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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency granted STD Chemicals Ltd, Marketing Authorisations for the medicinal products, Topiramate 25 mg, 50 mg, 100 mg and 200 mg Film-Coated Tablets (PL 36390/0069-72) on 24 January 2012. These prescription-only medicines (POM) belong to a group of medicines called “antiepileptic medicines”. They are used:

- alone to treat seizures in adults and children over the age of 6
- with other medicines to treat seizures in adults and children over the age of 2
- to prevent migraine headaches in adults

These applications are considered to be identical to the previously granted licences for Topiramate 25 mg, 50 mg, 100 mg and 200 mg Film-Coated Tablets (PL 08137/0243-0246) authorised to NeoLab Ltd on 12 August 2011.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Topiramate 25 mg, 50 mg, 100 mg and 200 mg Film-Coated Tablets (PL 36390/0069-72) outweigh the risks; hence Marketing Authorisations have been granted.
# SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted STD Chemicals Ltd., Marketing Authorisations for the medicinal products, Topiramate 25 mg, 50 mg, 100 mg and 200 mg Film-Coated Tablets (PL 36390/0069-72, on 24 January 2012. The products are prescription-only medicines.

These are simple, abridged, ‘informed consent’ applications submitted according to Article 10(c) of EC Directive 2001/83 (as amended), cross-referencing the Marketing Authorisation for Topiramate 25 mg, 50 mg, 100 mg and 200 mg Film-Coated Tablets (PL 08137/0243-0246) authorised to Neolab Ltd on 12 August 2011. The reference products cross-refer to the innovator products Topamax 25 mg, 50 mg 100 mg and 200 mg Tablets granted in 1995 to Janssen-Cilag Ltd, UK. The innovator products has been authorised in the EEA for over 10 years.

The active ingredient, topiramate, is classified as a sulphamate-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 neurons are subjected to a sustained depolarisation indicative of a state-dependent blockade of voltage-sensitive sodium channels. Topiramate enhances the activity of GABA at some types of GABA receptors. Topiramate weakly antagonises the excitatory activity of kainite/AMPA subtype of glutamate receptor but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype.

No new data were submitted nor were they necessary for these simple applications, as the data is identical to that of the previously granted cross-reference products. A Public Assessment Report (PAR) has been generated for the reference products Topiramate 25 mg, 50 mg, 100 mg and 200 mg Film-Coated Tablets (PL 08137/0243-0246).
1. INTRODUCTION
These are simple, informed consent applications for Topiramate 25 mg, 50 mg, 100 mg and 200 mg Film-Coated Tablets submitted under Article 10c of Directive 2001/83/EC. The proposed Marketing Authorisation Holder is STD Chemicals Ltd, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW, UK.

The applications cross-refer to Topiramate 25 mg, 50 mg, 100 mg and 200 mg Film-Coated Tablets (PL 08137/0243-246) authorised to Neolab Ltd since 12 August 2011. The current applications are considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM
2.1 Name
The proposed names of the products are Topiramate 25 mg, 50 mg, 100 mg and 200 mg Film-Coated Tablets. The products have been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
Each film coated tablet contains 25 mg, 50 mg, 100 mg and 200 mg respectively, of the active ingredient, topiramate. The medicinal products are licensed for marketing in either blister strips or bottles. The blister strips are composed of aluminium and coated with polyvinylchloride (PVC) and vinyl chloride vinyl acetate terpolyer resin (VMCH); the strips are packed with the Patient Information Leaflet (PIL) into cardboard outer cartons, in pack sizes of 28, 56, 60 & 84 tablets. The bottles are composed of opaque high density polyethylene, with white opaque polypropylene child resistant closures with a desiccant, the bottles are packed with the PIL into cardboard outer cartons, in pack sizes of 60, 100 & 200 tablets.

The container closure systems and pack sizes are identical to those for the reference products.

The approved shelf-life (2 years) with the storage instructions, “Store in original package” and “This medicinal product does not require any special storage conditions” and is identical to the details registered for the cross-reference product.

2.3 Legal status
These products are prescription-only medicines.

2.4 Marketing authorisation holder/Contact Persons/Company
The proposed Marketing Authorisation Holder is STD Chemicals Ltd, Hillbrow House, Hillbrow Road, Esher, Surrey, KT10 9NW, UK
The Quality Person (QP) responsible for pharmacovigilance is stated and their curriculum vita has been included.

2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference products and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference products.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The proposed finished product specification is in-line with the details registered for the cross-reference products.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference products.

2.10 TSE Compliance
With the exception of lactose monohydrate, none of the other excipients contained or used in the manufacturing process for the proposed products contain material derived from animal or human origin. The applicant has provided a declaration that milk used in the production of lactose is sourced from healthy animals under the same conditions as that for human consumption. None of the excipients are sourced from genetically modified organisms. This is consistent with the cross-reference product.

