

**TOPIRAMATE 25 MG, 50 MG, 100 MG AND 200 MG FILM-COATED
TABLETS**

PL 08137/0243-0246

UKPAR

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TOPIRAMATE 25 MG, 50 MG, 100 MG AND 200 MG FILM-COATED TABLETS

PL 08137/0243-0246

LAY SUMMARY

The Medicines Healthcare products Regulatory Agency granted Neolab Limited Marketing Authorisations (licences) for the medicinal products Topiramate 25 mg, 50 mg, 100 mg and 200 mg Film Coated Tablets (PL 08137/0243-0246) on 12th August 2011. These prescription-only medicines (POM) belong to a group of medicines called “antiepileptic medicines”. They are used:

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

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 Film-Coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.

TOPIRAMATE 25 MG, 50 MG, 100 MG AND 200 MG FILM-COATED TABLETS

PL 08137/0243-0246

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted Marketing Authorisations for the medicinal products Topiramate 25 mg, 50 mg, 100 mg and 200 mg Film-Coated Tablets (PL 08137/0243-0246) to Neolab Limited on 12th August 2011. These products are prescription-only medicines.

These applications were submitted as abridged applications according to Article 10(1) of Directive 2001/83/EC. The products are claimed to be generic medicinal products of the reference products, Topamax® 25 mg, 50 mg 100 mg and 200 mg Tablets (PL 00242/0301-0304), licensed to Janssen-Cilag Ltd, UK on 18th July 1995. The reference products have been authorised in the EEA for over 10 years.

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

No new 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 Film Coated Tablets (Neolab Limited) versus the reference product Topimax® 200 mg Tablets (Janssen-Cilag Ltd, UK) 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.

PHARMACEUTICAL ASSESSMENT

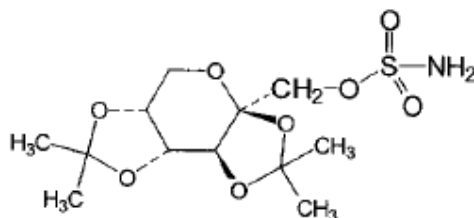
DRUG SUBSTANCE

Topiramate

INN/ BAN: Topiramate

Chemical name: 2,3:4,5-Bis-O-(1 methyl ethylidene)-β-D-fructopyranose-sulfamate

Structure



Molecular formula: C₁₂H₂₁NO₈S

Molecular weight: 339.37

General Properties

Description: White to off-white powder

Solubility: Freely soluble in dichloromethane

The active substance, topiramate, is the subject of a US Pharmacopoeia (USP) monograph.

Manufacture

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Appropriate data have been supplied to characterise the active substance. 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 specifications. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

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

Appropriate stability data have been generated to support a suitable re-test period when stored in the proposed packaging.

DRUG PRODUCT

Description and Composition

The product is presented as circular, biconvex film-coated tablets; each strength of tablet is coloured differently to help in identification (please refer to Section 3 of the SmPC for a full description of each tablet strength).

Other ingredients consist of pharmaceutical excipients, pre-gelatinised starch, lactose monohydrate, microcrystalline cellulose, sodium starch glycolate and magnesium stearate making up the tablet core; titanium dioxide, hypromellose, PEG 400, polysorbate 80, FD & C Blue #2/indigo carmine aluminium lake (25 mg strength only), iron oxide yellow and iron oxide red (50 mg and 100 mg strength only) and iron oxide red (200 mg strength only) making up the film-coating of the tablets. All ingredients within the tablet core comply with relevant Ph. Eur monographs; the ingredients within the film-coating comply with Ph.Eur, USP-NF or in-house specifications.

Appropriate justification for the inclusion of each excipient has been provided. Satisfactory Certificates of Analysis have been provided for all the excipients.

With the exception of lactose monohydrate and magnesium stearate none of the other excipients used contain material derived from animal or human origin. The applicant has provided a declaration that milk used in the production of lactose is sourced from healthy animals under the same conditions as that for human consumption and a valid TSE Certificate of Suitability for magnesium stearate has been presented confirming that there is no risk of TSE/BSE within this excipient. Furthermore, no genetically modified organisms are used in the manufacture of any of the excipients.

Pharmaceutical Development

The objective of the pharmaceutical development of this product was to develop bioequivalent and stable formulations comparable to the innovator's products Topamax® 25 mg, 50 mg, 100 mg and 200mg tablets. The applicant has provided suitable product development sections.

Comparative dissolution and impurity profiles were provided for test and reference products and were found to be similar.

Manufacture

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. The manufacturing process has been validated on pilot/production scale batches and has shown satisfactory results. In addition, a commitment is made to perform process validation on the first three commercial scale batches for all strengths.

Finished Product Specification

Finished product specifications are provided for both release and shelf-life, and are satisfactory. Acceptance limits have been justified with respect to conventional

pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The finished products are licensed for marketing in either polyvinylchloride/aluminium blister strips in pack sizes of 28, 56, 60 and 84 tablets or in opaque, high density polyethylene bottle packs with white, opaque, polypropylene, child-resistant closures in pack sizes of 60, 100 and 200 tablets; the blisters and bottles are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs; the cap comply with child resistant packaging legislation.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set. Storage conditions are 'This medicinal product does not require any special storage conditions' and 'Store in the original package'.

Bioequivalence Study

A bioequivalence study was presented comparing the test product, Topiramate 200 mg Film-Coated Tablets, to the reference product; Topamax® 200 mg tablets (Janssen-Cilag Ltd, UK).

An evaluation of the bioequivalence study is found in the Clinical Aspects section.

