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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Lupin (UK) Limited Marketing Authorisations for the medicinal products Topiramate 25mg, 50 mg, 100 mg and 200 mg Tablets (PL 20092/0060-3) on 05 July 2011. Topiramate Tablets are only available on prescription from your doctor and are used:

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

Topiramate Tablets contain the active ingredient topiramate, which belongs to a group of medicines called “antiepileptic medicines”.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Topiramate 25 mg, 50 mg, 100 mg and 200 mg Tablets outweigh the risks; hence Marketing Authorisations were granted.

These licences subsequently went through a Change of Ownership (CoA) procedure on 26 August 2011 and are authorised to the current Marketing Authorisation Holder, Lupin (Europe) Limited (Topiramate 25mg, 50 mg, 100 mg and 200 mg Tablets, PL 35507/0072-5).
TOPIRAMATE 25 MG TABLETS
TOPIRAMATE 50 MG TABLETS
TOPIRAMATE 100 MG TABLETS
TOPIRAMATE 200 MG TABLETS
PL 35507/0072-5

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Lupin (UK) Limited Marketing Authorisations for the medicinal products Topiramate 25 mg, 50 mg, 100 mg and 200 mg Tablets (PL 20092/0060-3) on 05 July 2011. The products are prescription-only medicines for:

- monotherapy in adults, adolescents and children over 6 years of age with partial seizures with or without secondary generalised seizures, and primary generalised tonic-clonic seizures.
- adjunctive therapy in children aged 2 years and above, adolescents and adults with partial onset seizures with or without secondary generalization or primary generalised tonic-clonic seizures and for the treatment of seizures associated with Lennox-Gastaut syndrome.
- prophylaxis of migraine headache in adults after careful evaluation of possible alternative treatment options. Topiramate is not intended for acute treatment.

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Topamax 25 mg, 50 mg, 100 mg and 200 mg Tablets, which were first authorised in the UK on 18 July 1995 to Janssen-Cilag Limited.

The active ingredient, topiramate, is classified as a sulphamate-substituted monosaccharide. Three pharmacological properties of topiramate have been identified that may contribute to its anticonvulsant activity. Topiramate reduces the frequency at which action potentials are generated when neurones are subjected to a sustained depolarisation indicative of a state-dependent blockade of voltage-sensitive sodium channels. Topiramate enhances the activity of GABA at some types of GABA receptors. Topiramate weakly antagonises the excitatory activity of kainate/AMPA subtype of glutamate receptor but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype.

No new non-clinical data have been submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

A single-dose, bioequivalence study was submitted to support these applications, comparing the test product Topiramate 200 mg Tablets (Lupin (UK) Limited, UK) versus the reference product Epitomax 200 mg Tablets (Janssen Pharmaceutica N.V, France) under fasting conditions. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Topiramate 25 mg, 50 mg, 100 mg and 200 mg Tablets outweigh the risks; hence Marketing Authorisations were granted.
These licences subsequently went through a Change of Ownership (CoA) procedure on 26 August 2011 and are authorised to the current Marketing Authorisation Holder, Lupin (Europe) Limited (Topiramate 25mg, 50 mg, 100 mg and 200 mg Tablets, PL 35507/0072-5).
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE
INN: Topiramate
Chemical Name: 2,3:4,5-Bis-O-(1-methyl ethylidene)-β-D-fructopyranose sulfamate
2,3:4,5-Di-O-iso-propylidene-β-D-fructopyranose sulfamate
Structure

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{H}_3\text{C} & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

Molecular Formula: \( \text{C}_{12}\text{H}_{21}\text{NO}_8\text{S} \)
Molecular weight: 339.36
Appearance: A white to off-white powder, freely soluble in dichloromethane.

Topiramate is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification limits. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated to support a suitable retest period for the active substance when stored in the proposed packaging.

DRUG PRODUCT
Other Ingredients
Other ingredients consist of the pharmaceutical excipients in the tablet core and film coating, namely lactose monohydrate, pregelatinized starch, microcrystalline cellulose (E460), sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, Opacode Black (which contains shellac, glaze in ethanol, iron oxide black (E172), isopropyl alcohol, N-butyl alcohol, propylene glycol (E 1520) and ammonium
hydroxide (E 527)), and either Opadry White (25 mg tablet), Opadry Yellow (50 mg and 100 mg tablets) or Opadry Pink (200 mg tablet).

Opadry White (25 mg tablet), Opadry Yellow (50 mg and 100 mg tablet) and Opadry Pink (200 mg tablet) are made up of the excipients hypromellose (E 464), titanium dioxide (E 171), macrogol, polysorbate 80 (E 433), iron oxide yellow (E 172 - 50 mg, 100mg and 200 mg tablets only) and iron oxide red (E172 – 100 mg and 200 mg tablets only). Appropriate justifications for the inclusion of each excipient have been provided.

With the exception of Opacode Black, and Opadry White, Yellow and Pink, all excipients comply with their respective European Pharmacopoeia monographs. Opacode Black, and Opadry White, Yellow and Pink, are controlled to suitable in-house specifications. However, their components are controlled to their respective European Pharmacopoeia monographs, with the exception of iron oxide black (E172), iron oxide yellow (E172) and iron oxide red (E172), which are controlled to their respective National Formulary specifications. In addition, the specifications for iron oxide black (E172), iron oxide yellow (E172), iron oxide red (E172) are in compliance with current European Directives concerning use of colouring agents in foodstuff. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**

The objective of the development programme was to formulate safe, efficacious, stable products that could be considered generic medicinal products of the reference products Topamax 25mg, 50mg, 100mg and 200mg Tablets (Janssen-Cilag Limited).

Suitable pharmaceutical development data have been provided for these applications.

Comparative *in-vitro* dissolution and impurity profiles have been provided for these products and their respective reference products.

**Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of all strengths of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot scale and shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on the first 3 full-scale production batches.
Control of Finished Product
The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for the working standards used.

Container Closure System
The tablets are packaged in either:
1. polivinylchloride/polivinylidene chloride/aluminium (PVC/PVdC/Al) blisters or PVC/PVdC/Al blisters in aluminium pouches containing desiccant silica gel or polyamide/aluminium/polyethylene (OPA/Al/PE) desiccant blisters in pack sizes of 10, 14, 20, 28, 30, 50, 60, 84, 90, 98, 100, 120 and 200 tablets.
2. white high-density polyethylene (HDPE) tablet containers, with white polypropylene child-resistant closures, containing silica gel desiccant and polyester filler in a pack sizes of 60 tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability
Finished product stability studies were performed in accordance with current guidelines on batches of the finished products in the packaging proposed for marketing. Based on the results, the following shelf-life/storage conditions have been accepted:
- 2 years for product packaged in blister packs, with the storage conditions, “Store below 25°C. Store in the original package.”
- 2 years for product packaged in the HDPE tablet containers, with the storage conditions “Store below 25°C. Keep container tightly closed.”

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are pharmaceutically satisfactory. The Marketing Authorisation Holder has committed to submitting mock-ups to the UK regulatory authority for approval before marketing any pack size.
A 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, as amended. 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.

**MAA Forms**
The MAA forms are pharmaceutically satisfactory.

**Expert Report**
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
The grant of Marketing Authorisations is recommended.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
As the pharmacodynamic, pharmacokinetic and toxicological properties of topiramate are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT
The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the products are intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of Marketing Authorisations is recommended.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

The clinical pharmacology of topiramate is well-known. With the exception of data from the below bioequivalence study, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

Pharmacokinetics

In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence study:

A randomised, single-dose, open-label, two-treatment, two-period, two-way crossover study to compare the pharmacokinetics of the test product Topiramate 200 mg Tablets (Lupin (UK) Limited, UK) versus the reference product Epitomax 200 mg Tablets (Janssen Pharmaceutica NV, France) in healthy adult male subjects under fasting conditions.

The subjects were given 200 mg of either the test or reference product with 240 ml of water, after at least a 10-hour overnight fast. Blood samples were collected before and up to 192 hours after each administration. The washout period between the treatment arms was 11 days. The pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters (geometric least squares mean, ratios and confidence intervals [CI]) of topiramate</th>
<th>Topiramate 200 mg (Test)</th>
<th>Epitomax 200 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\text{max} (ng/ml)</td>
<td>5202.001</td>
<td>5206.123</td>
<td>99.9</td>
<td>96.04-103.96</td>
</tr>
<tr>
<td>AUC\text{0-t} (ng.h/ml)</td>
<td>173208.783</td>
<td>169803.733</td>
<td>102.0</td>
<td>98.96-105.15</td>
</tr>
<tr>
<td>AUC\text{0-inf} (ng.h/ml)</td>
<td>180147.424</td>
<td>176898.632</td>
<td>101.8</td>
<td>98.91-104.85</td>
</tr>
</tbody>
</table>

AUC\text{0-t}, area under the plasma concentration-time curve from time zero to t hours
AUC\text{0-inf}, area under the plasma concentration-time curve from time zero to infinity
C\text{max}, maximum plasma concentration
90% geometric CI calculated from ln-transformed data

The ‘Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) defines the confidence limits as 80% to 125% for C\text{max} and AUC ratios. The 90% confidence intervals of the test/reference ratio of geometric means for AUC\text{0-t}, AUC\text{0-inf} and C\text{max} lie within the acceptable limits. Thus, the data support the claim that the test product Topiramate 200 mg Tablets (Lupin (UK) Limited, UK) is bioequivalent to the reference product Epitomax 200 mg Tablets (Janssen Pharmaceutica NV, France).

As the 25 mg, 50 mg, 100 mg and 200 mg strength products meet the criteria specified in the ‘Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions from the bioequivalence study with the 200 mg tablet strength can be extrapolated to the 25 mg, 50 mg and 100 mg tablet strengths.
EFFICACY
The efficacy of topiramate is well-known. No new efficacy data have been submitted and none are required for applications of this type.

SAFETY
With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues were raised by the bioequivalence data.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPCs, PIL and labelling are clinically acceptable. The SmPCs are consistent with those for the reference products. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

CLINICAL EXPERT REPORT
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a risk management plan for these products.

CONCLUSION
The grant of Marketing Authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Topiramate 25 mg, 50 mg, 100 mg and 200 mg Tablets 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.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of topiramate are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new efficacy data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s 200 mg strength tablet and the reference product. As the 25 mg, 50 mg, 100 mg and 200 mg strengths of the product meet the biowaiver criteria specified in the ‘Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions from the bioequivalence study with the 200 mg tablet strength can be extrapolated to the 25 mg, 50 mg and 100 mg tablet strengths.

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for applications of this type. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are acceptable. The SmPCs are consistent with those for the reference products. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data provided support the claim that these products are generic medicinal products of the reference products, Topamax 25 mg, 50 mg, 100 mg and 200 mg Tablets (Janssen-Cilag Limited, UK). Extensive clinical experience with topiramate is considered to have demonstrated the therapeutic value of the products. The benefit/risk is, therefore, considered to be positive.
TOPIRAMATE 25 MG TABLETS
TOPIRAMATE 50 MG TABLETS
TOPIRAMATE 100 MG TABLETS
TOPIRAMATE 200 MG TABLETS

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation applications on 07 May 2007.
2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 27 July 2007.
3 Following assessment of the applications the MHRA requested further information relating to the clinical dossier on 12 October 2007 and on the quality dossier on 04 April 2008, 09 April 2010 and 04 August 2010.
4 The applicant responded to the MHRA’s requests, providing further information on the clinical dossier on 26 February 2010 and on the quality dossier on 01 March 2010, 13 July 2010 and 09 November 2010.
5 The applications were determined and granted on 05 July 2011.
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Topiramate 25 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains 25 mg of Topiramate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablets
White to off white, circular, biconvex film coated tablets, imprinted “25” (in black ink) on one side and plain on the other side

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

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

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

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

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

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

Topiramate Tablets can be taken without regard to meals.

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

Monotherapy epilepsy
General
When concomitant antiepileptic drugs (AEDs) are withdrawn to achieve monotherapy with topiramate, consideration should be given to the effects this may have on seizure control. Unless safety concerns require an abrupt withdrawal of the concomitant AED, a gradual discontinuation at the rate of approximately one-third of the concomitant AED dose every 2 weeks is recommended.
When enzyme inducing medicinal products are withdrawn, topiramate levels will increase. A decrease in Topiramate Tablets (topiramate) dosage may be required if clinically indicated.

**Adults**

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

The recommended initial target dose for topiramate monotherapy in adults is 100 mg/day to 200 mg/day in 2 divided doses. The maximum recommended daily dose is 500 mg/day in 2 divided doses. Some patients with refractory forms of epilepsy have tolerated topiramate monotherapy at doses of 1,000 mg/day. These dosing recommendations apply to all adults including the elderly in the absence of underlying renal disease.