3. EXPERT REPORT
A satisfactory quality overall summary has been prepared by an appropriately qualified expert. The CV of the expert was provided.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product name. The appearances of the products are identical to that of the cross-reference products. For more details of the colours and shapes of tablets for each strength please refer to Section 3 of the SmPC.

5. SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
The approved SmPCs are consistent with the details registered for the cross-reference products.

6. PATIENT INFORMATION LEAFLET (PIL)/LABELLING
PIL
The PIL is satisfactory and in line with the approved SmPCs and has been prepared in the user-tested format.
To support the proposed patient leaflet, a user testing report has been provided for the approved reference products, Topiramate 25 mg, 50 mg, 100 mg and 200 mg Film-Coated Tablets (PL 08137/0243-0246) authorised to Neolab Ltd. The patient leaflet for the reference products met all criteria for successful user testing. The proposed layout and content of the proposed patient leaflet is identical to that of the approved reference product. As a result, bridging justification is accepted for the proposed products without the need for further user testing.

Labelling
Mock-ups of the labelling have been provided and are satisfactory. The approved artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements. In line with current legislation the applicant has included the name of the product in Braille on the outer packaging.

7. CONCLUSIONS
The data submitted with these applications are acceptable. Marketing Authorisations were, therefore, granted.
NON-CLINICAL ASSESSMENT

These are simple, abridged, ‘informed consent’ applications made under Article 10c of EC Directive 2001/83 (as amended). These applications are identical to the reference products Topiramate 25 mg, 50 mg, 100 mg and 200 mg Film-Coated Tablets (PL 08137/0243-0246) authorised to Neolab Ltd on 12 August 2011 in the UK, therefore, no new non-clinical data has been supplied with these applications and none are required. A non-clinical overview report has been written by a suitably qualified person and is satisfactory. The CV of the non-clinical expert has been supplied.

The marketing authorisation holder has provided adequate justification for not submitting an Environment Risk Assessment (ERA). As these applications are identical to already authorised reference products, it is not expected that the environmental exposure to topiramate will increase following the marketing approval of the proposed product.
CLINICAL ASSESSMENT

These are simple, abridged, ‘informed consent’ applications made under Article 10c of EC Directive 2001/83 (as amended), cross-referring to Topiramate 25 mg, 50 mg, 100 mg and 200 mg Film-Coated Tablets (PL 08137/0243-0246) authorised to Neolab Ltd on 12 August 2011 in the UK.

No new clinical data has been supplied with these applications and none are required. A clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the clinical expert has been supplied.

The marketing authorisation holder (MAH) has provided adequate justification for not submitting a Risk Management Plan (RMP). As these applications are identical to already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

The MAH has provided a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for these applications are consistent with those previously assessed for the cross-reference products and as such has been judged to be satisfactory.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
These applications are considered identical to the previously granted licences for Topiramate 25 mg, 50 mg, 100 mg and 200 mg Film-Coated Tablets (PL 08137/0243-0246) authorised to Neolab Ltd on 12 August 2011 in the UK.

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The approved SmPCs, PILs and labelling are satisfactory, and consistent with those for the cross-reference products.

A user testing report has been provided for the approved reference products, Topiramate 25 mg, 50 mg, 100 mg and 200 mg Film-Coated Tablets (PL 08137/0243-0246) authorised to Neolab Ltd. The patient leaflet for the reference products met all criteria for successful user testing. The proposed layout and content of the new patient leaflet is identical to that of the approved reference products. As a result, bridging justification is accepted for the proposed products without the need for further user testing.

Mock-ups of the labeling have been provided and are satisfactory. The labeling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging. The MAH has committed to submitting mock-ups for currently unmarketed packs to the UK regulatory authority for approval before those packs are commercially marketed.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products. The benefit, risk ratio is, therefore, considered to be positive.
TOPIRAMATE 25 MG, 50 MG, 100 MG & 200 MG FILM-COATED TABLETS

PL 36390/0069-72

**STEPS TAKEN FOR ASSESSMENT**

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 27 September 2011</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 19 October 2011</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 5 January 2012.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 18 January 2012.</td>
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<tr>
<td>5</td>
<td>The application was determined on 30 January 2012.</td>
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</table>
TOPIRAMATE 25 MG, 50 MG, 100 MG & 200 MG FILM-COATED TABLETS

PL 36390/0069-72

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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</table>
TOPIRAMATE 25 MG, 50 MG, 100 MG & 200 MG FILM-COATED TABLETS

PL 36390/0069-72

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Topiramate 25 mg, 50 mg, 100 mg and 200 mg Film-Coated Tablets (PL 36390/0069-72) are as follows: Differences between the SmPCs are highlighted in yellow.

