitching, muscular weakness, musculoskeletal chest pain	joint swelling*, musculoskeletal stiffness, flank pain, muscle fatigue	limb discomfort*
Renal and urinary disorders		nephrolithiasis, pollakiuria, dysuria	calculus urinary, urinary incontinence, haematuria, incontinence, micturition urgency, renal colic, renal pain	calculus ureteric, renal tubular acidosis*
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, influenza like illness*, sluggishness, peripheral coldness, feeling drunk, feeling jittery	face oedema
Investigations	weight decreased	weight increased*	crystal urine present, tandem gait test abnormal, white blood cell count decreased, Increase in liver enzymes	blood bicarbonate decreased
Social circumstances			learning disability	

Identified as an adverse reaction from postmarketing spontaneous reports. Its frequency was calculated based on the incidence in clinical trials, or was calculated if the event did not occur in clinical trials.

Congenital malformations and fetal growth restrictions).

Paediatric population

Adverse reactions reported more frequently (≥2-fold) in children than in adults in double-blind controlled studies include:

- Decreased appetite
- Increased appetite
- Hyperchloraemic acidosis
- 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
- Gait disturbance.

Adverse reactions that were reported in children but not in adults in double-blind controlled studies include:

- Eosinophilia
- Psychomotor hyperactivity
- Vertigo
- Vomiting
- Hyperthermia
- Pyrexia
- Learning disability.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this Medicine.

4.9 Overdose

Signs and symptoms

Overdoses of topiramate have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbances, 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 overdoses with multiple medicinal products including topiramate.

Topiramate overdose can result in severe metabolic acidosis.

Treatment

In acute topiramate overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has been shown to adsorb topiramate in vitro. Treatment should be appropriately supportive and the patient should be well hydrated. Haemodialysis has been shown to be an effective means of removing topiramate from the body.

5. Pharmacological properties

5.1 Mechanism of Action

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

5.2Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, other antiepileptics, antimigraine preparations, ATC code: N03AX11.

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

Action potentials elicited repetitively by a sustained depolarization of the neurons were blocked by topiramate in a time-dependent manner, suggestive of a state-dependent sodium channel blocking action. Topiramate increased the frequency at which γaminobutyrate (GABA) activated GABAA receptors, and enhanced the ability of GABA to induce a flux of chloride ions into neurons, suggesting that topiramate potentiates the activity of this inhibitory neurotransmitter.

This effect was not blocked by flumazenil, a benzodiazepine antagonist, nor did topiramate increase the duration of the channel open time, differentiating topiramate from barbiturates that modulate GABAA receptors.

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

In addition, topiramate inhibits some isoenzymes of carbonic anhydrase. This pharmacologic effect is much weaker than that of acetazolamide, a known carbonic anhydrase inhibitor, and is not thought to be a major component of topiramate's antiepileptic activity.

In animal studies, topiramate exhibits anticonvulsant activity in rat and mouse maximal electroshock seizure (MES) tests and is effective in rodent models of epilepsy, which include tonic and absence-like seizures in the spontaneous epileptic rat (SER) and tonic and clonic seizures induced in rats by kindling of the amygdala or by global ischemia. Topiramate is only weakly effective in blocking clonic seizures induced by the GABAA receptor antagonist, pentylenetetrazole.

Studies in mice receiving concomitant administration of topiramate and carbamazepine or phenobarbital showed synergistic anticonvulsant activity, while combination with phenytoin showed additive anticonvulsant activity. In well-controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations of topiramate and its clinical efficacy. No evidence of tolerance has been demonstrated in man.

Absence seizures

Two small one arm studies were carried out with children aged 4-11 years old (CAPSS326 and TOPAMAT-ABS-001). One included 5 children and the other included 12 children before it was terminated early due to lack of therapeutic response. The doses used in these reportedd studies were up to approximately 12 mg/kg in study TOPAMAT-ABS-001 and a maximum of the lesser of 9 mg/kg/day or 400 mg/day in study CAPSS-326. These studies do not provide sufficient evidence to reach conclusion regarding efficacy or safety in the paediatric population.

5.3 Pharmacokinetic properties

The film-coated tablet and hard capsule formulations are bioequivalent.

The pharmacokinetic profile of topiramate compared to other AEDs shows a long plasma half-life, linear pharmacokinetics, predominantly renal clearance, absence of significant protein binding, and lack of clinically relevant active metabolites.

