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PL 20176/0058-61

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) for the medicinal products Topiramate 25 mg, 50 mg, 100 mg and 200 mg Tablets (Product Licence numbers: 20176/0058-61).

Topiramate affects chemicals in the brain that are involved in sending signals to the nerves. Topiramate belongs to a group of medicines used to treat epilepsy and may also be used to prevent frequently recurring migraine headaches.

Topiramate 25 mg, 50 mg, 100 mg and 200 mg Tablets raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.
TOPIRAMATE 25 MG TABLETS
TOPIRAMATE 50 MG TABLETS
TOPIRAMATE 100 MG TABLETS
TOPIRAMATE 200 MG TABLETS

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Topiramate 25 mg, 50 mg, 100 mg and 200 mg Tablets to TechnoPharm Limited on 28 April 2009. This medicine is only available on prescription.

The applicant claims that Topiramate 25 mg, 50 mg, 100 mg and 200 mg Tablets are generic versions of Topamax 25, 50, 100 and 200 mg Tablets (PL 00242/0301-0304), authorised in 18 July 1995 to Janssen-Cilag Limited, UK. The legal bases of these applications are acceptable and the ten year rule is complied with.

Topiramate 25 mg, 50 mg, 100 mg and 200 mg Tablets are indicated for the monotherapy of adults and children aged 6 years and above with newly diagnosed epilepsy who have generalised tonic-clonic seizures or partial seizures with or without secondarily generalised seizures. Topiramate Tablets are also indicated as adjunctive therapy for adults and children over 2 years of age who are inadequately controlled on conventional first line antiepileptic drugs for: partial seizures with or without secondarily generalised seizures; seizures associated with Lennox Gastaut Syndrome and primary generalised tonic-clonic seizures.

Topiramate Tablets are also indicated in adults for the prophylaxis of migraine headache.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE: TOPIRAMATE

INN: Topiramate
Chemical Name: 2,3;4,5-Bis-O-(1-methyl ethylidene)-β-D-fructopyranose-sulfamate
CAS No: 97240-79-4

Molecular formula: C_{12}H_{21}NO_{8}S
Relative molecular mass: 339.37
Physical form: White to off-white powder
Solubility: Freely soluble in dichloromethane

An appropriate specification has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active topiramate is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 2 years.

DRUG PRODUCT

Description and Composition of the Drug Product
The tablets are round, biconvex and debossed with TO on one side and a number showing the tablet’s strength (i.e. 25, 50, 100 or 200) on the other side. The 25 mg tablets are about 6 mm in diameter and coated with white film, the 50 mg tablets are about 7 mm in diameter and coated with light yellow film, the 100 mg tablets are about 10 mm in diameter and coated with yellow film and the 200 mg tablets are about 13 mm in diameter and coated with salmon film.
The tablet cores contain the following inactive ingredients: lactose monohydrate, regelatinized starch, partially pregelatinized starch, microcrystalline cellulose, sodium starch glycollate and magnesium stearate.

The 25 mg tablet’s film coating comprises: hypromellose, polysorbate 80, talc and titanium dioxide (E171). The 50 mg and 100 mg tablets’ coating is identical to that for the 25 mg tablet, apart from it also contains iron oxide yellow (E172). The 200 mg tablet’s coating is identical to that for the 25 mg tablet, apart from it also contains iron oxide red (E172). Appropriate justification for the inclusion of each excipient has been provided.

The excipients in the Topiramate Tablets are all Ph. Eur. grade, with the exception of the colourants (in the absence of relevant Ph Eur monographs, this is acceptable). Certificate of analysis for all excipients are provided in support of the proposed specifications.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Magnesium stearate used is of vegetable origin.

**Dissolution and impurity profiles**

Dissolution and impurity profiles for all strengths of drug product were found to be similar to those for the reference products.

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

**Finished product specification**

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container Closure System**

Topiramate tablets are packaged in OPA 25 µm / aluminium 45 µm / PVC 60 µm / aluminium 20 µm blisters in cartons containing 28 or 60 tablets. Not all pack sizes may be marketed.

Specifications, including identity testing, are given for packaging materials and these are supported by certificates of analysis. These packaging materials are widely used components, which are utilised for packaging of numerous pharmaceutical products.
The suitability of the packaging materials has been demonstrated by the absence of any interaction between the product and pack during stability testing. The results obtained have shown that the package gave good protection to the tablets throughout the testing time. Certificates and statements on the suitability of foils to be used in contact with food and the compliance of its quality with EU regulations are provided.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. There are no special storage conditions.

**Bioequivalence / Bioavailability**
A bioequivalence study is reported using the generic Topiramate 200 mg Tablets and Topamax 200 mg Tablets from Janssen –Cilag Ltd, UK.

A validated method has been used to assay the topiramate drug in subject plasma using an internal standard (celecoxib). The method has been validated for linearity range (49.76 ng/ml to 4979.94 ng/ml), selectivity, sensitivity, precision and accuracy and solution stability.

90% CI indicate that the two products are bioequivalent in-vivo. As all tablet strengths are scale-up and scale-down versions of each other, drug kinetics are linear and all strengths exhibit similar dissolution profiles the 200mg results can be extrapolated to 25 mg, 50 mg and 100 mg strength tablets too.

**PRODUCT LITERATURE**
All product literature (SPC, PILs and labelling) are satisfactory. The package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (“user testing”), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY**
These products are satisfactory and Marketing Authorisations may be granted.
PRECLINICAL ASSESSMENT

These applications are for generic versions of Topamax tablets (Janssen-Cilag Limited), which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with these applications and none are required for an application of this type.
CLINICAL ASSESSMENT

INDICATIONS
The applicant has submitted the following:

“Epilepsy
Topiramate 25 mg (200 mg) Tablets is indicated as monotherapy in adults and children aged 6 years and above with newly diagnosed epilepsy who have generalised tonic-clonic seizures or partial seizures with or without secondarily generalised seizures.

Topiramate 25 mg (200 mg) Tablets is indicated as adjunctive therapy for adults and children over 2 years of age who are inadequately controlled on conventional first line antiepileptic drugs for: partial seizures with or without secondarily generalised seizures; seizures associated with Lennox Gastaut Syndrome and primary generalised tonic-clonic seizures. The efficacy and safety of conversion from adjunctive therapy to Topiramate 25 mg (200 mg) Tablets monotherapy has not been demonstrated.

Migraine
Topiramate 25 mg (200 mg) Tablets is indicated in adults for the prophylaxis of migraine headache. Initiation of treatment with topiramate should be restricted to specialist care and treatment should be managed under specialist supervision or shared care arrangements.

Prophylactic treatment of migraine may be considered in situations such as: Adults experiencing three or more migraine attacks per month; frequent migraine attacks that significantly interfere with the patient's daily routine.

Continuing therapy should be reviewed every six months.
The usefulness of Topiramate 25 mg (200 mg) Tablets in the acute treatment of migraine has not been studied.”

The proposed indications are identical to those for the licensed indications approved for the UK reference product Topamax tablets and are, therefore, satisfactory.

DOSE & DOSE SCHEDULE
The proposed posology is fully consistent with the text of section 4.2 of the SPC approved for the UK reference product.

CLINICAL PHARMACOLOGY
A bioequivalence study was performed on healthy volunteers to compare the bioavailability of Topiramate 200 mg Tablets with that of the reference product Topamax 200 mg Tablets, produced by Janssen-Cilag Ltd (supplied from UK market).

According to Note to guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), if a new application concerns several strengths of the active substance only one bioequivalence study using the highest strength is necessary if given conditions hold. Considering that the 25 mg, 50 mg and 100 mg tablets are direct scale downs of the Topiramate tablets 200 mg, and the
pharmacokinetics of the drug are linear over the therapeutic range, a single bioequivalence study conducted on the highest strength (200 mg) is satisfactory.

The study was performed according to Good Clinical Practice.

**Study design**
This was a randomised, crossover, open-label, single dose bioequivalence study of conventional design in healthy volunteers under fasting conditions, comparing Topiramate 200 mg tablets to the corresponding strength of innovator product, Topamax® tablets from the UK market.

The randomisation scheme is provided and appears truly random.

Topiramate has a long half life (approximately 21 hours) and a long washout period is therefore necessary to avoid carryover into period two. The washout period of 14 days in this study was sufficient to ensure zero plasma levels at the beginning of period two.

For statistical evaluation of bioequivalence, ANOVA with 90% confidence intervals was used for AUC0-t, AUC0-∞ and Cmax. The data was transformed prior to analysis using a logarithmic transformation. For evaluation of (untransformed) tmax, a non-parametric test was used. The bioequivalence acceptance ranges were 0.80 - 1.25 for the parameters AUC0-t and Cmax. See comment in results section below.

**Population(s) studied**
Twenty-six healthy, normal weight, non-smoking, male volunteers were enrolled in the study and completed the protocol.

**Results**
The 90% CI for the Test/Reference ratio of AUC0-t, AUC0-inf and Cmax fell within the pre-specified acceptance limits of 80-125%.

Tighter 90-111% acceptance limits are advocated for certain anticonvulsants. Topiramate however does not have a particularly narrow therapeutic index compared, for example, to phenytoin and carbamazepine and dose titration is less critical. The normal 80-125% criteria may, therefore, be applied.

Topiramate has a long half life. As a result, the extrapolated part of the AUC estimate exceeded the AUC0-inf more than 20% in a number of subjects. However, as the last time point for blood sampling was 72 hours, the absorption phase has been completely covered.

Conclusions
From the results of the study it can be concluded that bioequivalence of the test product containing 200 mg of topiramate and the reference products Topamax® 200 mg (Janssen-Cilag UK) has been satisfactorily demonstrated in accordance with CPMP criteria.

EFFICACY
No new data are submitted and none are required for this type of application.
SAFETY
No new data are submitted and none are required for this type of application.

EXPERT REPORTS
A satisfactory expert report is provided by an appropriately qualified individual.

PRODUCT LITERATURE
All product literature (SPCs, PILs and labelling) are satisfactory. The package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

DISCUSSION
The assessor considers that bioequivalence has been adequately demonstrated.

MEDICAL CONCLUSION
A marketing authorisation may be granted for these preparations.

ASSESSOR’S OVERALL CONCLUSIONS
It is recommended that marketing authorisations can be granted.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Topiramate 25 mg, 50 mg, 100 mg and 200 mg are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Topiramate 200 mg Tablets and Topamax 200 mg Tablets (Janssen-Cilag Ltd). Given that linear kinetics apply between the 25 mg, 50 mg, 100mg and 200mg tablets, that proportional formulae for the tablets have been used and that similar dissolution results have been shown for the four strengths, a separate bioequivalence study using the other tablet strengths is not considered necessary.

No new or unexpected safety concerns arise from these applications.

The SPCs, PIL and labelling are satisfactory and consistent with that for Topamax Tablets.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with topiramate is considered to have demonstrated the therapeutic value of the compound. The risk benefit ratio is, therefore, considered to be acceptable.
TOPIRAMATE 25 MG TABLETS

TOPIRAMATE 50 MG TABLETS

TOPIRAMATE 100 MG TABLETS

TOPIRAMATE 200 MG TABLETS

PL 20176/0058-61

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the marketing authorisation application on 22 December 2006

2. Following standard checks and communication with the applicant the MHRA considered the application valid on 4 March 2007

3. Following assessment of the application the MHRA requested further information relating to the quality dossier on 22 May 2007

4. The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 28 October 2007

5. Following assessment of the response the MHRA requested further information relating to the quality dossier on 4 February 2008 and the clinical dossier on 13 February 2008

6. The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 3 June 2008

7. Following assessment of the response the MHRA requested further information relating to the quality dossier on 5 December 2008

8. The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 19 February 2009 and the clinical dossier on 27 April 2009

9. The application was determined on 28 April 2009
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Topiramate 25 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 25 mg of topiramate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Topiramate 25 mg Tablets are white, round, biconvex film-coated tablets engraved with TO on one side and 25 on the other side, about 6 mm in diameter.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications

Epilepsy
Topiramate 25 mg Tablets is indicated as monotherapy in adults and children aged 6 years and above with newly diagnosed epilepsy who have generalised tonic-clonic seizures or partial seizures with or without secondarily generalised seizures.

Topiramate 25 mg Tablets is indicated as adjunctive therapy for adults and children over 2 years of age who are inadequately controlled on conventional first line antiepileptic drugs for: partial seizures with or without secondarily generalised seizures; seizures associated with Lennox Gastaut Syndrome and primary generalised tonic-clonic seizures.

The efficacy and safety of conversion from adjunctive therapy to Topiramate 25 mg Tablets monotherapy has not been demonstrated.

Migraine
Topiramate 25 mg Tablets is indicated in adults for the prophylaxis of migraine headache. Initiation of treatment with topiramate should be restricted to specialist care and treatment should be managed under specialist supervision or shared care arrangements.

Prophylactic treatment of migraine may be considered in situations such as: Adults experiencing three or more migraine attacks per month; frequent migraine attacks that significantly interfere with the patient's daily routine.
Continuing therapy should be reviewed every six months. The usefulness of Topiramate 25 mg Tablets in the acute treatment of migraine has not been studied.

4.2 Posology and method of administration

**General**
For optimal seizure control in both adults and children, it is recommended that therapy be initiated at a low dose followed by titration to an effective dose. Tablets should not be broken. Topiramate 25 mg Tablets can be taken without regard to meals. It is not necessary to monitor topiramate plasma concentrations to optimise topiramate therapy.

The dosing recommendations apply to children and to all adults, including the elderly, in the absence of underlying renal disease. (See 4.4 Special warnings and special precautions for use.) Since topiramate is removed from plasma by haemodialysis, a supplemental dose of topiramate 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.

**Epilepsy**

a) Monotherapy

**Adults and children over 16 years**

Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased at 1- or 2-week intervals by increments of 25 or 50 mg/day, administered in two divided doses. If the patient is unable to tolerate the titration regimen, smaller increments or longer intervals between increments can be used. Dose and titration rate should be guided by clinical outcome.

The recommended initial target dose for topiramate monotherapy in adults with newly diagnosed epilepsy is 100 mg/day and the maximum recommended daily dose is 400 mg. These dosing recommendations apply to all adults including the elderly in the absence of underlying renal disease.

**Children aged 6-16 years**

Treatment of children aged 6 years and above should begin at 0.5 to 1 mg/kg nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 0.5 to 1 mg/kg/day, administered in two divided doses. If the child is unable to tolerate the titration regimen, smaller increments or longer intervals between dose increments can be used. Dose and dose titration rate should be guided by clinical outcome.