1 NAME OF THE MEDICINAL PRODUCT
Topiramate 25 mg Film-coated Tablets.
Topiramate 50 mg Film-coated Tablets.
Topiramate 100 mg Film-coated Tablets.
Topiramate 200 mg Film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 25 mg/50 mg/100 mg/200 mg of topiramate respectively.
Each film-coated tablet contains 24.8 mg/49.5 mg/99 mg/198 mg of lactose monohydrate respectively.
For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Topiramate 25 mg Tablets are white coloured, circular, biconvex film-coated tablets.
Topiramate 50 mg Tablets are light orange coloured, circular, biconvex film-coated tablets.
Topiramate 100 mg Tablets are orange coloured, circular, biconvex film-coated tablets.
Topiramate 200 mg Tablets are pink coloured, biconvex, caplet-shaped film-coated tablets.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Epilepsy

Monotherapy in adults, adolescents and children over 6 years of age with partial seizures with or without secondary generalised seizures, and primary generalised tonic-clonic seizures.

Adjunctive therapy in children aged 2 years and above, adolescents and adults with partial onset seizures with or without secondary generalisation or primary generalised tonic-clonic seizures and for the treatment of seizures associated with Lennox-Gastaut syndrome.

Topiramate is indicated in adults for the prophylaxis of migraine headache after careful evaluation of possible alternative treatment options. Topiramate is not intended for acute treatment.

4.2 Posology and method of administration
General
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.

Topiramate Tablets are film-coated tablets. It is recommended that film-coated tablets should not be broken.

It is not necessary to monitor topiramate plasma concentrations to optimise therapy with Topiramate Tablets. 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 Topiramate Tablets may require adjustment of the dose of Topiramate Tablets.
Topiramate Tablets can be taken without regard to meals.

In patients with or without a history of seizures or epilepsy, antiepileptic drugs 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 antiepileptic drugs (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 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 100mg/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 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 bi-weekly 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 (see section 4.4).

**Paediatric population (children aged 2 years and above)**

The recommended total daily dose of 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.

**Migraine**

**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 of benefit in some patients, nevertheless, caution is advised due to an increase incidence of side effects.

**Paediatric population**
Topiramate is not recommended for treatment or prevention of migraine in children due to insufficient data on safety and efficacy.

**General dosing recommendations for Topiramate Tablets in special patient populations**

**Renal impairment**
In patients with impaired renal function (CLCR \( \leq \) 60mL/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.

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

**4.3 Contraindications**
Hypersensitivity to the active substance or to any of the excipients.

Migraine prophylaxis in pregnancy and in women of child bearing potential if not using effective methods of contraception.

**4.4 Special warnings and precautions for use**
In situations where rapid withdrawal of topiramate is medically required, appropriate monitoring is recommended (see section 4.2 for further details).

As with other anti-epileptic drugs, 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 anti-epileptics, 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 (see section 4.8).
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 anti-epileptic drugs 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.

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 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. Ophthalmological findings include myopia, anterior chamber shallowing, ocular hyperaemia (redness) and increased intra-ocular 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 the start 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 judgement 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 a history of eye disorders should be treated with topiramate.

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. 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 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 treatment that represent a risk factor for the appearance of metabolic acidosis.

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

4.5 Interaction with other medicinal products and other forms of interaction

Effects of Topiramate Tablets on other antiepileptic drugs
The addition of topiramate to other antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no effect on their steady-state plasma concentrations, except in the occasional patient, where the addition of topiramate 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 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 Topiramate Tablets
Phenytoin and carbamazepine decrease the plasma concentration of topiramate. The addition or withdrawal of phenytoin or carbamazepine to topiramate 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 topiramate and, therefore, does not warrant dosage adjustment of topiramate. The results of these interactions are summarised in the following table:

<table>
<thead>
<tr>
<th>AED Coadministered</th>
<th>AED Concentration</th>
<th>Topiramate Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>↔, ↔, ↔</td>
<td>↓</td>
</tr>
<tr>
<td>Carbamazepine (CBZ)</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>↔</td>
<td>NS</td>
</tr>
</tbody>
</table>
**Primidone**

| **↔** | 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 single-dose study, serum digoxin area under plasma concentration curve (AUC) decreased 12% due to concomitant administration of topiramate. The clinical relevance of this observation has not been established. When topiramate is added or withdrawn in patients on digoxin therapy, careful attention should be given to the routine monitoring of serum digoxin.

**CNS Depressants**

Concomitant administration of topiramate and alcohol or other CNS depressant medicinal products has not been evaluated in clinical studies. It is recommended that topiramate 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 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), topiramate 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 epilepsy patients taking valproic acid. In both studies, topiramate (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 these changes observed is not known. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with topiramate. 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 9-hydroxyrisperidone) 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 drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg q24h) and topiramate (96 mg q12h) when administered alone and concomitantly. The results of this 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 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 topiramate 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 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_τ,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_τ,ss respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in C_max,ss and AUC_τ,ss of the active keto-metabolite. The clinical significance of these findings is not known. When topiramate is added to pioglitazone therapy or pioglitazone is added to topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

**Glyburide**

A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glyburide (5 mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 25% reduction in glyburide 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 glyburide.