**Paediatric population (children over 6 years of age)**

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

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

**Adjunctive therapy epilepsy (partial onset seizures with or without secondary generalization, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome).**

**Adults**

Therapy should begin at 25-50 mg nightly for one week. Use of lower initial doses has been reported, but has not been studied systematically. Subsequently, at weekly or bi-weekly intervals, the dose should be increased by 25-50 mg/day and taken in two divided doses. Some patients may achieve efficacy with once-a-day dosing.

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

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

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

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

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

**Migraine**

**Adults**

The recommended total daily dose of topiramate for prophylaxis of migraine headache is 100 mg/day administered in two divided doses. Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased in increments of 25 mg/day administered at 1-week intervals. If the patient is unable to tolerate the titration regimen, longer intervals between dose adjustments can be used.
Some patients may experience a benefit at a total daily dose of 50 mg/day. Patients have received a total daily dose up to 200 mg/day. This dose may be benefit in some patients, nevertheless, caution is advised due to an increase incidence of side effects.

Paediatric population

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

General dosing recommendations for Topiramate Tablets in special patient populations

Renal impairment

In patients with impaired renal function (CL_{CR} \leq 60 \text{ mL/min}) topiramate should be administered with caution as the plasma and renal clearance of topiramate are decreased. Subjects with known renal impairment may require a longer time to reach steady-state at each dose.

In patients with end-stage renal failure, since topiramate is removed from plasma by haemodialysis, a supplemental dose of Topiramate Tablets equal to approximately one-half the daily dose should be administered on haemodialysis days. The supplemental dose should be administered in divided doses at the beginning and completion of the haemodialysis procedure. The supplemental dose may differ based on the characteristics of the dialysis equipment being used.

Hepatic impairment

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

Elderly

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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

4.4 Special warnings and precautions for use

In situations where rapid withdrawal of topiramate is medically required, appropriate monitoring is recommended (see section 4.2 for further details).

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

Adequate hydration while using topiramate is very important. Hydration can reduce the risk of nephrolithiasis (see below). Proper hydration prior to and during activities such as exercise or exposure to warm temperatures may reduce the risk of heat-related adverse reactions (see section 4.8).

Mood disturbances/depression

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

Suicide/suicide ideation

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic drugs has shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for topiramate.
In double blind clinical trials, suicide related events (SREs) (suicidal ideation, suicide attempts and suicide) occurred at a frequency of 0.5% in topiramate treated patients (46 out of 8,652 patients treated) and at a nearly 3 fold higher incidence than those treated with placebo (0.2%; 8 out of 4,045 patients treated).

Patients therefore should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

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

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

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

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

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

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

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

Chronic metabolic acidosis increases the risk of renal stone formation and may potentially lead to osteopenia.
Chronic metabolic acidosis in paediatric patients can reduce growth rates. The effect of topiramate on bone-related sequelae has not been systematically investigated in paediatric or adult populations.

Depending on underlying conditions, appropriate evaluation including serum bicarbonate levels is recommended with topiramate therapy. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering).

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

**Nutritional supplementation**

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

**Lactose intolerance**

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

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

**Effects of Topiramate Tablets on other antiepileptic medicinal products**

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

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

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

**Effects of other antiepileptic medicinal products on Topiramate Tablets**

Phenytoin and carbamazepine decrease the plasma concentration of topiramate. The addition or withdrawal of phenytoin or carbamazepine to Topiramaate Tablets 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 Tablets and, therefore, does not warrant dosage adjustment of Topiramate Tablets. The results of these interactions are summarized below:
AED Coadministered | AED Concentration | Topiramate Tablets Concentration
---|---|---
Phenytoin | ↔** | ↓
Carbamazepine (CBZ) | ↔ | ↓
Valproic acid | ↔ | ↔
Lamotrigine | ↔ | ↔
Phenobarbital | ↔ | NS
Primidone | ↔ | NS

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

Other medicinal product interactions

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

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

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

**Lithium**
In healthy volunteers, there was an observed reduction (18% for AUC) in systemic exposure for lithium during concomitant administration with topiramate 200 mg/day. In patients with bipolar disorder, the pharmacokinetics of lithium were unaffected during treatment with topiramate at doses of 200 mg/day; however, there was an observed increase in systemic
exposure (26% for AUC) following topiramate doses of up to 600 mg/day. Lithium levels should be monitored when co-administered with topiramate.

**Risperidone**
Drug-drug interaction studies conducted under single dose conditions in healthy volunteers and multiple dose conditions in patients with bipolar disorder, yielded similar results. When administered concomitantly with topiramate at escalating doses of 100, 250 and 400 mg/day there was a reduction in risperidone (administered at doses ranging from 1 to 6 mg/day) systemic exposure (16% and 33% for steady-state AUC at the 250 and 400 mg/day doses, respectively). However, differences in AUC for the total active moiety between treatment with risperidone alone and combination treatment with topiramate were not statistically significant. Minimal alterations in the pharmacokinetics of the total active moiety (risperidone plus 9-hydroxyrisperidone) and no alterations for 9-hydroxyrisperidone were observed. There were no significant changes in the systemic exposure of the risperidone total active moiety or of topiramate. When topiramate was added to existing risperidone (1-6 mg/day) treatment, adverse events were reported more frequently than prior to topiramate (250-400 mg/day) introduction (90% and 54 % respectively). The most frequently reported AE’s when topiramate was added to risperidone treatment were: somnolence (27% and 12%), paraesthesia (22% and 0%) and nausea (18% and 9% respectively).

**Hydrochlorothiazide (HCTZ)**
A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg q24h) and topiramate (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that topiramate \( C_{\text{max}} \) 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 and topiramate in plasma when metformin was given alone and when metformin and topiramate were given simultaneously. The results of this study indicated that metformin mean \( C_{\text{max}} \) 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 Tablets 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\( t_{\text{ss}} \) 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\( t_{\text{ss}} \) respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in \( C_{\text{max,ss}} \) and AUC\( t_{\text{ss}} \) of the active keto-metabolite. The clinical significance of these findings is not known. When Topiramate Tablets is added to pioglitazone therapy or pioglitazone is added to Topiramate Tablets therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.
Glyburide
A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glyburide (5 mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 25% reduction in glyburide AUC$_{24}$ during topiramate administration. Systemic exposure of the active metabolites, 4-trans-hydroxy-glyburide (M1) and 3-cis-hydroxyglyburide (M2), were also reduced by 13% and 15%, respectively. The steady-state pharmacokinetics of topiramate were unaffected by concomitant administration of glyburide.

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

Other forms of interactions
Agents predisposing to nephrolithiasis
Topiramate Tablets, when used concomitantly with other agents predisposing to nephrolithiasis, may increase the risk of nephrolithiasis. While using Topiramate Tablets, agents like these should be avoided since they may create a physiological environment that increases the risk of renal stone formation.

Valproic acid
Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either medicinal product alone. In most cases, symptoms and signs abated with discontinuation of either medicinal product. This adverse reaction is not due to a pharmacokinetic interaction. 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$_{max}$ 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</th>
<th>Topiramate Concentration&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>↔ 20% increase in C&lt;sub&gt;max&lt;/sub&gt; 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&lt;sub&gt;max&lt;/sub&gt; for 4-OH propranolol (TPM 50 mg q12h)</td>
<td>9% and 16% increase in C&lt;sub&gt;max&lt;/sub&gt;, 9% and 17% increase in AUC (40 and 80 mg propranolol q12h respectively)</td>
</tr>
<tr>
<td>Sumatriptan (Oral and Subcutaneous)</td>
<td>↔</td>
<td>NS</td>
</tr>
<tr>
<td>Pizotifen</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>25% decrease in AUC of diltiazem and 18% decrease in DEA, and ↔ for DEM*</td>
<td>20% increase in AUC</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Flunarizine</td>
<td>16% increase in AUC (TPM 50 mg q12h)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>↔</td>
</tr>
</tbody>
</table>

<sup>a</sup> % values are the changes in treatment mean C<sub>max</sub> or AUC with respect to monotherapy

↔ = No effect on C<sub>max</sub> and AUC (≤ 15% change) of the parent compound

NS = Not studied

*DEA = des acetyl diltiazem, DEM = N-demethyl diltiazem

<sup>b</sup> Flunarizine AUC increased 14% in subjects taking flunarizine alone. Increase in exposure may be attributed to accumulation during achievement of steady state.

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### 4.6 Pregnancy and lactation

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

There are no adequate and well-controlled studies with Topiramate Tablets in pregnant women.

Pregnancy registry data suggest that there may be an association between the use of Topiramate Tablets during pregnancy and congenital malformations (e.g., craniofacial defects, such as cleft lip/palate, hypospadias, and anomalies involving various body systems). This has been reported with topiramate monotherapy and topiramate as part of a polytherapy regimen. This data should be interpreted with caution, as more data is needed to identify increased risks for malformations.

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

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

Animal studies have shown excretion of topiramate in milk. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggest an extensive excretion of topiramate into breast milk. Since many medicinal products are excreted into human milk, a decision must be made whether to suspend breast-feeding or...
to discontinue/ abstain from topiramate therapy taking into account the importance of the medicinal product to the mother (section 4.4).

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

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

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

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

4.8 **Undesirable effects**
The safety of topiramate was evaluated from a clinical trial database consisting of 4,111 patients (3,182 on topiramate and 929 on placebo) who participated in 20 double-blind trials and 2,847 patients who participated in 34 open-label trials, respectively, for topiramate as adjunctive treatment of primary generalized tonic-clonic seizures, partial onset seizures, seizures associated with Lennox-Gastaut syndrome, monotherapy for newly or recently diagnosed epilepsy or migraine prophylaxis. The majority of ADRs were mild to moderate in severity. ADRs identified in clinical trials, and during post-marketing experience (as indicated by “*”) are listed by their incidence in clinical trials in Table 1. Assigned frequencies are as follows:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>≥ 1/10</td>
</tr>
<tr>
<td>Common</td>
<td>≥ 1/100 to &lt;1/10</td>
</tr>
<tr>
<td>Uncommon</td>
<td>≥ 1/1,000 to &lt;1/100</td>
</tr>
<tr>
<td>Rare</td>
<td>≥ 1/10,000 to &lt;1/1,000</td>
</tr>
<tr>
<td>Not known</td>
<td>cannot be estimated from the available data</td>
</tr>
</tbody>
</table>

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

**Paediatric population**
ADRs reported more frequently (≥2-fold) in children than in adults in double-blind controlled studies include: decreased appetite, increased appetite, acidosis hyperchlaemaic, hypokalaemia, abnormal behaviour, aggression, apathy, initial insomnia, suicidal ideation, disturbance in attention, lethargy, circadian rhythm sleep disorder, poor quality sleep, laceration increased, sinus bradycardia, feeling abnormal, and gait disturbance.

ADRs that were reported in children but not in adults in double-blind controlled studies include: eosinophilia, psychomotor hyperactivity, vertigo, vomiting, hyperthermia, pyrexia, and learning disability.
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td>Weight decreased</td>
<td>Weight increased*</td>
<td>Crystal urine present, tandem gait test abnormal, white blood cell count decreased</td>
<td>Blood bicarbonate decreased</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight increased*</td>
<td>Weight increased*</td>
<td>Crystal urine present, tandem gait test abnormal, white blood cell count decreased</td>
<td>Blood bicarbonate decreased</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Anaemia</td>
<td>Anaemia</td>
<td>Leucopenia, thrombocytopenia, lymphadenopathy, eosinophilia</td>
<td>Neutropenia*</td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Anaemia</td>
<td>Anaemia</td>
<td>Leucopenia, thrombocytopenia, lymphadenopathy, eosinophilia</td>
<td>Neutropenia*</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Paraesthesia, somnolence</td>
<td>Disturbance in attention, memory impairment, amnesia, cognitive disorder, mental impairment, psychomotor skills impaired, convulsion, coordination abnormal, tremor, lethargy, hypoesthesia, nystagmus, dysgeusia, balance disorder, dysarthria, intention tremor, sedation</td>
<td>Depressed level of consciousness, grand mal convulsion, visual field defect, complex partial seizures, speech disorder, psychomotor hyperactivity, syncope, sensory disturbance, drooling, hypersonnia, aphasia, repetitive speech, hypokinesia, dyskinesia, dizziness postural, poor quality sleep, burning sensation, sensory loss, parosmia, cerebellar syndrome, dysesthesia, hypogeusia, stupor, clumsiness, aura, ageusia, dysgraphia, dysphasia, neuropathy peripheral, presyncope, dystonia, ataxia, tremor</td>
<td>Apraxia, circadian rhythm sleep disorder, hyperaesthesia, hypoisosmia, anosmia, essential tremor, akinesia, unresponsive to stimuli</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Vision blurred diplopia, visual disturbance</td>
<td>Vision blurred diplopia, visual disturbance</td>
<td>Visual acuity reduced, scotoma, myopia*, abnormal sensation in eye*, dry eye, photophobia, blepharospasm, lacrimation increased, photopsia, mydriasis, presbyopia, blindness unilateral, blindness transient, glaucoma, accommodation disorder, altered visual depth perception, scintillating scotoma, eyelid oedema*, night blindness, amblyopia</td>
<td>Angle closure glaucoma*, Maculopathy*, eye movement disorder*</td>
<td></td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Very common</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Not known</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------</td>
<td>--------</td>
<td>----------</td>
<td>------</td>
<td>-----------</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Vertigo, tinnitus, ear pain</td>
<td>Deafness, deafness unilateral, deafness neurosensory, ear discomfort, hearing impaired</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnoea, epistaxis, nasal congestion, rhinorrhea</td>
<td>Dyspnoea exertional, Paramasal sinus hypersecretion, dysphonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, diarrhoea</td>
<td>Vomiting, constipation, abdominal pain upper, dyspepsia, abdominal pain, dry mouth, stomach discomfort, paraesthesia oral, gastritis, abdominal discomfort</td>
<td>Pancreatitis, flatulence, gastrooesophageal reflux disease, abdominal pain lower, hypoaesthesia oral, gingival bleeding, abdominal distension, epigastric discomfort, abdominal tenderness, salivary hypersecretion, oral pain, breath odour, glossodynia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Calculus urinary, urinary incontinence, haematuria, incontinence, micturition urgency, renal colic, renal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Nephrolithiasis, pollakiuria, dysuria</td>
<td>Calculus ureteric, renal tubular acidosis*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia, rash, pruritus</td>
<td>Anhidrosis, hypoaesthesia facial, urticaria, erythema, pruritus generalised, rash macular, skin discolouration, dermatitis allergic, swelling face</td>
<td>Stevens-Johnson syndrome* erythema multiforme*, skin odour abnormal, periorbital oedema*, urticaria localised</td>
<td>Toxic epidermal necrolysis*</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia, muscle spasms, myalgia, muscle twitching, muscular weakness, musculoskeletal chest pain</td>
<td>Joint swelling*, musculoskeletal stiffness, flank pain, muscle fatigue</td>
<td></td>
<td>Limb discomfort*</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia, decreased appetite</td>
<td>Metabolic acidosis, Hypokalaemia, increased appetite, polydipsia</td>
<td>Acidosis hyperchloraemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations Vascular disorders</td>
<td>Nasopharyngitis*</td>
<td>Hypotension, orthostatic hypotension flushing, hot flush</td>
<td>Raynaud's phenomenon</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.9 Overdose