The recommended initial target dose range for topiramate monotherapy in children with newly diagnosed epilepsy aged 6 years and above is 3 to 6 mg/kg/day. Higher doses have been tolerated and rarely doses up to 16 mg/kg/day have been given.

The tablet formulations are not appropriate for children requiring doses of less than 25 mg/day. A suitable formulation should be prescribed.

b) Adjunctive Therapy

**Adults and children over 16 years**
The minimal effective dose as adjunctive therapy is 200 mg per day. The usual total daily dose is 200 mg to 400 mg in two divided doses. Some patients may require doses up to 800 mg per day, which is the maximum recommended dose. It is recommended that therapy be initiated at a low dose, followed by titration to an effective dose. Titration should begin at 25 mg daily for one week. The total daily dose should then be increased by 25-50 mg increments at one to two weekly intervals and should be taken in two divided doses. If the patient is unable to tolerate the titration regimen then lower increments or longer intervals between increments may be used. Dose titration should be guided by clinical outcome.

**Children aged 2 - 16 years**
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 nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses), to achieve optimal clinical response. Dose titration should be guided by clinical outcome. Daily doses up to 30 mg/kg/day have been studied and were generally well tolerated.

**Migraine**

**Adults and children over 16 years**
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.
The recommended total daily dose of topiramate as treatment for the prophylaxis of migraine headache is 100 mg/day administered in two divided doses. Some patients may experience a benefit at a total daily dose of 50 mg/day. No extra benefit has been demonstrated from the administration of doses higher than 100 mg/day. Dose and titration rate should be guided by clinical outcome.

**Children**
Topiramate in migraine prophylaxis has not been studied in children under 16 years.

4.3 **Contraindications**
Hypersensitivity to any component of this medicinal product.

4.4 **Special warnings and precautions for use**

**General**
In patients with or without a history of seizures or epilepsy, antiepileptic drugs, including topiramate, should be gradually withdrawn to minimise the potential for seizures or increased seizure frequency. In clinical trials, daily dosages were decreased in weekly intervals by 50-100 mg in adults with epilepsy and by 25-50 mg in adults receiving topiramate at doses up to 100 mg/day for migraine prophylaxis. In clinical trials of children, topiramate was gradually withdrawn over a 2-8 week period. In situations where rapid
withdrawal of topiramate is medically required, appropriate monitoring is recommended.

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Renal elimination is dependent on renal function and is independent of age. Patients with moderate or severe renal impairment may take 10 to 15 days to reach steady-state plasma concentrations as compared to 4 to 8 days in patients with normal renal function. As with all patients, the titration schedule should be guided by clinical outcome (e.g. seizure control, avoidance of side effects, prophylaxis of migraine headache) with the knowledge that subjects with known renal impairment may require a longer time to reach steady state at each dose. 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. Adequate hydration whilst using topiramate is very important as it can reduce the risk of developing renal stones. In addition, it may reduce the risk of heat-related adverse events during exercise and exposure to particularly warm environments (see section 4.8).

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 medication associated with nephrolithiasis may be at increased risk.

In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased. Depression and mood alterations have been reported in patients treated with 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 (43 out of 7,999 patients treated) and at a 3 fold higher incidence than in those treated with placebo (0.15%; 5 out of 3,150 patients treated).

Patients should be monitored for signs of depression and referred for appropriate treatment if necessary. Patients (and caregivers of patients) should be advised to seek medical advice immediately should suicidal thoughts emerge.

In accordance with good clinical practice, patients with a history of depression and/or suicidal behaviour, adolescents and young adults may be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Acute myopia with secondary angle-closure glaucoma has been reported rarely in both children and adults receiving topiramate. Symptoms typically occur within 1 month of the start of treatment and include decreased visual acuity and/or ocular pain. Ophthalmological findings include bilateral myopia, anterior chamber shallowing, hyperaemia and increased intra-ocular pressure with or without mydriasis. There may be supraciliary effusion resulting in anterior displacement of the lens and iris. Treatment includes discontinuation of topiramate as rapidly as is clinically feasible and appropriate measures to reduce intraocular pressure. These measures generally result in a decrease in intraocular pressure. If increased intraocular pressure is suspected, immediate specialist advice should be sought.
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 drugs) may be additive to the bicarbonate lowering effects of topiramate.

Chronic metabolic acidosis in paediatric patients can reduce growth rates. The effect of topiramate on growth and 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).

A dietary supplement or increased food intake may be considered if the patient is losing weight or has inadequate weight gain while on this medication. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Migraine Prophylaxis
In migraine prophylaxis, before discontinuation of treatment, dosage should be gradually reduced over at least 2 weeks to minimise the possibility of rebound migraine headaches.

Weight loss
During the double-blind treatment with topiramate 100 mg/day, the mean change from baseline to the final visit in body weight was -2.5 kg, compared to -0.1 kg in the placebo group. Overall, 68% of patients treated with topiramate 100 mg/day lost weight during the trials, compared to 33% of patients receiving placebo. Weight decrease was reported as an adverse event in 1% of all placebo-treated patients and in 9% of all patients receiving topiramate 100 mg/day.

Significant weight loss may occur during long-term topiramate treatment for migraine prophylaxis. In clinical studies of topiramate 100 mg in migraine prophylaxis, a continuing weight decrease was observed with a mean weight decrease of 5.5 kg over 20 months. Twenty-five per cent of patients treated with topiramate for migraine prophylaxis had a weight loss of ≥10% of their body weight.

It is recommended that patients on long term topiramate for migraine prophylaxis should be regularly weighed and monitored for continuing weight loss.

4.5 Interaction with other medicinal products and other forms of interaction
For purposes of this section, a no effect dose is defined as a ≤15% change.
Effects of Topiramate on Other Antiepileptic Drugs

The addition of Topiramate to other antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no clinically significant effect on their steady-state plasma concentrations, except in some patients where the addition of Topiramate to phenytoin may result in an increase of plasma concentrations of phenytoin. Consequently, it is advised that any patient on phenytoin 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).

Effects of Other Antiepileptic Drugs on Topiramate

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 tablets.

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>
<tr>
<td>Primidone</td>
<td>↔</td>
<td>NS</td>
</tr>
</tbody>
</table>

↔ = No effect on plasma concentration (≤15% change)

** = Plasma concentrations increase in some patients

↓ = Plasma concentrations decrease

NS = Not studied

AED = antiepileptic drug
Other Drug 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 drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, topiramate should be used with caution if used in combination with alcohol and other CNS depressants.

Oral Contraceptives: In an interaction study with a combined oral contraceptive, Topiramate increased plasma clearance of the oestrogenic component significantly. Consequently, and bearing in mind the potential risk of teratogenicity, patients should receive a preparation containing not less than 50 µg of oestrogen or use some alternative non-hormonal method of contraception. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns.

Lithium: In healthy volunteers, there was an observed reduction (18 % for AUC) in systemic exposure for lithium during concomitant administration with topiramate 200 mg/kg. 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.

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 Cmax 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 500mg bd and topiramate 100mg bd in plasma when metformin was given alone and when metformin and topiramate were given simultaneously. The results of this study indicated that metformin mean Cmax and mean AUC0-12h increased by 18% and 25%, respectively, while mean CL/F decreased 20% when metformin was co-administered with topiramate. Topiramate did not affect metformin tmax. 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 $\text{AUC}_{\text{τ,ss}}$ of pioglitazone with no alteration in $\text{C}_{\text{max,ss}}$ was observed. This finding was not statistically significant. In addition, a 13% and 16% decrease in $\text{C}_{\text{max,ss}}$ and $\text{AUC}_{\text{τ,ss}}$, respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in $\text{C}_{\text{max,ss}}$ and $\text{AUC}_{\text{τ,ss}}$ 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.

**Glibenclamide:** A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glibenclamide (5mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 25% reduction in glibenclamide $\text{AUC}_{24}$ during topiramate administration. Systemic exposure of the active metabolites, 4-trans-hydroxy-glibenclamide (M1) and 3-cis-hydroxy-glibenclamide (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.

**Others:** 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. The interaction with benzodiazepines has not been studied.

**Valproic Acid:** Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. In most cases, symptoms and signs abated with discontinuation of either drug. 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 $\text{C}_{\text{max}}$ or $\text{AUC}$ 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.

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>Concomitant Drug Concentrationa</th>
<th>Topiramate Concentrationa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>↔</td>
<td>NS</td>
</tr>
</tbody>
</table>
Interaction studies showed that Topiramate did not significantly alter the serum levels of amitriptyline, propranolol or dihydroergotamine mesylate. The combination of Topiramate with each of these drugs was well tolerated and no dose adjustments were necessary.

**Laboratory Tests:**
Clinical trial data indicates that topiramate has been associated with an average decrease of 4 mmol/L in the serum bicarbonate level (see Section 4.4 Special warnings and special precautions for use Metabolic Acidosis).

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

There are no studies using Topiramate in pregnant women. However, Topiramate should not be used during pregnancy unless, in the opinion of the physician, the potential benefit outweighs the potential risk to the foetus.

Before starting Topiramate, women of childbearing potential should be fully informed of the possible effects of Topiramate on the unborn foetus and the risks should be discussed with the patient in relation to the benefits of Topiramate treatment in migraine prophylaxis.

In post-marketing experience, hypospadias has been reported in male infants exposed in-utero to topiramate, with or without other anticonvulsants; however, a causal relationship with topiramate has not been established. It is recommended that women of child bearing potential use adequate contraception.

Topiramate is excreted in the milk of lactating rats. 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. Topiramate should not be used during breast feeding.

4.7 **Effects on ability to drive and use machines**

Topiramate can produce central nervous system related adverse events and may be more sedative than other antiepileptic drugs. Drowsiness is a likelihood. In addition, there have been reports of visual disturbances/blurred vision. Patients should be warned of these and advised that if affected, they should not drive, operate machinery and/or take part in activities where such reactions could put themselves or others at risk.

4.8 **Undesirable effects**

Reported adverse events were classified using a modified WHO-ART dictionary. The majority of the most common adverse events in clinical trials were mild-moderate in severity and dose-related. These dose-related adverse events typically began in the titration phase and often persisted into the maintenance phase but infrequently began in the maintenance phase. Rapid titration rate and higher initial dose were associated with higher incidences of adverse events leading to discontinuation.

**Epilepsy**

*a) Monotherapy*

Qualitatively, the types of adverse events observed in monotherapy trials were generally similar to those observed during adjunctive therapy trials (see below). With the exception of paraesthesia and fatigue in adults, these adverse events were reported at similar or lower incidence rates in monotherapy trials.

**Adults:**

In double-blind monotherapy clinical trials, the most common adverse events, i.e., those occurring in 10% or more of the topiramate-treated adult patients were paraesthesia, headache, fatigue, dizziness, somnolence, weight decrease, nausea and anorexia.

Adverse events occurring at 5% or more but less than 10% included: insomnia, difficulty with memory, depression, difficulty with concentration/attention, abdominal pain, nervousness, hypoesthesia, mood problems and anxiety.

**Children:**

In double-blind monotherapy clinical trials, the most common adverse events, i.e., those occurring in 10% or more of the topiramate-treated children were headache, anorexia and somnolence.

Adverse events occurring at 5% or more but less than 10% included: difficulty with concentration/attention, fatigue, weight decrease, dizziness, paraesthesia, insomnia and nervousness.

*b) Adjunctive Therapy*

**Adults:**

Since Topiramate has most frequently been co-administered with other antiepileptic agents, it is not possible to determine which agents, if any, are associated with adverse effects. In double blind clinical trials, some of which included a rapid titration period, adverse events which occurred with a frequency greater than or equal to 5% and with a higher incidence in the topiramate-treated adult patients than in placebo included: abdominal pain, ataxia, anorexia, asthenia, confusion, difficulty with concentration/attention, difficulty with memory, diplopia, dizziness, fatigue, language problems,
nausea, nystagmus, paraesthesia, psychomotor slowing, somnolence, speech disorders/related speech problems, abnormal vision and weight decrease. Topiramate may cause agitation and emotional lability (which may manifest mood problems and nervousness) and depression. Other less common adverse effects include, gait abnormal, aggressive reaction, apathy, cognitive problems, co-ordination problems, leucopenia, psychotic symptoms (such as hallucinations) and taste perversion.

Isolated cases of venous thromboembolic events have been reported. A causal association with the drug has not been established.

Reports of increases in liver enzymes in patients taking Topiramate with and without other medications have been received. Isolated reports have been received of hepatitis and hepatic failure occurring in patients taking multiple medications while being treated with Topiramate.

Children

In double blind clinical trials, some of which included a rapid titration period, adverse events which occurred with a frequency greater than or equal to 5% and with a higher incidence in the topiramate-treated children than in placebo included: somnolence, anorexia, fatigue, insomnia, nervousness, personality disorder (behaviour problems), difficulty with concentration/attention, aggressive reaction, weight decrease, gait abnormal, mood problems, ataxia, saliva increased, nausea, difficulty with memory, hyperkinesia, dizziness, speech disorders/related speech problems and paraesthesia.

Adverse events that occurred less frequently but were considered potentially medically relevant included: emotional lability, agitation, apathy, cognitive problems, psychomotor slowing, confusion, hallucination, depression and leucopenia.

Migraine prophylaxis

In double-blind clinical trials, clinically relevant adverse events which occurred at a frequency of 5% or more and seen at a higher incidence in topiramate-treated patients than placebo-treated patients included: fatigue, paraesthesia, dizziness, hypoesthesia, language problems, nausea, diarrhoea, dyspepsia, dry mouth, weight decrease, anorexia, somnolence, difficulty with memory, difficulty with concentration/attention, insomnia, anxiety, mood problems, depression, taste perversion, abnormal vision. Fifty per cent of patients in these trials experienced paraesthesia.

During 6-month double-blind treatment with topiramate 100 mg/day for migraine prophylaxis, weight decrease was reported as an adverse event in 1% of all placebo treated patients and in 9% of all patients receiving topiramate 100 mg/day. Weight loss continued with long-term topiramate treatment (see Section 4.4 Special warnings and special precautions for use).

Children

The effect of Topiramate in children less than 16 years old with migraine has not been studied.

Post-marketing and Other Experience

Adverse drug reactions from spontaneous reports during the worldwide post-marketing experience with Topiramate are included in Table below. The adverse drug reactions are ranked by frequency, using the following convention (all calculated per patient-years of estimated exposure):

- Very common ≥1/10
- Common ≥1/100 and < 1/10
The frequencies provided below reflect reporting rates for adverse drug reactions from spontaneous reports, and do not represent more precise estimates that might be obtained in clinical or experimental studies.