Expert Report

A satisfactory quality overall summary is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels

The SmPC, PIL and labelling are pharmaceutically acceptable. Colour mock-ups of the labelling and PIL have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test show that the patients/users are able to act upon the information that the leaflet contains.

MAA Forms

The MAA forms are pharmaceutically satisfactory.

Conclusion

There are no objections to approval of Topiramate 25 mg, 50 mg, 100 mg and 200 mg Film-Coated Tablets from a pharmaceutical point of view.

NON-CLINICAL ASSESSMENT

These abridged applications, submitted under Article 10(1) of Directive 2001/83/EC, as amended, are for Topiramate 25 mg, 50 mg, 100 mg and 200 mg Film-Coated Tablets claiming to be generic versions of the reference products Topamax® 25 mg, 50 mg, 100 mg and 200 mg tablets authorised to Janssen-Cilag, UK on the 18 July 1995.

No new non-clinical data have been supplied with these applications and none are required for applications of this type. A non-clinical overview has been written by a suitably qualified person and is satisfactory.

CLINICAL ASSESSMENT

BACKGROUND

Topiramate is well characterised in the literature. It is an antiepileptic (ATC code N03 AX11), registered for the treatment of epilepsy. Topiramate is indicated as an adjunctive therapy for partial onset seizures and/or generalised tonic clonic seizures. Topiramate is indicated as monotherapy in adults and children aged 12 and older with partial onset seizures and/or generalised tonic-clonic seizures. Topiramate is indicated as second line treatment for migraine prophylaxis in adults.

Topiramate displays linear kinetics (tested till 400 mg single dose), and is largely absorbed. There is no clinically significant effect of food on topiramate absorption. In humans, the major route of elimination of unchanged topiramate and its metabolites is via the kidney.

THERAPEUTIC INDICATIONS

Epilepsy

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

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

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

POSODOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPCs. The posology is identical to that for the reference product Topamax SmPC and is satisfactory.

TOXICOLOGY

The toxicology of topiramate is well-known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

Pharmacokinetics

The applications are supported by a bioequivalence study comparing the pharmacokinetic profile of the test product Topiramate 200 mg Tablets, to that of the reference product Topamax® 200 mg tablets (Janssen-Cilag Ltd) sourced from the UK market. The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis have been provided for both the test and reference products.

This was an open label, balanced, randomised, two-treatment, two-period, two-sequence single dose, crossover oral bioavailability study of conventional design in healthy

volunteers under fasting conditions. Following an overnight fast, a single dose of either the test or reference product was administered orally to each subject in each period. A washout period of at least 210 hours was maintained between the two dosing days in each group as topiramate has a long half life (approximately 21 hours); the washout period in this study was sufficient to ensure zero plasma levels at the beginning of the next period of dosing.

Blood samples were taken pre-dose and at specified time points up to 96 hours after administration of test or reference products. Plasma levels of topiramate were detected by a validated LC MS/MS analytical method.

The primary pharmacokinetic parameters for this study were C_{max} , AUC_{0-t} and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference products was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-125 for log-transformed C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ ratios.

Results

A summary of the results of the bioequivalence study is tabulated below:

Pharmacokinetic results for topiramate for an open label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, crossover oral bioavailability study between the 200 mg strength test and reference products.

Parameters	Least square mean		T/R	90 % Confidence Interval for ln-transformed data
	Test (T)	Reference (R)		
C_{max} (µg/mL)	4.804	4.764	100.84	93.43 – 108.84
AUC_{0-t} (h.µg/mL)	157.28	155.64	101.05	94.51 – 108.05
$AUC_{0 \rightarrow \infty}$ (h.µg/mL)	174.72	172.98	101.00	94.22 – 108.27

C_{max}	maximum plasma concentration
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity

Conclusion on Bioequivalence

The results of the bioequivalence study show that the test and the reference products are bioequivalent, under fasting conditions, as the 90% confidence intervals for C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ ratios for topiramate, fall within the acceptance criteria ranges of 80-125% in line with the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98).

Satisfactory justification is provided for a bio-waiver for Topiramate 25 mg, 50 mg and 100 mg Film-Coated Tablets. As Topiramate 25 mg, 50 mg, 100 mg and 200 mg Film-Coated Tablets 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 of the bioequivalence study on the 200 mg strength can be extrapolated to the 25 mg, 50 mg and 100 mg strength tablets.

EFFICACY

No new data have been submitted and none are required. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of topiramate is well-established from its extensive use in clinical practice.

SAFETY

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of topiramate is well-known.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The approved SmPCs are consistent with those for the reference products and are acceptable.

Patient Information Leaflet (PIL)

The PIL is in line with the approved SmPCs and is satisfactory.

Labelling

The labelling is satisfactory.

Clinical Overview

A satisfactory clinical overview was provided and prepared by an appropriately qualified expert. The CV of the clinical expert was supplied.

CONCLUSIONS

Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was therefore recommended.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Topiramate 25 mg, 50 mg, 100 mg and 200 mg Film Coated 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 and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Topiramate 200 mg Film Coated Tablets and Topamax 200 mg Tablets (Janssen-Cilag Ltd, UK). Given that linear kinetics apply over the therapeutic dose range, that proportional formulae for the tablets have been used and that similar dissolution results have been shown for the all strengths, separate bioequivalence studies using the 25 mg, 50 mg and 100 mg tablets are not considered necessary.

No new or unexpected safety concerns arise from these applications.

The SmPC, PIL and labelling are satisfactory and consistent with those for the innovator product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with topiramate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

**TOPIRAMATE 25 MG, 50 MG, 100 MG AND 200 MG FILM-COATED
TABLETS**

PL 08137/0243-0246

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 19 th March 2009.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 20 th March 2009.
3	Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 21 st August 2009.
4	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 8 th September 2010.
5	The application was determined on 12 th August 2011.

**TOPIRAMATE 25 MG, 50 MG, 100 MG AND 200 MG FILM-COATED
TABLETS**

PL 08137/0243-0246

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

TOPIRAMATE 25 MG, 50 MG, 100 MG AND 200 MG FILM-COATED TABLETS

PL 08137/0243-0246

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Topiramate 25 mg Film-coated Tablets
Topiramate 50 mg Film-coated Tablets
Topiramate 100 mg Film-coated Tablets
Topiramate 200 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

For PL 08137/0243- Topiramate 25 mg Film-coated Tablets

Each film-coated tablet contains 25 mg of topiramate.
Each film-coated tablet contains 24.8 mg of lactose monohydrate.

For PL 08137/0244- Topiramate 50 mg Film-coated Tablets

Each film-coated tablet contains 50 mg of topiramate.
Each film-coated tablet contains 49.5 mg of lactose monohydrate.

For PL 08137/0245- Topiramate 100 mg Film-coated Tablets

Each film-coated tablet contains 100 mg of topiramate.
Each film-coated tablet contains 99 mg of lactose monohydrate.

For PL 08137/0246- Topiramate 200 mg Film-coated Tablets

Each film-coated tablet contains 200 mg of topiramate.
Each film-coated tablet contains 198 mg of lactose monohydrate.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Epilepsy

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

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

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

4.2 Posology and method of administration

General

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

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

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

Topiramate Tablets can be taken without regard to meals.

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

Monotherapy Epilepsy

General

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

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

Adults

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

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

Paediatric population (children over 6 years of age)

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

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

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

Adults

Therapy should begin at 25-50 mg nightly for one week. Use of lower initial doses has been reported, but has not been studied systematically. Subsequently, at weekly or bi-weekly intervals,

the dose should be increased by 25-50 mg/day and taken in two divided doses. Some patients may achieve efficacy with once-a-day dosing.

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

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

Paediatric population (children aged 2 years and above)

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

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

Migraine

Adults

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

Paediatric population

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

General dosing recommendations for Topiramate Tablets in special patient populations

Renal impairment

In patients with impaired renal function ($CL_{CR} \leq 60\text{mL/min}$) 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 child bearing potential if not using effective methods of contraception.

4.4 **Special warnings and precautions for use**

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

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

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

Mood disturbances/depression

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

Suicide/suicide ideation

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

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

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

Nephrolithiasis

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

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

Decreased hepatic function

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

Acute myopia and secondary angle closure glaucoma

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

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

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

Metabolic Acidosis

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

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

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

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

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

Nutritional supplementation

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

Lactose intolerance

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

4.5 Interaction with other medicinal products and other forms of interaction

Effects of Topiramate Tablets on other antiepileptic drugs

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

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

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

Effects of other antiepileptic medicinal products on Topiramate Tablets

Phenytoin and carbamazepine decrease the plasma concentration of topiramate. The addition or withdrawal of phenytoin or carbamazepine to topiramate therapy may require an adjustment in dosage of the latter. This should be done by titrating to clinical effect.

The addition or withdrawal of valproic acid does not produce clinically significant changes in plasma concentrations of topiramate and, therefore, does not warrant dosage adjustment of topiramate. The results of these interactions are summarised in the following table:

AED Coadministered	AED Concentration	Topiramate 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. The clinical relevance of this observation has not been established. When topiramate is added or withdrawn in patients on digoxin therapy, careful attention should be given to the routine monitoring of serum digoxin.

CNS Depressants

Concomitant administration of topiramate and alcohol or other CNS depressant medicinal products has not been evaluated in clinical studies. It is recommended that topiramate not be used concomitantly with alcohol or other CNS depressant medicinal products.

St John's Wort (Hypericum perforatum)

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

Oral Contraceptives

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

Lithium

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

Risperidone

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

Hydrochlorothiazide (HCTZ)

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg q24h) and topiramate (96 mg q12h) when administered alone and concomitantly. The results of this study indicate that topiramate C_{max} increased by 27% and AUC increased by 29% when HCTZ was added to topiramate. The clinical significance of this change is unknown. The addition of HCTZ to topiramate therapy may require an adjustment of the topiramate dose. The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicated decreases in serum potassium after topiramate or HCTZ administration, which were greater when HCTZ and topiramate were administered in combination.

Metformin

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin and topiramate in plasma when metformin was given alone and when metformin and topiramate were given simultaneously. The results of this study indicated that metformin mean C_{max} and mean AUC_{0-12h} increased by 18% and 25%, respectively, while mean CL/F decreased 20% when metformin was co-administered with topiramate. Topiramate did not affect metformin t_{max} . The clinical significance of the effect of topiramate on metformin pharmacokinetics is unclear. Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The extent of change in the clearance is unknown. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear.

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

Pioglitazone

A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of topiramate and pioglitazone when administered alone and concomitantly. A 15% decrease in the $AUC_{\tau,ss}$ of pioglitazone with no alteration in $C_{max,ss}$ was observed. This finding was not statistically significant. In addition, a 13% and 16% decrease in $C_{max,ss}$ and $AUC_{\tau,ss}$ respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in $C_{max,ss}$ and $AUC_{\tau,ss}$ of the active keto-metabolite. The clinical significance of these findings is not known. When topiramate is added to pioglitazone therapy or pioglitazone is added to topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Glyburide

A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glyburide (5 mg/day) alone and concomitantly with topiramate (150 mg/day). There was a 25% reduction in glyburide 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, when used concomitantly with other agents predisposing to nephrolithiasis, may increase the risk of nephrolithiasis. While using topiramate, agents like these should be avoided since they may create a physiological environment that increases the risk of renal stone formation.

Valproic Acid

Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either medicinal product alone. In most cases, symptoms and signs abated with discontinuation of either medicinal product. This adverse event is not due to a pharmacokinetic interaction. An association of hyperammonemia with topiramate monotherapy or concomitant treatment with other anti-epileptics has not been established.

Additional pharmacokinetic drug interaction studies

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

Summary of Results from Additional Clinical Pharmacokinetic Drug Interaction Studies

Concomitant Drug	Concomitant Drug Concentration^a	Topiramate Concentration^a
Amitriptyline	↔ 20% increase in C _{max} and AUC of nortriptyline metabolite	NS
Dihydroergotamine (Oral and Subcutaneous)	↔	↔
Haloperidol	↔ 31% increase in AUC of the reduced metabolite	NS
Propranolol	↔ 17% increase in C _{max} for 4-OH propranolol (TPM 50 mg q12h)	9% and 16% increase in C _{max} , 9% and 17% increase in AUC (40 and 80 mg propranolol q12h respectively)
Sumatriptan (Oral and Subcutaneous)	↔	NS
Pizotifen	↔	↔
Diltazem	25% decrease in AUC of diltiazem and 18% decrease in	20% increase in AUC

	DEA, and ↔ for DEM*	
Venlafaxine	↔	↔
Flunarizine	16% increase in AUC (TPM 50 mg q12h) ^b	↔

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

↔ = No effect on C_{max} and AUC (≤15% change) of the parent compound

NS = Not studied

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

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

4.6 Pregnancy and lactation

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

There are no adequate and well-controlled studies using topiramate in pregnant women.

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

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

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

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

Indication Epilepsy

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

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 is established.

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

4.8 Undesirable effects

The safety of topiramate was evaluated from a clinical trial database consisting of 4,111 patients (3,182 on topiramate and 929 on placebo) who participated in 20 double-blind trials and 2,847 patients who participated in 34 open-label trials, respectively, for topiramate as adjunctive treatment of primary generalized tonic-clonic seizures, partial onset seizures, seizures associated with Lennox-Gastaut syndrome, monotherapy for newly or recently diagnosed epilepsy or migraine prophylaxis.

The majority of ADRs were mild to moderate in severity. ADRs identified in clinical trials, and during post-marketing experience (as indicated by“*”) are listed by their incidence in clinical trials in Table 1. Assigned frequencies are as follows:

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

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

Paediatric population

ADRs reported more frequently (≥ 2-fold) in children than in adults in double-blind controlled studies include: decreased appetite, increased appetite, acidosis hyperchloreaemic, 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

System Organ Class	Very common	Common	Uncommon	Rare	Not known
Investigations	Weight decreased	Weight increased*	Crystal urine present, Tandem gait test abnormal, White blood cell count decreased	Blood bicarbonate decreased	
Cardiac disorders			Bradycardia, Sinus bradycardia, Palpitations		
Blood and lymphatic system disorders		Anaemia	Leucopenia, Thrombocytopenia, Lymphadenopathy, Eosinophilia	Neutropenia*	
Nervous system disorders	Paraesthesia, Somnolence, Dizziness	Disturbance in attention, Memory impairment, Amnesia, Cognitive disorder, Mental impairment, Psychomotor skills impaired, Convulsion, Coordination abnormal, Tremor, Lethargy,	Depressed level of consciousness, Grand mal convulsion, Visual field defect, Complex partial seizures, Speech disorder, Psychomotor hyperactivity, Syncope, Sensory disturbance, Drooling, Hypersomnia, Aphasia, Repetitive speech, Hypokinesia,	Apraxia, Circadian rhythm sleep disorder, Hyperaesthesia, Hyposmia, Anosmia, Essential tremor, Akinesia, Unresponsive to stimuli	

		Hypoaesthesia, Nystagmus, Dysgeusia, Balance disorder, Dysarthria, Intention tremor, Sedation	Dyskinesia, Dizziness postural, Poor quality sleep, Burning sensation, Sensory loss, Parosmia, Cerebellar syndrome, Dysaesthesia, Hypogeusia, Stupor, Clumsiness, Aura, Ageusia, Dysgraphia, Dysphasia, Neuropathy peripheral, Presyncope, Dystonia formication		
Eye disorders		Vision blurred, Diplopia, Visual disturbance	Visual acuity reduced, Scotoma, Myopia*, Abnormal sensation in eye*, Dry eye, Photophobia, Blepharospasm, Lacrimation increased, Photopsia, Mydriasis, Presbyopia	Blindness unilateral, Blindness transient, Glaucoma, Accommodation disorder, Altered visual depth perception, Scintillating scotoma, Eyelid oedema*, Night blindness, Amblyopia	Angle closure glaucoma*, Maculopathy*, Eye movement disorder*
Ear and Labyrinth disorders		Vertigo, Tinnitus, Ear pain	Deafness, Deafness unilateral, Deafness neurosensory, Ear discomfort, Hearing impaired		
Respiratory thoracic and mediastinal disorders		Dyspnoea, Epistaxis, Nasal congestion, Rhinorrhoea	Dyspnoea exertional, Paranasal sinus, Hypersecretion, Dysphonia		
Gastrointestinal disorders	Nausea, Diarrhoea	Vomiting, Constipation, Abdominal pain upper, Dyspepsia, Abdominal pain, Dry mouth, Stomach discomfort, Paraesthesia oral, Gastritis, Abdominal discomfort	Pancreatitis, Flatulence, Gastrooesophageal reflux disease, Abdominal pain lower, Hypoaesthesia oral, Gingival bleeding, Abdominal distention, Epigastric discomfort, Abdominal tenderness, Salivary hypersecretion, Oral pain, Breath odour, Glossodynia		
Renal and urinary		Nephrolithiasis, Pollakiuria,	Calculus urinary, Urinary incontinence,	Calculus ureteric, Renal tubular	

disorders		Dysuria	Haematuria, Incontinence, Micturition urgency, Renal colic, Renal pain	acidosis*	
Skin and subcutaneous tissue disorders		Alopecia, Rash, Pruritus	Anhidrosis, Hypoaesthesia facial, Urticaria, Erythema, Pruritus generalised, Rash macular, Skin discolouration, Dermatitis allergic, Swelling face	Stevens-Johnson syndrome*, Erythema multiforme*, Skin odour abnormal, Periorbital oedema*, Urticaria localised	Toxic epidermal necrolysis*
Musculoskeletal and connective tissue disorders		Arthralgia, Muscle spasms, Myalgia, Muscle twitching, Muscular weakness, Musculoskeletal chest pain	Joint swelling*, Musculoskeletal stiffness, Flank pain, Muscle fatigue	Limb discomfort*	
Metabolism and nutrition disorders		Anorexia, Decreased appetite	Metabolic acidosis, Hypokalaemia, Increased appetite, Polydipsia	Acidosis hyperchloraemic	
Infections and infestations	Nasopharyngitis*				
Vascular disorders			Hypotension, Orthostatic hypotension, Flushing, Hot flush	Raynaud's phenomenon	
General disorders and administration site conditions	Fatigue	Pyrexia, Asthenia, Irritability, Gait disturbance, Feeling abnormal, Malaise	Hyperthermia, Thirst, Influenza like illness*, Sluggishness, Peripheral coldness, Feeling drunk, Feeling jittery	Face oedema, Calcinosis	
Social circumstances			Learning disability		
Immune system disorders		Hypersensitivity			Allergic oedema*, Conjunctival oedema*
Reproductive system and breast disorders			Erectile dysfunction, Sexual dysfunction		
Psychiatric disorders	Depression	Bradyphrenia, Insomnia, Expressive language disorder, Anxiety, Confusional state, Disorientation, Aggression, Mood altered, Agitation, Mood swings,	Suicidal ideation, Suicide attempt, Hallucination, Psychotic disorder, Hallucination auditory, Hallucination visual, Apathy Lack of spontaneous speech, Sleep disorder, Affect lability,	Mania, Anorgasmia, Panic disorder, Disturbance in sexual arousal, Feeling of despair*, Orgasm abnormal, Hypomania, Orgasmic sensation decreased.	

		Depressed mood, Anger, Abnormal behaviour	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, Distractability, Early morning awakening, Panic reaction, Elevated mood		
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* identified as an ADR from postmarketing spontaneous reports. Its frequency was calculated based on clinical trial data.

4.9 Overdose

Signs and Symptoms

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

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

Treatment

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Action potentials elicited repetitively by a sustained depolarization of the neurons were blocked by topiramate in a time-dependent manner, suggestive of a state-dependent sodium channel blocking action. Topiramate increased the frequency at which γ -aminobutyrate (GABA) activated GABA_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.

The effect was not blocked by flumazenil, a benzodiazepine antagonist, nor did topiramate increase the duration of the channel open time, differentiating topiramate from barbiturates that modulate GABA_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 μ M to 200 μ M, with minimum activity observed at 1 μ M to 10 μ 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 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 μ g/ml was achieved within 2 to 3 hours (T_{max}).

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

Distribution

Generally 13-17% of topiramate is bound to plasma proteins. A low capacity binding site for topiramate in/on erythrocytes that is saturable above plasma concentrations of 4 μ 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 metabolised (~20%) in healthy volunteers. It is metabolised up to 50% in patients receiving concomitant antiepileptic therapy with known inducers of drug metabolising enzymes. Six metabolites, formed through hydroxylation, hydrolysis and glucuronidation, have been isolated, characterised and identified from plasma, urine and faeces of humans. Each metabolite represents less than 3% of the total radioactivity excreted following administration of ¹⁴C-topiramate. Two metabolites, which retained most of the structure of topiramate, were tested and found to have little or no anticonvulsant activity.

Elimination

In humans, the major route of elimination of unchanged topiramate and its metabolites is via the kidney (at least 81% of the dose). Approximately 66% of a dose of ^{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_{max} following multiple, twice a day oral doses of 100 mg to healthy subjects was 6.76 $\mu\text{g/ml}$. 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 shorter elimination half-life. Consequently, the plasma concentrations of topiramate for the same mg/kg dose may be lower in children compared to adults. As in adults, hepatic enzyme inducing anti-epileptic drugs decrease the steady-state plasma concentrations.

5.3 Preclinical safety data

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

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

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

The teratogenic effects seen in rats and rabbits were similar to those seen with carbonic anhydrase inhibitors, which have not been associated with malformations in humans. Effects on growth were

also indicated by lower weights at birth and during lactation for pups from female rats treated with 20 or 100 mg/kg/day during gestation and lactation. In rats, topiramate crosses the placental barrier.

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Pre-gelatinised Starch (PA 5PH)

Lactose monohydrate

Microcrystalline cellulose (Avicel PH 101)

Sodium starch glycolate (Type A)

Magnesium stearate

Film-coating (for PL 08137/0243)

Opadry White containing:

Titanium dioxide

Hypromellose

PEG 400

Polysorbate 80

FD & Blue #2/ Indigo Carmine Aluminum Lake

Film-coating (PL 08137/0244-5)

Opadry Beige containing:

Titanium dioxide

Hypromellose

PEG 400

Polysorbate 80

Iron oxide yellow

Iron oxide red

Film-coating (PL 08137/0246)

Opadry Pink containing:

Titanium dioxide

Hypromellose

PEG 400

Polysorbate 80

Iron oxide red

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

Store in the original package.

6.5 Nature and contents of container

Blisters:

Packed in push-through blister strips composed of 3-ply alu-alu laminated film and 25 micron plain aluminium foil (heat sealable against PVC with VMCH coating).
Pack sizes of 28, 56, 60 & 84 tablets.

Bottles:

Bottle packs of the following composition: Opaque, high density polyethylene bottles.
White, opaque, polypropylene, child-resistant closures and a desiccant.
Pack sizes of 60, 100 & 200 tablets.
(Not all pack sizes will be marketed).

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Neolab Limited
57 High Street
Odiham
Hants
RG29 1LF
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 08137/0243

PL 08137/0244

PL 08137/0245

PL 08137/0246

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/08/2011

10 DATE OF REVISION OF THE TEXT

12/08/2011

PATIENT INFORMATION LEAFLET

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4. POSSIBLE SIDE EFFECTS

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

Very common side effects (affects more than 1 user in 10):

- weight loss
- tingling in the arms and legs
- drowsiness or sleepiness; tiredness; dizziness
- diarrhoea; nausea (feeling sick)
- stuffy, runny nose and sore throat
- depression

Common side effects (affects 1 to 10 users in 100):

- changes in mood or behaviour, including anger, nervousness, sadness
- weight gain; decrease or loss of appetite
- reduced number of red blood cells
- changes in thinking and alertness, including confusion, problems with concentration, memory or slowness in thinking; slurred speech
- clumsiness, or problems with walking; involuntary shaking in the arms, hands or legs
- reduced sense of touch or sensation
- involuntary movement of the eyes; visual disturbances, blurred vision, double vision
- distorted sense of taste
- ringing sound in the ears; ear pain
- shortness of breath
- nose bleeds
- vomiting (being sick); constipation; stomach pain; indigestion
- dry mouth; tingling or numbness of the mouth
- kidney stones; frequent urination; painful urination
- hair loss
- skin rash or itchy skin
- joint pain; muscle spasms, muscle twitching or muscle weakness
- chest pain
- fever
- loss of strength
- general feeling of feeling unwell
- allergic reaction

Uncommon side effects (affects 1 to 10 users in 1,000):

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

- hot flushing; flu like illness; cold extremities (e.g. hands and face)
- problems with learning
- disturbances in sexual function (erectile dysfunction, loss of libido)
- hallucinations
- decreased verbal communication

Rare side effects (affects 1 to 10 users in 10,000):

- excessive skin sensitivity
- impaired sense of smell
- **glaucoma which is a blockage of fluid in the eye causing increased pressure in the eye, pain and decreased vision**
- renal tubular acidosis
- severe skin reaction, including Stevens-Johnson syndrome, a life threatening skin condition in which the upper layer of the skin separates from the lower, and erythema multiforma, a condition of raised red spots that can blister
- odour
- 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 (calcinosis)

Side effects of unknown frequency:

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

If any of these side effects gets 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 take this medicine after the expiry date (Exp.) stated. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Store in the original package.

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

6. FURTHER INFORMATION

What Topiramate Tablets contain:

The active ingredient is topiramate.

Tablet core:

The ingredients are lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate and magnesium stearate.

Film-coating:

Topiramate 25 mg Tablets are coated with OPADRY® White, the ingredients of which are titanium dioxide, hypromellose, polysorbate 80 and indigo carmine aluminium lake (E132).

Topiramate 50 & 100 mg Tablets are coated with OPADRY® Beige YS-1-171174-A, the ingredients of which are titanium dioxide, hypromellose, polysorbate 80, iron oxide yellow (E172) and iron oxide red (E172).

Topiramate 200 mg Tablets are coated with OPADRY® Pink YS-1-14778A, the ingredients of which are titanium dioxide, hypromellose, polysorbate 80 and iron oxide red (E172).

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

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

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

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

Topiramate 200 mg: pink coloured, biconvex, caplet-shaped film-coated tablets.

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

Marketing Authorisation Holder and Manufacturer:
Neolab Limited, 57 High Street, Odiham, Hants, RG29 1LF

This leaflet was last approved in March 2011.

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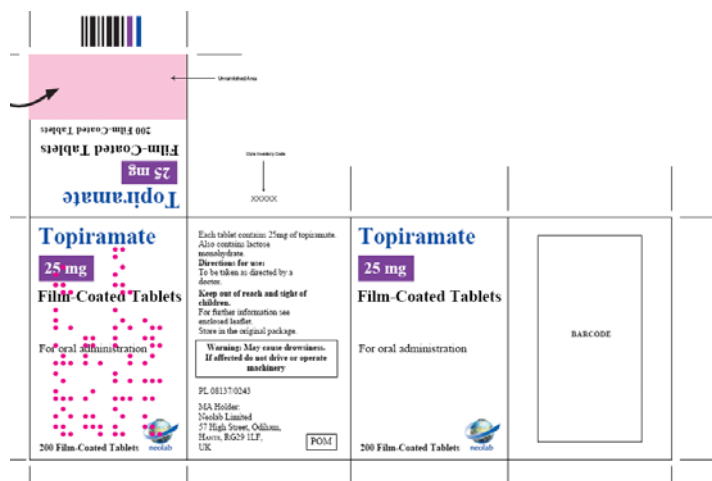
TOPIRAMATE 25 MG, 50 MG, 100 MG AND 200 MG FILM-COATED TABLETS

PL 08137/0243-0246

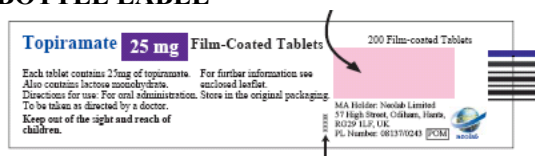
LABELLING

PLEASE NOTE: Other labels for this strength are identical apart from the number of tablets.

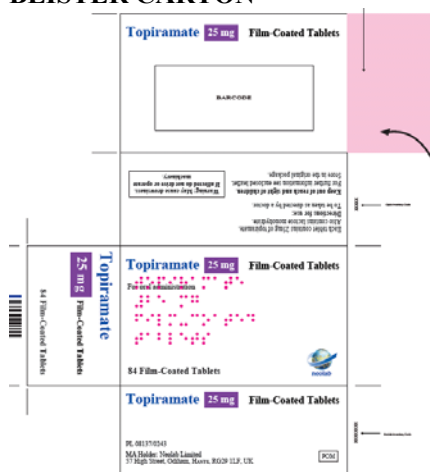
BOTTLE CARTON



BOTTLE LABEL



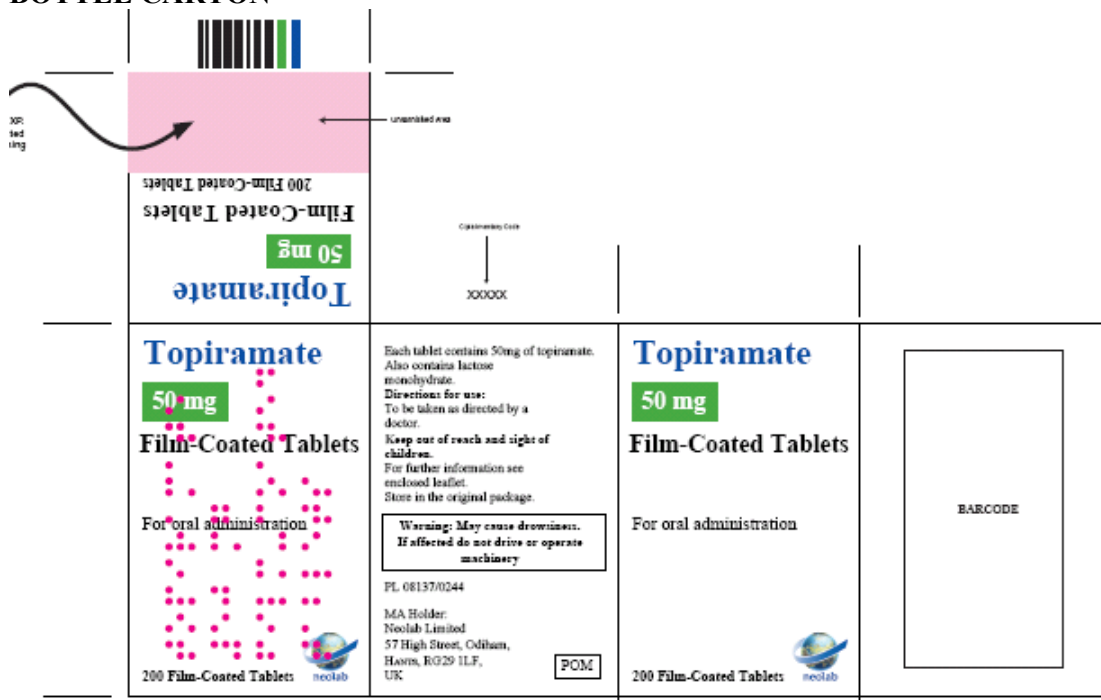
BLISTER CARTON



BLISTER FOIL



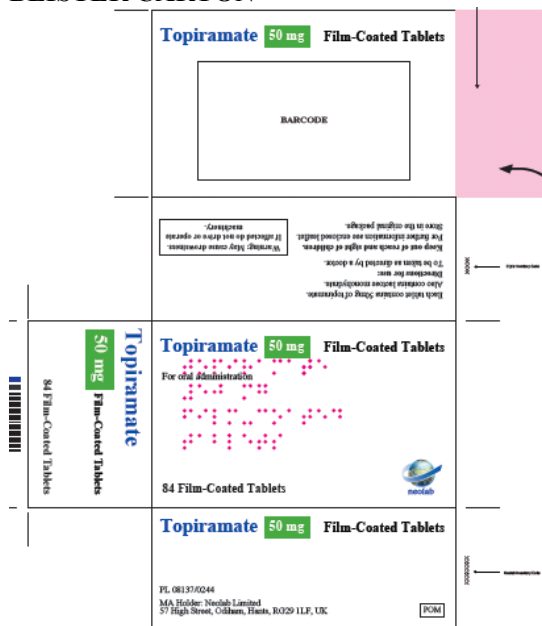
BOTTLE CARTON



BOTTLE LABEL



BLISTER CARTON



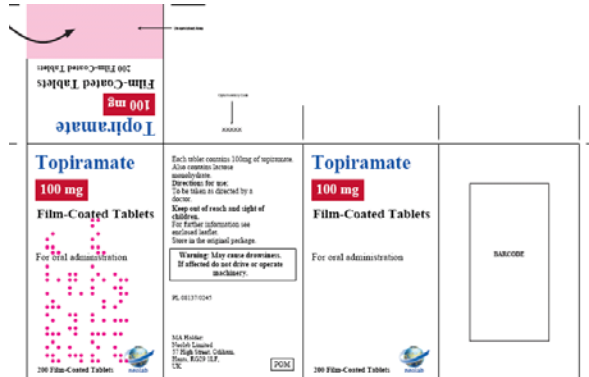
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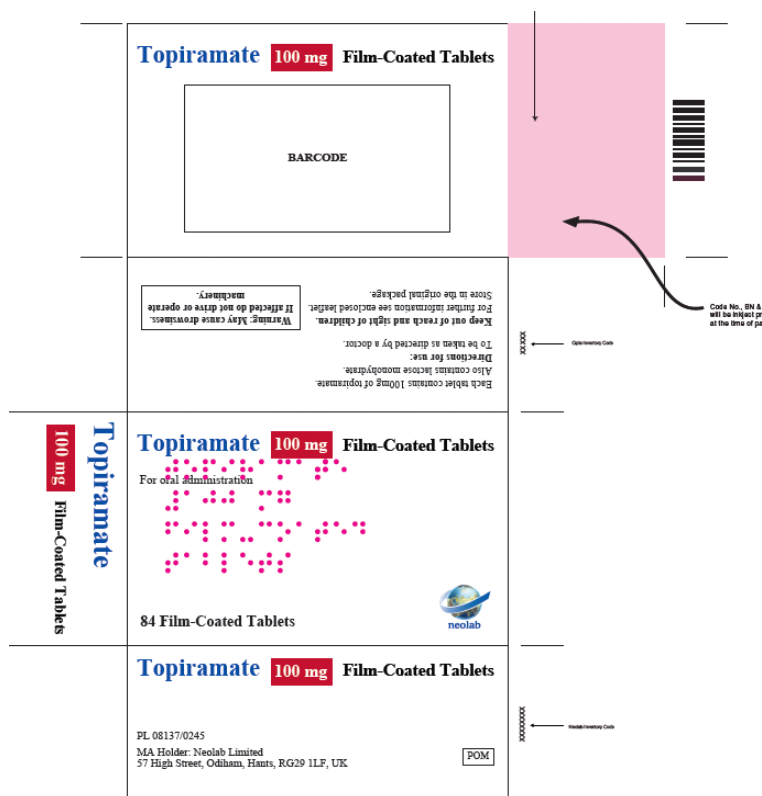
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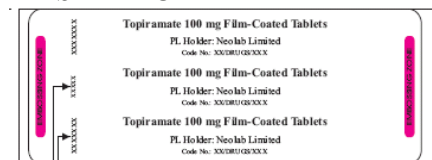
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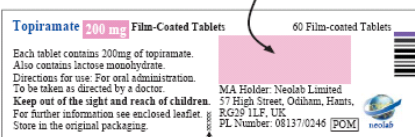
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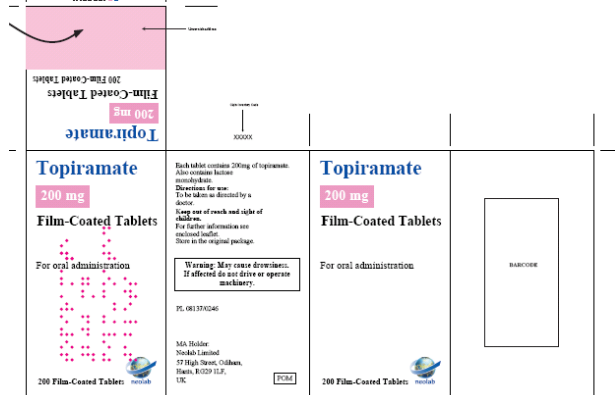
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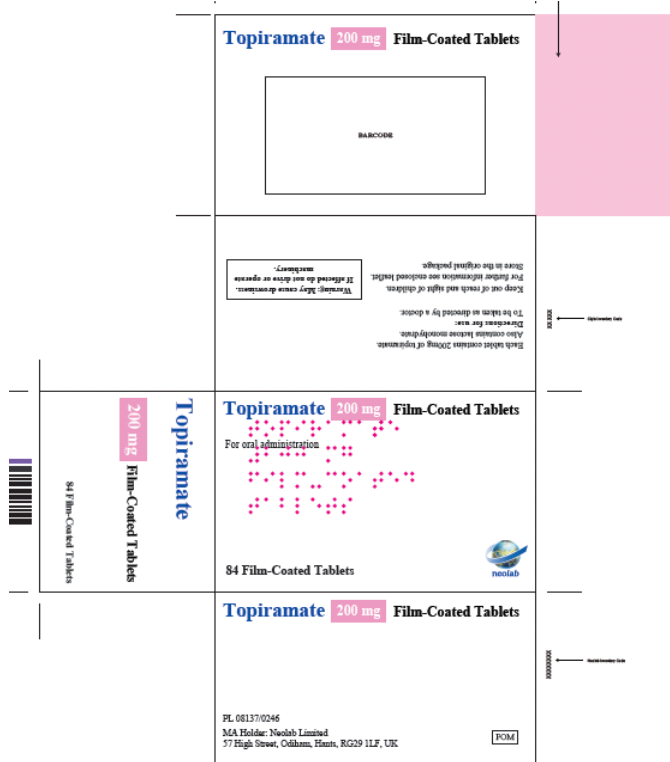
BOTTLE LABEL



BOTTLE CARTON



BLISTER CARTON



BLISTER FOIL