Signs and symptoms
Overdoses of topiramate have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbances, blurred vision, diplopia, impaired mentation, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. The clinical consequences were not severe in most cases, but deaths have been reported after overdoses with multiple medicinal products including topiramate.

Topiramate overdose can result in severe metabolic acidosis (see section 4.4).

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

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

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

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

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

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

5.2 Pharmacokinetic properties

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

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

Topiramate is not a potent inducer of drug metabolizing enzymes, can be administered without regard to meals, and routine monitoring of plasma topiramate concentrations is not necessary. In clinical studies, there was no consistent relationship between plasma concentrations and efficacy or adverse events.
Absorption
Topiramate is rapidly and well absorbed. Following oral administration of 100 mg topiramate to healthy subjects, a mean peak plasma concentration ($C_{\text{max}}$) of 1.5 $\mu$g/ml was achieved within 2 to 3 hours ($T_{\text{max}}$).

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

Distribution
Generally, 13 to 17% of topiramate is bound to plasma protein. A low capacity binding site for topiramate in/on erythrocytes that is saturable above plasma concentrations of 4 $\mu$g/ml has been observed. The volume of distribution varied inversely with the dose. The mean apparent volume of distribution was 0.80 to 0.55 l/kg for a single dose range of 100 to 1200 mg. An effect of gender on the volume of distribution was detected, with values for females circa 50% of those for males. This was attributed to the higher percent body fat in female patients and is of no clinical consequence.

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

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

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

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

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

Plasma clearance of topiramate is decreased in patients with moderate to severe hepatic impairment.
Plasma clearance of topiramate is unchanged in elderly subjects in the absence of underlying renal disease.

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

The pharmacokinetics of topiramate in children, as in adults receiving add-on therapy, are linear, with clearance independent of dose and steady-state plasma concentrations increasing in proportion to dose. Children, however, have a higher clearance and a shorter elimination half-life. Consequently, the plasma concentrations of topiramate for the same mg/kg dose may be lower in children compared to adults. As in adults, hepatic enzyme inducing anti-epileptic drugs decrease the steady-state plasma concentrations.

### 5.3 Preclinical safety data

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

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

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

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

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

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

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

- Lactose monohydrate
- Pregelatinized starch
- Microcrystalline cellulose (E 460)
- Sodium starch glycolate
- Colloidal silicon dioxide
- Magnesium stearate

Opadry White contains Hypromellose (E 464), Titanium dioxide (E 171), Macrogol, and polysorbate 80 (E 433).

**Ink Composition:** Opacode Black.

OPACODE contains, Shellac Glaze in ethanol, Iron Oxide Black (E 172), Isopropyl Alcohol, N-butyl alcohol, Propylene glycol (E 1520) and Ammonium hydroxide (E 527).
6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 25°C.
HDPE tablet containers: Keep container tightly closed.
Blisters: Store in the original package.

6.5 Nature and contents of container
PVC/PVdC/Al blisters
PVC/PVdC/Al blisters in aluminium pouch containing desiccant silica gel
OPA/Al/PE desiccant blister
Pack sizes: 10, 14, 20, 28, 30, 50, 60, 84, 90, 98, 100, 120 and 200 tablets

HDPE tablet containers with PP child-resistant closures, containing silica gel desiccant and polyester filler.
Pack sizes: 60 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Lupin (Europe) Limited
Victoria Court
Bexton Road
Knutsford
Cheshire WA16 0PF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 35507/0072

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
05/07/2011

10 DATE OF REVISION OF THE TEXT
05/07/2011
1 NAME OF THE MEDICINAL PRODUCT
Topiramate 50 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains 50 mg of Topiramate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablets
Light yellow, circular, biconvex film coated tablets, imprinted “50” (in black ink) on one side and plain on the other side

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

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

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

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

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

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

Topiramate Tablets can be taken without regard to meals.

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

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

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

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

The recommended initial target dose for topiramate monotherapy in adults is 100 mg/day to 200 mg/day in 2 divided doses. The maximum recommended daily dose is 500 mg/day in 2 divided doses. Some patients with refractory forms of epilepsy have tolerated topiramate monotherapy at doses of 1,000 mg/day. These dosing recommendations apply to all adults including the elderly in the absence of underlying renal disease.

**Paediatric population (children over 6 years of age)**

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

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

**Adjunctive therapy epilepsy (partial onset seizures with or without secondary generalization, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome).**

**Adults**

Therapy should begin at 25-50 mg nightly for one week. Use of lower initial doses has been reported, but has not been studied systematically. Subsequently, at weekly or bi-weekly intervals, the dose should be increased by 25-50 mg/day and taken in two divided doses. Some patients may achieve efficacy with once-a-day dosing.

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

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

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

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

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

**Migraine**

**Adults**

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

Some patients may experience a benefit at a total daily dose of 50 mg/day. Patients have received a total daily dose up to 200 mg/day. This dose may be benefit in some patients, nevertheless, caution is advised due to an increase incidence of side effects.
Paediatric population
Topiramate Tablets (topiramate) is not recommended for treatment or prevention of migraine in children due to insufficient data on safety and efficacy.

General dosing recommendations for Topiramate Tablets in special patient populations
Renal impairment
In patients with impaired renal function (CL\textsubscript{CR} ≤ 60 mL/min) topiramate should be administered with caution as the plasma and renal clearance of topiramate are decreased. Subjects with known renal impairment may require a longer time to reach steady-state at each dose.

In patients with end-stage renal failure, since topiramate is removed from plasma by haemodialysis, a supplemental dose of Topiramate Tablets equal to approximately one-half the daily dose should be administered on haemodialysis days. The supplemental dose should be administered in divided doses at the beginning and completion of the haemodialysis procedure. The supplemental dose may differ based on the characteristics of the dialysis equipment being used.

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

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

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

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

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

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

Adequate hydration while using topiramate is very important. Hydration can reduce the risk of nephrolithiasis (see below). Proper hydration prior to and during activities such as exercise or exposure to warm temperatures may reduce the risk of heat-related adverse reactions (see section 4.8).

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

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

In double blind clinical trials, suicide related events (SREs) (suicidal ideation, suicide attempts and suicide) occurred at a frequency of 0.5% in topiramate treated patients (46 out of 8,652 patients treated) and at a nearly 3 fold higher incidence than those treated with placebo (0.2%; 8 out of 4,045 patients treated).
Patients therefore should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

**Nephrolithiasis**

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

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

**Decreased hepatic function**

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

**Acute myopia and secondary angle closure glaucoma**

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

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

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

**Metabolic acidosis**

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

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

Chronic metabolic acidosis in paediatric patients can reduce growth rates. The effect of topiramate on bone-related sequelae has not been systematically investigated in paediatric or adult populations. Depending on underlying conditions, appropriate evaluation including serum bicarbonate levels is recommended with topiramate therapy. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering).
Topiramate should be used with caution in patients with conditions or treatments that represent a risk factor for the appearance of metabolic acidosis.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

**Effects of other antiepileptic medicinal products on Topiramate Tablets**
Phenytoin and carbamazepine decrease the plasma concentration of topiramate. The addition or withdrawal of phenytoin or carbamazepine to Topiramate Tablets 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 Tablets and, therefore, does not warrant dosage adjustment of Topiramate Tablets. The results of these interactions are summarized below:
### AED Coadministered

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

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

### Other medicinal product interactions

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

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

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

#### Lithium
In healthy volunteers, there was an observed reduction (18% for AUC) in systemic exposure for lithium during concomitant administration with topiramate 200 mg/day. In patients with bipolar disorder, the pharmacokinetics of lithium were unaffected during treatment with topiramate at doses of 200 mg/day; however, there was an observed increase in systemic exposure (26% for AUC) following topiramate doses of up to 600 mg/day. Lithium levels should be monitored when co-administered with topiramate.
Risperidone
Drug-drug interaction studies conducted under single dose conditions in healthy volunteers and multiple dose conditions in patients with bipolar disorder, yielded similar results. When administered concomitantly with topiramate at escalating doses of 100, 250 and 400 mg/day there was a reduction in risperidone (administered at doses ranging from 1 to 6 mg/day) systemic exposure (16% and 33% for steady-state AUC at the 250 and 400 mg/day doses, respectively). However, differences in AUC for the total active moiety between treatment with risperidone alone and combination treatment with topiramate were not statistically significant. Minimal alterations in the pharmacokinetics of the total active moiety (risperidone plus 9-hydroxyrisperidone) and no alterations for 9-hydroxyrisperidone were observed. There were no significant changes in the systemic exposure of the risperidone total active moiety or of topiramate. When topiramate was added to existing risperidone (1-6 mg/day) treatment, adverse events were reported more frequently than prior to topiramate (250-400 mg/day) introduction (90% and 54 % respectively). The most frequently reported AE’s when topiramate was added to risperidone treatment were: somnolence (27% and 12%), paraesthesia (22% and 0%) and nausea (18% and 9% respectively).

Hydrochlorothiazide (HCTZ)
A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg q24h) and topiramate (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that topiramate 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 and topiramate in plasma when metformin was given alone and when metformin and topiramate were given simultaneously. The results of this study indicated that metformin mean 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 Tablets 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\(_{t,ss}\) 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\(_{t,ss}\) respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in C\(_{max,ss}\) and AUC\(_{t,ss}\) of the active keto-metabolite. The clinical significance of these findings is not known. When Topiramate Tablets is added to pioglitazone therapy or pioglitazone is added to Topiramate Tablets therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.
**Glyburide**
A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glyburide (5 mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 25% reduction in glyburide \( \text{AUC}_{24} \) during topiramate administration. Systemic exposure of the active metabolites, 4-\textit{trans}\-hydroxy-glyburide (M1) and 3-\textit{cis}\-hydroxyglyburide (M2), were also reduced by 13% and 15%, respectively. The steady-state pharmacokinetics of topiramate were unaffected by concomitant administration of glyburide.

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

**Other forms of interactions**

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

**Valproic acid**
Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either medicinal product alone. In most cases, symptoms and signs abated with discontinuation of either medicinal product. This adverse reaction is not due to a pharmacokinetic interaction. 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 \( \text{AUC} \) 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.
### Summary of Results from Additional Clinical Pharmacokinetic Drug Interaction Studies

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>Concomitant Drug Concentration</th>
<th>Topiramate Concentrationa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>↔ 20% increase in Cmax 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 Cmax for 4-OH propranolol (TPM 50 mg q12h)</td>
<td>9% and 16% increase in Cmax, 9% and 17% increase in AUC (40 and 80 mg propranolol q12h respectively)</td>
</tr>
<tr>
<td>Sumatriptan (Oral and Subcutaneous)</td>
<td>↔</td>
<td>NS</td>
</tr>
<tr>
<td>Pizotifen</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>25% decrease in AUC of diltiazem and 18% decrease in DEA, and ↔ for DEM*</td>
<td>20% increase in AUC</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Flunarizine</td>
<td>16% increase in AUC (TPM 50 mg q12h)b</td>
<td>↔</td>
</tr>
</tbody>
</table>

- % values are the changes in treatment mean Cmax or AUC with respect to monotherapy
- ↔ = No effect on Cmax and AUC (≤ 15% change) of the parent compound
- NS = Not studied
- *DEA = des acetyl diltiazem, DEM = N-demethyl diltiazem
- b Flunarizine AUC increased 14% in subjects taking flunarizine alone. Increase in exposure may be attributed to accumulation during achievement of steady state.