Topiramate increases the risk of nephrolithiasis especially in those with a predisposition (see 4.4 Special warnings and special precautions for use). In the initial clinical trials none of the calculi required open surgery and three-quarters were passed spontaneously. Most of the patients opted to continue treatment despite nephrolithiasis.

Reduced sweating has been rarely reported. The majority of cases have been in children and some have been associated with flushing and raised temperature.

Very rarely, reports have been received for bullous skin and mucosal reactions (including erythema multiforme, pemphigus, Stevens-Johnson syndrome and toxic epidermal necrolysis). The majority of these reports have occurred in patients taking other medications also associated with bullous skin and mucosal reactions.

Post marketing reports of adverse drug reactions

<table>
<thead>
<tr>
<th>Blood and Lymphatic System Disorders</th>
<th>Very rare: leucopenia and neutropenia, thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Rare: anorexia</td>
</tr>
<tr>
<td></td>
<td>Very rare: metabolic acidosis (see section 4.4. Special warnings and Special precautions); decreased appetite, hyperammonemia (see section 4.5 Interactions with Other Medicinal Products and Other Forms of Interaction)</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Uncommon: suicidal ideation, attempts, and suicide (see section 4.4. Special warnings and Special precautions)</td>
</tr>
<tr>
<td></td>
<td>Rare: depression (see section 4.4. Special warnings and Special precautions); agitation; somnolence</td>
</tr>
<tr>
<td></td>
<td>Very rare: insomnia, confusional state, psychotic disorder, aggression, hallucination, expressive language disorder</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Rare: paresthesia, convulsion, headache</td>
</tr>
<tr>
<td></td>
<td>Very rare: speech disorder, dysgeusia, amnesia, memory impairment, drug withdrawal convulsion (see section 4.4. Special warnings and Special precautions)</td>
</tr>
</tbody>
</table>
Eye Disorders
Rare: visual disturbance, vision blurred
Very rare: myopia, angle closure glaucoma (see section 4.4. Special warnings and Special precautions), eye pain

Gastrointestinal Disorders
Rare: nausea
Very rare: diarrhoea, abdominal pain, vomiting

Skin and Subcutaneous Tissue Disorders
Rare: alopecia
Very rare: rash

Renal and Urinary Disorders
Rare: nephrolithiasis (see section 4.4. Special warnings and Special precautions)

General Disorders and Administration Site Conditions
Rare: fatigue
Very rare: pyrexia, feeling abnormal, asthenia

Investigations
Rare: weight decreased

4.9 Overdose

Signs and Symptoms
Overdoses of topiramate have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbances, blurred vision, diplopia, mentation impaired, 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 polydrug overdoses involving topiramate.
Topiramate overdose can result in severe metabolic acidosis.
A patient who ingested a dose calculated to be between 96 and 110 g topiramate was admitted to hospital with coma lasting 20-24 hours followed by full recovery after 3 to 4 days.

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. Haemodialysis has been shown to be an effective means of removing topiramate from the body. The patient should be well hydrated.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antiepileptics, other antiepileptics
ATC classification: N03AX11
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 neurones are subjected to a sustained depolarisation indicative of a state-dependent blockade of voltage-sensitive sodium channels.
Topiramate markedly enhances the activity of GABA at some types of GABA receptors but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype.
Topiramate weakly antagonises the excitatory activity of kainate/AMPA subtype of glutamate receptor.
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.

5.2 Pharmacokinetic properties
Topiramate is rapidly and well absorbed. Based on recovery of radioactivity from the urine, the mean extent of absorption of a 100 mg dose of 14C topiramate was at least 81%. There is no clinically significant effect of food on topiramate. Generally 13-17% of topiramate is bound to plasma proteins. The mean apparent volume of distribution has been measured as 0.55-0.8 L/kg for single doses up to 1200 mg. There is an effect of gender on the volume of distribution. Values for females are circa 50% of those for males.
Topiramate is not extensively metabolised (=20%) in healthy volunteers. Topiramate is metabolised up to 50% in patients receiving concomitant antiepileptic therapy with known inducers of drug metabolising enzymes. Six metabolites have been isolated, characterised and identified from plasma, urine and faeces of humans. Two metabolites, which retained most of the structure of topiramate, were tested and found to have little or no anticonvulsant activity.
In humans, the major route of elimination of unchanged topiramate and its metabolites is via the kidney. 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.
The plasma and renal clearance of topiramate are decreased in patients with impaired renal function (CLCR $\leq 60$ mL/min), and the plasma clearance is decreased in patients with end-stage renal disease. Plasma clearance of topiramate is unchanged in elderly subjects in the absence of underlying renal disease. Plasma clearance of topiramate is decreased in patients with moderate to severe hepatic impairment. 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 antiepileptic drugs decrease the steady-state plasma concentrations. Topiramate modestly reduces the bioavailability of risperidone, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance. Topiramate modestly reduces the bioavailability of diltiazem and one of its active metabolites. This is unlikely to be of clinical significance.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity. As with other antiepileptic drugs, topiramate was teratogenic in mice, rats and rabbits. Overall numbers of foetal malformations in mice were increased for all drug-treated groups, but no significant differences or dosage-response relationships were observed for overall or specific malformations, suggesting that other factors such as maternal toxicity may be involved.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Topiramate 25 mg Tablets contain the following inactive ingredients:

*Tablet core:*
Lactose monohydrate
Starch, pregelatinized
Starch, partially pregelatinized
Microcrystalline cellulose
Sodium starch glycylate
Magnesium stearate

*Tablet film-coating*
Hypromellose
Polysorbate 80
Talc
Titanium dioxide (E171)
6.2 **Incompatibilities**
None known

6.3 **Shelf life**
3 years.

6.4 **Special precautions for storage**
This medicinal product does not require any special storage conditions.

6.5 **Nature and contents of container**
Topiramate 25 mg Tablets are packed in OPA 25 µm / aluminium 45 µm / PVC 60 µm // aluminium 20 µm blisters in cartons containing 28 or 60 tablets. Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
Not applicable

7 **MARKETING AUTHORISATION HOLDER**
TechnoPharm Limited
Fannin House
South County Business Park
Leopardstown
Dublin 18
Ireland

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 20176/0058

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
28/04/2009

10 **DATE OF REVISION OF THE TEXT**
28/04/2009

1 **NAME OF THE MEDICINAL PRODUCT**
Topiramate 50 mg Tablets

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each tablet contains 50 mg of topiramate.

For a full list of excipients, see section 6.1.
3 PHARMACEUTICAL FORM

Film-coated tablet.

Topiramate 50 mg Tablets are light yellow, round, biconvex film-coated tablets engraved with TO on one side and 50 on the other side, about 7 mm in diameter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Epilepsy

Topiramate 50 mg Tablets is indicated as monotherapy in adults and children aged 6 years and above with newly diagnosed epilepsy who have generalised tonic-clonic seizures or partial seizures with or without secondarily generalised seizures.

Topiramate 50 mg Tablets is indicated as adjunctive therapy for adults and children over 2 years of age who are inadequately controlled on conventional first line antiepileptic drugs for: partial seizures with or without secondarily generalised seizures; seizures associated with Lennox Gastaut Syndrome and primary generalised tonic-clonic seizures.

The efficacy and safety of conversion from adjunctive therapy to Topiramate 50 mg Tablets monotherapy has not been demonstrated.

Migraine

Topiramate 50 mg Tablets is indicated in adults for the prophylaxis of migraine headache. Initiation of treatment with topiramate should be restricted to specialist care and treatment should be managed under specialist supervision or shared care arrangements.

Prophylactic treatment of migraine may be considered in situations such as: Adults experiencing three or more migraine attacks per month; frequent migraine attacks that significantly interfere with the patient's daily routine.

Continuing therapy should be reviewed every six months.

The usefulness of Topiramate 50 mg Tablets in the acute treatment of migraine has not been studied.

4.2 Posology and method of administration

General

For optimal seizure control in both adults and children, it is recommended that therapy be initiated at a low dose followed by titration to an effective dose. Tablets should not be broken. Topiramate 50 mg Tablets can be taken without regard to meals.

It is not necessary to monitor topiramate plasma concentrations to optimise topiramate therapy.

The dosing recommendations apply to children and to all adults, including the elderly, in the absence of underlying renal disease. (See 4.4 Special warnings and special precautions for use.)
Since topiramate is removed from plasma by haemodialysis, a supplemental dose of topiramate 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.

**Epilepsy**

a) **Monotherapy**

**Adults and children over 16 years**

Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased at 1- or 2-week intervals by increments of 25 or 50 mg/day, administered in two divided doses. If the patient is unable to tolerate the titration regimen, smaller increments or longer intervals between increments can be used. Dose and titration rate should be guided by clinical outcome. The recommended initial target dose for topiramate monotherapy in adults with newly diagnosed epilepsy is 100 mg/day and the maximum recommended daily dose is 400 mg. These dosing recommendations apply to all adults including the elderly in the absence of underlying renal disease.

**Children aged 6-16 years**

Treatment of children aged 6 years and above should begin at 0.5 to 1 mg/kg nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 0.5 to 1 mg/kg/day, administered in two divided doses. If the child is unable to tolerate the titration regimen, smaller increments or longer intervals between dose increments can be used. Dose and dose titration rate should be guided by clinical outcome. The recommended initial target dose range for topiramate monotherapy in children with newly diagnosed epilepsy aged 6 years and above is 3 to 6 mg/kg/day. Higher doses have been tolerated and rarely doses up to 16 mg/kg/day have been given.

The tablet formulations are not appropriate for children requiring doses of less than 25 mg/day. A suitable formulation should be prescribed.

b) **Adjunctive Therapy**

**Adults and children over 16 years**

The minimal effective dose as adjunctive therapy is 200 mg per day. The usual total daily dose is 200 mg to 400 mg in two divided doses. Some patients may require doses up to 800 mg per day, which is the maximum recommended dose. It is recommended that therapy be initiated at a low dose, followed by titration to an effective dose. Titration should begin at 25 mg daily for one week. The total daily dose should then be increased by 25-50 mg increments at one to two weekly intervals and should be taken in two divided doses. If the patient is unable to tolerate the titration regimen then lower increments or longer intervals between increments may be used. Dose titration should be guided by clinical outcome.

**Children aged 2 - 16 years**

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 nightly for the first week. The dosage should then be increased at 1-
or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses), to achieve optimal clinical response. Dose titration should be guided by clinical outcome. Daily doses up to 30 mg/kg/day have been studied and were generally well tolerated.

**Migraine**

**Adults and children over 16 years**

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.

The recommended total daily dose of topiramate as treatment for the prophylaxis of migraine headache is 100 mg/day administered in two divided doses. Some patients may experience a benefit at a total daily dose of 50 mg/day. No extra benefit has been demonstrated from the administration of doses higher than 100 mg/day. Dose and titration rate should be guided by clinical outcome.

**Children**

Topiramate in migraine prophylaxis has not been studied in children under 16 years.

### 4.3 Contraindications

Hypersensitivity to any component of this medicinal product.

### 4.4 Special warnings and precautions for use

**General**

In patients with or without a history of seizures or epilepsy, antiepileptic drugs, including topiramate, should be gradually withdrawn to minimise the potential for seizures or increased seizure frequency. In clinical trials, daily dosages were decreased in weekly intervals by 50-100 mg in adults with epilepsy and by 25-50 mg in adults receiving topiramate at doses up to 100 mg/day for migraine prophylaxis. In clinical trials of children, topiramate was gradually withdrawn over a 2-8 week period. In situations where rapid withdrawal of topiramate is medically required, appropriate monitoring is recommended.

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Renal elimination is dependent on renal function and is independent of age. Patients with moderate or severe renal impairment may take 10 to 15 days to reach steady-state plasma concentrations as compared to 4 to 8 days in patients with normal renal function.

As with all patients, the titration schedule should be guided by clinical outcome (e.g. seizure control, avoidance of side effects, prophylaxis of migraine headache) with the knowledge that subjects with known renal impairment may require a longer time to reach steady state at each dose. 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. Adequate hydration whilst using topiramate is very important as it can reduce the risk of developing renal stones. In addition, it may reduce the risk of heat-related
adverse events during exercise and exposure to particularly warm environments (see section 4.8). 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 medication associated with nephrolithiasis may be at increased risk.

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

Depression and mood alterations have been reported in patients treated with 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 (43 out of 7,999 patients treated) and at a 3 fold higher incidence than in those treated with placebo (0.15%; 5 out of 3,150 patients treated).

Patients should be monitored for signs of depression and referred for appropriate treatment if necessary. Patients (and caregivers of patients) should be advised to seek medical advice immediately should suicidal thoughts emerge.

In accordance with good clinical practice, patients with a history of depression and/or suicidal behaviour, adolescents and young adults may be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Acute myopia with secondary angle-closure glaucoma has been reported rarely in both children and adults receiving topiramate. Symptoms typically occur within 1 month of the start of treatment and include decreased visual acuity and/or ocular pain. Ophthalmological findings include bilateral myopia, anterior chamber shallowing, hyperaemia and increased intra-ocular pressure with or without mydriasis. There may be supraciliary effusion resulting in anterior displacement of the lens and iris. Treatment includes discontinuation of topiramate as rapidly as is clinically feasible and appropriate measures to reduce intraocular pressure. These measures generally result in a decrease in intraocular pressure. If increased intraocular pressure is suspected, immediate specialist advice should be sought.

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 drugs) may be additive to the bicarbonate lowering effects of topiramate.

Chronic metabolic acidosis in paediatric patients can reduce growth rates. The effect of topiramate on growth and 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).

A dietary supplement or increased food intake may be considered if the patient is losing weight or has inadequate weight gain while on this medication.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Migraine Prophylaxis**

In migraine prophylaxis, before discontinuation of treatment, dosage should be gradually reduced over at least 2 weeks to minimise the possibility of rebound migraine headaches.

**Weight loss**

During the double-blind treatment with topiramate 100 mg/day, the mean change from baseline to the final visit in body weight was -2.5 kg, compared to -0.1 kg in the placebo group. Overall, 68% of patients treated with topiramate 100 mg/day lost weight during the trials, compared to 33% of patients receiving placebo. Weight decrease was reported as an adverse event in 1% of all placebo-treated patients and in 9% of all patients receiving topiramate 100 mg/day.

Significant weight loss may occur during long-term topiramate treatment for migraine prophylaxis. In clinical studies of topiramate 100 mg in migraine prophylaxis, a continuing weight decrease was observed with a mean weight decrease of 5.5 kg over 20 months. Twenty-five per cent of patients treated with topiramate for migraine prophylaxis had a weight loss of ≥10% of their body weight.

It is recommended that patients on long term topiramate for migraine prophylaxis should be regularly weighed and monitored for continuing weight loss.