When topiramate is added to glyburide therapy or glyburide 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**
Topiramate, when used concomitantly with other agents predisposing to nephrolithiasis, may increase the risk of nephrolithiasis. While using topiramate, 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 event is not due to a pharmacokinetic interaction. An association of hyperammonemia with topiramate monotherapy or concomitant treatment with other anti-epileptics has not been established.

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 $C_{\text{max}}$ 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

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>Concomitant Drug Concentration$^a$</th>
<th>Topiramate Concentration$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>↔ 20% increase in $C_{\text{max}}$ and AUC of nortriptyline metabolite</td>
<td>NS</td>
</tr>
<tr>
<td>Dihydroergotamine (Oral and Subcutaneous)</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>↔ 31% increase in AUC of the reduced metabolite</td>
<td>NS</td>
</tr>
<tr>
<td>Propranolol</td>
<td>↔ 17% increase in $C_{\text{max}}$ for 4-OH propranolol (TPM 50 mg q12h)</td>
<td>9% and 16% increase in $C_{\text{max}}$, 9% and 17% increase in AUC (40 and 80 mg propranolol q12h respectively)</td>
</tr>
<tr>
<td>Sumatriptan (Oral and Subcutaneous)</td>
<td>↔</td>
<td>NS</td>
</tr>
<tr>
<td>Pizotifen</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>25% decrease in AUC of diltiazem and 18% decrease in DEA, and ↔ for DEM$^*$</td>
<td>20% increase in AUC</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Flunarizine</td>
<td>16% increase in AUC (TPM 50 mg q12h)$^b$</td>
<td>↔</td>
</tr>
</tbody>
</table>

$^a$ % values are the changes in treatment mean $C_{\text{max}}$ or AUC with respect to monotherapy

↔ = No effect on $C_{\text{max}}$ and AUC ($\leq 15\%$ change) of the parent compound
NS = Not studied

*DUA = 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 Pregnancy and lactation

Topiramate was teratogenic in mice, rats and rabbits. In rats, topiramate crosses the placental barrier.

There are no adequate and well-controlled studies using topiramate in pregnant women.
Pregnancy registry data suggest that there may be an association between the use of topiramate during pregnancy and 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. This data should be interpreted with caution, as more data is needed to identify increased risks for malformations.

In addition, data from these registries and other studies suggest that, compared with monotherapy, there may be an increased risk of teratogenic effects associated with the use of anti-epileptic drugs in combination therapy.

It is recommended that women of child bearing potential use adequate contraception.

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 breast milk. Since many medicinal products are excreted into human milk, a decision must be made whether to suspend breast-feeding or to discontinue/abstain from topiramate therapy, taking into account the importance of the medicinal product to the mother (section 4.4).

**Indication: Epilepsy**

During pregnancy, topiramate should be prescribed after fully informing the woman of the known risks of uncontrolled epilepsy to the pregnancy and the potential risks of the medicinal product to the foetus.

**Indication: Migraine Prophylaxis**

Topiramate is contraindicated in pregnancy, and in women of childbearing potential if an effective method of contraception is not used (see section 4.3 and 4.5 Interactions with oral contraceptives).

### 4.7 Effects on 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 product is established.

No studies on the effects on the ability to drive and use machines have been performed.

### 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 ADRs were mild to moderate in severity. ADRs 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 ADRs (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, bradycardia, depression, expressive language disorder, insomnia, coordination abnormal, disturbance in attention, dizziness, dysarthria, dysgeusia, hypotension, lethargy, memory impairment, nystagmus, paresthesia, somnolence, tremor, diplopia, blurred vision, diarrhoea, nausea, fatigue, irritability, and weight decrease.
Paediatric population
ADRs reported more frequently (>2-fold) in children than in adults in double-blind controlled studies include: decreased appetite, increased appetite, acidosis hyperchloremic, hypokalemia, abnormal behavior, aggression, apathy, initial insomnia, suicidal ideation, disturbance in attention, lethargy, circadian rhythm sleep disorder, poor quality sleep, lacrimation increased, sinus bradycardia, feeling abnormal, and gait disturbance.