### 4.6 Pregnancy and Lactation

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

There are no adequate and well-controlled studies with Topiramate Tablets in pregnant women.

Pregnancy registry data suggest that there may be an association between the use of Topiramate Tablets during pregnancy and congenital malformations (e.g., craniofacial defects, such as cleft lip/palate, hypospadias, and anomalies involving various body systems). This has been reported with topiramate monotherapy and topiramate as part of a polytherapy regimen. This data should be interpreted with caution, as more data is needed to identify increased risks for malformations.

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

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

Animal studies have shown excretion of topiramate in milk. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggest an extensive excretion of topiramate into breast milk. Since many medicinal products are excreted into human milk, a decision must be made whether to suspend breast-feeding or
to discontinue/ abstain from topiramate therapy taking into account the importance of the medicinal product to the mother (section 4.4).

**Indication Epilepsy**

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

**Indication Migraine Prophylaxis**

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

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

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

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

### 4.9 Undesirable effects

The safety of topiramate was evaluated from a clinical trial database consisting of 4,111 patients (3,182 on topiramate and 929 on placebo) who participated in 20 double-blind trials and 2,847 patients who participated in 34 open-label trials, respectively, for topiramate as adjunctive treatment of primary generalized tonic-clonic seizures, partial onset seizures, seizures associated with Lennox-Gastaut syndrome, monotherapy for newly or recently diagnosed epilepsy or migraine prophylaxis. The majority of ADRs were mild to moderate in severity. ADRs identified in clinical trials, and during post-marketing experience (as indicated by “*”) are listed by their incidence in clinical trials in Table 1. Assigned frequencies are as follows:

- **Very common** ≥ 1/10
- **Common** ≥ 1/100 to <1/10
- **Uncommon** ≥ 1/1,000 to <1/100
- **Rare** ≥ 1/10,000 to <1/1,000
- **Not known** cannot be estimated from the available data

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

**Paediatric population**

ADRs reported more frequently (≥2-fold) in children than in adults in double-blind controlled studies include: decreased appetite, increased appetite, acidosis hyperchloremic, hypokalaemia, abnormal behaviour, aggression, apathy, initial insomnia, suicidal ideation, disturbance in attention, lethargy, circadian rhythm sleep disorder, poor quality sleep, lacrimation increased, sinus bradycardia, feeling abnormal, and gait disturbance.

ADRs that were reported in children but not in adults in double-blind controlled studies include: eosinophilia, psychomotor hyperactivity, vertigo, vomiting, hyperthermia, pyrexia, and learning disability.
# Table 1: Topiramate Adverse Drug Reactions

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigations</strong></td>
<td><strong>Weight decreased</strong></td>
<td><strong>Weight increased</strong>*</td>
<td>Crystal urine present, tandem gait test abnormal, white blood cell count decreased Brachyctria, sinus bradycardia, palpitations</td>
<td>Blood bicarbonate decreased</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Anaemia</td>
<td></td>
<td>Leucopenia, thrombocytopenia lymphadenopathy, eosinophilia</td>
<td>Neutropenia*</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Paraesthesia, somnolence Dizziness</td>
<td>Disturbance in attention, memory impairment, amnesia, cognitive disorder, mental impairment, psychomotor skills impaired, convulsion, coordination abnormal, tremor, lethargy, hypoesthesia, nystagmus, dysgeusia, balance disorder, dysarthria, intention tremor, sedation</td>
<td>Depressed level of consciousness, grand mal convulsion, visual field defect, complex partial seizures, speech disorder, psychomotor hyperactivity, syncpe, sensory disturbance, drooling, hypersonnia, aphasia, repetitive speech, hypokinesia, dyskinesia, dizziness postural, poor quality sleep, burning sensation, sensory loss, parosmia, cerebellar syndrome, dysesthesia, hypogeusia, stupor, clumsiness, aura, ageusia, dysgraphia, dysphasia, neuropathy peripheral, presyncope, dystonia, formication</td>
<td>Apraxia, circadian rhythm sleep disorder, hyperaesthesia, hyposmia, anosmia, essential tremor, akinesia, unresponsive to stimuli</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Vision blurred diplopia, visual disturbance</td>
<td>Visual acuity reduced, scotoma, myopia*, abnormal sensation in eye*, dry eye, photophobia, blepharospasm, lacrimation increased, photopsia, mydriasis, presbyopia</td>
<td>Blindness unilateral, blindness transient, glaucoma, accommodation disorder, altered visual depth perception, scintillating scotoma, eyelid oedema*, night blindness, amblyopia</td>
<td>Angle closure glaucoma*, Maculopathy*, eye movement disorder*</td>
<td></td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Very common</td>
<td>Common</td>
<td>Uknown</td>
<td>Rare</td>
<td>Not known</td>
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<tr>
<td>---------------------------------------------------------</td>
<td>-------------</td>
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</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Vertigo, tinnitus, ear pain</td>
<td>Deafness, deafness unilateral, deafness neurosensory, ear discomfort, hearing impaired</td>
<td>Dyspnoea exertional,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnoea, epistaxis, nasal congestion, rhinorrhea</td>
<td>Pancreatitis, flatulence, gastrooesophageal reflux disease, abdominal pain lower, hypoaesthesia oral, gingival bleeding, abdominal distension, epigastric discomfort, abdominal tenderness, salivary hypersecretion, oral pain, breath odour, glossodynia</td>
<td>Dyspnoea exertional,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, diarrhoea</td>
<td>Vomiting, constipation, abdominal pain upper, dyspepsia, abdominal pain, dry mouth, stomach discomfort, paraesthesia oral, gastritis, abdominal discomfort</td>
<td>Pancreatitis, flatulence, gastrooesophageal reflux disease, abdominal pain lower, hypoaesthesia oral, gingival bleeding, abdominal distension, epigastric discomfort, abdominal tenderness, salivary hypersecretion, oral pain, breath odour, glossodynia</td>
<td>Dyspnoea exertional,</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Nephrolithiasis, pollakiuria, dysuria</td>
<td>Calculus urinary, urinary incontinence, haematuria, incontinence, micturition urgency, renal colic, renal pain</td>
<td>Calculus ureteric, renal tubular acidosis*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia, rash, pruritus</td>
<td>Anhidrosis, hypoaesthesia facial, urticaria, erythema, pruritus generalised, rash macular, skin discoloration, dermatitis allergic, swelling face</td>
<td>Stevens-Johnson syndrome*, erythema multiforme*, skin odour abnormal, periorbital oedema*, urticaria localised</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia, muscle spasms, myalgia, muscle twiching, muscular weakness, musculoskeletal chest pain</td>
<td>Joint swelling*, musculoskeletal stiffness, flank pain, muscle fatigue</td>
<td>Limb discomfort*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia, decreased appetite</td>
<td>Metabolic acidosis, Hypokalaemia, increased appetite, polydipsia</td>
<td>Acidosi hyperchloaemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Nasopharyngitis*</td>
<td>Hypotension, orthostatic hypotension flushing, hot flush</td>
<td>Raynad's phenomenon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Very common</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Not known</td>
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<td>-----------------------------------------</td>
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</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>Pyrexia, asthenia, irritability, gait disturbance, feeling abnormal, malaise</td>
<td>Hyperthermia, thirst, influenza like illness*, sluggishness, peripheral coldness, feeling drunk, feeling jittery</td>
<td>Face oedema, calcinosi</td>
<td></td>
</tr>
<tr>
<td>Social circumstances</td>
<td></td>
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<tr>
<td>Immune system disorders</td>
<td></td>
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<td></td>
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<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Depression</td>
<td>Bradyphrenia, insomnia, expressive language disorder, anxiety, confusional state, disorientation, aggression, mood altered, agitation, mood swings, depressed mood, anger, abnormal behaviour</td>
<td>Erectile dysfunction, sexual dysfunction</td>
<td>Suicidal ideation, suicide attempt, hallucination, psychotic disorder, hallucination auditory, hallucination visual, apathy, lack of spontaneous speech, sleep disorder, affect lability, libido decreased, restlessness, crying, dysphemia, euphoric mood, paranoia, perseveration, panic attack, tearfulness, reading disorder, initial insomnia, flat affect, thinking abnormal, loss of libido, listless, middle insomnia, distractibility, early morning awakening, panic reaction, elevated mood</td>
<td>Mania, anorgasmia, panic disorder, disturbance in sexual arousal, feeling of despair*, orgasm abnormal, hypomania, orgasmic sensation decreased</td>
</tr>
</tbody>
</table>

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

### 4.9 Overdose

#### Signs and symptoms

Overdoses of topiramate have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbances, blurred vision, diplopia, impaired mentation, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. The clinical consequences were not severe in most cases, but deaths have been reported after overdoses with multiple medicinal products including topiramate.

Topiramate overdose can result in severe metabolic acidosis (see section 4.4).

#### Treatment

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

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

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

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

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

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

5.2 Pharmacokinetic properties

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

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

Topiramate is not a potent inducer of drug metabolizing enzymes, can be administered without regard to meals, and routine monitoring of plasma topiramate concentrations is not necessary. In clinical studies, there was no consistent relationship between plasma concentrations and efficacy or adverse events.
Absorption
Topiramate is rapidly and well absorbed. Following oral administration of 100 mg topiramate to healthy subjects, a mean peak plasma concentration (C_{max}) of 1.5 μg/ml was achieved within 2 to 3 hours (T_{max}).

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

Distribution
Generally, 13 to 17% of topiramate is bound to plasma protein. A low capacity binding site for topiramate in/on erythrocytes that is saturable above plasma concentrations of 4 μg/ml has been observed. The volume of distribution varied inversely with the dose. The mean apparent volume of distribution was 0.80 to 0.55 l/kg for a single dose range of 100 to 1200 mg. An effect of gender on the volume of distribution was detected, with values for females circa 50% of those for males. This was attributed to the higher percent body fat in female patients and is of no clinical consequence.

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

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

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

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

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

Plasma clearance of topiramate is decreased in patients with moderate to severe hepatic impairment.
Plasma clearance of topiramate is unchanged in elderly subjects in the absence of underlying renal disease.

Paediatric population (pharmacokinetics, up to 12 years of age)
The pharmacokinetics of topiramate in children, as in adults receiving add-on therapy, are linear, with clearance independent of dose and steady-state plasma concentrations increasing in proportion to dose. Children, however, have a higher clearance and a shorter elimination half-life. Consequently, the plasma concentrations of topiramate for the same mg/kg dose may be lower in children compared to adults. As in adults, hepatic enzyme inducing anti-epileptic drugs decrease the steady-state plasma concentrations.

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

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

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

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

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

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

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose monohydrate  
Pregelatinized starch  
Microcrystalline cellulose (E 460)  
Sodium starch glycolate  
Colloidal silicon dioxide  
Magnesium stearate  
Opadry Yellow contains Hypromellose (E 464), Titanium dioxide (E 171), Macrogol, Iron Oxide Yellow (E 172) and polysorbate 80 (E 433).

Ink Composition: Opacode Black.  
OPACODE contains, Shellac Glaze in ethanol, Iron Oxide Black (E 172), Isopropyl Alcohol, N-butyl alcohol, Propylene glycol (E 1520) and Ammonium hydroxide (E 527).
6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 25°C.
HDPE tablet containers: Keep container tightly closed.
Blisters: Store in the original package.

6.5 Nature and contents of container
PVC/PVdC/Al blisters
PVC/PVdC/Al blisters in aluminium pouch containing desiccant silica gel
OPA/Al/PE desiccant blister
Pack sizes: 10, 14, 20, 28, 30, 50, 60, 84, 90, 98, 100, 120 and 200 tablets
HDPE tablet containers with PP child-resistant closures, containing silica gel desiccant and polyester filler.
Pack sizes: 60 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Lupin (Europe) Limited
Victoria Court
Bexton Road
Knutsford
Cheshire WA16 0PF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 35507/0073

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
05/07/2011

10 DATE OF REVISION OF THE TEXT
05/07/2011
1 NAME OF THE MEDICINAL PRODUCT
Topiramate 100 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains 100 mg of Topiramate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablets
Dark yellow, circular, biconvex film coated tablets, imprinted “100” (in black ink) on one side and plain on the other side

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

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

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

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

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

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

Topiramate Tablets can be taken without regard to meals.