4.5 **Interaction with other medicinal products and other forms of interaction**

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

**Effects of Topiramate on Other Antiepileptic Drugs**

The addition of Topiramate to other antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no clinically significant effect on their steady-state plasma concentrations, except in some patients where the addition of Topiramate to phenytoin may result in an increase of plasma concentrations of phenytoin. Consequently, it is advised that any patient on phenytoin 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).

**Effects of Other Antiepileptic Drugs on Topiramate**

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 tablets. 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>
<tr>
<td>Primidone</td>
<td>↔</td>
<td>NS</td>
</tr>
</tbody>
</table>

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

**Other Drug 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 drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, topiramate should be used with caution if used in combination with alcohol and other CNS depressants.

Oral Contraceptives: In an interaction study with a combined oral contraceptive, Topiramate increased plasma clearance of the oestrogenic component significantly. Consequently, and bearing in mind the potential risk of teratogenicity, patients should receive a preparation containing not less than 50 µg of oestrogen or use some alternative non-hormonal method of...
contraception. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns.

**Lithium:** In healthy volunteers, there was an observed reduction (18% for AUC) in systemic exposure for lithium during concomitant administration with topiramate 200 mg/kg. 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.

**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 Cmax 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 500mg bd and topiramate 100mg bd in plasma when metformin was given alone and when metformin and topiramate were given simultaneously. The results of this study indicated that metformin mean Cmax and mean AUC0-12h increased by 18% and 25%, respectively, while mean CL/F decreased 20% when metformin was co-administered with topiramate. Topiramate did not affect metformin tmax. 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 AUCt,ss of pioglitazone with no alteration in Cmax,ss was observed. This finding was not statistically significant. In addition, a 13% and 16% decrease in Cmax,ss and AUCt,ss respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in Cmax,ss and AUCt,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.

**Glibenclamide:** A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glibenclamide.
(5mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 25% reduction in glibenclamide AUC\textsubscript{24} during topiramate administration. Systemic exposure of the active metabolites, 4-trans-hydroxy-glibenclamide (M1) and 3-cis-hydroxy-glibenclamide (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.

**Others:** 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. The interaction with benzodiazepines has not been studied.

**Valproic Acid:** Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. In most cases, symptoms and signs abated with discontinuation of either drug. 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\textsubscript{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>↔</td>
<td>20% increase in C\textsubscript{max} and AUC of nortriptyline metabolite</td>
</tr>
<tr>
<td>Dihydroergotamine (Oral and Subcutaneous)</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>↔</td>
<td>31% increase in AUC of the reduced metabolite</td>
</tr>
<tr>
<td>Propranolol</td>
<td>↔</td>
<td>17% increase in C\textsubscript{max} for 4-OH propranolol (TPM 50 mg q12h)</td>
</tr>
</tbody>
</table>

\(^a\) Reference concentration.
Interaction studies showed that Topiramate did not significantly alter the serum levels of amitriptyline, propranolol or dihydroergotamine mesylate. The combination of Topiramate with each of these drugs was well tolerated and no dose adjustments were necessary.

**Laboratory Tests:**
Clinical trial data indicates that topiramate has been associated with an average decrease of 4 mmol/L in the serum bicarbonate level (see Section 4.4 Special warnings and special precautions for use Metabolic Acidosis).

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

There are no studies using Topiramate in pregnant women. However, Topiramate should not be used during pregnancy unless, in the opinion of the physician, the potential benefit outweighs the potential risk to the foetus. Before starting Topiramate, women of childbearing potential should be fully informed of the possible effects of Topiramate on the unborn foetus and the risks should be discussed with the patient in relation to the benefits of Topiramate treatment in migraine prophylaxis.

In post-marketing experience, hypospadias has been reported in male infants exposed in-utero to topiramate, with or without other anticonvulsants; however, a causal relationship with topiramate has not been established. It is recommended that women of child bearing potential use adequate contraception.

Topiramate is excreted in the milk of lactating rats. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggests an extensive excretion of topiramate into breast milk. Topiramate should not be used during breast feeding.

### 4.7 Effects on ability to drive and use machines
Topiramate can produce central nervous system related adverse events and may be more sedative than other antiepileptic drugs. Drowsiness is a likelihood. In addition, there have been reports of visual disturbances/blurred vision. Patients should be warned of these and advised that if affected, they should not drive, operate machinery and/or take part in activities where such reactions could put themselves or others at risk.
4.8 Undesirable effects
Reported adverse events were classified using a modified WHO-ART dictionary. The majority of the most common adverse events in clinical trials were mild-moderate in severity and dose-related. These dose-related adverse events typically began in the titration phase and often persisted into the maintenance phase but infrequently began in the maintenance phase. Rapid titration rate and higher initial dose were associated with higher incidences of adverse events leading to discontinuation.

Epilepsy
a) Monotherapy
Qualitatively, the types of adverse events observed in monotherapy trials were generally similar to those observed during adjunctive therapy trials (see below). With the exception of paraesthesia and fatigue in adults, these adverse events were reported at similar or lower incidence rates in monotherapy trials.

Adults:
In double-blind monotherapy clinical trials, the most common adverse events, i.e., those occurring in 10% or more of the topiramate-treated adult patients were paraesthesia, headache, fatigue, dizziness, somnolence, weight decrease, nausea and anorexia. Adverse events occurring at 5% or more but less than 10% included: insomnia, difficulty with memory, depression, difficulty with concentration/attention, abdominal pain, nervousness, hypoaesthesia, mood problems and anxiety.

Children:
In double-blind monotherapy clinical trials, the most common adverse events, i.e., those occurring in 10% or more of the topiramate-treated children were headache, anorexia and somnolence. Adverse events occurring at 5% or more but less than 10% included: difficulty with concentration/attention, fatigue, weight decrease, dizziness, paraesthesia, insomnia and nervousness.

b) Adjunctive Therapy
Adults:
Since Topiramate has most frequently been co-administered with other antiepileptic agents, it is not possible to determine which agents, if any, are associated with adverse effects. In double blind clinical trials, some of which included a rapid titration period, adverse events which occurred with a frequency greater than or equal to 5% and with a higher incidence in the topiramate-treated adult patients than in placebo included: abdominal pain, ataxia, anorexia, asthenia, confusion, difficulty with concentration/attention, difficulty with memory, diplopia, dizziness, fatigue, language problems, nausea, nystagmus, paraesthesia, psychomotor slowing, somnolence, speech disorders/related speech problems, abnormal vision and weight decrease. Topiramate may cause agitation and emotional lability (which may manifest mood problems and nervousness) and depression. Other less common adverse effects include, gait abnormal, aggressive reaction, apathy, cognitive problems, co-ordination problems, leucopenia, psychotic symptoms (such as hallucinations) and taste perversion. Isolated cases of venous thromboembolic events have been reported. A causal association with the drug has not been established. Reports of increases in liver enzymes in patients taking Topiramate with and without other medications have been received. Isolated reports have been
received of hepatitis and hepatic failure occurring in patients taking multiple medications while being treated with Topiramate.

Children

In double blind clinical trials, some of which included a rapid titration period, adverse events which occurred with a frequency greater than or equal to 5% and with a higher incidence in the topiramate-treated children than in placebo included: somnolence, anorexia, fatigue, insomnia, nervousness, personality disorder (behaviour problems), difficulty with concentration/attention, aggressive reaction, weight decrease, gait abnormal, mood problems, ataxia, saliva increased, nausea, difficulty with memory, hyperkinesia, dizziness, speech disorders/related speech problems and paraesthesia.

Adverse events that occurred less frequently but were considered potentially medically relevant included: emotional lability, agitation, apathy, cognitive problems, psychomotor slowing, confusion, hallucination, depression and leucopenia.

Migraine prophylaxis

In double-blind clinical trials, clinically relevant adverse events which occurred at a frequency of 5% or more and seen at a higher incidence in topiramate-treated patients than placebo-treated patients included: fatigue, paraesthesia, dizziness, hypoaesthesia, language problems, nausea, diarrhoea, dyspepsia, dry mouth, weight decrease, anorexia, somnolence, difficulty with memory, difficulty with concentration/attention, insomnia, anxiety, mood problems, depression, taste perversion, abnormal vision. Fifty per cent of patients in these trials experienced paraesthesia.

During 6-month double-blind treatment with topiramate 100 mg/day for migraine prophylaxis, weight decrease was reported as an adverse event in 1% of all placebo treated patients and in 9% of all patients receiving topiramate 100 mg/day. Weight loss continued with long-term topiramate treatment (see Section 4.4 Special warnings and special precautions for use).

Children

The effect of Topiramate in children less than 16 years old with migraine has not been studied.

Post-marketing and Other Experience

Adverse drug reactions from spontaneous reports during the worldwide post-marketing experience with Topiramate are included in Table below. The adverse drug reactions are ranked by frequency, using the following convention (all calculated per patient-years of estimated exposure):

- Very common ≥1/10
- Common ≥1/100 and < 1/10
- Uncommon ≥1/1,000 and < 1/100
- Rare ≥1/10,000 and < 1/1000
- Very rare <1/10,000

The frequencies provided below reflect reporting rates for adverse drug reactions from spontaneous reports, and do not represent more precise estimates that might be obtained in clinical or experimental studies.

Topiramate increases the risk of nephrolithiasis especially in those with a predisposition (see 4.4 Special warnings and special precautions for use). In the initial clinical trials none of the calculi required open surgery and three-quarters were passed spontaneously. Most of the patients opted to continue treatment despite nephrolithiasis.
Reduced sweating has been rarely reported. The majority of cases have been in children and some have been associated with flushing and raised temperature. Very rarely, reports have been received for bullous skin and mucosal reactions (including erythema multiforme, pemphigus, Stevens-Johnson syndrome and toxic epidermal necrolysis). The majority of these reports have occurred in patients taking other medications also associated with bullous skin and mucosal reactions.

Post marketing reports of adverse drug reactions

<table>
<thead>
<tr>
<th>Blood and Lymphatic System Disorders</th>
<th>Very rare: leucopenia and neutropenia, thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Rare: anorexia</td>
</tr>
<tr>
<td></td>
<td>Very rare: metabolic acidosis (see section 4.4. Special warnings and Special precautions); decreased appetite, hyperammonemia (see section 4.5 Interactions with Other Medicinal Products and Other Forms of Interaction)</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Uncommon: suicidal ideation, attempts, and suicide (see section 4.4. Special warnings and Special precautions)</td>
</tr>
<tr>
<td></td>
<td>Rare: depression (see section 4.4. Special warnings and Special precautions); agitation; somnolence</td>
</tr>
<tr>
<td></td>
<td>Very rare: insomnia, confusional state, psychotic disorder, aggression, hallucination, expressive language disorder</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Rare: paresthesia, convulsion, headache</td>
</tr>
<tr>
<td></td>
<td>Very rare: speech disorder, dysgeusia, amnesia, memory impairment, drug withdrawal convulsion (see section 4.4. Special warnings and Special precautions)</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>Rare: visual disturbance, vision blurred</td>
</tr>
<tr>
<td></td>
<td>Very rare: myopia, angle closure glaucoma (see section 4.4. Special warnings and Special precautions), eye pain</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Rare: nausea</td>
</tr>
<tr>
<td></td>
<td>Very rare: diarrhoea, abdominal pain, vomiting</td>
</tr>
</tbody>
</table>
Skin and Subcutaneous Tissue Disorders
Rare: alopecia
Very rare: rash

Renal and Urinary Disorders
Rare: nephrolithiasis (see section 4.4. Special warnings and Special precautions)

General Disorders and Administration Site Conditions
Rare: fatigue
Very rare: pyrexia, feeling abnormal, asthenia

Investigations
Rare: weight decreased

4.9 Overdose

Signs and Symptoms
Overdoses of topiramate have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbances, blurred vision, diplopia, mentation impaired, 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 polydrug overdoses involving topiramate. Topiramate overdose can result in severe metabolic acidosis. A patient who ingested a dose calculated to be between 96 and 110 g topiramate was admitted to hospital with coma lasting 20-24 hours followed by full recovery after 3 to 4 days.

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. Haemodialysis has been shown to be an effective means of removing topiramate from the body. The patient should be well hydrated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antiepileptics, other antiepileptics
ATC classification: N03AX11
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 neurones are subjected to a sustained depolarisation indicative of a state-dependent blockade of voltage-sensitive sodium channels.
Topiramate markedly enhances the activity of GABA at some types of GABA receptors but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype. Topiramate weakly antagonises the excitatory activity of kainate/AMPA subtype of glutamate receptor. 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.

5.2 Pharmacokinetic properties
Topiramate is rapidly and well absorbed. Based on recovery of radioactivity from the urine, the mean extent of absorption of a 100 mg dose of $^{14}$C topiramate was at least 81%. There is no clinically significant effect of food on topiramate. Generally 13-17% of topiramate is bound to plasma proteins. The mean apparent volume of distribution has been measured as 0.55-0.8 L/kg for single doses up to 1200 mg. There is an effect of gender on the volume of distribution. Values for females are circa 50% of those for males. Topiramate is not extensively metabolised (=20%) in healthy volunteers. Topiramate is metabolised up to 50% in patients receiving concomitant antiepileptic therapy with known inducers of drug metabolising enzymes. Six metabolites have been isolated, characterised and identified from plasma, urine and faeces of humans. Two metabolites, which retained most of the structure of topiramate, were tested and found to have little or no anticonvulsant activity.

In humans, the major route of elimination of unchanged topiramate and its metabolites is via the kidney. 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 $C_{max}$ 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.

The plasma and renal clearance of topiramate are decreased in patients with impaired renal function (CLCR ≤60 mL/min), and the plasma clearance is decreased in patients with end-stage renal disease. Plasma clearance of topiramate is unchanged in elderly subjects in the absence of underlying renal disease. Plasma clearance of topiramate is decreased in patients with moderate to severe hepatic impairment. 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 antiepileptic drugs decrease the steady-state plasma concentrations. Topiramate modestly reduces the bioavailability of risperidone, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance. Topiramate modestly reduces the bioavailability of diltiazem and one of its active metabolites. This is unlikely to be of clinical significance.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity. As with other antiepileptic drugs, topiramate was teratogenic in mice, rats and rabbits. Overall numbers of foetal malformations in mice were increased for all drug-treated groups, but no significant differences or dosage-response relationships were observed for overall or specific malformations, suggesting that other factors such as maternal toxicity may be involved.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Topiramate 50 mg Tablets contain the following inactive ingredients:

*Tablet core:*
Lactose monohydrate
Starch, pregelatinized
Starch, partially pregelatinized
Microcrystalline cellulose
Sodium starch glycollate
Magnesium stearate

*Tablet film-coating*
Hypromellose
Polysorbate 80
Talc
Titanium dioxide (E171)
Iron oxide yellow (E172)

6.2 Incompatibilities
None known

6.3 Shelf life
3 years.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.
6.5 Nature and contents of container
Topiramate 50 mg Tablets are packed in OPA 25 µm / aluminium 45 µm / PVC 60 µm // aluminium 20 µm blisters in cartons containing 28 or 60 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Not applicable

7 MARKETING AUTHORISATION HOLDER
TechnoPharm Limited
Fannin House
South County Business Park
Leopardstown
Dublin 18
Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 20176/0059

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28/04/2009

10 DATE OF REVISION OF THE TEXT
28/04/2009

1 NAME OF THE MEDICINAL PRODUCT
Topiramate 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 100 mg of topiramate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Topiramate 100 mg Tablets are yellow, round, biconvex film-coated tablets engraved with TO on one side and 100 on the other side, about 10 mm in diameter.
4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Epilepsy
Topiramate 100 mg Tablets is indicated as monotherapy in adults and children aged 6 years and above with newly diagnosed epilepsy who have generalised tonic-clonic seizures or partial seizures with or without secondarily generalised seizures.

Topiramate 100 mg Tablets is indicated as adjunctive therapy for adults and children over 2 years of age who are inadequately controlled on conventional first line antiepileptic drugs for: partial seizures with or without secondarily generalised seizures; seizures associated with Lennox Gastaut Syndrome and primary generalised tonic-clonic seizures.

The efficacy and safety of conversion from adjunctive therapy to Topiramate 100 mg Tablets monotherapy has not been demonstrated.

Migraine
Topiramate 100 mg Tablets is indicated in adults for the prophylaxis of migraine headache. Initiation of treatment with topiramate should be restricted to specialist care and treatment should be managed under specialist supervision or shared care arrangements.

Prophylactic treatment of migraine may be considered in situations such as: Adults experiencing three or more migraine attacks per month; frequent migraine attacks that significantly interfere with the patient's daily routine.
Continuing therapy should be reviewed every six months.

The usefulness of Topiramate 100 mg Tablets in the acute treatment of migraine has not been studied.

4.2 Posology and method of administration

General
For optimal seizure control in both adults and children, it is recommended that therapy be initiated at a low dose followed by titration to an effective dose. Tablets should not be broken. Topiramate 100 mg Tablets can be taken without regard to meals.
It is not necessary to monitor topiramate plasma concentrations to optimise topiramate therapy.
The dosing recommendations apply to children and to all adults, including the elderly, in the absence of underlying renal disease. (See 4.4 Special warnings and special precautions for use.)

Since topiramate is removed from plasma by haemodialysis, a supplemental dose of topiramate 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.

Epilepsy
a) Monotherapy
Adults and children over 16 years
Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased at 1- or 2-week intervals by increments of 25 or 50 mg/day, administered in two divided doses. If the patient is unable to tolerate the titration regimen, smaller increments or longer intervals between increments can be used. Dose and titration rate should be guided by clinical outcome. The recommended initial target dose for topiramate monotherapy in adults with newly diagnosed epilepsy is 100 mg/day and the maximum recommended daily dose is 400 mg. These dosing recommendations apply to all adults including the elderly in the absence of underlying renal disease.

**Children aged 6-16 years**

Treatment of children aged 6 years and above should begin at 0.5 to 1 mg/kg nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 0.5 to 1 mg/kg/day, administered in two divided doses. If the child is unable to tolerate the titration regimen, smaller increments or longer intervals between dose increments can be used. Dose and dose titration rate should be guided by clinical outcome. The recommended initial target dose range for topiramate monotherapy in children with newly diagnosed epilepsy aged 6 years and above is 3 to 6 mg/kg/day. Higher doses have been tolerated and rarely doses up to 16 mg/kg/day have been given.

The tablet formulations are not appropriate for children requiring doses of less than 25 mg/day. A suitable formulation should be prescribed.

**b) Adjunctive Therapy**

**Adults and children over 16 years**

The minimal effective dose as adjunctive therapy is 200 mg per day. The usual total daily dose is 200 mg to 400 mg in two divided doses. Some patients may require doses up to 800 mg per day, which is the maximum recommended dose. It is recommended that therapy be initiated at a low dose, followed by titration to an effective dose.

Titration should begin at 25 mg daily for one week. The total daily dose should then be increased by 25-50 mg increments at one to two weekly intervals and should be taken in two divided doses. If the patient is unable to tolerate the titration regimen then lower increments or longer intervals between increments may be used. Dose titration should be guided by clinical outcome.

**Children aged 2 - 16 years**

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 nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses), to achieve optimal clinical response. Dose titration should be guided by clinical outcome. Daily doses up to 30 mg/kg/day have been studied and were generally well tolerated.

**Migraine**

**Adults and children over 16 years**

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.
The recommended total daily dose of topiramate as treatment for the prophylaxis of migraine headache is 100 mg/day administered in two divided doses. Some patients may experience a benefit at a total daily dose of 50 mg/day. No extra benefit has been demonstrated from the administration of doses higher than 100 mg/day. Dose and titration rate should be guided by clinical outcome.

**Children**
Topiramate in migraine prophylaxis has not been studied in children under 16 years.

### 4.3 Contraindications
Hypersensitivity to any component of this medicinal product.

### 4.4 Special warnings and precautions for use

**General**
In patients with or without a history of seizures or epilepsy, antiepileptic drugs, including topiramate, should be gradually withdrawn to minimise the potential for seizures or increased seizure frequency. In clinical trials, daily dosages were decreased in weekly intervals by 50-100 mg in adults with epilepsy and by 25-50 mg in adults receiving topiramate at doses up to 100 mg/day for migraine prophylaxis. In clinical trials of children, topiramate was gradually withdrawn over a 2-8 week period. In situations where rapid withdrawal of topiramate is medically required, appropriate monitoring is recommended.

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Renal elimination is dependent on renal function and is independent of age. Patients with moderate or severe renal impairment may take 10 to 15 days to reach steady-state plasma concentrations as compared to 4 to 8 days in patients with normal renal function.

As with all patients, the titration schedule should be guided by clinical outcome (e.g. seizure control, avoidance of side effects, prophylaxis of migraine headache) with the knowledge that subjects with known renal impairment may require a longer time to reach steady state at each dose. 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. Adequate hydration whilst using topiramate is very important as it can reduce the risk of developing renal stones. In addition, it may reduce the risk of heat-related adverse events during exercise and exposure to particularly warm environments (see section 4.8).

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 medication associated with nephrolithiasis may be at increased risk.

In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased.
Depression and mood alterations have been reported in patients treated with 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 (43 out of 7,999 patients treated) and at a 3 fold higher incidence than in those treated with placebo (0.15%; 5 out of 3,150 patients treated).

Patients should be monitored for signs of depression and referred for appropriate treatment if necessary. Patients (and caregivers of patients) should be advised to seek medical advice immediately should suicidal thoughts emerge.

In accordance with good clinical practice, patients with a history of depression and/or suicidal behaviour, adolescents and young adults may be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Acute myopia with secondary angle-closure glaucoma has been reported rarely in both children and adults receiving topiramate. Symptoms typically occur within 1 month of the start of treatment and include decreased visual acuity and/or ocular pain. Ophthalmological findings include bilateral myopia, anterior chamber shallowing, hyperaemia and increased intra-ocular pressure with or without mydriasis. There may be supraciliary effusion resulting in anterior displacement of the lens and iris. Treatment includes discontinuation of topiramate as rapidly as is clinically feasible and appropriate measures to reduce intraocular pressure. These measures generally result in a decrease in intraocular pressure. If increased intraocular pressure is suspected, immediate specialist advice should be sought.

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 drugs) may be additive to the bicarbonate lowering effects of topiramate.

Chronic metabolic acidosis in paediatric patients can reduce growth rates. The effect of topiramate on growth and 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).

A dietary supplement or increased food intake may be considered if the patient is losing weight or has inadequate weight gain while on this medication. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Migraine Prophylaxis
In migraine prophylaxis, before discontinuation of treatment, dosage should be gradually reduced over at least 2 weeks to minimise the possibility of rebound migraine headaches.

Weight loss
During the double-blind treatment with topiramate 100 mg/day, the mean change from baseline to the final visit in body weight was -2.5 kg, compared to -0.1 kg in the placebo group. Overall, 68% of patients treated with topiramate 100 mg/day lost weight during the trials, compared to 33% of patients receiving placebo. Weight decrease was reported as an adverse event in 1% of all placebo-treated patients and in 9% of all patients receiving topiramate 100 mg/day.

Significant weight loss may occur during long-term topiramate treatment for migraine prophylaxis. In clinical studies of topiramate 100 mg in migraine prophylaxis, a continuing weight decrease was observed with a mean weight decrease of 5.5 kg over 20 months. Twenty-five per cent of patients treated with topiramate for migraine prophylaxis had a weight loss of ≥10% of their body weight.

It is recommended that patients on long term topiramate for migraine prophylaxis should be regularly weighed and monitored for continuing weight loss.

4.5 Interaction with other medicinal products and other forms of interaction
For purposes of this section, a no effect dose is defined as a ≤15% change.

Effects of Topiramate on Other Antiepileptic Drugs
The addition of Topiramate to other antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no clinically significant effect on their steady-state plasma concentrations, except in some patients where the addition of Topiramate to phenytoin may result in an increase of plasma concentrations of phenytoin. Consequently, it is advised that any patient on phenytoin 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).

Effects of Other Antiepileptic Drugs on Topiramate
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 tablets.

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>
</table>

MHRA PAR; TOPIRAMATE 25 MG, 50 MG, 100 MG AND 200 MG TABLETS, PL 20176/0058-61 51
Phenytoin ↔** ↓

Carbamazepine (CBZ) ↔ ↓

Valproic Acid ↔ ↔

Lamotrigine ↔ ↔

Phenobarbital ↔ NS

Primidone ↔ NS

↔ = No effect on plasma concentration (≤15% change)

** = Plasma concentrations increase in some patients

↓ = Plasma concentrations decrease

NS = Not studied

AED = antiepileptic drug

Other Drug 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 drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, topiramate should be used with caution if used in combination with alcohol and other CNS depressants.

Oral Contraceptives: In an interaction study with a combined oral contraceptive, Topiramate increased plasma clearance of the oestrogenic component significantly. Consequently, and bearing in mind the potential risk of teratogenicity, patients should receive a preparation containing not less than 50 µg of oestrogen or use some alternative non-hormonal method of contraception. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns.

Lithium: In healthy volunteers, there was an observed reduction (18 % for AUC) in systemic exposure for lithium during concomitant administration with topiramate 200 mg/kg. 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.

**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 $C_{\text{max}}$ 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 500mg bd and topiramate 100mg bd in plasma when metformin was given alone and when metformin and topiramate were given simultaneously. The results of this study indicated that metformin mean $C_{\text{max}}$ 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 $t_{\text{max}}$. 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$_{\text{τ,ss}}$ of pioglitazone with no alteration in $C_{\text{max,ss}}$ was observed. This finding was not statistically significant. In addition, a 13% and 16% decrease in $C_{\text{max,ss}}$ and AUC$_{\text{τ,ss}}$ respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in $C_{\text{max,ss}}$ and AUC$_{\text{τ,ss}}$ 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.

**Glibenclamide:** A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glibenclamide (5mg/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-glibenclamide (M1) and 3-cis-hydroxy-glibenclamide (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.

**Others:** 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. The interaction with benzodiazepines has not been studied.

**Valproic Acid:** Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. In most cases, symptoms and signs abated with discontinuation of either drug. 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>↔</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>20% increase in C(_{\text{max}}) and AUC of nortriptyline metabolite</td>
<td></td>
</tr>
<tr>
<td>Dihydroergotamine (Oral and Subcutaneous)</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>↔</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>31% increase in AUC of the reduced metabolite</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>↔</td>
<td>16% increase in C(_{\text{max}}),</td>
</tr>
<tr>
<td></td>
<td>17% increase in C(_{\text{max}}) for 4-OH propranolol (TPM 50 mg q12h)</td>
<td>17% increase in AUC (80 mg propranolol q12h)</td>
</tr>
<tr>
<td>Sumatriptan (Oral and Subcutaneous)</td>
<td>↔</td>
<td>NS</td>
</tr>
<tr>
<td>Pizotifen</td>
<td>↔</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

Interaction studies showed that Topiramate did not significantly alter the serum levels of amitriptyline, propranolol or dihydroergotamine mesylate. The combination of Topiramate with each of these drugs was well tolerated and no dose adjustments were necessary.

**Laboratory Tests:**
Clinical trial data indicates that topiramate has been associated with an average decrease of 4 mmol/L in the serum bicarbonate level (see Section 4.4 Special warnings and special precautions for use Metabolic Acidosis).

### 4.6 Pregnancy and lactation

Topiramate was teratogenic in mice, rats and rabbits. In rats, topiramate crosses the placental barrier.
There are no studies using Topiramate in pregnant women. However, Topiramate should not be used during pregnancy unless, in the opinion of the physician, the potential benefit outweighs the potential risk to the foetus.
Before starting Topiramate, women of childbearing potential should be fully informed of the possible effects of Topiramate on the unborn foetus and the risks should be discussed with the patient in relation to the benefits of Topiramate treatment in migraine prophylaxis.
In post-marketing experience, hypospadias has been reported in male infants exposed in-utero to topiramate, with or without other anticonvulsants; however, a causal relationship with topiramate has not been established.
It is recommended that women of child bearing potential use adequate contraception.
Topiramate is excreted in the milk of lactating rats. The excretion of topiramate in human milk has not been evaluated in controlled studies.
Limited observations in patients suggests an extensive excretion of topiramate into breast milk. Topiramate should not be used during breast feeding.

### 4.7 Effects on ability to drive and use machines

Topiramate can produce central nervous system related adverse events and may be more sedative than other antiepileptic drugs. Drowsiness is a likelihood. In addition, there have been reports of visual disturbances/blurred vision. Patients should be warned of these and advised that if affected, they should not drive, operate machinery and/or take part in activities where such reactions could put themselves or others at risk.

### 4.8 Undesirable effects

Reported adverse events were classified using a modified WHO-ART dictionary. The majority of the most common adverse events in clinical trials were mild-moderate in severity and dose-related. These dose-related adverse events typically began in the titration phase and often persisted into the maintenance phase but infrequently began in the maintenance phase. Rapid titration rate and higher initial dose were associated with higher incidences of adverse events leading to discontinuation.

**Epilepsy**
a) Monotherapy
Qualitatively, the types of adverse events observed in monotherapy trials were generally similar to those observed during adjunctive therapy trials (see below). With the exception of paraesthesia and fatigue in adults, these adverse events were reported at similar or lower incidence rates in monotherapy trials.

Adults:
In double-blind monotherapy clinical trials, the most common adverse events, i.e., those occurring in 10% or more of the topiramate-treated adult patients were paraesthesia, headache, fatigue, dizziness, somnolence, weight decrease, nausea and anorexia.
Adverse events occurring at 5% or more but less than 10% included: insomnia, difficulty with memory, depression, difficulty with concentration/attention, abdominal pain, nervousness, hypoesthesia, mood problems and anxiety.

Children:
In double-blind monotherapy clinical trials, the most common adverse events, i.e., those occurring in 10% or more of the topiramate-treated children were headache, anorexia and somnolence.
Adverse events occurring at 5% or more but less than 10% included: difficulty with concentration/attention, fatigue, weight decrease, dizziness, paraesthesia, insomnia and nervousness.

b) Adjunctive Therapy
Adults:
Since Topiramate has most frequently been co-administered with other antiepileptic agents, it is not possible to determine which agents, if any, are associated with adverse effects. In double-blind clinical trials, some of which included a rapid titration period, adverse events which occurred with a frequency greater than or equal to 5% and with a higher incidence in the topiramate-treated adult patients than in placebo included: abdominal pain, ataxia, anorexia, asthenia, confusion, difficulty with concentration/attention, difficulty with memory, diplopia, dizziness, fatigue, language problems, nausea, nystagmus, paraesthesia, psychomotor slowing, somnolence, speech disorders/related speech problems, abnormal vision and weight decrease.
Topiramate may cause agitation and emotional lability (which may manifest mood problems and nervousness) and depression. Other less common adverse effects include, gait abnormal, aggressive reaction, apathy, cognitive problems, co-ordination problems, leucopenia, psychotic symptoms (such as hallucinations) and taste perversion.
Isolated cases of venous thromboembolic events have been reported. A causal association with the drug has not been established.
Reports of increases in liver enzymes in patients taking Topiramate with and without other medications have been received. Isolated reports have been received of hepatitis and hepatic failure occurring in patients taking multiple medications while being treated with Topiramate.

Children
In double-blind clinical trials, some of which included a rapid titration period, adverse events which occurred with a frequency greater than or equal to 5% and with a higher incidence in the topiramate-treated children than in placebo included: somnolence, anorexia, fatigue, insomnia, nervousness, personality disorder (behaviour problems), difficulty with concentration/attention, aggressive reaction, weight decrease, gait abnormal, mood problems, ataxia,
saliva increased, nausea, difficulty with memory, hyperkinesia, dizziness, speech disorders/related speech problems and paraesthesia. Adverse events that occurred less frequently but were considered potentially medically relevant included: emotional lability, agitation, apathy, cognitive problems, psychomotor slowing, confusion, hallucination, depression and leucopenia.

**Migraine prophylaxis**
In double-blind clinical trials, clinically relevant adverse events which occurred at a frequency of 5% or more and seen at a higher incidence in topiramate-treated patients than placebo-treated patients included: fatigue, paraesthesia, dizziness, hypoaesthesia, language problems, nausea, diarrhoea, dyspepsia, dry mouth, weight decrease, anorexia, somnolence, difficulty with memory, difficulty with concentration/attention, insomnia, anxiety, mood problems, depression, taste perversion, abnormal vision. Fifty per cent of patients in these trials experienced paraesthesia.
During 6-month double-blind treatment with topiramate 100 mg/day for migraine prophylaxis, weight decrease was reported as an adverse event in 1% of all placebo-treated patients and in 9% of all patients receiving topiramate 100 mg/day. Weight loss continued with long-term topiramate treatment (see Section 4.4 Special warnings and special precautions for use).

**Children**
The effect of Topiramate in children less than 16 years old with migraine has not been studied.

**Post-marketing and Other Experience**
Adverse drug reactions from spontaneous reports during the worldwide post-marketing experience with Topiramate are included in Table below. The adverse drug reactions are ranked by frequency, using the following convention (all calculated per patient-years of estimated exposure):

- **Very common** ≥1/10
- **Common** ≥1/100 and < 1/10
- **Uncommon** ≥1/1,000 and < 1/100
- **Rare** ≥1/10,000 and < 1/1000
- **Very rare** <1/10,000

The frequencies provided below reflect reporting rates for adverse drug reactions from spontaneous reports, and do not represent more precise estimates that might be obtained in clinical or experimental studies.
Topiramate increases the risk of nephrolithiasis especially in those with a predisposition (see 4.4 Special warnings and special precautions for use). In the initial clinical trials none of the calculi required open surgery and three-quarters were passed spontaneously. Most of the patients opted to continue treatment despite nephrolithiasis.
Reduced sweating has been rarely reported. The majority of cases have been in children and some have been associated with flushing and raised temperature. Very rarely, reports have been received for bullous skin and mucosal reactions (including erythema multiforme, pemphigus, Stevens-Johnson syndrome and toxic epidermal necrolysis). The majority of these reports have occurred in patients taking other medications also associated with bullous skin and mucosal reactions.
Post marketing reports of adverse drug reactions
<table>
<thead>
<tr>
<th>Blood and Lymphatic System Disorders</th>
<th>Very rare: leucopenia and neutropenia, thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Rare: anorexia</td>
</tr>
<tr>
<td></td>
<td>Very rare: metabolic acidosis (see section 4.4. Special warnings and Special precautions); decreased appetite, hyperammonemia (see section 4.5 Interactions with Other Medicinal Products and Other Forms of Interaction)</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Uncommon: suicidal ideation, attempts, and suicide (see section 4.4. Special warnings and Special precautions)</td>
</tr>
<tr>
<td></td>
<td>Rare: depression (see section 4.4. Special warnings and Special precautions); agitation; somnolence</td>
</tr>
<tr>
<td></td>
<td>Very rare: insomnia, confusional state, psychotic disorder, aggression, hallucination, expressive language disorder</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Rare: paresthesia, convulsion, headache</td>
</tr>
<tr>
<td></td>
<td>Very rare: speech disorder, dysgeusia, amnesia, memory impairment, drug withdrawal convulsion (see section 4.4. Special warnings and Special precautions)</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>Rare: visual disturbance, vision blurred</td>
</tr>
<tr>
<td></td>
<td>Very rare: myopia, angle closure glaucoma (see section 4.4. Special warnings and Special precautions), eye pain</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Rare: nausea</td>
</tr>
<tr>
<td></td>
<td>Very rare: diarrhoea, abdominal pain, vomiting</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Rare: alopecia</td>
</tr>
<tr>
<td></td>
<td>Very rare: rash</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>Rare: nephrolithiasis (see section 4.4. Special warnings and Special precautions)</td>
</tr>
<tr>
<td>General Disorders and</td>
<td>Rare: fatigue</td>
</tr>
</tbody>
</table>
Administration Site Conditions Very rare: pyrexia, feeling abnormal, asthenia

Investigations Rare: weight decreased

4.9 Overdose

Signs and Symptoms
Overdoses of topiramate have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbances, blurred vision, diplopia, mentation impaired, 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 polydrug overdoses involving topiramate.
Topiramate overdose can result in severe metabolic acidosis.
A patient who ingested a dose calculated to be between 96 and 110 g topiramate was admitted to hospital with coma lasting 20-24 hours followed by full recovery after 3 to 4 days.

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. Haemodialysis has been shown to be an effective means of removing topiramate from the body. The patient should be well hydrated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antiepileptics, other antiepileptics
ATC classification: N03AX11
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 neurones are subjected to a sustained depolarisation indicative of a state-dependent blockade of voltage-sensitive sodium channels.
Topiramate markedly enhances the activity of GABA at some types of GABA receptors but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype.
Topiramate weakly antagonises the excitatory activity of kainate/AMPA subtype of glutamate receptor.
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.

5.2 Pharmacokinetic properties
Topiramate is rapidly and well absorbed. Based on recovery of radioactivity from the urine, the mean extent of absorption of a 100 mg dose of $^{14}$C
Topiramate was at least 81%. There is no clinically significant effect of food on topiramate. Generally 13-17% of topiramate is bound to plasma proteins. The mean apparent volume of distribution has been measured as 0.55-0.8 L/kg for single doses up to 1200 mg. There is an effect of gender on the volume of distribution. Values for females are circa 50% of those for males.

Topiramate is not extensively metabolised (~20%) in healthy volunteers. Topiramate is metabolised up to 50% in patients receiving concomitant antiepileptic therapy with known inducers of drug metabolising enzymes. Six metabolites have been isolated, characterised and identified from plasma, urine and faeces of humans. Two metabolites, which retained most of the structure of topiramate, were tested and found to have little or no anticonvulsant activity.

In humans, the major route of elimination of unchanged topiramate and its metabolites is via the kidney. 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.

The plasma and renal clearance of topiramate are decreased in patients with impaired renal function (CLCR $\leq$ 60 mL/min), and the plasma clearance is decreased in patients with end-stage renal disease. Plasma clearance of topiramate is unchanged in elderly subjects in the absence of underlying renal disease. Plasma clearance of topiramate is decreased in patients with moderate to severe hepatic impairment.

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. Topiramate modestly reduces the bioavailability of risperidone, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance.

Topiramate modestly reduces the bioavailability of diltiazem and one of its active metabolites. This is unlikely to be of clinical significance.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity.
As with other antiepileptic drugs, topiramate was teratogenic in mice, rats and rabbits. Overall numbers of foetal malformations in mice were increased for all drug-treated groups, but no significant differences or dosage-response relationships were observed for overall or specific malformations, suggesting that other factors such as maternal toxicity may be involved.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Topiramate 100 mg Tablets contain the following inactive ingredients:

*Tablet core:*
- Lactose monohydrate
- Starch, pregelatinized
- Starch, partially pregelatinized
- Microcrystalline cellulose
- Sodium starch glycollate
- Magnesium stearate

*Tablet film-coating*
- Hyromellose
- Polysorbate 80
- Talc
- Titanium dioxide (E171)
- Iron oxide yellow (E172)

6.2 Incompatibilities
None known

6.3 Shelf life
3 years.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Topiramate 100 mg Tablets are packed in OPA 25 µm / aluminium 45 µm / PVC 60 µm // aluminium 20 µm blisters in cartons containing 28 or 60 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Not applicable

7 MARKETING AUTHORITY HOLDER
TechnoPharm Limited
Fannin House
South County Business Park
Leopardstown
1 NAME OF THE MEDICINAL PRODUCT
Topiramate 200 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 200 mg of topiramate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Topiramate 200 mg Tablets are salmon coloured, round, biconvex film-coated tablets engraved with TO on one side and 200 on the other side, about 13 mm in diameter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Epilepsy
Topiramate 200 mg Tablets is indicated as monotherapy in adults and children aged 6 years and above with newly diagnosed epilepsy who have generalised tonic-clonic seizures or partial seizures with or without secondarily generalised seizures.

Topiramate 200 mg Tablets is indicated as adjunctive therapy for adults and children over 2 years of age who are inadequately controlled on conventional first line antiepileptic drugs for: partial seizures with or without secondarily generalised seizures; seizures associated with Lennox Gastaut Syndrome and primary generalised tonic-clonic seizures.
The efficacy and safety of conversion from adjunctive therapy to Topiramate 200 mg Tablets monotherapy has not been demonstrated.

**Migraine**

Topiramate 200 mg Tablets is indicated in adults for the prophylaxis of migraine headache. Initiation of treatment with topiramate should be restricted to specialist care and treatment should be managed under specialist supervision or shared care arrangements.

Prophylactic treatment of migraine may be considered in situations such as:
- Adults experiencing three or more migraine attacks per month; frequent migraine attacks that significantly interfere with the patient's daily routine.
- Continuing therapy should be reviewed every six months.

The usefulness of Topiramate 200 mg Tablets in the acute treatment of migraine has not been studied.

### 4.2 Posology and method of administration

**General**

For optimal seizure control in both adults and children, it is recommended that therapy be initiated at a low dose followed by titration to an effective dose. Tablets should not be broken. Topiramate 200 mg Tablets can be taken without regard to meals.

It is not necessary to monitor topiramate plasma concentrations to optimise topiramate therapy.

The dosing recommendations apply to children and to all adults, including the elderly, in the absence of underlying renal disease. (See 4.4 Special warnings and special precautions for use.)

Since topiramate is removed from plasma by haemodialysis, a supplemental dose of topiramate 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.

**Epilepsy**

a) **Monotherapy**

**Adults and children over 16 years**

Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased at 1- or 2-week intervals by increments of 25 or 50 mg/day, administered in two divided doses. If the patient is unable to tolerate the titration regimen, smaller increments or longer intervals between increments can be used. Dose and titration rate should be guided by clinical outcome.

The recommended initial target dose for topiramate monotherapy in adults with newly diagnosed epilepsy is 100 mg/day and the maximum recommended daily dose is 400 mg. These dosing recommendations apply to all adults including the elderly in the absence of underlying renal disease.

**Children aged 6-16 years**

Treatment of children aged 6 years and above should begin at 0.5 to 1 mg/kg nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 0.5 to 1 mg/kg/day, administered in two divided doses. If the child is unable to tolerate the titration regimen, smaller
increments or longer intervals between dose increments can be used. Dose and
dose titration rate should be guided by clinical outcome.
The recommended initial target dose range for topiramate monotherapy in
children with newly diagnosed epilepsy aged 6 years and above is 3 to 6
mg/kg/day. Higher doses have been tolerated and rarely doses up to 16
mg/kg/day have been given.
The tablet formulations are not appropriate for children requiring doses of less
than 25 mg/day. A suitable formulation should be prescribed.

b) Adjunctive Therapy
Adults and children over 16 years
The minimal effective dose as adjunctive therapy is 200 mg per day. The usual
total daily dose is 200 mg to 400 mg in two divided doses. Some patients may
require doses up to 800 mg per day, which is the maximum recommended
dose. It is recommended that therapy be initiated at a low dose, followed by
titration to an effective dose.
Titration should begin at 25 mg daily for one week. The total daily dose
should then be increased by 25-50 mg increments at one to two weekly
intervals and should be taken in two divided doses. If the patient is unable to
tolerate the titration regimen then lower increments or longer intervals
between increments may be used. Dose titration should be guided by clinical
outcome.
Children aged 2 - 16 years
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 nightly for the first week. The dosage should then be increased at 1-
or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two
divided doses), to achieve optimal clinical response. Dose titration should be
guided by clinical outcome.
Daily doses up to 30 mg/kg/day have been studied and were generally well
tolerated.

Migraine
Adults and children over 16 years
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.
The recommended total daily dose of topiramate as treatment for the
prophylaxis of migraine headache is 100 mg/day administered in two divided
doses. Some patients may experience a benefit at a total daily dose of 50
mg/day. No extra benefit has been demonstrated from the administration of
doses higher than 100 mg/day. Dose and titration rate should be guided by
clinical outcome.
Children
Topiramate in migraine prophylaxis has not been studied in children under 16
years.

4.3 Contraindications
Hypersensitivity to any component of this medicinal product.
4.4 Special warnings and precautions for use

General

In patients with or without a history of seizures or epilepsy, antiepileptic drugs, including topiramate, should be gradually withdrawn to minimise the potential for seizures or increased seizure frequency. In clinical trials, daily dosages were decreased in weekly intervals by 50-100 mg in adults with epilepsy and by 25-50 mg in adults receiving topiramate at doses up to 100 mg/day for migraine prophylaxis. In clinical trials of children, topiramate was gradually withdrawn over a 2-8 week period. In situations where rapid withdrawal of topiramate is medically required, appropriate monitoring is recommended.

The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Renal elimination is dependent on renal function and is independent of age. Patients with moderate or severe renal impairment may take 10 to 15 days to reach steady-state plasma concentrations as compared to 4 to 8 days in patients with normal renal function.

As with all patients, the titration schedule should be guided by clinical outcome (e.g. seizure control, avoidance of side effects, prophylaxis of migraine headache) with the knowledge that subjects with known renal impairment may require a longer time to reach steady state at each dose.

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. Adequate hydration whilst using topiramate is very important as it can reduce the risk of developing renal stones. In addition, it may reduce the risk of heat-related adverse events during exercise and exposure to particularly warm environments (see section 4.8).

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 medication associated with nephrolithiasis may be at increased risk.

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

Depression and mood alterations have been reported in patients treated with 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 (43 out of 7,999 patients treated) and at a 3 fold higher incidence than in those treated with placebo (0.15%; 5 out of 3,150 patients treated).

Patients should be monitored for signs of depression and referred for appropriate treatment if necessary. Patients (and caregivers of patients) should be advised to seek medical advice immediately should suicidal thoughts emerge.

In accordance with good clinical practice, patients with a history of depression and/or suicidal behaviour, adolescents and young adults may be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.
Acute myopia with secondary angle-closure glaucoma has been reported rarely in both children and adults receiving topiramate. Symptoms typically occur within 1 month of the start of treatment and include decreased visual acuity and/or ocular pain. Ophthalmological findings include bilateral myopia, anterior chamber shallowing, hyperaemia and increased intraocular pressure with or without mydriasis. There may be supraciliary effusion resulting in anterior displacement of the lens and iris. Treatment includes discontinuation of topiramate as rapidly as is clinically feasible and appropriate measures to reduce intraocular pressure. These measures generally result in a decrease in intraocular pressure. If increased intraocular pressure is suspected, immediate specialist advice should be sought.

**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 drugs) may be additive to the bicarbonate lowering effects of topiramate. Chronic metabolic acidosis in paediatric patients can reduce growth rates. The effect of topiramate on growth and 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). A dietary supplement or increased food intake may be considered if the patient is losing weight or has inadequate weight gain while on this medication. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Migraine Prophylaxis**
In migraine prophylaxis, before discontinuation of treatment, dosage should be gradually reduced over at least 2 weeks to minimise the possibility of rebound migraine headaches.

**Weight loss**
During the double-blind treatment with topiramate 100 mg/day, the mean change from baseline to the final visit in body weight was -2.5 kg, compared to -0.1 kg in the placebo group. Overall, 68% of patients treated with topiramate 100 mg/day lost weight during the trials, compared to 33% of patients receiving placebo. Weight decrease was reported as an adverse event in 1% of all placebo-treated patients and in 9% of all patients receiving topiramate 100 mg/day.
Significant weight loss may occur during long-term topiramate treatment for migraine prophylaxis. In clinical studies of topiramate 100 mg in migraine prophylaxis, a continuing weight decrease was observed with a mean weight decrease of 5.5 kg over 20 months. Twenty-five per cent of patients treated with topiramate for migraine prophylaxis had a weight loss of ≥10% of their body weight.

It is recommended that patients on long term topiramate for migraine prophylaxis should be regularly weighed and monitored for continuing weight loss.

4.5 Interaction with other medicinal products and other forms of interaction

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

Effects of Topiramate on Other Antiepileptic Drugs

The addition of Topiramate to other antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no clinically significant effect on their steady-state plasma concentrations, except in some patients where the addition of Topiramate to phenytoin may result in an increase of plasma concentrations of phenytoin. Consequently, it is advised that any patient on phenytoin 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).

Effects of Other Antiepileptic Drugs on Topiramate

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 tablets.

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>
<tr>
<td>Primidone</td>
<td>↔</td>
<td>NS</td>
</tr>
</tbody>
</table>
↔ = No effect on plasma concentration (≤15% change)
** = Plasma concentrations increase in some patients
↓ = Plasma concentrations decrease
NS = Not studied
AED = antiepileptic drug

Other Drug 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 drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, topiramate should be used with caution if used in combination with alcohol and other CNS depressants.

Oral Contraceptives: In an interaction study with a combined oral contraceptive, Topiramate increased plasma clearance of the oestrogenic component significantly. Consequently, and bearing in mind the potential risk of teratogenicity, patients should receive a preparation containing not less than 50 µg of oestrogen or use some alternative non-hormonal method of contraception. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns.

Lithium: In healthy volunteers, there was an observed reduction (18 % for AUC) in systemic exposure for lithium during concomitant administration with topiramate 200 mg/kg. 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.

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 Cmax 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 500mg bd and topiramate 100mg bd 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.

**Glibenclamide:** A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glibenclamide (5mg/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-glibenclamide (M1) and 3-cis-hydroxy-glibenclamide (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.

**Others:** 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. The interaction with benzodiazepines has not been studied.

**Valproic Acid:** Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. In most cases, symptoms and signs abated with discontinuation of either drug. 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 Concentrationa</th>
<th>Topiramate Concentrationa</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>16% increase in $C_{\text{max}}$, 17% increase in AUC (80 mg propranolol q12h)</td>
</tr>
<tr>
<td>Sumatriptan (Oral and Subcutaneous)</td>
<td>↔</td>
<td>NS</td>
</tr>
<tr>
<td>Pizotifen</td>
<td>↔</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

Interaction studies showed that Topiramate did not significantly alter the serum levels of amitriptyline, propranolol or dihydroergotamine mesylate. The combination of Topiramate with each of these drugs was well tolerated and no dose adjustments were necessary.

**Laboratory Tests:**

Clinical trial data indicates that topiramate has been associated with an average decrease of 4 mmol/L in the serum bicarbonate level (see Section 4.4 Special warnings and special precautions for use Metabolic Acidosis).
4.6 Pregnancy and lactation
Topiramate was teratogenic in mice, rats and rabbits. In rats, topiramate crosses the placental barrier.
There are no studies using Topiramate in pregnant women. However, Topiramate should not be used during pregnancy unless, in the opinion of the physician, the potential benefit outweighs the potential risk to the foetus. Before starting Topiramate, women of childbearing potential should be fully informed of the possible effects of Topiramate on the unborn foetus and the risks should be discussed with the patient in relation to the benefits of Topiramate treatment in migraine prophylaxis.
In post-marketing experience, hypospadias has been reported in male infants exposed in-utero to topiramate, with or without other anticonvulsants; however, a causal relationship with topiramate has not been established.
It is recommended that women of child bearing potential use adequate contraception.
Topiramate is excreted in the milk of lactating rats. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggests an extensive excretion of topiramate into breast milk. Topiramate should not be used during breast feeding.

4.7 Effects on ability to drive and use machines
Topiramate can produce central nervous system related adverse events and may be more sedative than other antiepileptic drugs. Drowsiness is a likelihood. In addition, there have been reports of visual disturbances/blurred vision. Patients should be warned of these and advised that if affected, they should not drive, operate machinery and/or take part in activities where such reactions could put themselves or others at risk.

4.8 Undesirable effects
Reported adverse events were classified using a modified WHO-ART dictionary. The majority of the most common adverse events in clinical trials were mild-moderate in severity and dose-related. These dose-related adverse events typically began in the titration phase and often persisted into the maintenance phase but infrequently began in the maintenance phase. Rapid titration rate and higher initial dose were associated with higher incidences of adverse events leading to discontinuation.

Epilepsy
a) Monotherapy
Qualitatively, the types of adverse events observed in monotherapy trials were generally similar to those observed during adjunctive therapy trials (see below). With the exception of paraesthesia and fatigue in adults, these adverse events were reported at similar or lower incidence rates in monotherapy trials.

Adults:
In double-blind monotherapy clinical trials, the most common adverse events, i.e., those occurring in 10% or more of the topiramate-treated adult patients were paraesthesia, headache, fatigue, dizziness, somnolence, weight decrease, nausea and anorexia.
Adverse events occurring at 5% or more but less than 10% included: insomnia, difficulty with memory, depression, difficulty with concentration/attention, abdominal pain, nervousness, hypoaesthesia, mood problems and anxiety.
Children:
In double-blind monotherapy clinical trials, the most common adverse events, i.e., those occurring in 10% or more of the topiramate-treated children were headache, anorexia and somnolence.
Adverse events occurring at 5% or more but less than 10% included: difficulty with concentration/attention, fatigue, weight decrease, dizziness, paraesthesia, insomnia and nervousness.

b) Adjunctive Therapy

Adults:
Since Topiramate has most frequently been co-administered with other antiepileptic agents, it is not possible to determine which agents, if any, are associated with adverse effects. In double blind clinical trials, some of which included a rapid titration period, adverse events which occurred with a frequency greater than or equal to 5% and with a higher incidence in the topiramate-treated adult patients than in placebo included: abdominal pain, ataxia, anorexia, asthenia, confusion, difficulty with concentration/attention, difficulty with memory, diplopia, dizziness, fatigue, language problems, nausea, nystagmus, paraesthesia, psychomotor slowing, somnolence, speech disorders/related speech problems, abnormal vision and weight decrease.
Topiramate may cause agitation and emotional lability (which may manifest mood problems and nervousness) and depression. Other less common adverse effects include, gait abnormal, aggressive reaction, apathy, cognitive problems, co-ordination problems, leucopenia, psychotic symptoms (such as hallucinations) and taste perversion.
Isolated cases of venous thromboembolic events have been reported. A causal association with the drug has not been established.
Reports of increases in liver enzymes in patients taking Topiramate with and without other medications have been received. Isolated reports have been received of hepatitis and hepatic failure occurring in patients taking multiple medications while being treated with Topiramate.

Children
In double blind clinical trials, some of which included a rapid titration period, adverse events which occurred with a frequency greater than or equal to 5% and with a higher incidence in the topiramate-treated children than in placebo included: somnolence, anorexia, fatigue, insomnia, nervousness, personality disorder (behaviour problems), difficulty with concentration/attention, aggressive reaction, weight decrease, gait abnormal, mood problems, ataxia, saliva increased, nausea, difficulty with memory, hyperkinesia, dizziness, speech disorders/related speech problems and paraesthesia.
Adverse events that occurred less frequently but were considered potentially medically relevant included: emotional lability, agitation, apathy, cognitive problems, psychomotor slowing, confusion, hallucination, depression and leucopenia.

Migraine prophylaxis
In double-blind clinical trials, clinically relevant adverse events which occurred at a frequency of 5% or more and seen at a higher incidence in topiramate-treated patients than placebo-treated patients included: fatigue, paraesthesia, dizziness, hypoesthesia, language problems, nausea, diarrhoea, dyspepsia, dry mouth, weight decrease, anorexia, somnolence, difficulty with memory, difficulty with concentration/attention, insomnia, anxiety, mood
problems, depression, taste perversion, abnormal vision. Fifty per cent of patients in these trials experienced paraesthesia.

During 6-month double-blind treatment with topiramate 100 mg/day for migraine prophylaxis, weight decrease was reported as an adverse event in 1% of all placebo treated patients and in 9% of all patients receiving topiramate 100 mg/day. Weight loss continued with long-term topiramate treatment (see Section 4.4 Special warnings and special precautions for use).

**Children**

The effect of Topiramate in children less than 16 years old with migraine has not been studied.

**Post-marketing and Other Experience**

Adverse drug reactions from spontaneous reports during the worldwide post-marketing experience with Topiramate are included in Table below. The adverse drug reactions are ranked by frequency, using the following convention (all calculated per patient-years of estimated exposure):

- **Very common** ≥1/10
- **Common** ≥1/100 and < 1/10
- **Uncommon** ≥1/1,000 and < 1/100
- **Rare** ≥1/10,000 and < 1/1000
- **Very rare** <1/10,000

The frequencies provided below reflect reporting rates for adverse drug reactions from spontaneous reports, and do not represent more precise estimates that might be obtained in clinical or experimental studies.

Topiramate increases the risk of nephrolithiasis especially in those with a predisposition (see 4.4 Special warnings and special precautions for use). In the initial clinical trials none of the calculi required open surgery and three-quarters were passed spontaneously. Most of the patients opted to continue treatment despite nephrolithiasis.

Reduced sweating has been rarely reported. The majority of cases have been in children and some have been associated with flushing and raised temperature. Very rarely, reports have been received for bullous skin and mucosal reactions (including erythema multiforme, pemphigus, Stevens-Johnson syndrome and toxic epidermal necrolysis). The majority of these reports have occurred in patients taking other medications also associated with bullous skin and mucosal reactions.

Post marketing reports of adverse drug reactions

<table>
<thead>
<tr>
<th>Blood and Lymphatic System Disorders</th>
<th>Very rare: leucopenia and neutropenia, thrombocytopenia</th>
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<tbody>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Rare: anorexia</td>
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<td></td>
<td>Very rare: metabolic acidosis (see section 4.4. Special warnings and Special precautions); decreased appetite, hyperammonemia (see section 4.5 Interactions with Other Medicinal Products and Other Forms of Interaction)</td>
</tr>
</tbody>
</table>
Psychiatric Disorders  Uncommon: suicidal ideation, attempts, and suicide (see section 4.4. Special warnings and Special precautions)
Rare: depression (see section 4.4. Special warnings and Special precautions); agitation; somnolence
Very rare: insomnia, confusional state, psychotic disorder, aggression, hallucination, expressive language disorder

Nervous System Disorders  Rare: paresthesia, convulsion, headache
Very rare: speech disorder, dysgeusia, amnesia, memory impairment, drug withdrawal convulsion (see section 4.4. Special warnings and Special precautions)

Eye Disorders  Rare: visual disturbance, vision blurred
Very rare: myopia, angle closure glaucoma (see section 4.4. Special warnings and Special precautions), eye pain

Gastrointestinal Disorders  Rare: nausea
Very rare: diarrhoea, abdominal pain, vomiting

Skin and Subcutaneous Tissue Disorders  Rare: alopecia
Very rare: rash

Renal and Urinary Disorders  Rare: nephrolithiasis (see section 4.4. Special warnings and Special precautions)

General Disorders and Administration Site Conditions  Rare: fatigue
Very rare: pyrexia, feeling abnormal, asthenia

Investigations  Rare: weight decreased

4.9  Overdose
  Signs and Symptoms
Overdoses of topiramate have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbances, blurred vision, diplopia, mentation impaired, 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 polydrug overdoses involving topiramate.

Topiramate overdose can result in severe metabolic acidosis.

A patient who ingested a dose calculated to be between 96 and 110 g topiramate was admitted to hospital with coma lasting 20-24 hours followed by full recovery after 3 to 4 days.

**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. Haemodialysis has been shown to be an effective means of removing topiramate from the body. The patient should be well hydrated.

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5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Pharmacotherapeutic group: Antiepileptics, other antiepileptics

ATC classification: N03AX11

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 neurones are subjected to a sustained depolarisation indicative of a state-dependent blockade of voltage-sensitive sodium channels.

Topiramate markedly enhances the activity of GABA at some types of GABA receptors but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype.

Topiramate weakly antagonises the excitatory activity of kainate/AMPA subtype of glutamate receptor.

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.

5.2 **Pharmacokinetic properties**

Topiramate is rapidly and well absorbed. Based on recovery of radioactivity from the urine, the mean extent of absorption of a 100 mg dose of $^{14}$C topiramate was at least 81%. There is no clinically significant effect of food on topiramate. Generally 13-17% of topiramate is bound to plasma proteins. The mean apparent volume of distribution has been measured as 0.55-0.8 L/kg for single doses up to 1200 mg. There is an effect of gender on the volume of distribution. Values for females are circa 50% of those for males.

Topiramate is not extensively metabolised (=20%) in healthy volunteers.

Topiramate is metabolised up to 50% in patients receiving concomitant antiepileptic therapy with known inducers of drug metabolising enzymes. Six metabolites have been isolated, characterised and identified from plasma, urine and faeces of humans. Two metabolites, which retained most of the structure
of topiramate, were tested and found to have little or no anticonvulsant activity.
In humans, the major route of elimination of unchanged topiramate and its metabolites is via the kidney. 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.

The plasma and renal clearance of topiramate are decreased in patients with impaired renal function (CLCR \(\leq 60\) mL/min), and the plasma clearance is decreased in patients with end-stage renal disease. Plasma clearance of topiramate is unchanged in elderly subjects in the absence of underlying renal disease. Plasma clearance of topiramate is decreased in patients with moderate to severe hepatic impairment. 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 antiepileptic drugs decrease the steady-state plasma concentrations. Topiramate modestly reduces the bioavailability of risperidone, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance. Topiramate modestly reduces the bioavailability of diltiazem and one of its active metabolites. This is unlikely to be of clinical significance.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity. As with other antiepileptic drugs, topiramate was teratogenic in mice, rats and rabbits. Overall numbers of foetal malformations in mice were increased for all drug-treated groups, but no significant differences or dosage-response relationships were observed for overall or specific malformations, suggesting that other factors such as maternal toxicity may be involved.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Topiramate 200 mg Tablets contain the following inactive ingredients:
Tablet core:
Lactose monohydrate
Starch, pregelatinized
Starch, partially pregelatinized
Microcrystalline cellulose
Sodium starch glycollate
Magnesium stearate

Tablet film-coating
Hypromellose
Polysorbate 80
Talc
Titanium dioxide (E171)
Iron oxide red (E172)

6.2 Incompatibilities
None known

6.3 Shelf life
3 years.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Topiramate 200 mg Tablets are packed in OPA 25 µm / aluminium 45 µm /
PVC 60 µm // aluminium 20 µm blisters in cartons containing 28 or 60 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Not applicable

7 MARKETING AUTHORISATION HOLDER
TechnoPharm Limited
Fannin House
South County Business Park
Leopardstown
Dublin 18
Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 20176/0061

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION
28/04/2009
DATE OF REVISION OF THE TEXT
28/04/2009
Topiramate 25mg Tablets
Topiramate 50mg Tablets
Topiramate 100mg Tablets
Topiramate 200mg Tablets (Topiramate)

Read all of this leaflet carefully before you start taking this medicine.

- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in the leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Topiramate Tablets are and what they are used for
2. Before you take Topiramate Tablets
3. How to Take Topiramate Tablets
4. Possible side effects
5. How to store Topiramate Tablets
6. Further information

1 What Topiramate Tablets are and what they are used for

Topiramate affects chemicals in the brain that are involved in sending signals to the nerves. Topiramate belongs to a group of medicines used to treat epilepsy and may also be used to prevent migraine headaches. Topiramate should be taken continuously to prevent frequently recurring migraine headaches.

Epilepsy:
Topiramate is used to treat various types of epilepsy. This medicine may be used on its own to treat adults and children aged 6 years and over. It can also be used in combination with other anti-epileptic medicines in both adults and children aged 2 years and over.

Prevention of Migraines:
Topiramate is also used to prevent frequently recurring migraine headaches in adults and children over 16 years old. Treatment must be started under specialist care and continued under the supervision of a specialist. This medicine is not intended to treat an individual migraine attack.

2 Before you take Topiramate Tablets

Do not take Topiramate Tablets if you
- Have ever had an allergic reaction to topiramate or to any of the ingredients in this medicinal product.

Take special care and speak to your doctor before taking Topiramate Tablets if you
- Are a relative of one or have had kidney stones; you have a greater risk of kidney stone formation which may cause pain in the flank (side of the abdomen). Your doctor may want you to increase the amount of water you drink while you are taking this medicine to reduce the risk of kidney stone formation.
- Have liver problems.

Important information about your medicine
- You may notice a change in your mood, or experience feelings of depression while taking this medicine. Patients taking this medicine may sometimes have thoughts of harming themselves or taking their own lives. If you get these thoughts at any time, contact your doctor or go to a hospital straight away.
- Sudden blurring of vision, pain and redness of the eyes has occurred in both adults and children, typically during the first month of taking this medicine. This may indicate glaucoma (raised pressure in the eye). If you develop any eye symptoms tell your doctor immediately. If necessary your doctor will advise you how to stop taking this medicine and refer you to a specialist for eye treatment.
- Metabolic acidosis; Blood tests have sometimes shown an increase in acidity during treatment with this medicine. Your doctor will monitor this and may adjust the amount of topiramate you are taking if you notice weight loss or in the case of children not gaining enough weight, the amount of food being eaten should be increased. Patients, particularly those taking this medicine long term for migraine, should be weighed regularly and their weight monitored.

3 Taking other medicines
Tell your doctor before you are given this medicine if you are taking, or have recently taken, any of the following medicines:
- Other antiepileptic drugs such as phenytoin, carbamazepine or valproic acid.
- Digoxin (to treat various heart conditions).
- Antidepressants, including amitriptyline. The effect when taken with topiramate may make you less alert or sleepy.
- Oral contraceptives. If you notice a change in your bleeding pattern tell your doctor.
- Lithium (for depression or bipolar disorder).
- Hydrochlorothiazide (a diuretic).
- Metformin, Pioglitazone or Gilbertismide (used to treat diabetes).
- Haloperidol (for psychiatric disorders).
- Propranolol (a beta blocker).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines or dietary supplements obtained without a prescription.

Pregnancy
Do not take Topiramate Tablets if you are pregnant unless your doctor has specifically recommended it.

Breast-feeding
Your doctor may ask you to stop breast-feeding as this medicine may reach your baby through your breast milk. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
This medicine may cause drowsiness. You may also experience blurred vision. If affected do not drive, operate machinery or do anything else that could put you or others at risk.

Important information about some of the ingredients of this medicine
This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

4 How to take Topiramate Tablets
Always take topiramate exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure:

- Your doctor will start treatment with a low dose of this medicine and slowly increase the dose to the lowest amount needed to control your epilepsy.
- This medicine is for oral administration. Do not break the tablets. Swallow the tablets with plenty of water. You can take the tablets with or without food.

Epilepsy
Treatment using only this medicine:
Adults and children over 16 years: Your doctor will start treatment with a dose of 25mg to be taken nightly. Your doctor will then increase your dose to the lowest amount needed to control your epilepsy. The recommended target dose is 100mg/day but your doctor may tell you to use a higher or lower dose. The maximum recommended dose is 400mg/day.

Children aged 6 to 16 years: The recommended target dose is 3 to 6mg/kg/day but your doctor will tell you how much to take.

Treatment using this medicine and other antiepileptic drugs:
Adults and children over 16 years: Your doctor will start treatment with a dose of 25mg/day. Your doctor will then increase your dose to the lowest amount needed to control your epilepsy. The recommended target dose is 200 to 400mg/day but your doctor may tell you to use a higher or lower dose.

Children aged 2 to 16 years: The recommended target dose is 5 to 10mg/kg/day taken in two divided doses. Your doctor will tell you how much to take.

Prevention of Migraines
Adults and children over 16 years: Your doctor will start treatment with a dose of 25mg to be taken nightly. Your doctor will then increase your dose to the lowest amount needed to prevent frequently recurring migraine headaches. The recommended target dose is 100mg/day taken in two divided doses (50mg in the morning and 50mg at night) but your doctor may tell you to use a higher or lower dose. Your treatment will be reviewed routinely.
Children under 16 years: This medicine is not recommended in children under 16 years to prevent migraine headaches. If you take more Topiramate Tablets than you should if you accidentally take too many tablets, contact your doctor or nearest hospital casualty department immediately.

If you forget to take Topiramate Tablets
Do not take a double dose to make up for a forgotten dose if a dose is forgotten, it should be taken as soon as it is remembered. However, if it is nearly time for the next dose, miss the forgotten dose altogether and continue with the rest of the medicine as normal.

If you stop taking Topiramate Tablets
If you are to stop taking this medicine, your doctor will reduce the dose you are taking gradually in order to minimise the potential for seizures or increased seizure frequency. Do not suddenly stop taking this medicine without first consulting your doctor. If you have any further questions on the use of this product, ask your doctor or pharmacist.

Possible side effects
Like all medicines, topiramate can cause side effects, although not everybody gets them.

Stop taking Topiramate Tablets and consult your doctor or hospital immediately if you experience:
• High temperature or feel unwell with skin rash, blisters on the skin, eyes, genitals and sore mouth. This is a very rare allergic reaction.
• Thoughts of suicide and attempts to commit suicide.
• Tell your doctor if you experience:
• Any eye symptoms such as sudden blurring of vision, pain and redness of the eyes. This may indicate glaucoma (raised pressure in the eye) and may occur during the first month of using this medicine.
• High temperature or feel unwell with skin rash, blisters on the skin, eyes, genitals and sore mouth. This is a very rare allergic reaction.
• Thoughts of suicide and attempts to commit suicide.

Consider the following side effects if you are taking more than 1 in 100 people:
• Difficulty concentrating, changes in thinking including slow thinking, confusion, forgetfulness, speech problems, nervousness, anxiety, depression, difficulty sleeping.
• Increased sense of touch, vision problems.
• Diarrhoea, indigestion, change levels of salvia in mouth.
• Weakness, inability to keep still, changes in behaviour, mood swings.
• Uncommon side effects (affecting less than 1 in 100 people):
• Decrease in the white blood cells, problems with co-ordination, changes in taste.
• Agitation, fits.
• Hair loss, kidney problems.
• Very rare side effects (affecting less than 1 in 10,000 people):
• Short sightedness, eye pain, memory loss.

If someone taking Topiramate becomes flushed or overheated, they should relax in a cool place and drink plenty of water. Reduced sweating has occurred, mainly during exercise or in particular warm conditions and mostly in children. This occurs rarely.

The following side effects have been reported in adults and children treated for epilepsy and migraine:

Common side effects (affecting less than 1 in 10 people):
• Headache, dizziness, tiredness, drowsiness.
• Pins, needles and tingling sensation in the hands and feet.
• Feeling sick, weight loss and loss of appetite.

Side effects (affecting less than 1 in 100 people):
• Difficulty concentrating, changes in thinking including slow thinking, confusion, forgetfulness, speech problems, nervousness, anxiety, depression, difficulty sleeping.
• Increased sense of touch, vision problems.
• Diarrhoea, indigestion, change levels of salvia in mouth.
• Weakness, inability to keep still, changes in behaviour, mood swings.

Uncommon side effects (affecting less than 1 in 100 people):
• Decrease in the white blood cells, problems with co-ordination, changes in taste.
• Agitation, fits.
• Hair loss, kidney problems.

Very rare side effects (affecting less than 1 in 10,000 people):
• Short sightedness, eye pain, memory loss.

A few people have been reported with a minor change to the opening at the end of the penis after their mothers took toprimate while pregnant. However, it has not been proven that this was caused by toprimate.

Changes in the blood tests, which show how your liver is working, have been seen in patients taking toprimate with or without other medicines. Very rarely patients have had liver problems and liver failure when taking many medicines with toprimate.

If you experience any of the side effects listed, or you notice any not listed in this leaflet, please tell your doctor.

How to store Topiramate Tablets
This medicinal product does not require any special storage conditions. Keep out of the reach and sight of children. Do not use this medicinal product after the expiry date stated on the carton. The expiry date refers to the last day of that month. 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.

Further information
This Tramadol Tablets contains the active ingredient is topiramate. Each tablet contains either 25, 50, 100, or 200mg of topiramate. The other ingredients are lactose monohydrate, pregelatinised starch, partially pregelatinised starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate. The tablet coating ingredients are hypromellose, polyethylene 80, talc, titanium dioxide (E171) and iron oxide (E172) (except white tablets).

What Topiramate Tablets look like and contents of the pack
Topiramate 25mg Tablets are white round biconvex tablets, engraved with TO on one side and 25 on the other side. Topiramate 50mg Tablets are light yellow round biconvex tablets, engraved with TO on one side and 50 on the other side. Topiramate 100mg Tablets are yellow round biconvex tablets, engraved with TO on one side and 100 on the other side. Topiramate 200mg Tablets are salmon coloured round biconvex tablets, engraved with TO on one side and 200 on the other side. This medicinal product is available in blisters packed in cartons of 28 or 60 tablets. Not all pack sizes may be marketed.
25 mg tablets

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100 mg tablets

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200 mg tablets

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