Topiramate is not a potent inducer of drug metabolizing enzymes, can be administered without regard to meals, and routine monitoring of plasma topiramate concentrations is not necessary. In clinical studies, there was no consistent relationship between plasma concentrations and efficacy or adverse events.

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%. 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 1200 mg. An effect of gender on the volume of distribution was detected, with values for females circa 50% of those for males. This was attributed to the higher percent body fat in female patients and is of no clinical consequence.

Biotransformation

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

Elimination

In humans, the major route of elimination of unchanged topiramate and its metabolites is via the kidney (at least 81% of the dose). Approximately 66% of a dose of 14Ctopiramate was excreted unchanged in the urine within four days. Following twice a day dosing with 50 mg and 100 mg of topiramate the mean renal clearance was approximately 18 ml/min and 17 ml/min, respectively. There is evidence of renal tubular reabsorption of topiramate. This is supported by studies in rats where topiramate was co-administered with probenecid, and a significant increase in renal clearance of topiramate was observed. Overall, plasma clearance is approximately 20 to 30 ml/min in humans following oral administration.

Linearity/non-linearity

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

Use with other AEDs

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

Renal impairment

The plasma and renal clearance of topiramate are decreased in patients with moderate and severe impaired renal function (CLCR $\leq$ 70 ml/min). As a result, higher steadystate topiramate plasma concentrations are expected for a given dose in renal-impaired patients as compared to those with normal renal function. In addition, patients with renal impairment will require a longer time to reach steady-state at each dose. In patients with moderate and severe renal impairment, half of the usual starting and maintenance dose is recommended.

Topiramate is effectively removed from plasma by haemodialysis. A prolonged period of hemodialysis may cause topiramate concentration to fall below levels that are required to maintain an anti-seizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis, a supplemental dose of topiramate may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed.

Hepatic impairment

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

Elderly population

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

Paediatric population (pharmacokinetics, up to 12 years of age)

The pharmacokinetics of topiramate in children, as in adults receiving add-on therapy, are linear, with clearance independent of dose and steady-state plasma concentrations increasing

in proportion to dose. Children, however, have a higher clearance and a shorter elimination half-life. Consequently, the plasma concentrations of topiramate for the same mg/kg dose may be lower in children compared to adults. As in adults, hepatic enzyme inducing AEDs decrease the steady-state plasma concentrations.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

In nonclinical studies of fertility, despite maternal and paternal toxicity as low as 8 mg/kg/day, no effects on fertility were observed, in male or female rats with doses up to 100 mg/kg/day.

In preclinical studies, topiramate has been shown to have teratogenic effects in the species studied (mice, rats and rabbits). In mice, fetal weights and skeletal ossification were reduced at 500 mg/kg/day in conjunction with maternal toxicity. Overall numbers of fetal malformations in mice were increased for all drug-treated groups (20, 100 and 500 mg/kg/day).

In rats, dosage-related maternal and embryo/fetal toxicity (reduced fetal weights and/or skeletal ossification) were observed down to 20 mg/kg/day with teratogenic effects (limb and digit defects) at 400 mg/kg/day and above. In rabbits, dosage-related maternal toxicity was noted down to 10 mg/kg/day with embryo/fetal toxicity (increased lethality) down to 35 mg/kg/day, and teratogenic effects (rib and vertebral malformations) at 120 mg/kg/day.

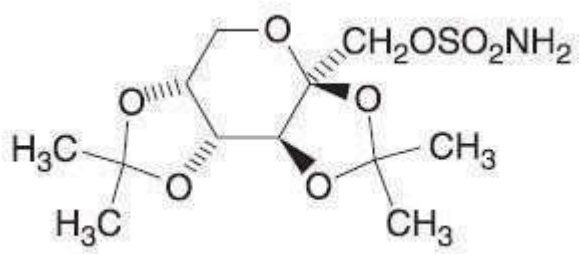
The teratogenic effects seen in rats and rabbits were similar to those seen with carbonic anhydrase inhibitors, which have not been associated with malformations in humans. Effects on growth were also indicated by lower weights at birth and during lactation for pups from female rats treated with 20 or 100 mg/kg/day during gestation and lactation. In rats, topiramate crosses the placental barrier.

In juvenile rats, daily oral administration of topiramate at doses up to 300 mg/kg/day during the period of development corresponding to infancy, childhood, and adolescence resulted in toxicities similar to those in adult animals (decreased food consumption with decreased body weight gain, centrolobullar hepatocellular hypertrophy). There were no relevant effects on long bone (tibia) growth or bone (femur) mineral density, preweaning and reproductive development, neurological development (including assessments on memory and learning), mating and fertility or hysterotomy parameters.

In a battery of *in vitro* and *in vivo* mutagenicity assays, topiramate did not show genotoxic potential.

7. Description

Topiramate has the molecular formula $C_{12}H_{21}NO_8S$ and a molecular weight of 339.36. Topiramate is designated chemically as 2, 3:4, 5-Di-O-isopropylidene-β-D-fructopyranose sulfamate and has the following structural formula:



Topiramate is a white to off-white powder which is freely soluble in ethyl acetate and in ethanol; slightly soluble in water.

NEXTOP 25
White to off white, round, biconvex, film coated tablets with breakline on one side and plain on other side. The excipients used are Lactose, Microcrystalline Cellulose, Pregelatinized Starch, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Talc, Magnesium Stearate, Hydroxypropyl Methyl Cellulose, Polyethylene Glycol, Titanium Dioxide.

NEXTOP 50
Yellow coloured, round, biconvex, film coated tablets with breakline on one side and plain on other side. The excipients used are Lactose, Microcrystalline Cellulose, Pregelatinized Starch, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Talc, Magnesium Stearate, Hydroxypropyl Methyl Cellulose, Polyethylene Glycol, Titanium Dioxide and Yellow Oxide of Iron.

NEXTOP 100
Light yellow coloured, round, biconvex, film coated tablets with breakline on one side and plain on other side. The excipients used are Lactose, Microcrystalline Cellulose, Pregelatinized Starch, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Talc, Magnesium Stearate, Hydroxypropyl Methyl Cellulose, Polyethylene Glycol, Titanium Dioxide and Yellow Oxide of Iron.

8. Pharmaceutical particulars

8.1 Incompatibilities
Not applicable.

8.2 Shelf-life
Do not use later than the date of expiry.

8.3 Packaging information
NEXTOP is packed in blister strips of 10 tablets.

8.4 Storage and handing instructions
- Store protected from moisture, at a temperature not exceeding 30^0C.
- Keep out of reach of children.

9. Patient Counselling Information

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What in this leaflet:

9.1 What NEXTOP is and what it is used for

NEXTOP belongs to a group of medicines called "anti-epileptic medicines". It is used:

- alone to treat seizures in adults and children over age 6
- with other medicines to treat seizures in adults and children aged 2 years and above
- to prevent migraine headaches in adults.

9.2 What you need to know before you take NEXTOP

Do not take NEXTOP:

- if you are allergic to topiramate or any of the other ingredients of this medicine.
- for migraine prevention: if you are pregnant or if you are a woman of childbearing potential unless you are using effective contraception. You should talk to your doctor about the best kind of contraception to use while you are taking NEXTOP.

If you are not sure if the above applies to you, talk to your doctor or pharmacist before using NEXTOP

Warnings and precautions

Talk to your doctor or pharmacist before taking NEXTOP if you:

- have kidney problems, especially kidney stones, or are getting kidney dialysis
- have a history of blood and body fluid abnormality (metabolic acidosis)
- have liver problems
- have eye problems, especially glaucoma
- have a growth problem
- are on a high fat diet (ketogenic diet).
- are taking NEXTOP to treat epilepsy and you are pregnant or a woman of childbearing potential.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using NEXTOP.

It is important that you do not stop taking your medicine without first consulting your doctor.

You should also talk to your doctor before taking any medicine containing topiramate that is given to you as an alternative to NEXTOP.

You may lose weight if you use NEXTOP so your weight should be checked regularly when using this medicine. If you are losing too much weight or a child using this medicine is not gaining enough weight, you should consult your doctor.

A small number of people being treated with anti-epileptic medicines such as NEXTOP have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

NEXTOP may in rare cases cause high levels of ammonia in the blood (seen in blood tests) which can lead to a change in brain function, especially if you are also taking a medicine called valproic acid or sodium valproate. Since this may be a severe condition, tell your doctor immediately if the following symptoms occur:
- difficulty thinking, remembering information, or solving problems
- being less alert or aware
- feeling very sleepy with low energy

At higher doses of NEXTOP, the risk of developing these symptoms may increase.

Other medicines and NEXTOP
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. NEXTOP and certain other medicines can affect each other. Sometimes the dose of some of your other medicines or NEXTOP will have to be adjusted.

Especially, tell your doctor or pharmacist if you are taking:
- other medicines that impair or decrease your thinking, concentration, or muscle coordination (e.g. central nervous system depressant medicines such as muscle relaxants and sedatives).
- birth control pills. NEXTOP may make your birth control pills less effective. You should talk to your doctor about the best kind of contraception to use while you are taking NEXTOP.

Tell your doctor if your menstrual bleeding changes while you are taking birth control pills and NEXTOP.

Keep a list of all the medicines you take. Show this list to your doctor and pharmacist before you start a new medicine.

Other medicines you should discuss with your doctor or pharmacist include other anti-epileptic medicines, risperidone, lithium, hydrochlorothiazide, metformin, pioglitazone, glibenclamide, amitriptyline, propranolol, diltiazem, venlafaxine, flunarazine, St. John's wort (Hypericum perforatum) (a herbal preparation used to treat depression), warfarin used to thin the blood.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using NEXTOP.

NEXTOP with food and drink
You can take NEXTOP with or without food. Drink plenty of fluids during the day to prevent kidney stones while taking NEXTOP. You should avoid drinking alcohol when taking NEXTOP.

Pregnancy and breast-feeding
Migraine prevention:
NEXTOP can harm an unborn baby. You must not use NEXTOP if you are pregnant. You must not use NEXTOP for migraine prevention if you are a woman of childbearing potential unless you are using effective contraception. Talk to your doctor about the best kind of contraception and whether NEXTOP is suitable for you. Before the start of treatment with NEXTOP a pregnancy test should be performed.

Treatment of epilepsy:
If you are a woman of childbearing potential you should talk to your doctor about other possible treatments instead of NEXTOP. If the decision is made to use NEXTOP, you should use effective contraception. Talk to your doctor about the best kind of contraception to use while you are taking NEXTOP. Before the start of treatment with NEXTOP a pregnancy test should be performed.

Talk to your doctor if you wish to become pregnant.
As with other anti-epileptic medicines, there is a risk of harm to the unborn child if NEXTOP is used during pregnancy. Make sure you are very clear about the risks and the benefits of using NEXTOP for epilepsy during pregnancy.

- If you take NEXTOP during pregnancy, your baby has a higher risk for birth defects, particularly, cleft lip (split in the top lip) and cleft palate (split in the roof of the mouth). Newborn boys may also have a malformation of the penis (hypospadia). These defects can develop early in pregnancy, even before you know you are pregnant.
- If you take NEXTOP during pregnancy, your baby may be smaller than expected at birth. Talk to your doctor if you have questions about this risk during pregnancy.
- There may be other medicines to treat your condition that have a lower risk of birth defects.
- Tell your doctor straight away if you become pregnant while taking NEXTOP. You and your doctor should decide if you will continue to take NEXTOP while you are pregnant.

Breast-feeding
The active substance in NEXTOP (topiramate) passes into human milk. Effects have been seen in breastfed babies of treated mothers, including diarrhea, feeling sleepy, feeling irritable, and poor weight gain.

Therefore, your doctor will discuss with you whether you abstain from breast-feeding or whether to abstain from treatment with NEXTOP. Your doctor will take into account the importance of the medicine to the mother and the risk for the baby.

Mothers who breast-feed while taking NEXTOP must tell the doctor as soon as possible if the baby experiences anything unusual.

Driving and using machines
Dizziness, tiredness, and vision problems may occur during treatment with NEXTOP. Do not drive or use any tools or machines without talking to your doctor first.

NEXTOP contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product

9.3 How to take NEXTOP

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

- Your doctor will usually start you on a low dose of NEXTOP and slowly increase your dose until the best dose is found for you.
- NEXTOP tablets are to be swallowed whole. Avoid chewing the tablets as they may leave a bitter taste.
- NEXTOP can be taken before, during, or after a meal. Drink plenty of fluids during the day to prevent kidney stones while taking NEXTOP.

If you take more NEXTOP than you should

- See a doctor right away. Take the medicine pack with you.
- You may feel sleepy, tired, or less alert; lack coordination; have difficulty speaking or concentrating; have double or blurred vision; feel dizzy due to low blood pressure; feel depressed or agitated; or have abdominal pain, or seizures (fits).

Overdose can happen if you are taking other medicines together with NEXTOP

If you forget to take NEXTOP

- If you forget to take a dose, take it as soon as you remember it. However, if it is almost time for your next dose, skip the missed dose and continue as usual. If you miss two or more doses, contact your doctor.
- Do not take a double dose (two doses at the same time) to make up for a forgotten dose.

If you stop taking NEXTOP
Do not stop taking this medicine unless told to do so by your doctor. Your symptoms may return. If your doctor decides to stop this medication, your dose may be decreased gradually over a few days.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor, or seek medical attention immediately if you have the following side effects:

Very common (may affect more than 1 in 10 people)

- Depression (new or worse)

Common (may affect up to 1 in 10 people)
- Seizures (fits)
- Anxiety, irritability, changes in mood, confusion, disorientation
- Problems with concentration, slowness of thinking, loss of memory, problems with memory (new onset, sudden change or increased severity)
- Kidney stone, frequent or painful urination

Uncommon (may affect up to 1 in 100 people)
- Increased acid level in the blood (may cause troubled breathing including shortness of breath, loss of appetite, nausea, vomiting, excessive tiredness, and fast or uneven heart beats)
- Decreased or loss of sweating (particularly in young children who are exposed to high temperatures)
- Having thoughts of serious self-harm, trying to cause serious self-harm
- Loss of part of the field of vision

Rare (may affect up to 1 in 1,000 people)
- Glaucoma – blockage of fluid in eye causing increased pressure in the eye, pain, or decreased vision
- Difficulty thinking, remembering information, or solving problems, being less alert or aware, feeling very sleepy with low energy – these symptoms may be a sign of a high level of ammonia in the blood (hyperammonemia), which can lead to a change in brain function (hyperammonemic encephalopathy)

Other side effects include the following, if they get serious, please tell your doctor or pharmacist:
Very common (may affect more than 1 in 10 people)
- Stuffy, runny nose or sore throat
- Tingling, pain and/or numbness of various body parts
- Sleepiness, tiredness
- Dizziness
- Nausea, diarrhoea
- Weight loss

Common (may affect up to 1 in 10 people)
- Anaemia (low blood count)
- Allergic reaction (such as skin rash, redness, itching, facial swelling, hives)
- Loss of appetite, decreased appetite
- Aggression, agitation, anger, abnormal behaviour
- Difficulty falling or staying asleep
- Problems with speech or speech disorder, slurred speech
- Clumsiness or lack of coordination, feeling of unsteadiness when walking
- Decreased ability to complete routine tasks
- Decreased, loss of, or no sense of taste
- Involuntary trembling or shaking; rapid, uncontrollable movements of the eyes
- Visual disturbance, such as double vision, blurred vision, decreased vision, difficulty focusing

- Sensation of spinning (vertigo), ringing in the ears, ear pain
- Shortness of breath
- Cough
- Nose bleeds
- Fever, not feeling well, weakness
- Vomiting, constipation, abdominal pain or discomfort, indigestion, stomach or intestinal infection
- Dry mouth
- Hair loss
- Itching
- Joint pain or swelling, muscle spasms or twitching, muscle aches or weakness, chest pain
- Weight gain

Uncommon (may affect up to 1 in 100 people)
- Decrease in platelets (blood cells that help stop bleeding), decrease in white blood cells that help to protect you against infection, decrease in potassium level in the blood
- Increase in liver enzymes, increase in eosinophils (a type of white blood cell) in the blood
- Swollen glands in the neck, armpit, or groin
- Increased appetite
- Elevated mood
- Hearing, seeing, or feeling things that are not there, severe mental disorder (psychosis)
- Showing and/or feeling no emotion, unusual suspiciousness, panic attack
- Problems with reading, speech disorder, problems with handwriting
- Restlessness, hyperactivity
- Slowed thinking, decreased wakefulness or alertness
- Reduced or slow body movements, involuntary abnormal or repetitive muscle movements
- Fainting
- Abnormal sense of touch; impaired sense of touch
- Impaired, distorted, or no sense of smell
- Unusual feeling or sensation that may precede a migraine or a certain type of seizure
- Dry eye, sensitivity of the eyes to light, eyelid twitching, watery eyes
- Decreased or loss of hearing, loss of hearing in one ear
- Slow or irregular heartbeat, feeling your heart beating in your chest
- Low blood pressure, low blood pressure upon standing (consequently, some people taking NEXTOP may feel faint, dizzy, or may pass out when they stand up or sit up suddenly)
- Flushing, feeling warm
- Pancreatitis (inflammation of the pancreas)
- Excessive passing of gas or wind, heartburn, abdominal fullness or bloating
- Bleeding gums, increased saliva, drooling, breath odour
- Excessive intake of fluids, thirst
- Skin discolouration
- Muscle stiffness, pain in side
- Blood in urine, incontinence (lack of control) of urine, urgent desire to urinate, flank or kidney pain
- Difficulty getting or keeping an erection, sexual dysfunction
- Flu-like symptoms
- Cold fingers and toes