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

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

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

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

The recommended initial target dose for topiramate monotherapy in adults is 100 mg/day to 200 mg/day in 2 divided doses. The maximum recommended daily dose is 500 mg/day in 2 divided doses. Some patients with refractory forms of epilepsy have tolerated topiramate monotherapy at doses of 1,000 mg/day. These dosing recommendations apply to all adults including the elderly in the absence of underlying renal disease.

**Paediatric population (children over 6 years of age)**

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

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

**Adjunctive therapy epilepsy (partial onset seizures with or without secondary generalization, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome).**

**Adults**

Therapy should begin at 25-50 mg nightly for one week. Use of lower initial doses has been reported, but has not been studied systematically. Subsequently, at weekly or bi-weekly intervals, the dose should be increased by 25-50 mg/day and taken in two divided doses. Some patients may achieve efficacy with once-a-day dosing.

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

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

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

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

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

**Migraine**

**Adults**

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

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

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

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

**Renal impairment**

In patients with impaired renal function (CLCR ≤ 60 mL/min) topiramate should be administered with caution as the plasma and renal clearance of topiramate are decreased. Subjects with known renal impairment may require a longer time to reach steady-state at each dose.

In patients with end-stage renal failure, since topiramate is removed from plasma by haemodialysis, a supplemental dose of Topiramate Tablets equal to approximately one-half the daily dose should be administered on haemodialysis days. The supplemental dose should be administered in divided doses at the beginning and completion of the haemodialysis procedure. The supplemental dose may differ based on the characteristics of the dialysis equipment being used.

**Hepatic impairment**

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

**Elderly**

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

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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

### 4.4 Special warnings and precautions for use

In situations where rapid withdrawal of topiramate is medically required, appropriate monitoring is recommended (see section 4.2 for further details).

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

Adequate hydration while using topiramate is very important. Hydration can reduce the risk of nephrolithiasis (see below). Proper hydration prior to and during activities such as exercise or exposure to warm temperatures may reduce the risk of heat-related adverse reactions (see section 4.8).

**Mood disturbances/depression**

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

**Suicide/suicide ideation**

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

In double blind clinical trials, suicide related events (SREs) (suicidal ideation, suicide attempts and suicide) occurred at a frequency of 0.5% in topiramate treated patients (46 out of 8,652 patients treated) and at a nearly 3 fold higher incidence than those treated with placebo (0.2%; 8 out of 4,045 patients treated).
Patients therefore should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

**Nephrolithiasis**

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

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

**Decreased hepatic function**

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

**Acute myopia and secondary angle closure glaucoma**

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

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

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

**Metabolic acidosis**

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

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

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

Depending on underlying conditions, appropriate evaluation including serum bicarbonate levels is recommended with topiramate therapy. If metabolic acidosis develops and persists,
consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering).

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

**Nutritional supplementation**

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

**Lactose intolerance**

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

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

**Effects of Topiramate Tablets on other antiepileptic medicinal products**

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

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

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

**Effects of other antiepileptic medicinal products on Topiramate Tablets**

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

<table>
<thead>
<tr>
<th>AED Coadministered</th>
<th>AED Concentration</th>
<th>Topiramate Tablets 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>Valproic acid</td>
<td>↔</td>
<td>↔</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 individual patients
↓ = Plasma concentrations decrease
NS = Not studied
AED = antiepileptic drug

### Other medicinal product interactions

**Digoxin**

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

**St John’s Wort (Hypericum perforatum).**

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

**Oral contraceptives**

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

**Lithium**

In healthy volunteers, there was an observed reduction (18% for AUC) in systemic exposure for lithium during concomitant administration with topiramate 200 mg/day. In patients with bipolar disorder, the pharmacokinetics of lithium were unaffected during treatment with topiramate at doses of 200 mg/day; however, there was an observed increase in systemic
exposure (26% for AUC) following topiramate doses of up to 600 mg/day. Lithium levels should be monitored when co-administered with topiramate.

**Risperidone**

Drug-drug interaction studies conducted under single dose conditions in healthy volunteers and multiple dose conditions in patients with bipolar disorder, yielded similar results. When administered concomitantly with topiramate at escalating doses of 100, 250 and 400 mg/day there was a reduction in risperidone (administered at doses ranging from 1 to 6 mg/day) systemic exposure (16% and 33% for steady-state AUC at the 250 and 400 mg/day doses, respectively). However, differences in AUC for the total active moiety between treatment with risperidone alone and combination treatment with topiramate were not statistically significant. Minimal alterations in the pharmacokinetics of the total active moiety (risperidone plus 9-hydroxyrisperidone) and no alterations for 9-hydroxyrisperidone were observed. There were no significant changes in the systemic exposure of the risperidone total active moiety or of topiramate. When topiramate was added to existing risperidone (1-6 mg/day) treatment, adverse events were reported more frequently than prior to topiramate (250-400 mg/day) introduction (90% and 54 % respectively). The most frequently reported AE’s when topiramate was added to risperidone treatment were: somnolence (27% and 12%), paraesthesia (22% and 0%) and nausea (18% and 9% respectively).

**Hydrochlorothiazide (HCTZ)**

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg q24h) and topiramate (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that topiramate C\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 and topiramate in plasma when metformin was given alone and when metformin and topiramate were given simultaneously. The results of this study indicated that metformin mean C\text{max} and mean AUC\text{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 Tablets 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{t,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{t,ss} respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in C\text{max,ss} and AUC\text{t,ss} of the active keto-metabolite. The clinical significance of these findings is not known. When Topiramate Tablets is added to pioglitazone therapy or pioglitazone is added to Topiramate Tablets therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.
Glyburide
A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glyburide (5 mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 25% reduction in glyburide AUC$_{24}$ during topiramate administration. Systemic exposure of the active metabolites, 4-trans-hydroxy-glyburide (M1) and 3-cis-hydroxyglyburide (M2), were also reduced by 13% and 15%, respectively. The steady-state pharmacokinetics of topiramate were unaffected by concomitant administration of glyburide.

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

Other forms of interactions
Agents predisposing to nephrolithiasis
Topiramate Tablets, when used concomitantly with other agents predisposing to nephrolithiasis, may increase the risk of nephrolithiasis. While using Topiramate Tablets, agents like these should be avoided since they may create a physiological environment that increases the risk of renal stone formation.

Valproic acid
Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either medicinal product alone. In most cases, symptoms and signs abated with discontinuation of either medicinal product. This adverse reaction is not due to a pharmacokinetic interaction. 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$_{max}$ 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>Topiramate Concentration&lt;sup&gt;a&lt;/sup&gt;</th>
<th>NS</th>
<th>↔ = No effect on C&lt;sub&gt;max&lt;/sub&gt; and AUC (&lt;sup&gt;b&lt;/sup&gt;≤ 15% change) of the parent compound</th>
<th>NS = Not studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>↔ 20% increase in C&lt;sub&gt;max&lt;/sub&gt; and AUC of nortriptyline metabolite</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dihydroergotamine (Oral and Subcutaneous)</td>
<td>↔</td>
<td>↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>↔ 31% increase in AUC of the reduced metabolite</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>↔ 17% increase in C&lt;sub&gt;max&lt;/sub&gt; for 4-OH propranolol (TPM 50 mg q12h)</td>
<td>9% and 16% increase in C&lt;sub&gt;max&lt;/sub&gt;, 9% and 17% increase in AUC (40 and 80 mg propranolol q12h respectively)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sumatriptan (Oral and Subcutaneous)</td>
<td>↔</td>
<td>↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pizotifen</td>
<td>↔</td>
<td>↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>25% decrease in AUC of diltiazem and 18% decrease in DEA, and ↔ for DEM&lt;sup&gt;*&lt;/sup&gt;</td>
<td>20% increase in AUC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>↔</td>
<td>↔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flunarizine</td>
<td>16% increase in AUC (TPM 50 mg q12h)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>↔</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*<sup>a</sup> % values are the changes in treatment mean C<sub>max</sub> or AUC with respect to monotherapy
*<sup>b</sup> = No effect on C<sub>max</sub> and AUC (<sup>b</sup>≤ 15% change) of the parent compound
NS = Not studied
*DEA = des acetyl diltiazem, DEM = N-demethyl diltiazem
<sup>b</sup> Flunarizine AUC increased 14% in subjects taking flunarizine alone. Increase in exposure may be attributed to accumulation during achievement of steady state.

### 4.6 Pregnancy and lactation

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

There are no adequate and well-controlled studies with Topiramate Tablets in pregnant women.

Pregnancy registry data suggest that there may be an association between the use of Topiramate Tablets during pregnancy and congenital malformations (e.g., craniofacial defects, such as cleft lip/palate, hypospadias, and anomalies involving various body systems). This has been reported with topiramate monotherapy and topiramate as part of a polytherapy regimen. This data should be interpreted with caution, as more data is needed to identify increased risks for malformations.

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

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

Animal studies have shown excretion of topiramate in milk. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggest an extensive excretion of topiramate into breast milk. Since many medicinal products are excreted into human milk, a decision must be made whether to suspend breast-feeding or...
to discontinue/ abstain from topiramate therapy taking into account the importance of the medicinal product to the mother (section 4.4).

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

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

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

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

4.10 **Undesirable effects**
The safety of topiramate was evaluated from a clinical trial database consisting of 4,111 patients (3,182 on topiramate and 929 on placebo) who participated in 20 double-blind trials and 2,847 patients who participated in 34 open-label trials, respectively, for topiramate as adjunctive treatment of primary generalized tonic-clonic seizures, partial onset seizures, seizures associated with Lennox-Gastaut syndrome, monotherapy for newly or recently diagnosed epilepsy or migraine prophylaxis. The majority of ADRs were mild to moderate in severity. ADRs identified in clinical trials, and during post-marketing experience (as indicated by “*”) are listed by their incidence in clinical trials in Table 1. Assigned frequencies are as follows:

Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1,000 to <1/100
Rare ≥1/10,000 to <1/1,000
Not known cannot be estimated from the available data

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

**Paediatric population**
ADRs reported more frequently (≥2-fold) in children than in adults in double-blind controlled studies include: decreased appetite, increased appetite, acidosis hyperchloaraemic, hypokalaemia, abnormal behaviour, aggression, apathy, initial insomnia, suicidal ideation, disturbance in attention, lethargy, circadian rhythm sleep disorder, poor quality sleep, lacrimation increased, sinus bradycardia, feeling abnormal, and gait disturbance.

ADRs that were reported in children but not in adults in double-blind controlled studies include: eosinophilia, psychomotor hyperactivity, vertigo, vomiting, hyperthermia, pyrexia, and learning disability.
### Table 1: Topiramate Adverse Drug Reactions

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td>Weight increased*</td>
<td>Crystall urine present, tandem gait test abnormal, white blood cell count decreased</td>
<td>Bradycardia, sinus bradycardia, palpitations</td>
<td>Blood bicarbonate decreased</td>
<td></td>
</tr>
</tbody>
</table>

| **Cardiac disorders** |             |        |          |      |           |
| Anaemia             |             |        |          |      |           |

| **Blood and lymphatic system disorders** |             |        |          |      |           |
| Anaemia             |             |        |          |      |           |

| **Nervous system disorders** | Paraesthesia, somnolence Dizziness | Disturbance in attention, memory impairment, amnesia, cognitive disorder, mental impairment, psychomotor skills impaired, convulsion, coordination abnormal, tremor, lethargy, hypoaesthesia, nystagmus, dysgeusia, balance disorder, dysarthria, intention tremor, sedation | Depressed level of consciousness, grand mal convolution, visual field defect, complex partial seizures, speech disorder, psychomotor hyperactivity, syncope, sensory disturbance, drooling, hypersonnia, aphasia, repetitive speech, hypokinesia, dyskinesia, dizziness postural, poor quality sleep, burning sensation, sensory loss, parosmia, cerebellar syndrome, dysesthesia, hypogeusia, stupor, clumsiness, aura, ageusia, dysgraphia, dysphasia, neuropathy peripheral, presyncope, dystonia, formication | Apraxia, circadian rhythm sleep disorder, hyperaesthesia, hyposmia, anosmia, essential tremor, akinesia, unresponsive to stimuli |