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

Table 1: Topiramate Adverse Drug Reactions

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td>Weight decreased</td>
<td>Weight increased*</td>
<td>Crystal urine present, Tandem gait test abnormal, White blood cell count decreased</td>
<td>Blood bicarbonate decreased</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Bradycardia, Sinus bradycardia, Palpitations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Anaemia</td>
<td>Leucopenia, Thrombocytopenia, Lymphadenopathy, Eosinophilia</td>
<td>Neutropenia*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Paraesthesia, Somnolence, Dizziness</td>
<td>Disturbance in attention, Memory impairment, Amnesia, Cognitive disorder, Mental impairment, Psychomotor skills impaired, Convulsion, Coordination abnormal, Tremor, Lethargy, Hypoaesthesia, Nystagmus, Dysgeusia, Balance disorder, Dysarthria, Intention tremor, Sedation</td>
<td>Depressed level of consciousness, Grand mal convulsion, Visual field defect, Complex partial seizures, Speech disorder, Psychomotor hyperactivity, Syncope, Sensory disturbance, Drooling, Hypersonnia, Aphasia, Repetitive speech, Hypokinesia, Dyskinesia, Dizziness postural, Poor quality sleep, Burning sensation, Sensory loss, Parosmia, Cerebellar syndrome, Dysaesthesia, Hypogeusia, Stupor, Clumsiness, Aura, Ageusia, Dysgraphia, Dysphasia, Neuropathy</td>
<td>Apraxia, Circadian rhythm sleep disorder, Hyperaesthesia, Hyposmia, Anosmia, Essential tremor, Akinesia, Unresponsive to stimuli</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Vision blurred, Diplopia, Visual disturbance</td>
<td>Visual acuity reduced, Scotoma, Myopia*, Abnormal sensation in eye*, Dry eye, Photophobia, Blepharospasm, Lacrimation increased, Photopsia, Mydriasis, Presbyopia</td>
<td>Blindness unilateral, Blindness transient, Glaucoma, Accommodation disorder, Altered visual depth perception, Scintillating scotoma, Eyelid oedema*, Night blindness, Amblyopia</td>
<td>Angle closure glaucoma*, Maculopathy*, Eye movement disorder*</td>
<td></td>
</tr>
<tr>
<td>Ear and Labyrinth disorders</td>
<td>Vertigo, Tinnitus, Ear pain</td>
<td>Deafness, Deafness unilateral, Deafness neurosensory, Ear discomfort, Hearing impaired</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory thoracic and mediastinal disorders</td>
<td>Dyspnoea, Epistaxis, Nasal congestion, Rhinorrhea</td>
<td>Dyspnoea exertional, Paranasal sinus, Hypersecretion, Dysphonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Nephrolithiasis, Pollakiuria, Dysuria</td>
<td>Calculus urinary, Urinary incontinence, Haematuria, Incontinence, Micturition urgency, Renal colic, Renal pain</td>
<td>Calculus ureteric, Renal tubular acidosis*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia, Rash, Pruritus</td>
<td>Anhidrosis, Hypoesthesia facial, Urticaria, Erythema, Pruritus generalised, Rash macular, Skin discolouration, Dermatitis allergic, Swelling face</td>
<td>Stevens-Johnson syndrome*, Erythema multiforme*, Skin odour abnormal, Periorbital oedema*, Urticaria localised</td>
<td>Toxic epidermal necrolysis*</td>
<td></td>
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<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia, Muscle spasms, Myalgia, Muscle twitching, Muscular weakness, Musculoskeletal chest pain</td>
<td>Joint swelling*, Musculoskeletal stiffness, Flank pain, Muscle fatigue</td>
<td></td>
<td>Limb discomfort*</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia, Decreased appetite</td>
<td>Metabolic acidosis, Hypokalaemia, Increased appetite, Polydipsia</td>
<td></td>
<td>Acidosis hyperchlaemic</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Nasopharyngitis*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td>Hypotension, Orthostatic hypotension, Flushing, Hot flush</td>
<td></td>
<td>Raynaud’s phenomenon</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>Hyperthermia, Thirst, Influenza like illness*, Sluggishness, Peripheral coldness, Feeling drunk, Feeling jittery</td>
<td></td>
<td>Face oedema, Calcinosis</td>
<td></td>
</tr>
<tr>
<td>Social circumstances</td>
<td></td>
<td></td>
<td></td>
<td>Learning disability</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity</td>
<td></td>
<td></td>
<td>Allergic oedema*, Conjunctival oedema*</td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td>Erectile dysfunction, Sexual dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Depression</td>
<td>Bradyphrenia, Insomnia, Expressive language disorder, Anxiety, Confusional state, Disorientation, Aggression, Mood altered, Agitation, Mood swings, Depressed mood, Anger, Suicidal ideation, Suicide attempt, Hallucination, Psychotic disorder, Hallucination auditory, Hallucination visual, Apathy Lack of spontaneous speech, Sleep disorder, Affect lability, Libido decreased, Restlessness, Crying, Mania, Anorgasmia, Panic disorder, Disturbance in sexual arousal, Feeling of despair*, Orgasm abnormal, Hypomania, Orgasmic sensation decreased.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MHRA-UKPAR – Topiramate 25mg, 50mg, 100mg & 200mg Film-Coated Tablets  PL 36390/0069-72  - 24 -
Abnormal behaviour | Dysphemia, Euphoric mood, Paranoia, Perseveration, Panic attack, Tearfulness, Reading disorder, Initial insomnia, Flat affect, Thinking abnormal, Loss of libido, Listless, Middle insomnia, Distractability, Early morning awakening, Panic reaction, Elevated mood

* identified as an ADR from postmarketing spontaneous reports. Its frequency was calculated based on clinical trial data.