- Feeling drunk
- Learning disability

Rare (may affect up to 1 in 1,000 people)
- Abnormally elevated mood
- Loss of consciousness
- Blindness in one eye, temporary blindness, night blindness
- Lazy eye
- Swelling in and around the eyes
- Numbness, tingling and colour change (white, blue then red) in fingers and toes when exposed to the cold
- Inflammation of the liver, liver failure
- Stevens Johnson syndrome, a potentially life-threatening condition that may present with sores in multiple mucosal sites (such as the mouth, nose, and eyes), a skin rash, and blistering
- Abnormal skin odour
- Discomfort in your arms or legs
- Kidney disorder

Not known (frequency cannot be estimated from the available data)
- Maculopathy is a disease of the macula, the small spot in the retina where vision is keenest. You should call your doctor if you notice a change or decrease in your vision.
- Toxic epidermal necrosis, a life-threatening condition related to, yet more severe than, Stevens-Johnson syndrome, characterized by widespread blistering and sloughing of the outer layers of the skin (see rare side effects)

Children
The side effects in children are generally similar to those seen in adults, but the following side effects may be more common in children than adults:
- Problems with concentration
- Increased acid level in the blood
- Having thoughts of serious self-harm
- Tiredness
- Decreased or increased appetite
- Aggression, abnormal behaviour
- Difficulty falling or staying asleep
- Feeling of unsteadiness when walking
- Not feeling well
- Decrease in potassium level in the blood
- Showing and/or feeling no emotion
- Watery eyes
- Slow or irregular heartbeat

Other side effects that may occur in children are:
Common (may affect up to 1 in 10 people)
- Sensation of spinning (vertigo)
- Vomiting

- Fever

Uncommon (may affect up to 1 in 100 people)
- Increase in eosinophils (a type of white blood cell) in the blood
- Hyperactivity
- Feeling warm
- Learning disability

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.
By reporting side effects, you can help provide more information on the safety of this Medicine.

9.5 How to store NEXTOP
- Store protected from moisture, at a temperature not exceeding 30^0C.
- Keep out of reach of children.
- Do not use this medicine after the expiry date which is stated on the bottle/carton after EXP. The expiry date refers to the last day of that month.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment

9.6 Contents of the pack and other information
What NEXTOP tablet contains
- The active substance is Topiramate.
- Each NEXTOP film-coated tablet contains 25, 50 or 100 mg of topiramate
- The other ingredients are:

NEXTOP 25
The excipients used are Lactose, Microcrystalline Cellulose, Pregelatinized Starch, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Talc, Magnesium Stearate, Hydroxypropyl Methyl Cellulose, Polyethylene Glycol, Titanium Dioxide.

NEXTOP 50 & 100
Lactose, Microcrystalline Cellulose, Pregelatinized Starch, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Talc, Magnesium Stearate, Hydroxypropyl Methyl Cellulose, Polyethylene Glycol, Titanium Dioxide and Yellow Oxide of Iron.

What NEXTOP looks like and contents of the pack
NEXTOP is packed in blister strips of 10 tablets

10. Details of manufacturer
NEXTOP 25
Torrent Pharmaceuticals ltd.
Vill.Bhud & Makhnu Majra,
The. Baddi-173 205, Dist. Solan(H.P.), INDIA.

NEXTOP 50 & 100
Ravenbhel Biotech
EPIP, SIDCO, Kartholi,
Bari-Brahmana, Jammu-181133

11. Details of permission or licence number with date

NEXTOP 25
MNB/05/183 issued on 01.07.2010

NEXTOP 50 & 100
JK/01/11-12/192 issued on 04.09.2015

12. Date of revision
APR 2021

MARKETED BY
TORRENT PHARMACEUTICALS LTD.
IN/NEXTOP 25, 50, 100mg/APR 2021/07/PI