<p>| <strong>Eye disorders</strong> | Vision blurred diplopia, visual disturbance | Visual acuity reduced, scotoma, myopia*, abnormal sensation in eye*, dry eye, photophobia, blepharospasm, lacrimation increased, photopsia, mydriasis, presbyopia | Blindness unilateral, blindness transient, glaucoma, accommodation disorder, altered visual depth perception, scintillating scotoma, eyelid oedema*, night blindness, amblyopia | Angle closure glaucoma*, Maculopathy*, eye movement disorder* |</p>
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Vertigo, tinnitus, ear pain</td>
<td>Deafness, deafness unilateral, deafness neurosensory, ear discomfort, hearing impaired</td>
<td>Dyspnoea exertional, Paramasal sinus hypersecretion, dysphonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnoea, epistaxis, nasal congestion, rhinorrhea</td>
<td>Pancreatitis, flatulence, gastroesophageal reflux disease, abdominal pain lower, hypoesthesia oral, gingival bleeding, abdominal distension, epigastric discomfort, abdominal tenderness, salivary hypersecretion, oral pain, breath odour, glossodynia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, diarrhoea</td>
<td>Vomiting, constipation, abdominal pain upper, dyspepsia, abdominal pain, dry mouth, stomach discomfort, paraesthesia oral, gastritis, abdominal discomfort</td>
<td>Pancreatitis, flatulence, gastroesophageal reflux disease, abdominal pain lower, hypoesthesia oral, gingival bleeding, abdominal distension, epigastric discomfort, abdominal tenderness, salivary hypersecretion, oral pain, breath odour, glossodynia</td>
<td></td>
<td></td>
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<tr>
<td>Nephrolithiasis, pollakiuria, dysuria</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia, rash, pruritus</td>
<td>Anhidrosis, hypoesthesia facial, urticaria, erythema, pruritus generalised, rash macular, skin discoloration, dermatitis allergic, swelling face</td>
<td>Stevens-Johnson syndrome*, erythema multiforme*, skin odour abnormal, periorbital oedema*, urticaria localised</td>
<td></td>
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</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia, muscle spasms, myalgia, muscle twitching, muscular weakness, musculoskeletal chest pain</td>
<td>Joint swelling*, musculoskeletal stiffness, flank pain, muscle fatigue</td>
<td></td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia, decreased appetite</td>
<td>Metabolic acidosis, Hypokalaemia, increased appetite, polydipsia</td>
<td>Acidosis hyperchloraemic</td>
<td></td>
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</tr>
<tr>
<td>Infections and infestations Vascular disorders</td>
<td>Nasopharyngitis*</td>
<td>Hypotension, orthostatic hypotension flushing, hot flush</td>
<td>Raynaud's phenomenon</td>
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</tr>
</tbody>
</table>
### 4.9 Overdose

#### Signs and symptoms

Overdoses of topiramate have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbances, blurred vision, diplopia, impaired mentation, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. The clinical consequences were not severe in most cases, but deaths have been reported after overdoses with multiple medicinal products including topiramate.

Topiramate overdose can result in severe metabolic acidosis (see section 4.4).

#### Treatment

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>Pyrexia, asthenia, irritability, gait disturbance, feeling abnormal, malaise</td>
<td>Hyperthermia, thirst, influenza like illness*, sluggishness, peripheral coldness, feeling drunk, feeling jittery</td>
<td>Face oedema, calcinosiss</td>
<td></td>
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<tr>
<td>Social circumstances</td>
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<tr>
<td>Immune system disorders</td>
<td></td>
<td>Hypersensitivity</td>
<td></td>
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<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td>Erectile dysfunction, sexual dysfunction</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Depression</td>
<td>Bradyphrenia, insomnia, expressive language disorder, anxiety, confusional state, disorientation, aggression, mood altered, agitation, mood swings, depressed mood, anger, abnormal behaviour</td>
<td>Suicidal ideation, suicide attempt, hallucination, psychotic disorder, hallucination auditory, hallucination visual, apathy, lack of spontaneous speech, sleep disorder, affect lability, libido decreased, restlessness, crying, dysphoria, euphoric mood, paranoia, perseveration, panic attack, tearfulness, reading disorder, initial insomnia, flat affect, thinking abnormal, loss of libido, listless, middle insomnia, distractibility, early morning awakening, panic reaction, elevated mood</td>
<td>Mania, anorgasmia, panic disorder, disturbance in sexual arousal, feeling of despair*, orgasm abnormal, hypomania, orgasmic sensation decreased</td>
<td></td>
</tr>
</tbody>
</table>

* identified as an ADR from postmarketing spontaneous reports. Its frequency was calculated based on clinical trial data.
should be well hydrated. Haemodialysis has shown to be an effective means of removing topiramate from the body.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

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

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

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

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

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

5.2 Pharmacokinetic properties

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

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

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

Absorption
Topiramate is rapidly and well absorbed. Following oral administration of 100 mg topiramate to healthy subjects, a mean peak plasma concentration ($C_{\text{max}}$) of 1.5 $\mu$g/ml was achieved within 2 to 3 hours ($T_{\text{max}}$).

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

Distribution
Generally, 13 to 17% of topiramate is bound to plasma protein. A low capacity binding site for topiramate in/on erythrocytes that is saturable above plasma concentrations of 4 $\mu$g/ml has been observed. The volume of distribution varied inversely with the dose. The mean apparent volume of distribution was 0.80 to 0.55 l/kg for a single dose range of 100 to 1200 mg. An effect of gender on the volume of distribution was detected, with values for females circa 50% of those for males. This was attributed to the higher percent body fat in female patients and is of no clinical consequence.

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

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

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

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

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

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

Paediatric population (pharmacokinetics, up to 12 years of age)
The pharmacokinetics of topiramate in children, as in adults receiving add-on therapy, are linear, with clearance independent of dose and steady-state plasma concentrations increasing in proportion to dose. Children, however, have a higher clearance and a shorter elimination half-life. Consequently, the plasma concentrations of topiramate for the same mg/kg dose may be lower in children compared to adults. As in adults, hepatic enzyme inducing anti-epileptic drugs decrease the steady-state plasma concentrations.

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

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

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Pregelatinized starch
Microcrystalline cellulose (E 460)
Sodium starch glycolate
Colloidal silicon dioxide
Magnesium stearate
Opadry Yellow contains Hypromellose (E 464), Titanium dioxide (E 171), Macrogol, Iron Oxide Red & Yellow (E 172) and polysorbate 80 (E 433).
Ink Composition: Opacode Black.
OPACODE contains, Shellac Glaze in ethanol, Iron Oxide Black (E 172), Isopropyl Alcohol, N-butyl alcohol, Propylene glycol (E 1520) and Ammonium hydroxide (E 527).

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 25°C.
HDPE tablet containers: Keep container tightly closed.
Blisters: Store in the original package.

6.5 Nature and contents of container
PVC/PVdC/Al blisters
PVC/PVdC/Al blisters in aluminium pouch containing desiccant silica gel
OPA/Al/PE desiccant blister
Pack sizes: 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100, 120 and 200 tablets

HDPE tablet containers with PP child-resistant closures, containing silica gel desiccant and polyester filler.
Pack sizes: 60 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Lupin (Europe) Limited
Victoria Court
Bexton Road
Knutsford
Cheshire WA16 0PF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 35507/0074

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
05/07/2011

10 DATE OF REVISION OF THE TEXT
05/07/2011
1 **NAME OF THE MEDICINAL PRODUCT**
Topiramate 200 mg Tablets

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each film coated tablet contains 200 mg of Topiramate.

For a full list of excipients, see section 6.1.

3 **PHARMACEUTICAL FORM**
Film-coated tablets
Reddish pink, oval shaped, biconvex film coated tablets, imprinted “200” (in black ink) on one side and plain on the other side.

4 **CLINICAL PARTICULARS**

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

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

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

4.2 **Posology and method of administration**

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

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

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

Topiramate Tablets can be taken without regard to meals.

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

**Monotherapy epilepsy**

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

When enzyme inducing medicinal products are withdrawn, topiramate levels will increase. A decrease in Topiramate Tablets (topiramate) dosage may be required if clinically indicated.
Adults
Dose and titration should be guided by clinical response. Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased at 1- or 2-week intervals by increments of 25 or 50 mg/day, administered in two divided doses. If the patient is unable to tolerate the titration regimen, smaller increments or longer intervals between increments can be used.

The recommended initial target dose for topiramate monotherapy in adults is 100 mg/day to 200 mg/day in 2 divided doses. The maximum recommended daily dose is 500 mg/day in 2 divided doses. Some patients with refractory forms of epilepsy have tolerated topiramate monotherapy at doses of 1,000 mg/day. These dosing recommendations apply to all adults including the elderly in the absence of underlying renal disease.

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

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

Adjunctive therapy epilepsy (partial onset seizures with or without secondary generalization, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome).

Adults
Therapy should begin at 25-50 mg nightly for one week. Use of lower initial doses has been reported, but has not been studied systematically. Subsequently, at weekly or bi-weekly intervals, the dose should be increased by 25-50 mg/day and taken in two divided doses. Some patients may achieve efficacy with once-a-day dosing.

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

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

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

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

Migraine

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

Some patients may experience a benefit at a total daily dose of 50 mg/day. Patients have received a total daily dose up to 200 mg/day. This dose may be benefit in some patients, nevertheless, caution is advised due to an increase incidence of side effects.
Paediatric population
Topiramate Tablets (topiramate) is not recommended for treatment or prevention of migraine in children due to insufficient data on safety and efficacy.

General dosing recommendations for Topiramate Tablets in special patient populations
Renal impairment
In patients with impaired renal function (CLCR ≤ 60 mL/min) topiramate should be administered with caution as the plasma and renal clearance of topiramate are decreased. Subjects with known renal impairment may require a longer time to reach steady-state at each dose.

In patients with end-stage renal failure, since topiramate is removed from plasma by haemodialysis, a supplemental dose of Topiramate Tablets equal to approximately one-half the daily dose should be administered on haemodialysis days. The supplemental dose should be administered in divided doses at the beginning and completion of the haemodialysis procedure. The supplemental dose may differ based on the characteristics of the dialysis equipment being used.

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

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

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.
Migraine prophylaxis in pregnancy and in women of childbearing potential if not using effective methods of contraception.

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

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

Adequate hydration while using topiramate is very important. Hydration can reduce the risk of nephrolithiasis (see below). Proper hydration prior to and during activities such as exercise or exposure to warm temperatures may reduce the risk of heat-related adverse reactions (see section 4.8).

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

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

In double blind clinical trials, suicide related events (SREs) (suicidal ideation, suicide attempts and suicide) occurred at a frequency of 0.5% in topiramate treated patients (46 out of 8,652 patients treated) and at a nearly 3 fold higher incidence than those treated with placebo (0.2%; 8 out of 4,045 patients treated).
Patients therefore should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

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

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

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

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

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

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

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

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

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

Depending on underlying conditions, appropriate evaluation including serum bicarbonate levels is recommended with topiramate therapy. If metabolic acidosis develops and persists,
consideration should be given to reducing the dose or discontinuing topiramate (using dose
tapering).
Topiramate should be used with caution in patients with conditions or treatments that
represent a risk factor for the appearance of metabolic acidosis.

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

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

4.5 Interaction with other medicinal products and other forms of interaction
Effects of Topiramate Tablets on other antiepileptic medicinal products
The addition of Topiramate Tablets to other antiepileptic drugs (phenytoin, carbamazepine,
valproic acid, phenobarbital, primidone) has no effect on their steady-state plasma
concentrations, except in the occasional patient, where the addition of Topiramate Tablets to
phenytoin may result in an increase of plasma concentrations of phenytoin. This is possibly
due to inhibition of a specific enzyme polymorphic isoform (CYP2C19). Consequently, any
patient on phenytoin showing clinical signs or symptoms of toxicity should have phenytoin
levels monitored.

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

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

Effects of other antiepileptic medicinal products on Topiramate Tablets
Phenytoin and carbamazepine decrease the plasma concentration of topiramate. The addition
or withdrawal of phenytoin or carbamazepine to Topiramaate Tablets 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 Tablets and, therefore, does not warrant dosage
adjustment of Topiramate Tablets. The results of these interactions are summarized below:
AED Coadministered | AED Concentration | Topiramate Tablets Concentration
---|---|---
Phenytoin | ↔** | ↓
Carbamazepine (CBZ) | ↔ | ↓
Valproic acid | ↔ | ↔
Lamotrigine | ↔ | ↔
Valproic acid | ↔ | ↔
Phenobarbital | ↔ | NS
Primidone | ↔ | NS

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

Other medicinal product interactions

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

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

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

**Lithium**
In healthy volunteers, there was an observed reduction (18% for AUC) in systemic exposure for lithium during concomitant administration with topiramate 200 mg/day. In patients with bipolar disorder, the pharmacokinetics of lithium were unaffected during treatment with topiramate at doses of 200 mg/day; however, there was an observed increase in systemic
exposure (26% for AUC) following topiramate doses of up to 600 mg/day. Lithium levels should be monitored when co-administered with topiramate.

**Risperidone**

Drug-drug interaction studies conducted under single dose conditions in healthy volunteers and multiple dose conditions in patients with bipolar disorder, yielded similar results. When administered concomitantly with topiramate at escalating doses of 100, 250 and 400 mg/day there was a reduction in risperidone (administered at doses ranging from 1 to 6 mg/day) systemic exposure (16% and 33% for steady-state AUC at the 250 and 400 mg/day doses, respectively). However, differences in AUC for the total active moiety between treatment with risperidone alone and combination treatment with topiramate were not statistically significant. Minimal alterations in the pharmacokinetics of the total active moiety (risperidone plus 9-hydroxyrisperidone) and no alterations for 9-hydroxyrisperidone were observed. There were no significant changes in the systemic exposure of the risperidone total active moiety of topiramate. When topiramate was added to existing risperidone (1-6 mg/day) treatment, adverse events were reported more frequently than prior to topiramate (250-400 mg/day) introduction (90% and 54% respectively). The most frequently reported AE’s when topiramate was added to risperidone treatment were: somnolence (27% and 12%), paraesthesia (22% and 9%) and nausea (18% and 9% respectively).