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 co-ordination, 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 (see section 4.4).

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 Pharmacodynamic properties

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

Topiramate is classified as a sulphamate-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 γ-aminobutyrate (GABA) activated GABA<sub>₆</sub> 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.

The 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 GABA<sub>₆</sub> receptors.

Because the antiepileptic profile of topiramate differs markedly from that of the benzodiazepines, it may modulate a benzodiazepine-insensitive subtype of GABA<sub>₆</sub> 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 GABA_A receptor antagonist, pentylentetrazole.

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.

5.2 Pharmacokinetic properties

The pharmacokinetic profile of topiramate compared to other antiepileptic drugs 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 (C_{max}) of 1.5 µg/ml was achieved within 2 to 3 hours (T_{max}).

Based on the recovery of radioactivity from the urine, the mean extent of absorption of a 100 mg oral dose of 14C-topiramate was at least 81%. There is no clinically significant effect of food on the bioavailability of topiramate.

Distribution

Generally 13-17% of topiramate is bound to plasma proteins. 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.

Metabolism

Topiramate is not extensively metabolised (~20%) in healthy volunteers. It is metabolised up to 50% in patients receiving concomitant antiepileptic therapy with known inducers of drug metabolising enzymes. Six metabolites, formed through hydroxylation, hydrolysis and glucuronidation, have been isolated, characterised 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 14C-topiramate 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.

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 $C_{\text{max}}$ 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.

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.

The plasma and renal clearance of topiramate are decreased in patients with impaired renal function ($CL_Cr \leq 60$ ml/min), and the plasma clearance is decreased in patients with end-stage renal disease. As a result, higher steady-state topiramate plasma concentrations are expected for a given dose in renal-impaired patients as compared to those with normal renal function. Topiramate is effectively removed from plasma by haemodialysis.

Plasma clearance of topiramate is decreased in patients with moderate to severe hepatic impairment.

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 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 drugs decrease the steady-state plasma concentrations.

5.3 Preclinical safety data

In non-clinical studies or 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, centrolobular 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Pre-gelatinised Starch (PA 5PH)
Lactose monohydrate
Microcrystalline cellulose (Avicel PH 101)
Sodium starch glycolate (Type A)
Magnesium stearate

**Film-coating for Topiramate 25 mg Film-Coated tablets**
Opadry White containing:
Titanium dioxide
Hypromellose
PEG 400
Polysorbate 80
FD & Blue #2
Indigo Carmine Aluminum Lake.

**Film-coating for Topiramate 50 mg and 100mg Film-Coated tablets**
Opadry Beige containing:
Titanium dioxide
Hypromellose
PEG 400
Polysorbate 80
Iron oxide yellow
Iron oxide red.

**Film-coating for Topiramate 200mg Film-Coated tablets**
Opadry Pink containing:
Titanium dioxide
Hypromellose
PEG 400
Polysorbate 80
Iron oxide red.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. Store in the original package.

6.5 Nature and contents of container

**Blisters:**
Packed in push-through blister strips composed of 3-ply alu-alu laminated film and 25 micron plain aluminium foil (heat sealable against PVC with VMCH coating).
Pack sizes of 28, 56, 60 & 84 tablets.
Bottles:
Bottle packs of the following composition: Opaque, high density polyethylene bottles.
White, opaque, polypropylene, child-resistant closures and a desiccant.
Pack sizes of 60, 100 & 200 tablets.
(Not all pack sizes will be marketed).

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
STD CHEMICALS LIMITED,
HILLBROW HOUSE,
HILLBROW ROAD,
ESHER,
SURREY,
KT10 9NW

8 MARKETING AUTHORISATION NUMBER(S)
PL 36390/0069
PL 36390/0070
PL 36390/0071
PL 36390/0072

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/01/2012

10 DATE OF REVISION OF THE TEXT
24/01/2012
TOPIRAMATE 25 MG, 50 MG, 100 MG & 200 MG FILM-COATED TABLETS
PL 36390/0069-72
PATIENT INFORMATION LEAFLET

1. WHAT TOPIRAMATE IS AND WHAT IT IS USED FOR

Topiramate Tablets belong to a group of medicines called ‘antiepileptic medicines’. They can be used:
- alone to treat seizures in adults and children over age 6
- with other medicines to treat seizures in adults and children over age 2
- to prevent migraine headaches in adults

2. BEFORE YOU TAKE TOPIRAMATE TABLETS

Do not take Topiramate Tablets:
- if you are allergic (hypersensitive) to topiramate, or any of the other ingredients in Topiramate Tablets (these are listed in section 6.4. Further Information).
- for genetic reasons if you are pregnant or you are about to become pregnant or are not using effective contraception. (see section Pregnancy and breast-feeding for further information).
- if you are not sure that the above applies to you, talk to your doctor or pharmacist before using Topiramate Tablets.

Talk special care with Topiramate Tablets

Before you take Topiramate Tablets you should tell your doctor if you:
- have kidney problems, especially kidney stones or are getting kidney disorders
- 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 not sure about any of the above applies to you, talk to your doctor or pharmacist before taking Topiramate Tablets

It is important that you do not stop taking this medicine without first consulting your doctor. You should also talk to your doctor before taking any medicine contains topiramate that is given to you as an alternative to Topiramate Tablets. You may lose weight while taking Topiramate Tablets so your weight should be checked regularly. If you are losing too much weight, or if a child using this medicine is not gaining enough weight, you should consult your doctor.

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

Talking other medicines

Please tell your doctor if you are taking or have recently taken any of the following medicines, including medicines obtained without a prescription, vitamin and herbal medicines. Topiramate Tablets and certain other medicines can affect each other. Sometimes the dose of some of your other medicines or Topiramate Tablets will have to be adjusted.

3. HOW TO TAKE TOPIRAMATE TABLETS

Always take Topiramate Tablets exactly as your doctor has told you to do so. You should check with your doctor or pharmacist if you are not sure.

Take Topiramate Tablets as prescribed. Your doctor will usually start you on a low dose of topiramate and slowly increase your dose until the best dose is found for you. Take your tablets in the evening or at bedtime. Do not change the tablets from your mouth to your hand. Do not break or crush tablets.

Topiramate Tablets are to be swallowed whole. Avoid chewing the tablets as they may be bitter. Do not take your tablets with food or milk, as this may affect the amount of the medicine in your body. Take your tablets at the same time each day. If you forget to take your tablets, take them as soon as you remember. If you miss a dose, do not take a double dose to make up for the missed dose.

Overdose can happen if you are taking other medicines together with Topiramate Tablets.

4. POSSIBLE SIDE EFFECTS

Some people taking Topiramate Tablets may have problems such as:
- blurred vision
- allergic reactions
- rash
- liver problems, fluid and salt balance problems
- kidney problems
- emotional problems
- suicidal thoughts
- mental health problems
- skin reaction

If you have any of these problems, contact your doctor immediately. If you experience any other problems while taking Topiramate Tablets, contact your doctor or pharmacist.

5. HOW TO DEAL WITH SIDE EFFECTS

If you have any more questions on the use of this product, ask your doctor or pharmacist.
4. POSSIBLE SIDE EFFECTS

Like all medicines, Topiramate Tablets can cause side effects, although not everybody gets them.

Very common side effects (affects more than 1 user in 10):
- weight loss
- tingling in the arms and legs
- dryness of the skin, tightness, itchiness
- dizziness, nausea (including drowsiness)
- stuffy, runny nose and sore throat
- depression

Common side effects (affects 1 to 10 users in 100):
- changes in mood or behaviour, including anger, nervousness, sadness
- weight gain, decrease or loss of appetite
- reduced number of red blood cells
- changes in thinking and alertness, including confusion, problems with concentration, memory or disorientation in thinking, slowed speech
- clumsiness, or problems with walking: involuntary shaking in the arms, hands or legs
- reduced sense of touch or sensation
- involuntary movement of the eyes, visual disturbances, blurred vision, double vision
- dilated pupils, taste
- ringing sound in the ears, ear pain
- shortness of breath
- nose bleed
- vomiting, constipation, diarrhea
- dry mouth, tingling or numbness of the mouth
- kidney stones, frequent urination, painful urination
- headache
- skin rash or itching skin
- joint pain, muscle spasm, muscle twitching or muscle weakness
- chest pain
- fever
- loss of strength
- persistent feeling of being unwell
- allergic reaction

Uncommon side effects (affects 1 to 10 users in 1,000):
- crystals in the urine
- abnormal blood counts, including reduced white blood cell count or platelet count, or increased eosinophils
- irregular heartbeat or slowing of the heart rate
- swollen glands in the neck, armpit or groin
- increase in size of tumours
- problems with verbal communication
- dizziness
- restlessness or increase in mental and physical activity
- loss of consciousness
- fainting
- slow or irregular movements
- disturbed or poor quality sleep
- impaired or distorted sense of smell
- problems with handwriting
- feeling of movement under the skin
- eye problems including dry eyes, light sensitivity, involuntary twitching, tearing and decreased vision
- decreased or loss of hearing
- hoarseness of the voice
- inflammation of the pancreas
- gas, heartburn
- loss of sensitivity to touch in the mouth, breathing gums, painful or burning sensations in the mouth, breath odour
- fullness or bloating
- leakage of urine and/or stool: urgent desire to urinate, pain in the kidney area and/or bladder caused by kidney stones
- decrease or loss of sweating
- skin discoloration: localized swelling in the skin
- swelling of the face, swelling of the joints
- muscular stiffness
- increased acid levels in the blood, low potassium levels in the blood
- increased appetite, increased thirst and drinking abnormally large amounts of fluid
- low blood pressure or decrease in blood pressure that occurs when you stand up

- hot flushes, cold extremities (e.g. hands and feet)
- problems with walking
- disturbances in sexual function (erection dysfunction, loss of libido)
- hallucinations
- decreased verbal communication

Rare side effects (affects 1 to 10 users in 10,000):
- excessive skin sensitivity
- impaired sense of smell
- glaucoma which is a blockage of fluid in the eye causing increased pressure in the eye, pain and decreased vision
- nasal turbinar adducts
- severe skin reaction, including Stevens-Johnson syndrome, a life-threatening skin condition in which the upper layer of the skin separates from the lower, and erythema multiforme, a condition of red, raised spots that can blister
- dizziness
- swelling of the tissues around the eye
- Raynaud's syndrome: A disorder affecting the blood vessels in the fingers, toes, ears and causing pain and cold sensitivity
- tissue calcification (dental)

Side effects of unknown frequency:
- Maculopathy: a disease of the macula, the small spot in the retina where vision is sharpest. You should tell your doctor if you notice a change or decrease in your vision.
- swelling of the conjunctiva of the eye
- Toxic epidermal necrolysis which is a severe form of Stevens-Johnson syndrome (see rare side effects).

If any of these side effects gets worse, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE TOPIRAMATE TABLETS

Keep out of the reach and sight of children.

Do not take this medicine after the expiry date (e.g. 31 January) stated. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Store in the original package.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Topiramate Tablets contain:

The active ingredient is topiramate.

Tablet cores:
The ingredients are lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycollate and magnesium stearate.

Film-coating:

Topiramate 25 mg Tablets are coated with OPADRY® White, the ingredients of which are titanium dioxide, hypromellose, polyethylene glycol and colloidal silicon dioxide (E172). Topiramate 50 & 100 mg Tablets are coated with OPADRY® Beige YS-1-17117-L-A, the ingredients of which are titanium dioxide, hypromellose, polyethylene glycol, iron oxide yellow (E172) and iron oxide red (E172).

Topiramate 200 mg Tablets are coated with OPADRY® Pink YS-1-14775-A, the ingredients of which are titanium dioxide, hypromellose, polyethylene glycol 80 and iron oxide red (E172).

What Topiramate Tablets look like and the contents of the pack:

Topiramate 25 mg: white-coloured, circular, bilayered film-coated tablets.

Topiramate 50 mg: light-orange coloured, bilayered film-coated tablets.

Topiramate 100 mg: orange coloured, circular, bilayered film-coated tablets.

Topiramate 200 mg: pink-coloured, bilayered film-coated tablets.

Topiramate Tablets are available in containers of 60, 100 and 200 film-coated tablets and blister packs of 28, 56, 60 and 84 film-coated tablets. Not all pack sizes will be marketed.

Marketing Authorisation Holder and Manufacturer:
The Product Licence Holder is Sano Pharmaceuticals Ltd., Hillview House, Hillview Road, Esher, Surrey, KT10 BNM.

The manufacturer responsible for batch release is Panmure UK Ltd, 57 High Street, Oxted, Surrey, RH8 1DF.

This leaflet was last reviewed in September 2011.
Topiramate 25 mg Film-Coated Tablets

Each tablet contains 25 mg of topiramate. Also contains lactose monohydrate.

Directions for use:
To be taken as directed by a doctor.
Keep out of reach of children.
For further information see enclosed leaflet.
Store in the original packaging.

MHRA-UKPAR – Topiramate 25mg, 50mg, 100mg & 200mg Film-Coated Tablets PL 36390/0069-72
Topiramate 50 mg Film-Coated Tablets

For oral administration.

Each tablet contains 50mg of topiramate.
Also contains lactose monohydrate.

Keep out of the sight and reach of children.
For further information see enclosed leaflet.
Store in the original packaging.

MHRA-UKPAR – Topiramate 25mg, 50mg, 100mg & 200mg Film-Coated Tablets PL 36390/0069-72
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Topiramate 100 mg Film-Coated Tablets

Each tablet contains 100 mg of topiramate. Also contains lactose monohydrate.

Directions for use: For oral administration. To be taken as directed by a doctor.

Keep out of reach and sight of children.

For further information see enclosed leaflet. Store in the original packaging.

MHRA-UKPAR – Topiramate 25mg, 50mg, 100mg & 200mg Film-Coated Tablets  PL 36390/0069-72

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