**Hydrochlorothiazide (HCTZ)**

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg q24h) and topiramate (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that topiramate 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 and topiramate in plasma when metformin was given alone and when metformin and topiramate were given simultaneously. The results of this study indicated that metformin mean 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 Tablets 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 AUCτ,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 AUCτ,ss respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in Cmax,ss and AUCτ,ss of the active keto-metabolite. The clinical significance of these findings is not known. When Topiramate Tablets is added to pioglitazone therapy or pioglitazone is added to Topiramate Tablets therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.
**Glyburide**
A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glyburide (5 mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 25% reduction in glyburide AUC₂₄ during topiramate administration. Systemic exposure of the active metabolites, 4-trans-hydroxy-glyburide (M1) and 3-cis-hydroxyglyburide (M2), were also reduced by 13% and 15%, respectively. The steady-state pharmacokinetics of topiramate were unaffected by concomitant administration of glyburide.

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

**Other forms of interactions**

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

**Valproic acid**
Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either medicinal product alone. In most cases, symptoms and signs abated with discontinuation of either medicinal product. This adverse reaction is not due to a pharmacokinetic interaction. 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</th>
<th>Topiramate Concentration*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>↔ 20% increase in C&lt;sub&gt;max&lt;/sub&gt; 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&lt;sub&gt;max&lt;/sub&gt; for 4-OH propranolol (TPM 50 mg q12h)</td>
<td>9% and 16% increase in C&lt;sub&gt;max&lt;/sub&gt;, 9% and 17% increase in AUC (40 and 80 mg propranolol q12h respectively)</td>
</tr>
<tr>
<td>Sumatriptan (Oral and Subcutaneous)</td>
<td>↔</td>
<td>NS</td>
</tr>
<tr>
<td>Pizotifen</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>25% decrease in AUC of diltiazem and 18% decrease in DEA, and ↔ for DEM*</td>
<td>20% increase in AUC</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Flunarizine</td>
<td>16% increase in AUC (TPM 50 mg q12h)b</td>
<td>↔</td>
</tr>
</tbody>
</table>

* % values are the changes in treatment mean C<sub>max</sub> or AUC with respect to monotherapy
↔ = No effect on C<sub>max</sub> and AUC (≤ 15% change) of the parent compound
NS = Not studied
*DEA = des acetyl diltiazem, DEM = N-demethyl diltiazem
b Flunarizine AUC increased 14% in subjects taking flunarizine alone. Increase in exposure may be attributed to accumulation during achievement of steady state.

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

There are no adequate and well-controlled studies with Topiramate Tablets in pregnant women.

Pregnancy registry data suggest that there may be an association between the use of Topiramate Tablets during pregnancy and congenital malformations (e.g., craniofacial defects, such as cleft lip/palate, hypospadias, and anomalies involving various body systems). This has been reported with topiramate monotherapy and topiramate as part of a polytherapy regimen. This data should be interpreted with caution, as more data is needed to identify increased risks for malformations.

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

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

Animal studies have shown excretion of topiramate in milk. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggest an extensive excretion of topiramate into breast milk. Since many medicinal products are excreted into human milk, a decision must be made whether to suspend breast-feeding or to discontinue/abstain from topiramate therapy taking into account the importance of the medicinal product to the mother (section 4.4).
Indication Epilepsy
During pregnancy, topiramate should be prescribed after fully informing the woman of the known risks of uncontrolled epilepsy to the pregnancy and the potential risks of the medicinal product to the foetus.

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

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

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

4.11 Undesirable effects
The safety of topiramate was evaluated from a clinical trial database consisting of 4,111 patients (3,182 on topiramate and 929 on placebo) who participated in 20 double-blind trials and 2,847 patients who participated in 34 open-label trials, respectively, for topiramate as adjunctive treatment of primary generalized tonic-clonic seizures, partial onset seizures, seizures associated with Lennox-Gastaut syndrome, monotherapy for newly or recently diagnosed epilepsy or migraine prophylaxis. The majority of ADRs were mild to moderate in severity. ADRs identified in clinical trials, and during post-marketing experience (as indicated by “*”) are listed by their incidence in clinical trials in Table 1. Assigned frequencies are as follows:

Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1,000 to <1/100
Rare ≥1/10,000 to <1/1,000
Not known cannot be estimated from the available data

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

Paediatric population
ADRs reported more frequently (≥2-fold) in children than in adults in double-blind controlled studies include: decreased appetite, increased appetite, acidosis hyperchloremic, hypokalaemia, abnormal behaviour, aggression, apathy, initial insomnia, suicidal ideation, disturbance in attention, lethargy, circadian rhythm sleep disorder, poor quality sleep, lacrimation increased, sinus bradycardia, feeling abnormal, and gait disturbance.

ADRs that were reported in children but not in adults in double-blind controlled studies include: eosinophilia, psychomotor hyperactivity, vertigo, vomiting, hyperthermia, pyrexia, and learning disability.
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td>Weight decreased</td>
<td>Weight increased*</td>
<td>Blood bicarbonate decreased</td>
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<td>Cardiac disorders</td>
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<tr>
<td>Blood and lymphatic system disorders</td>
<td>Anaemia</td>
<td>Leucopenia,</td>
<td>Neutropenia*</td>
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<td></td>
<td>thrombocytopenia</td>
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<td></td>
<td></td>
<td>eosinophilia</td>
<td></td>
</tr>
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<td>Nervous system disorders</td>
<td>Parasthesia, somnolence</td>
<td>Disturbance in</td>
<td>Apraxia, circadian rhythm</td>
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<td></td>
<td></td>
<td>attention,</td>
<td>sleep disorder,</td>
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<tr>
<td></td>
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<td>memory</td>
<td>hyperaesthesia,</td>
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<td>impairment,</td>
<td>anosmia, essential</td>
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<td></td>
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<td>amnesia,</td>
<td>tremor, akinesia,</td>
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<td>cognitive</td>
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<td>stimuli</td>
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<td>mental</td>
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<td>psychomotor</td>
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<td>skills impaired,</td>
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<td></td>
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<td>convulsion,</td>
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<td></td>
<td>coordination</td>
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<tr>
<td></td>
<td></td>
<td>tremor,</td>
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<td></td>
<td>lethargy,</td>
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<td>hypoaesthesia,</td>
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<td>nystagmus,</td>
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<td></td>
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<td>dysgeusia,</td>
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<td></td>
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<td></td>
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<td>intention</td>
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<td></td>
<td></td>
<td>tremor,</td>
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<tr>
<td></td>
<td></td>
<td>sedation</td>
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<td>Eye disorders</td>
<td>Vision blurred diplopia, visual disturbance</td>
<td>Visual acuity</td>
<td>Blindness unilateral,</td>
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<td></td>
<td></td>
<td>reduced, scotoma,</td>
<td>blindness transient,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>myopia*, abnormal</td>
<td>glaucoma,</td>
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<td></td>
<td></td>
<td>sensation in eye*</td>
<td>accommodation disorder,</td>
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<td></td>
<td>dry eye,</td>
<td>altered</td>
</tr>
<tr>
<td></td>
<td></td>
<td>photophobia,</td>
<td>visual depth</td>
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<td></td>
<td>blepharospasm,</td>
<td>perception,</td>
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<td>lacrimation</td>
<td>scintillating</td>
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<td>increased,</td>
<td>scotoma, eyelid</td>
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<td></td>
<td></td>
<td>photopsia,</td>
<td>oedema*, night blindness,</td>
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<tr>
<td></td>
<td></td>
<td>mydriasis,</td>
<td>amblyopia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>presbyopia</td>
<td></td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Very common</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>--------------------</td>
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<td>----------</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Vertigo, tinnitus, ear pain</td>
<td>Deafness, deafness unilateral, deafness neurosensory, ear discomfort, hearing impaired</td>
<td>Dysexia</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnoea, epistaxis, nasal congestion, rhinorrhea</td>
<td>Dysexia, exertional, Parasana, sinus hypoxia, dysphonia</td>
<td>Pancreatitis, flatulence, gastroesophageal reflux disease, abdominal pain lower, hypoesthesia oral, gingival bleeding, abdominal distension, epigastric discomfort, abdominal tenderness, salivary hyposecretion, oral pain, breath odour, glossodynia</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, diarrhoea, vomiting, constipation, abdominal pain upper, dyspepsia, abdominal pain, dry mouth, stomach discomfort, paraesthesia oral, gastritis, abdominal discomfort</td>
<td>Pancreatitis, flatulence, gastroesophageal reflux disease, abdominal pain lower, hypoesthesia oral, gingival bleeding, abdominal distension, epigastric discomfort, abdominal tenderness, salivary hyposecretion, oral pain, breath odour, glossodynia</td>
<td>Pancreatitis, flatulence, gastroesophageal reflux disease, abdominal pain lower, hypoesthesia oral, gingival bleeding, abdominal distension, epigastric discomfort, abdominal tenderness, salivary hyposecretion, oral pain, breath odour, glossodynia</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Nephrolithiasis, pollakuria, dysuria</td>
<td>Calculus urinary, incontinence, haematuria, incontinence, micturition urgency, renal colic, renal pain</td>
<td>Calcium stone</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia, rash, pruritus</td>
<td>Anhidrosis, hypoesthesia facial, urticaria, erythema, pruritus generalised, rash macular, skin discoloration, dermatitis allergic, swelling face</td>
<td>Stevens-Johnson syndrome, erythema multiforme, skin odour abnormal, peri-orbital oedema, urticaria localised</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia, muscle spasms, myalgia, muscle twitching, muscular weakness, musculoskeletal chest pain</td>
<td>Joint swelling, musculoskeletal stiffness, flank pain, muscle fatigue</td>
<td>Limb discomfort</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia, decreased appetite</td>
<td>Metabolic acidosis, hypokalaemia, increased appetite, polydipsia</td>
<td>Acidosis hyperchloraemic</td>
</tr>
<tr>
<td>Infections and infestations Vascular disorders</td>
<td>Nasopharyngitis</td>
<td>Hypotension, orthostatic hypotension flushing, hot flush</td>
<td>Raynaud's phenomenon</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Very common</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>--------------------</td>
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<td>----------</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>Pyrexia, asthenia, irritability, gait disturbance, feeling abnormal, malaise</td>
<td>Hyperthermia, thirst, influenza like illness*, sluggishness, peripheral coldness, feeling drunk, feeling jittery</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social circumstances</td>
<td>Hypersensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Erectile dysfunction, sexual dysfunction</td>
<td>Bradyphrenia, insomnia, expressive language disorder, anxiety, confusional state, disorientation, aggression, mood altered, agitation, mood swings, depressed mood, anger, abnormal behaviour</td>
<td>Suicidal ideation, suicide attempt, hallucination, psychotic disorder, hallucination auditory, hallucination visual, apathy, lack of spontaneous speech, sleep disorder, affect lability, libido decreased, restlessness, crying, dysphoria, euphoric mood, paranoia, perseveration, panic attack, tearfulness, reading disorder, initial insomnia, flat affect, thinking abnormal, loss of libido, listless, middle insomnia, distractibility, early morning awakening, panic reaction, elevated mood</td>
</tr>
</tbody>
</table>

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

### 4.9 Overdose

#### Signs and symptoms

Overdoses of topiramate have been reported. Signs and symptoms included convulsions, drowsiness, speech disturbances, blurred vision, diplopia, impaired mentation, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness and depression. The clinical consequences were not severe in most cases, but deaths have been reported after overdoses with multiple medicinal products including topiramate.

Topiramate overdose can result in severe metabolic acidosis (see section 4.4).
Treatment
In acute topiramate overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has been shown to adsorb topiramate in vitro. Treatment should be appropriately supportive and the patient should be well hydrated. Haemodialysis has been shown to be an effective means of removing topiramate from the body.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: other antiepileptics, antimigraine preparations, ATC code: N03AX11

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

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

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

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

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

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

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

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

The pharmacokinetic profile of topiramate compared to other antiepileptic drugs shows a long plasma half-life, linear pharmacokinetics, predominantly renal clearance, absence of significant protein binding, and lack of clinically relevant active metabolites.
Topiramate is not a potent inducer of drug metabolizing enzymes, can be administered without regard to meals, and routine monitoring of plasma topiramate concentrations is not necessary. In clinical studies, there was no consistent relationship between plasma concentrations and efficacy or adverse events.

Absorption
Topiramate is rapidly and well absorbed. Following oral administration of 100 mg topiramate to healthy subjects, a mean peak plasma concentration ($C_{\text{max}}$) of 1.5 $\mu$g/ml was achieved within 2 to 3 hours ($T_{\text{max}}$).

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

Distribution
Generally, 13 to 17% of topiramate is bound to plasma protein. A low capacity binding site for topiramate in/on erythrocytes that is saturable above plasma concentrations of 4 $\mu$g/ml has been observed. The volume of distribution varied inversely with the dose. The mean apparent volume of distribution was 0.80 to 0.55 l/kg for a single dose range of 100 to 1200 mg. An effect of gender on the volume of distribution was detected, with values for females circa 50% of those for males. This was attributed to the higher percent body fat in female patients and is of no clinical consequence.

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

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

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

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

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

Paediatric population (pharmacokinetics, up to 12 years of age)
The pharmacokinetics of topiramate in children, as in adults receiving add-on therapy, are linear, with clearance independent of dose and steady-state plasma concentrations increasing in proportion to dose. Children, however, have a higher clearance and a shorter elimination half-life. Consequently, the plasma concentrations of topiramate for the same mg/kg dose may be lower in children compared to adults. As in adults, hepatic enzyme inducing anti-epileptic drugs decrease the steady-state plasma concentrations.

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

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

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

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

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

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

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose monohydrate
Pregelatinized starch
Microcrystalline cellulose (E 460)
Sodium starch glycolate
Colloidal silicon dioxide
Magnesium stearate
Opadry Pink contains Hypromellose (E 464), Titanium dioxide (E 171), Macrogol, Iron Oxide Red & Yellow (E 172) and polysorbate 80 (E 433).
Ink Composition: Opacode Black. OPACODE contains, Shellac Glaze in ethanol, Iron Oxide Black (E 172), Isopropyl Alcohol, N-butyl alcohol, Propylene glycol (E 1520) and Ammonium hydroxide (E 527).

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 25°C.
HDPE tablet containers: Keep container tightly closed.
Blisters: Store in the original package.

6.5 Nature and contents of container
PVC/PVdC/Al blisters
PVC/PVdC/Al blisters in aluminium pouch containing desiccant silica gel
OPA/Al/PE desiccant blister
Pack sizes: 10, 14, 20, 28, 30, 50, 56, 60, 84, 90, 98, 100, 120 and 200 tablets
HDPE tablet containers with PP child-resistant closures, containing silica gel desiccant and polyester filler.
Pack sizes: 60 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Lupin (Europe) Limited
Victoria Court
Bexton Road
Knutsford
Cheshire WA16 0PF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 35507/0075

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
05/07/2011

10 DATE OF REVISION OF THE TEXT
05/07/2011
UKPAR Topiramate 25 mg, 50 mg, 100 mg and 200 mg Tablets

PL 35507/0072-5

PACKAGE LEAFLET: INFORMATION FOR THE USER
Topiramate 25, 50, 100 and 200 mg 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 get serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

In this leaflet:
1. What Topiramate Tablets are and 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 Tablets belong to a group of medicines called 'antiepileptic medicines.' They are used:
- to treat seizures in adults and children over age 6
- with other medicines to treat seizures in adults and children over age 2
- to prevent migraine headaches in adults

2. BEFORE YOU TAKE TOPIRAMATE TABLETS

Do not take Topiramate Tablets:
- if you are allergic (hypersensitive) to topiramate or any of the other ingredients of Topiramate Tablets listed in section 6,
- if you have a history of kidney problems, or if you are getting kidney dialysis
- if you have a history of blood and body fluid abnormality (metabolic acidosis)
- if you have liver problems
- if you have eye problems, especially glaucoma
- if you have a history of any of the above apply to you, talk to your doctor or pharmacist before using Topiramate Tablets.

Take special care with Topiramate Tablets:
Check with your doctor or pharmacist before taking Topiramate Tablets if you:
- take diuretics, especially kidney stones, or are getting kidney dialysis
- have a history of kidney problems, or if you are getting kidney dialysis
- have a history of blood and body fluid abnormality (metabolic acidosis)
- have liver problems
- have had problems with your eyes, especially glaucoma
- have a history of any of the above apply to you, talk to your doctor or pharmacist before using Topiramate Tablets.

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

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

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

Especially, tell your doctor or pharmacist if you are taking:
- other medicines that affect your brain (bleeding or bleeding tendency, or muscle coordination or central nervous system depressant medicines such as some medicines to treat depression or anxiety),
- oral birth control pills. Topiramate Tablets may make your birth control pills less effective.

Tell your doctor if your menstrual period changes while you are taking birth control pills and Topiramate Tablets.

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

Other medicines you should discuss with your doctor or pharmacist include:
- other anti-epileptic medicines, including: carbamazepine, lamotrigine, oxcarbazepine, phenytoin, sodium valproate, levetiracetam, lacosamide, zonisamide, gabapentin, pregabalin, topiramate,
- other medicines may interact with Topiramate Tablets and make your medicine less effective.

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

3. HOW TO TAKE TOPIRAMATE TABLETS

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

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

4. POSSIBLE SIDE EFFECTS

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

3. HOW TO TAKE TOPIRAMATE TABLETS

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

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

If you take more Topiramate Tablets than you should:
- See a doctor right away. Take the medicine pack with you.
- You may feel dizzy, drowsy, or have abnormal body movements, problems standing and walking, feel dizzy due to low blood pressure, or have abnormal heart beats or fits.

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

- If you forget to take Topiramate Tablets:
- If you forget to take a dose, take it as soon as you remember it. However, if it is almost time for your next dose, skip the missed dose and continue as usual. If you miss two or more doses, contact your doctor.

- Do not take a double dose (two doses at the same time) to make up for a forgotten dose.

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

- If you have any further questions on the use of this product, ask your doctor or pharmacist.
UKPAR Topiramate 25 mg, 50 mg, 100 mg and 200 mg Tablets

Common side effects include:

- Changes in mood or behaviour, including anger, nervousness, sadness
- Weight loss
- Decrease or loss of appetite
- Reduced number of red blood cells
- Changes in thinking and alertness, including confusion, problems with concentration, memory or slowness in thinking
- Slurred speech
- Trembling, or problems with walking
- Involuntary shaking of the arms, hands or legs
- Reduced sense of touch or sensation
- Involuntary movement in the eyes
- Disturbed sense of taste
- Localised sensation, blurred vision, double vision
- Ringing sound in the ears
- Ear pain
- Shortness of breath
- Numbness
- Vomiting
- Constipation
- Stomach pain
- Indigestion
- Dry mouth
- Tingling or numbness of the mouth
- Kidney stones
- Fitting or convulsion
- Fatigue
- Pain
- Fatigue
- Redness and/or itchy skin
- Jittery
- Muscle spasms, muscle twitching or muscle weakness
- Chest pain
- Fever
- Loss of strength
- General feeling of feeling unwell

Uncommon side effects include:

- Crystals in the urine
- Abnormal blood counts, including reduced white blood cell count or platelet count, or increased eosinophils
- Irregular heartbeat or slowness of the heart beat
- Swollen glands in the neck, armpit or groin
- Increase in seizures
- Problems with verbal communication
- Dizziness
- Restlessness or increased mental or physical activity
- Loss of concentration
- Fainting
- Stiff or diminished movement
- Disturbed or poor quality sleep
- Improved or disturbed sense of smell
- Problems with handwriting
- Feeling of unreassurance under the skin
- Eye problems including dry eyes, light sensitivity, involuntary twitching, tearing and decreased vision

- Headache in the ears
- Inflammation of the pancreas
- Gas
- Heartburn
- Loss of sensitivity to touch in the mouth
- Blood clots
- Fainting or blacking
- Pain or burning sensations in the mouth
- Swollen arms
- Leakage of urine and/or stools
- Urge to urinate
- Pain in the kidney area and/or bladder caused by kidney stones
- Decrease or loss of sweating
- Skin discoloration
- Localised swelling in the skin
- Swelling of the face
- Swelling of the joints
- Muscle stiffness
- Increased acid levels in the blood
- Low potassium levels in the blood
- Increased appetite
- Increased thirst and drinking
- Inclination of large amounts of fluid
- Low blood pressure or decrease in blood pressure that occurs when you stand up
- Hot flushing
- Feeling of fatness
- Cold extremities (e.g. hands and face)
- Problems with hearing
- Disturbances in general function (medication dysfunction, loss of balance)
- Hallucinations
- Drowsiness
- Decreased verbal communication

Rare side effects include:

- Excessive skin sensitivity
- Increased sense of smell
- Glaucoma which causes a buildup of fluid in the eye causing increased pressure in the eye, pain and decreased vision
- Retail behaviour
- Stevens-Johnson syndrome, a rare skin condition which causes the upper layer of the skin separates from the lower, and erythema multiforme, a condition of raised red spots that can blister
- Stopt
- Swelling in the tissues around the eye
- Raynaud's syndrome. A disorder affecting the blood vessels, in the fingers, toes, ears and causing pain and cold sensitivity
- Tissue calcification (calcification)

Side effects of unknown frequency

- Maculopatity is a disease of the macula, the small spot in the retina where vision is sharpest. You should visit your doctor if you notice a change or decreased vision in your vision.
- Swelling of the conjunctiva of the eye.
- Torsor epidermal melanocytosis which is a severe form of Stevens-Johnson syndrome (see uncommon side effects).

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

5. HOW TO STORE TOPIRAMATE TABLETS

Keep out of the reach and sight of children.

Do not use Topiramate tablets after the expiry date which is on the label. This expiry date refers to the last day of that month.

Store below 25°C.

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

6. FURTHER INFORMATION

What Topiramate Tablets contain

The active substance is topiramate.

- Each Topiramate Tablet contains 25, 50, 100, 200 mg of topiramate.

The other ingredients are listed below:

- Lactose monohydrate, microcrystalline cellulose (E460), Avicel PH 101, pregelatinised starch, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, Opadry White, Yellow, Pink, (depending on the colour), contains Hypromellose (E464), Titanium dioxide (E171), Macrogol, Iron Oxide (E172) and polyethylene 80 (E450), and Opadex 3-1.613 MF Black, Opadex contains, Shellac Glaze 47.5 % (2 % Extender) in IMS 74 OP Iron Oxide Black JIE (E 172) Industrial methylated Spirit 74 OP, Lecithine (Goyen) NF (E 322) Andifam DC 1510 (Food grade).

What Topiramate Tablets look like and contents of the pack

Topiramate 25 mg Tablets: White to off white, circular, brown viscous film coated tablets, imprinted “25” (in black ink) on one side and plain on the other side.

Topiramate 50 mg Tablets: Light yellow, circular, brown viscous film coated tablets, imprinted “50” (in black ink) on one side and plain on the other side.

Topiramate 100 mg Tablets: Dark yellow, circular, brown viscous film coated tablets, imprinted “100” (in black ink) on one side and plain on the other side.

Topiramate 200 mg Tablets: Reddish pink, oval shaped, brown viscous film coated tablets, imprinted “200” on one side and plain on the other side.

Topiramate Tablets are packed in:

- Blister packs

Pack Sizes: 10, 14, 20, 28, 30, 50, 60, 80, 90, 100, 120, 200 tablets

- Bottle with child-resistant closure

Pack Sizes: 60 tablets

Net pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Lupin (Europe) Limited
Victoria Court
Bexley Road
Knutsford
Chester CH61 8PQ

Limited Kingdom.

Date of preparation: June 2010

This leaflet was last approved in
MODULE 4

Please note that representative labelling for Topiramate 25 mg Tablets (PL 35507/0072) is shown below. The labelling text details for Topiramate 50 mg, 100 mg and 200 mg Tablets (PL 35507/0073-5) are consistent with these labels, with the exception of the product licence numbers.

Cartons:
Bottle label:

each tablet contains 25 mg Topiramate.
Also contains lactose monohydrate (see leaflet for further information).
Read the package leaflet before use.
It contains important information about how and when you take your tablet.

For oral use.
Use as directed by your doctor.
Store below 25°C.
Keep container tightly closed.
Keep out of the reach and sight of children.

Topiramate 25 mg Tablets
Topiramate

PL 35507/0072
Lupin (Europe) Limited
Vicotora Court, Benson Road, Nutfield, Cheeks, WA10 1FF,
UNITED KINGDOM

Code No. GO/DRUGS/064
### Aluminium pouch labelling:

<table>
<thead>
<tr>
<th></th>
<th>Topiramate 25 mg Tablets</th>
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<tbody>
<tr>
<td><strong>Pack contains a desiccant-</strong></td>
<td><strong>DO NOT SWALLOW</strong></td>
</tr>
<tr>
<td><strong>POM</strong></td>
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<tr>
<td>PL 35507/0072</td>
<td></td>
</tr>
<tr>
<td><strong>Batch No.</strong></td>
<td></td>
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<tr>
<td><strong>Expiry Date</strong></td>
<td></td>
</tr>
<tr>
<td>Lupin (Europe) Ltd</td>
<td>XXXXXXX</td>
</tr>
</tbody>
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<td>XXXXXXX</td>
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</table>
Blister labels: