Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

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

(topiramate)

UK/H/1438/001-004/DC
UK licence numbers: PL 20075/0145-0148

Accord Healthcare Limited

LAY SUMMARY

On 20th October 2009, the MHRA granted Accord Healthcare Limited Marketing Authorisations (licences) for the medicinal products Topiramate 25mg, 50mg, 100mg, and 200mg film-coated tablets (PL 20075/0145-0148). These are prescription-only medicines (POM).

Topiramate belongs to a group of medicines called "antiepileptic medicines." It is used:

- alone to treat seizures in adults and children over age 6
- with other medicines to treat seizures in adults and children over age 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 25mg, 50mg, 100mg, and 200mg film-coated tablets outweigh the risks; hence Marketing Authorisations have been granted.

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Module 1

Information about Initial Procedure

Product Name	Topiramate 25mg film-coated tablets Topiramate 50mg film-coated tablets Topiramate 100mg film-coated tablets Topiramate 200mg film-coated tablets
Type of Application	Generic, Article 10.1
Active Substance	Topiramate
Form	Film-coated tablets
Strength	25mg, 50mg, 100mg, and 200mg
MA Holder	Accord Healthcare Limited Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF, United Kingdom
Reference Member State (RMS)	UK
Concerned Member State / s (CMS)	BG, DE, ES, IT, LT, NL, PL, and PT
Procedure Number	UK/H/1438/001-004/DC
Timetable	Day 210 – 20th September 2009

Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Topiramate 25mg, 50mg, 100mg, and 200mg film-coated tablets (PL 20075/0145-0148) is as follows – Differences are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

Topiramate 25 mg film-coated tablets
Topiramate 50 mg film-coated tablets
Topiramate 100 mg film-coated tablets
Topiramate 200 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 25 / 50 / 100 / 200 mg topiramate

Excipients:

25 mg: Each film-coated tablet contains 28.405 mg of lactose.
50mg: Each film-coated tablet contains 56.810 mg of lactose.
100mg: Each film-coated tablet contains 113.62 mg of lactose.
200mg: Each film-coated tablet contains 227.24 mg of lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Round, biconvex film-coated tablets with bevelled edges.

25 mg: The white tablets are embossed TP on one side and 25 on the other side.
50mg: The light yellow tablets are embossed TP on one side and 50 on the other side.
100mg: The dark yellow tablets are embossed TP on one side and 100 on the other side.
200mg: The red tablets are embossed TP on one side and 200 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 gradual titration to an effective dose. Dose and titration rate should be guided by clinical response.

Topiramate film-coated tablet is available in film-coated tablets formulation. It is recommended that film-coated tablets not be broken.

It is not necessary to monitor topiramate plasma concentrations to optimize therapy with Topiramate film-coated tablet. 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 film-coated tablet may require adjustment of the dose of Topiramate film-coated tablet.

Topiramate film-coated tablet 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 film-coated tablet (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 film-coated tablet (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 film-coated tablet (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 film-coated tablet 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 film-coated tablet 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 topiramate or to any of the excipients.

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

4.4 Special warnings and precautions for use

In situations where rapid withdrawal of topiramate is medically required, appropriate monitoring is recommended (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
There is an increased risk of renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain, especially in patients with a predisposition to nephrolithiasis.

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 syndrome
Secondary angle-closure glaucoma with acute myopia has been reported in patients receiving topiramate (see also section 4.8). 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 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 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 in early treatment although it can occur at any time during treatment. This decrease 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 enhances 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.

Weight loss
Loss of weight or absence of weight gain has been observed in clinical trials with topiramate in growing children. It is recommended that their weight is monitored whilst undergoing treatment with topiramate. In patients with weight loss during therapy supplemental nutrition should be considered.

Excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

The container contains desiccant that must not be swallowed.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of topiramate on other antiepileptic medicinal product

The addition of topiramate to other antiepileptic drug (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no effect on their steady-state plasma concentrations, except in the occasional patients, 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 product on topiramate

Phenytoin and carbamazepine decrease the plasma concentration of topiramate. The addition or withdrawal of phenytoin or carbamazepine to topiramate therapy may require an adjustment in dosage of the latter. This should be done by titrating to clinical effect. The addition or withdrawal of valproic acid does not produce clinically significant changes in plasma concentrations of topiramate and, therefore, does not warrant dosage adjustment of topiramate. The results of these interactions are summarized below:

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 interactions with medicinal products

Digoxin
The AUC for a single digoxin dose decreases by 12% due to concomitant administration of topiramate. When patients are simultaneously treated with digoxin and topiramate, serum digoxin should be carefully monitored. Serum digoxin should also be carefully monitored after discontinuation of topiramate.

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 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 was 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
An interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin 500 mg twice daily and topiramate 100 mg twice daily in plasma when metformin and topiramate were given simultaneously. The results of this study indicated that metformin mean Cmax and mean AUC_{0-12h} increased by 18% and 25%, respectively, while mean CL/F decreased by 20% when metformin was co-administered with topiramate. The clinical significance of the effect of topiramate on metformin pharmacokinetics is unclear. The oral plasma clearance of topiramate appears to be reduced when administered with metformin. The extent of the change in 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 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 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 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 Cmax 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 Cmax for 4-OH propranolol (TPM 50 mg q12h)	9% and 16% increase in Cmax, 9% and17% increase in AUC (40 and 80 mg propranolol q12h respectively)
Sumatriptan (Oral and Subcutaneous)	↔	NS
Pizotifen	↔	↔
Diltiazem	25% decrease in AUC of diltiazem and 18% decrease in DEA, and ↔for DEM*	20% increase in AUC
Venlafaxine	↔	↔
Flunarizine	16% increase in AUC (TPM 50 mg q12h)[b]	↔

[a] % values are the changes in treatment mean C_{max} or AUC with respect to monotherapy
↔= No effect on 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

Pregnancy

An increased frequency of malformations (distal extremity and cranio-facial malformations, heart failure) has been observed subsequent to use of certain antiepileptic agents during the first trimester of pregnancy.

Combination treatment appears to increase the risk of malformation and therefore it is important that monotheraphy is practised whenever possible.

Topiramate has been shown to have teratogenic effects in the species studied (mice, rats and rabbits). In rats, topiramate crosses the placental barrier.

Specialist advice should be given to women who are likely to become pregnant, or who are of child-bearing potential. It is recommended that women of child-bearing potential use adequate contraception. The need for antiepileptic treatment should be reviewed when a woman is planning to become pregnant.

Epilepsy:

There are no studies using topiramate in pregnant women. However, topiramate should be used during pregnancy only if the potential benefit outweighs the potential risk.

In post-marketing experience, cases of hypospadias have been reported in male infants exposed in utero to topiramate, either as monotherapy or as add-on to other anti-epileptic agents. It has not been established whether a causal relationship exists with topiramate.

If, however, the seizure prophylaxis is impaired or discontinued, this may bring about a considerable risk for the mother as well as for the fetus, which probably is more severe than the risk for malformation. During pregnancy, antiepileptic therapy should consequently be prescribed with consideration for what is said above.

Migraine prophylaxis:

Treatment for prophylaxis of migraine: topiramate is contraindicated in pregnancy, and in women of child-bearing potential if an effective method of contraception is not used (see section 4.3).

Lactation

Topiramate is excreted in human breast milk. Limited observations suggest a milk/plasma ratio of 1:1.Taking into account the potential harmful effects to infants, breast-feeding is not recommended if continuing therapy is required for the mother.

4.7 Effects on ability to drive and use machines

Topiramate has a major influence on the ability to drive and use machines.

Topiramate acts on the central nervous system and may cause somnolence, dizziness, visual disturbance and other related symptoms These adverse events could potentially be dangerous in patients driving a vehicle or operating machinery, particularly until such time as the individual patient's experience with the active substance is established.

4.8 Undesirable effects

The safety of topiramate was evaluated from a clinical trial database consisting of 4,111 patients (3,182 on topiramate and 929 on placebo) who participated in 20 double-blind trials and 2,847 patients who participated in 34 open-label trials, respectively, for topiramate as adjunctive treatment of primary generalized tonic-clonic seizures, partial onset seizures, seizures associated with Lennox-Gastaut syndrome, monotherapy for newly or recently diagnosed epilepsy or migraine prophylaxis. The majority of 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);
very rare	(< 1/10,000)
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 hyperchloraemic, 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.

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, hypoaesthesia, nystagmus, dysgeusia, balance disorder, dysarthria, intention tremor, sedation ,	Depressed level of consciousness, grand mal convulsion, visual field defect, complex partial seizures, speech disorder, psychomotor hyperactivity, syncope, sensory disturbance, drooling, hypersomnia, aphasia, repetitive speech, hypokinesia, dyskinesia, 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	Apraxia, circadian rhythm sleep disorder, hyperaesthesia, hyposmia, anosmia, essential tremor, akinesia, unresponsive to stimuli	
Eye disorders		Vision blurred, diplopia, visual disturbance	Visual acuity reduced, scotoma, myopia*, abnormal sensation in eye*, dry eye, photophobia, blepharospasm, lacrimation increased, photopsia, mydriasis,	Blindness unilateral, blindness transient, glaucoma, accommodation disorder, altered visual depth perception, scintillating	Angle closure glaucoma*, Maculopathy *, eye movement disorder*

			presbyopia	scotoma, eyelid oedema*, night blindness, amblyopia	
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 distension, epigastric discomfort, abdominal tenderness, salivary hypersecretion, oral pain, breath odour, glossodynia		
Renal and urinary disorders		Nephrolithiasis, pollakiuria, dysuria	Calculus urinary, urinary incontinence, haematuria, incontinence, micturition urgency, renal colic, renal pain	Calculus ureteric, renal tubular 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*	
Metabolis		Anorexia,	Metabolic acidosis,	Acidosis	

m and nutrition disorders		decreased appetite	Hypokalaemia, increased appetite, polydipsia	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, depressed mood, anger, abnormal behaviour	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	Mania, anorgasmia, panic disorder, disturbance in sexual arousal, feeling of despair*, orgasm abnormal, hypomania, orgasmic sensation decreased	

			awakening, panic reaction, elevated mood		
* identified as an ADR from postmarketing spontaneous reports. Its frequency was calculated based on clinical trial data.					

4.9 Overdose

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

Topiramate overdose can result in severe metabolic acidosis (see section 4.4). A patient who ingested a dose calculated to be between 96 and 110 g topiramate was admitted to hospital with coma lasting 20-24 hours followed by full recovery after 3 to 4 days.

Treatment
Treatment should be appropriately supportive. Unabsorbed active substance should be removed from the gastro-intestinal tract by lavage or activated charcoal, if it is considered to be necessary in the clinical perspective. Haemodialysis has been shown to be an effective means of removing topiramate from the body. The patient should be well hydrated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antiepileptics

ATC code: N03A X11

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 sustained depolarisation, indicative of 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 the 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. In addition, topiramate inhibits some isoenzymes of carbonic anhydrase. This effect is not thought to be a major component of the antiepileptic activity of topiramate.

The efficacy of topiramate in prophylaxis of migraine was evaluated in two multicentre, randomized, double-blind placebo-controlled, parallel group trials. The pooled results of the trials evaluating topiramate doses of 50 (N=233), 100 (N=244) and 200 mg/day (N=228) found a median percent reduction in the primary efficacy endpoint, average monthly migraine period rate, of 35%, 51% and 49% respectively, compared to 21% for the placebo group (N=229). The 100 and 200 mg/day doses of topiramate were statistically superior to placebo, while the differences for the 50 mg/day dose compared to placebo were not statistically significant. 27% of patients administered topiramate 100 mg/day achieved at least a 75% reduction in migraine frequency (placebo 11%), whilst 52% achieved at least a 50% reduction. (placebo 23%).

In a third multicentre, randomized, double-blind, parallel group study it was shown that the monthly frequency of migraine periods (the primary endpoint) decreased by -0.8 periods/month when compared to the base period under a placebo. The reduction under topiramate 100 mg/day was -1.6 periods/month, and under topiramate 200 mg/day it was -1.1 periods/month. These differences were not statistically significant.

In a further supplemental study, from the primary efficacy analysis no statistically significant differences were found between the topiramate 200 mg target dose and placebo (change in the monthly migraine episode rate versus the baseline).

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 (Cmax) of 1.5 μg/ml was achieved within 2 to 3 hours (Tmax).

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

Distribution

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

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 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 Cmax following multiple, twice a day oral doses of 100 mg to healthy subjects was 6.76 μg/ml. Following administration of multiple doses of 50 mg and 100 mg of topiramate twice a day, the mean plasma elimination half-life was approximately 21 hours.

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 ≤ 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 general toxicity studies, topiramate-induced toxicity was identified, with target organs being the stomach, kidney, urinary bladder and blood (anaemia). Toxicity was evident in animals at systemic exposures which were those expected in patients given recommended doses. The clinical relevance of these findings is unknown, but cannot be excluded.

Reproductive toxicity studies showed that topiramate was teratogenic in the species studied (mice, rats and rabbits), at systemic exposure levels below those expected in patients given recommended doses. The human risk is unknown but cannot be excluded.

Moderate blockade of calcium channels was demonstrated in vitro, which may lead to a risk of QT prolongation at high doses and in patients with other arrhythmogenic factors.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

- Lactose monohydrate
- Pregelatinised starch (i.e. potato starch)
- Microcrystalline cellulose
- Croscarmellose sodium
- Magnesium stearate

Coating:

25 mg: Hypromellose, titanium dioxide (E171), macrogol 6000
50 mg: Opadry yellow 03F52057 (Hypromellose, macrogol 6000, titanium dioxide E 171, iron oxide yellow E172)
100 mg: Opadry yellow 03F52056 (Hypromellose, macrogol 6000, titanium dioxide E 171, iron oxide yellow E 172)
200 mg: Opadry pink 03F54045 (Hypromellose, macrogol 6000, titanium dioxide E 171, iron oxide red E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C. Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Topiramate film-coated tablets are available in aluminium/aluminium blisters in packs sizes of 10, 14, 20, 28, 30, 50, 56, 60, 100, 120 and 200 film-coated tablets or in high density polyethylene (HDPE) bottles fitted with a white opaque polypropylene child resistant closure with wad having induction sealing liner supplied in cardboard cartons in pack sizes of 14, 30, 60, 100 and 200 film-coated tablets. In each container there is a silica gel desiccant, which should not be swallowed.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal & and other handling

No special requirements

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House,
319 Pinner Road,
North Harrow,
Middlesex, HA1 4HF,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/ 0145
PL 20075/ 0146
PL 20075/ 0147
PL 20075/ 0148

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/10/2009

10 DATE OF REVISION OF THE TEXT

20/10/2009

Module 3

Product Information Leaflet

accord

PACKAGE LEAFLET:
INFORMATION FOR THE USER

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

Topiramate

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

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Topiramate is and what it is used for

Topiramate belongs to a group of medicines called "antiepileptic medicines." It is used:

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

2. Before you take Topiramate

Do NOT take Topiramate

- if you are allergic (hypersensitive) to topiramate or any of the other ingredients of Topiramate (see section 6, Further information).
- to prevent a migraine headache if you are pregnant, think you may be pregnant or are of child-bearing age and not using an effective method of contraception.

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

Take special care with Topiramate

Check with your doctor or pharmacist before taking topiramate if you:

- have kidney problems, especially kidney stones, or are getting kidney dialysis
- have a history of blood and body fluid abnormality (metabolic acidosis)
- have liver problems
- have eye problems, especially glaucoma
- have a growth problem
- are on a high fat diet (ketogenic diet)

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

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

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

You may loss weight if you use topiramate 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 have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Taking 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 and certain other medicines can affect each other. Sometimes the dose of some of your other medicines or topiramate will have to be adjusted.

Especially, tell your doctor or pharmacist if you are taking:

- other medicines that impair or decrease your thinking, concentration, or muscle coordination (e.g. central nervous system depressant medicines such as muscle relaxants and sedatives).
- birth control pills. Topiramate may make your birth control pills less effective.

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

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 antiepileptic medicines, risperidone, lithium, hydrochlorothiazide, metformin, pioglitazone, glyburide, amitriptyline, propranolol, diltiazem, venlafaxine, flunarazine

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

Taking Topiramate with food and drink

You can take topiramate with or without food.

It is recommended not to drink alcohol whilst you are taking topiramate as this can increase the risk of side effects.

It is important to drink plenty of water whilst you are taking topiramate especially if you are taking exercise or the weather is hot.

Pregnancy and breast-feeding

Talk to your doctor before using topiramate if you are pregnant, trying to become pregnant or breast-feeding. Your doctor will decide if you can take topiramate. As with other antiepilepsy medicines, there is a risk of harm to the unborn child if topiramate is used during pregnancy. Make sure you are very clear about the risks and the benefits of using topiramate for epilepsy during pregnancy.

You should not take topiramate for migraine prevention if you are pregnant or you are able to become pregnant and you are not using effective contraception.

Mothers who breastfeed while taking topiramate must tell the doctor as soon as possible if the baby experiences anything unusual.

Ask your doctor or pharmacist for advice before taking any medicine.

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

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

Warning! Each tablet bottle contains a desiccant capsule. This a small canister on which "Do not eat" is written. Do not eat this.

3. How to take Topiramate

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

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

If you take more Topiramate than you should
- See a doctor right away. Take the medicine pack with you.
- You may feel sleepy or tired, 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.

If you forget to take Topiramate
Take the missed dose as soon as you remember. If it is almost time for your next dose, do not take the missed dose but simply take your next dose at the normal time. If you miss two or more doses, contact your doctor.
Do not take a double dose to make up for the one you missed.

If you stop taking Topiramate
You may have more fits or sudden worsening of the headaches. It is important that you keep taking your tablets until your doctor tells you to stop. If the doctor decides to stop your treatment with topiramate they will usually do so gradually over a period of a few weeks. It is important that you follow what the doctor tells you to do.

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

4. Possible side effects

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

If you notice a rash, itching, blistering or other effects on the skin, eyes, mouth or genitals or you get a high temperature, you should stop taking the tablets and contact your doctor immediately.

Patients taking topiramate can have thoughts of harming themselves or taking their own lives. If you get these thoughts at **any time, contact your doctor or go to a hospital immediately.**

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data).

The following side effects have been reported:
Very common side effects (probably affecting more than 1 in 10 people):
- weight loss
- tingling in the arms and legs
- drowsiness or sleepiness
- dizziness
- diarrhoea
- nausea (feeling sick)
- stuffy, runny nose and sore throat
- tiredness

Common side effects (probably affecting fewer than 1 in 10 people):
- 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
- Distorted sense of taste
- Visual disturbance, blurred vision, double vision
- Ringing sound in the ears
- Ear pain
- Shortness of breath
- Nose bleeds
- Vomiting
- Constipation
- Stomach pain
- Indigestion
- Dry mouth
- Tingling or numbness of the mouth
- Kidney stones
- Frequent urination
- Painful urination
- Hair loss
- Skin rash and/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 (probably affecting fewer than 1 in 100 people):
- 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 increased 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

- Fullness or bloating
- Painful or burning sensations in the mouth
- Breath odour
- 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 (probably affecting fewer than 1 in 1,000 people):
- 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 erythma multiforme, 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 uncommon side effects).

If any of the 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 use Topiramate tablets after the expiry date, which is stated on the carton and bottle or blister after EXP. The expiry date refers to the last day of that month.
Do not store above 25ºC. Keep the container tightly closed in order to protect from moisture.
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 contains

The active substance is topiramate.

Topiramate 25 mg Film-coated Tablets: Each film-coated tablet contains 25 mg topiramate.
Topiramate 50 mg Film-coated Tablets: Each film-coated tablet contains 50 mg topiramate.
Topiramate 100 mg Film-coated Tablets: Each film-coated tablet contains 100 mg topiramate.
Topiramate 200 mg Film-coated Tablets: Each film-coated tablet contains 200 mg topiramate.

The other ingredients are lactose monohydrate (see section 2: important information about some of the ingredients of Topiramate tablets), Cellulose microcrystalline, Starch, Pregelatinised (i.e. potato starch), croscarmellose sodium, magnesium stearate.
- The 25 mg tablets are coated with hypromellose, titanium dioxide (E171) and macrogol 6000.
- The 50 mg and 100 mg tablets are coated with hypromellose, titanium dioxide (E171), macrogol 6000 and iron oxide yellow (E172)
- The 200 mg tablets are coated with hypromellose, titanium dioxide (E171), macrogol 6000 and iron oxide red (E172).

What Topiramate tablets looks like and content of the pack

Film-coated tablet.

The 25 mg film-coated tablets are white round and biconvex, with bevelled edges and embossed TP on one side and 25 on the other.

The 50 mg film-coated tablets are light yellow round and biconvex with bevelled edges and embossed TP on one side and 50 on the other.

The 100 mg film-coated tablets are dark yellow round and biconvex, with bevelled edges and embossed TP on one side and 100 on the other.

The 200 mg film-coated tablets are red, round and biconvex, with bevelled edges and embossed TP on one side and 200 on the other.

Topiramate film-coated tablets are available in aluminium/aluminium blisters in packs sizes of 10, 14, 20, 28, 30, 50, 56, 60, 100, 120 and 200 film-coated tablets or in high density polyethylene (HDPE) bottles fitted with a white opaque polypropylene child resistant closure with wad having induction sealing liner supplied in cardboard cartons in pack sizes of 14,30,60,100 and 200 film-coated tablets. In each container there is a desiccant canister, which should not be swallowed.

Not all pack sizes may be marketed.

Topiramate is available in four strengths containing either 25 mg, 50 mg, 100 mg and 200 mg topiramate.

Marketing authorization holder

Accord Healthcare Limited,
Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF, United Kingdom

Manufacturer:

Accord Healthcare Limited,
Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF, United Kingdom

or
Cemelog BRS Limited,
2040 Budaörs, Vasút u. 13., Hungary.

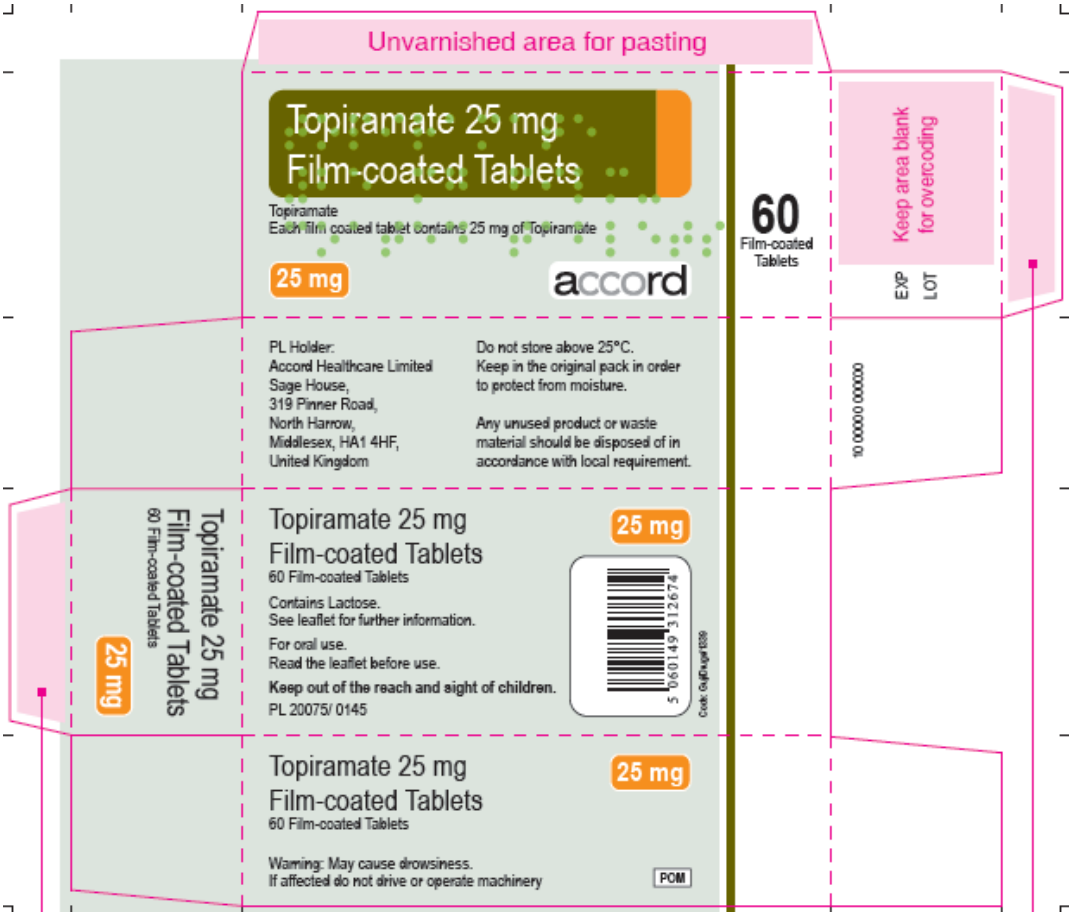
This leaflet was last approved in 10/2009

Module 4

Labelling

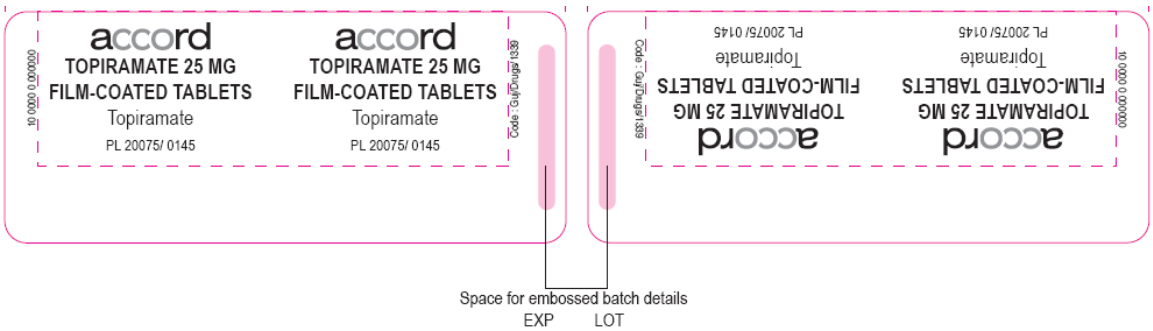
Topiramate 25mg film-coated tablets

Blister carton - pack size 60 tablets

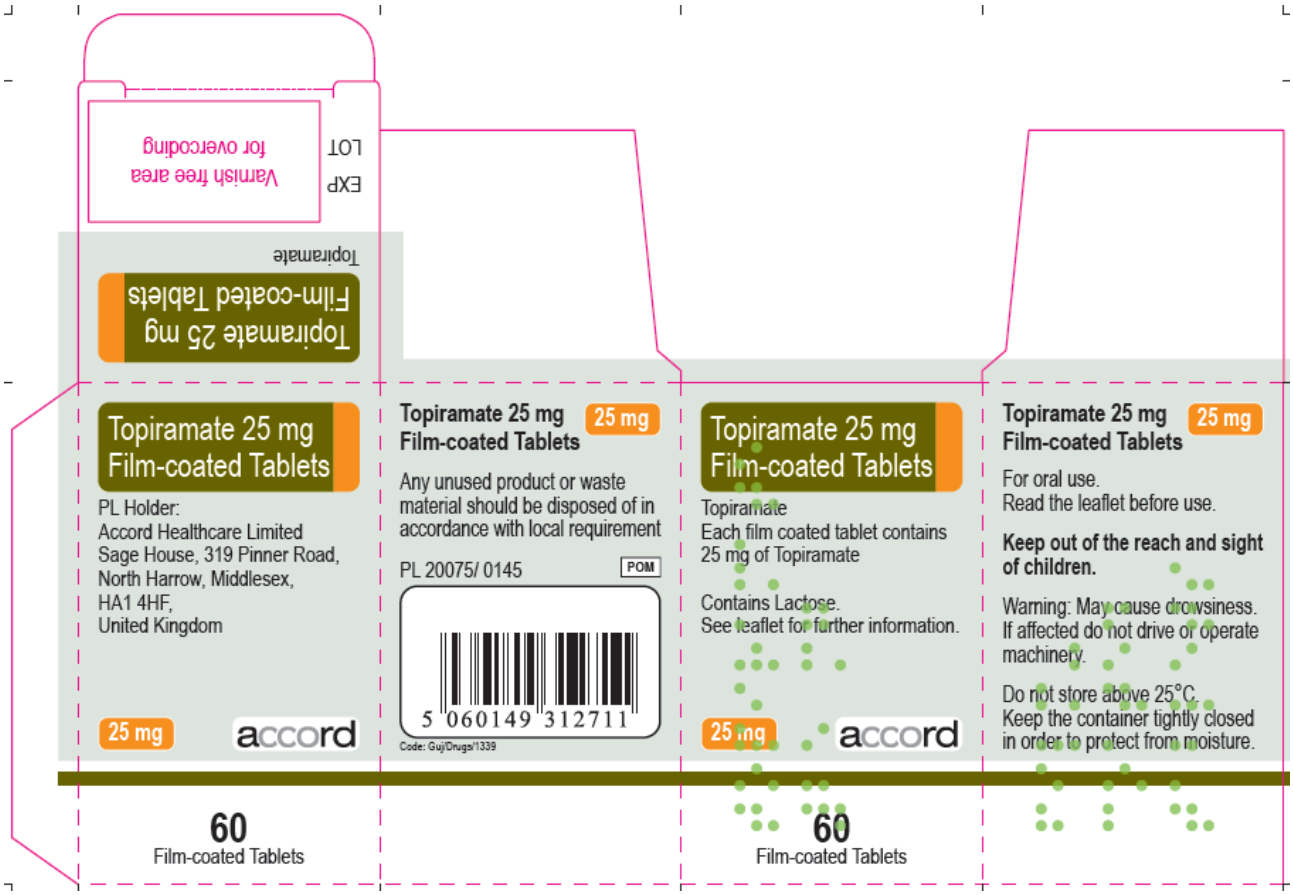


Braille translation

Blister foil



Bottle carton – pack size 60 tablets

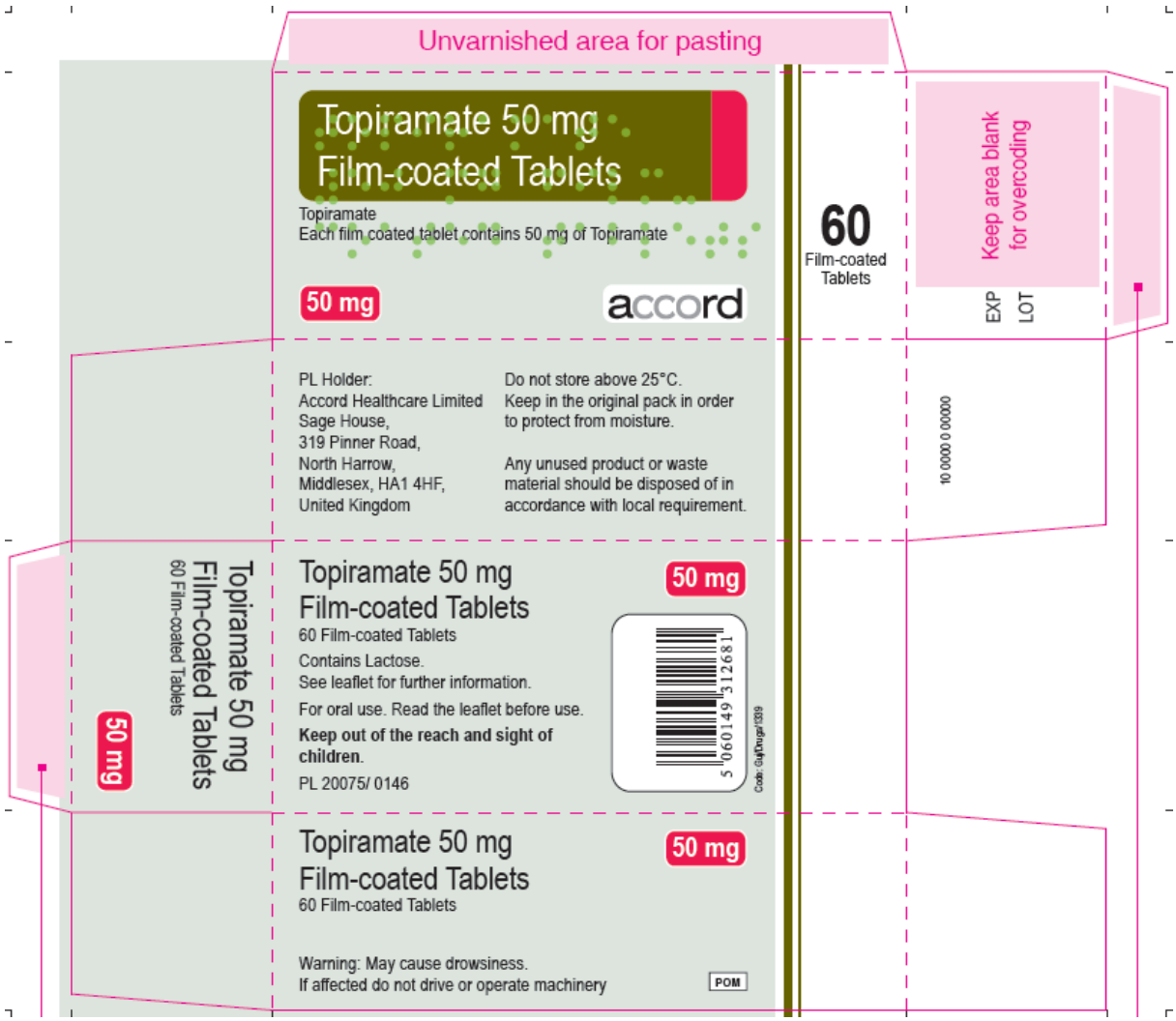


Braille translation

Bottle label

Topiramate 50mg film-coated tablets

Blister carton - pack size 60 tablets



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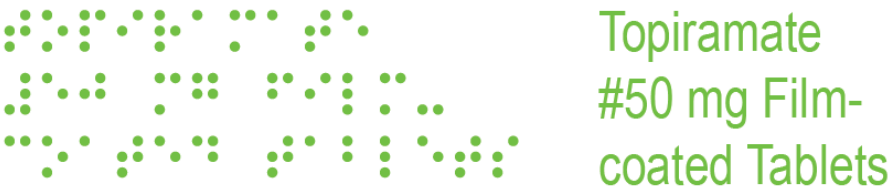
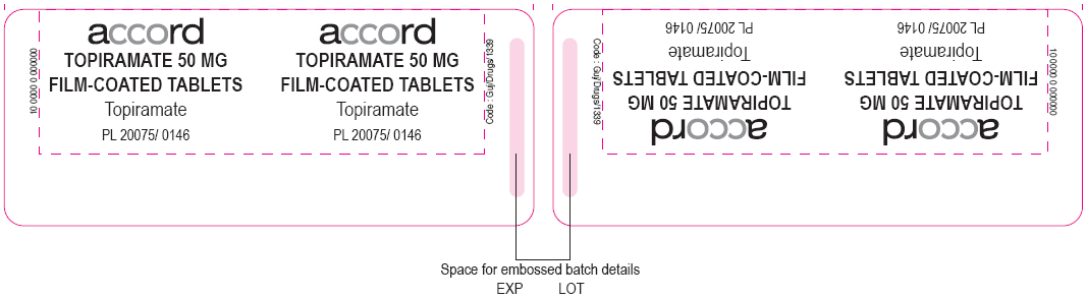
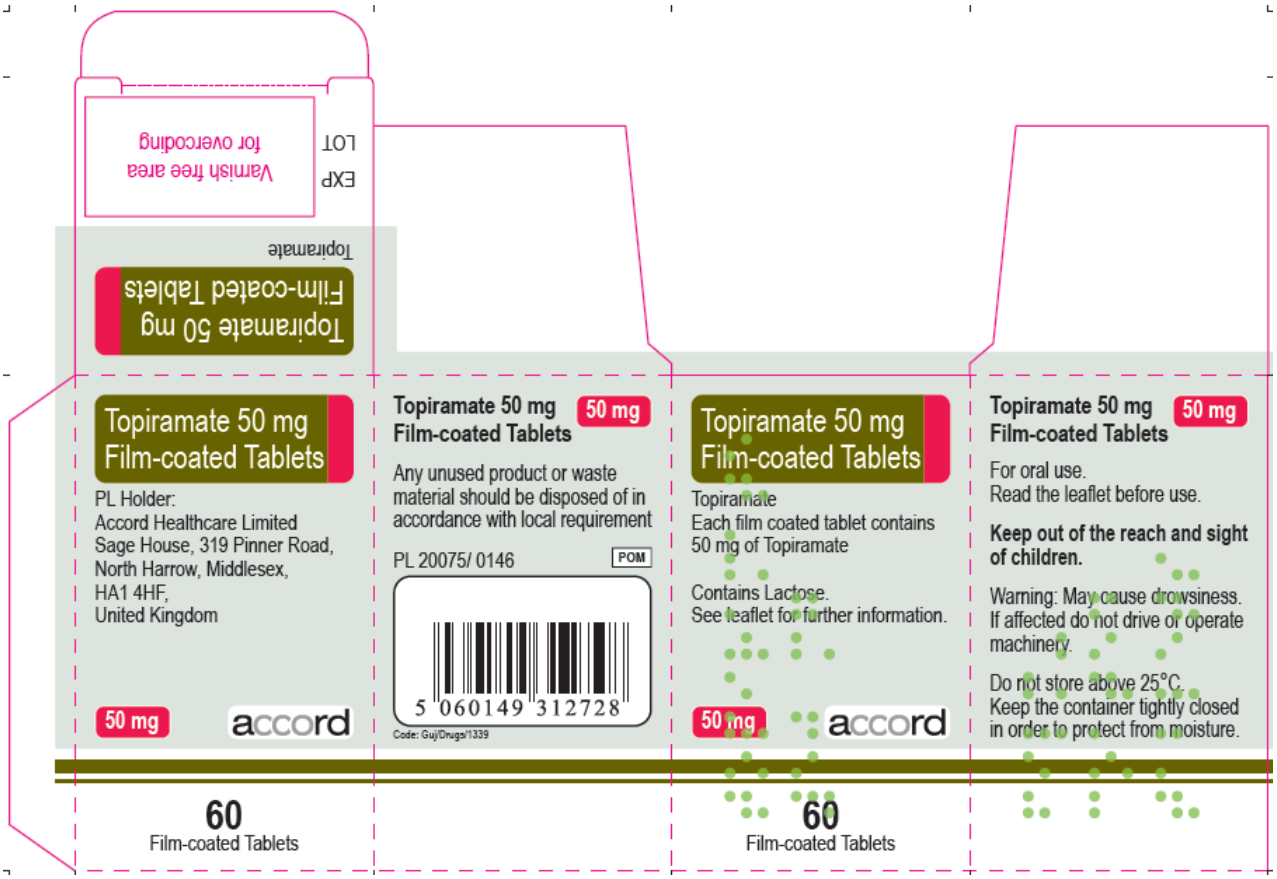


Blister foil



Bottle carton – pack size 60 tablets

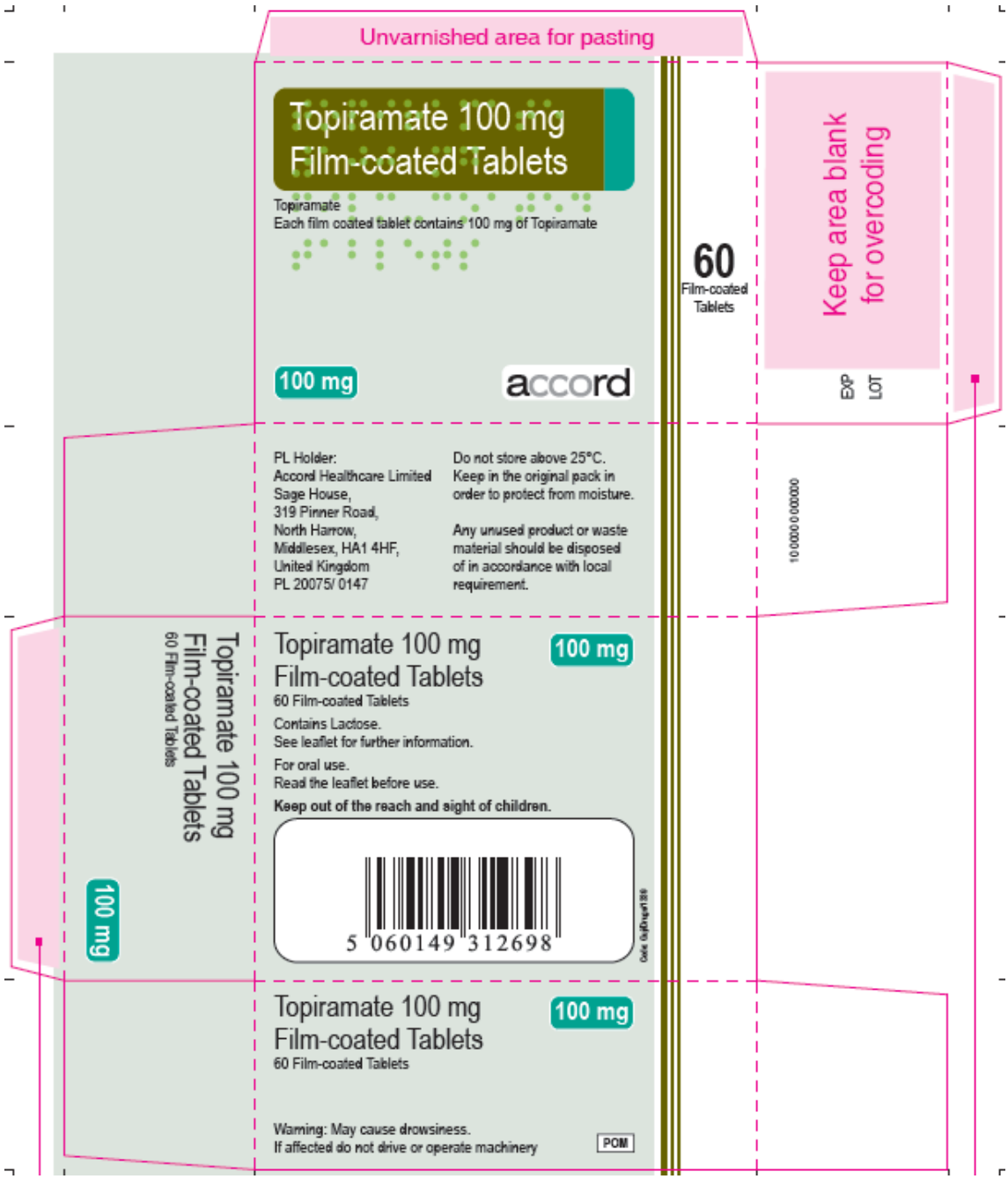


Braille translation

Bottle label

Topiramate 100mg film-coated tablets

Blister carton - pack size 60 tablets



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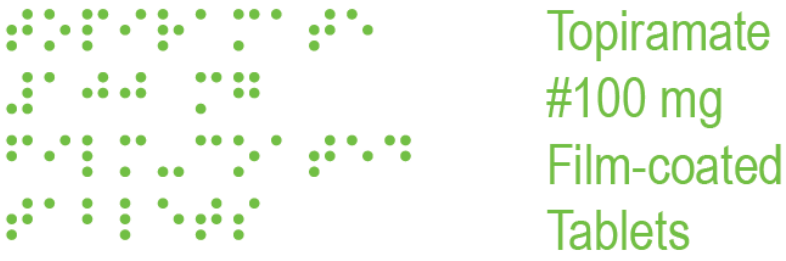
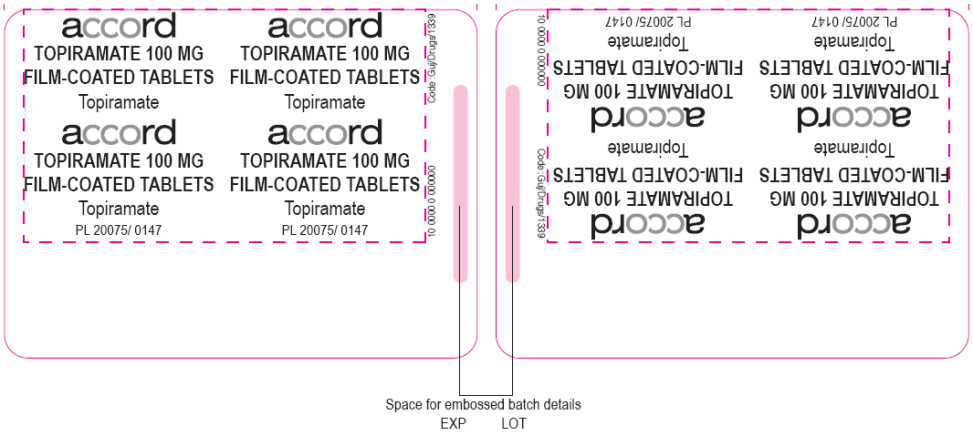
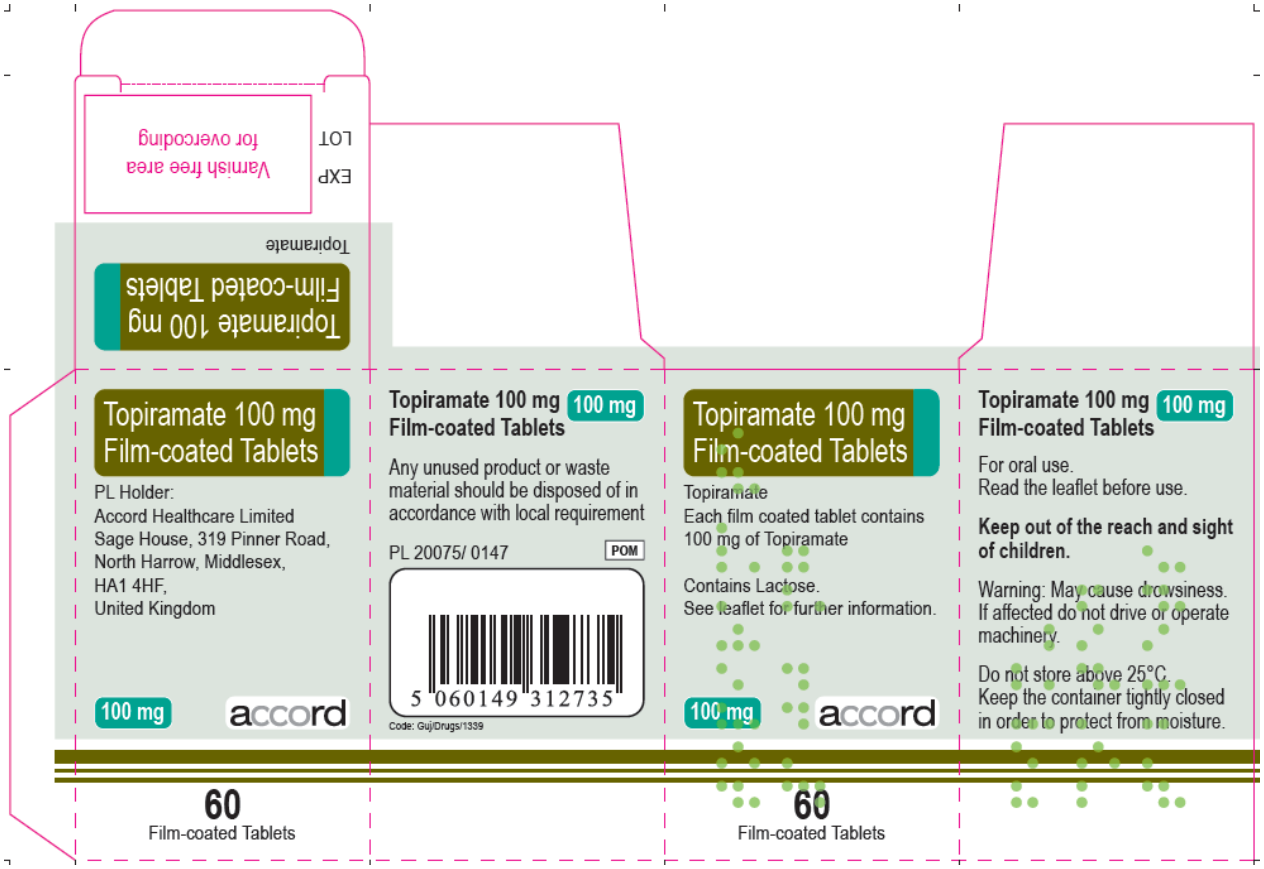


Blister foil



Bottle carton – pack size 60 tablets



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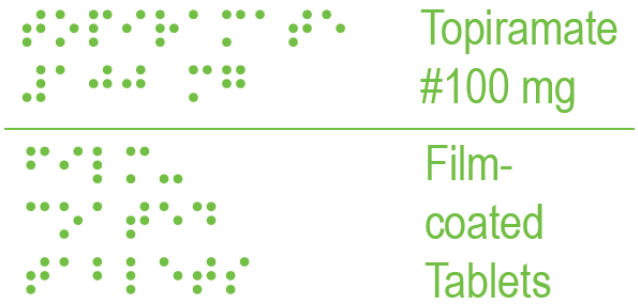
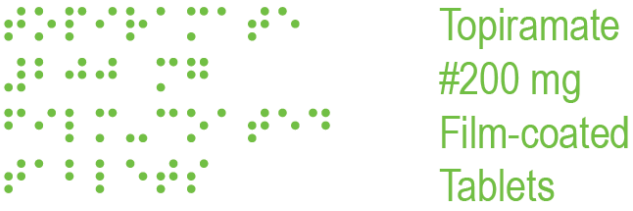


Bottle label

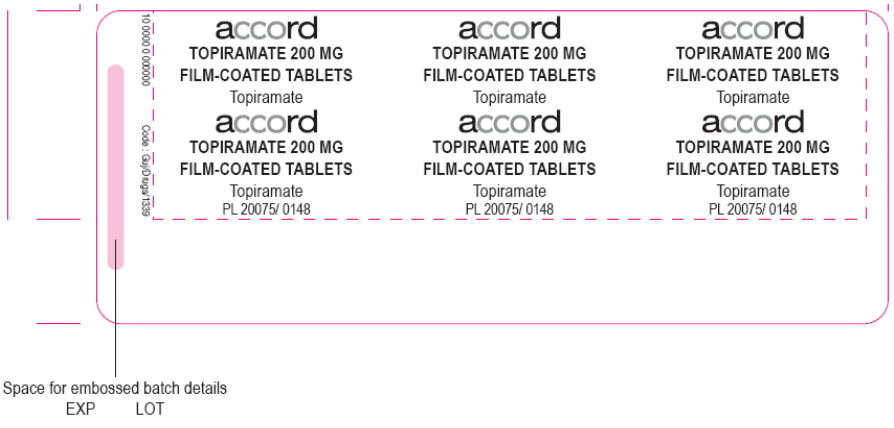
Topiramate 200mg film-coated tablets

Blister carton - pack size 60 tablets

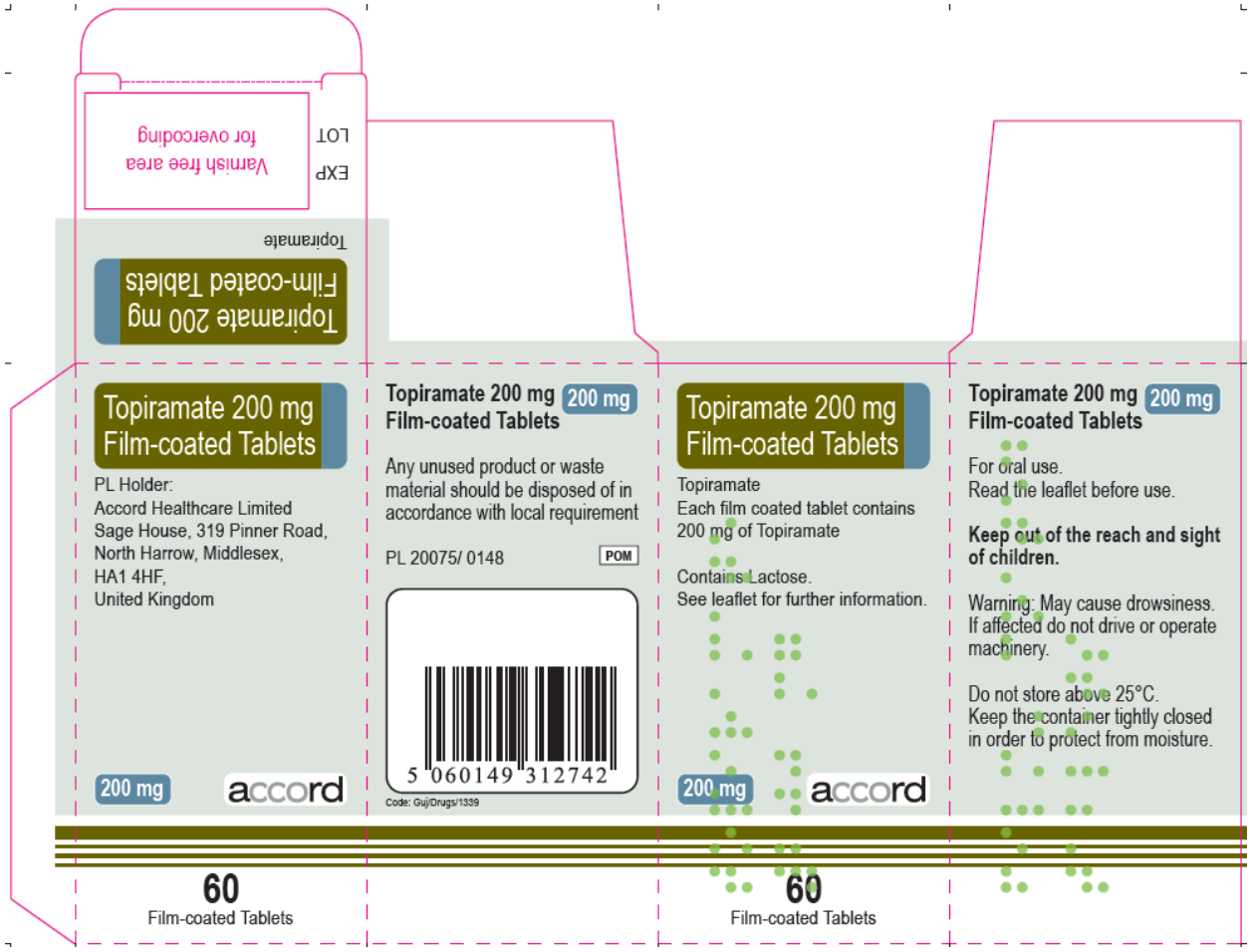
Braille translation



Blister foil



Bottle carton – pack size 60 tablets



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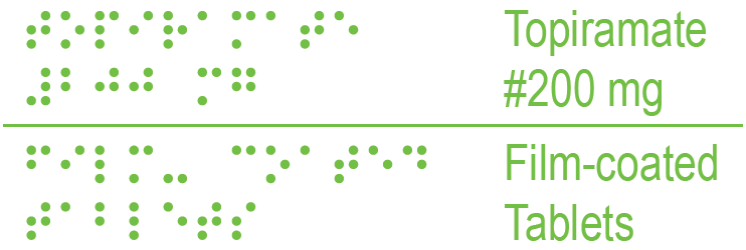
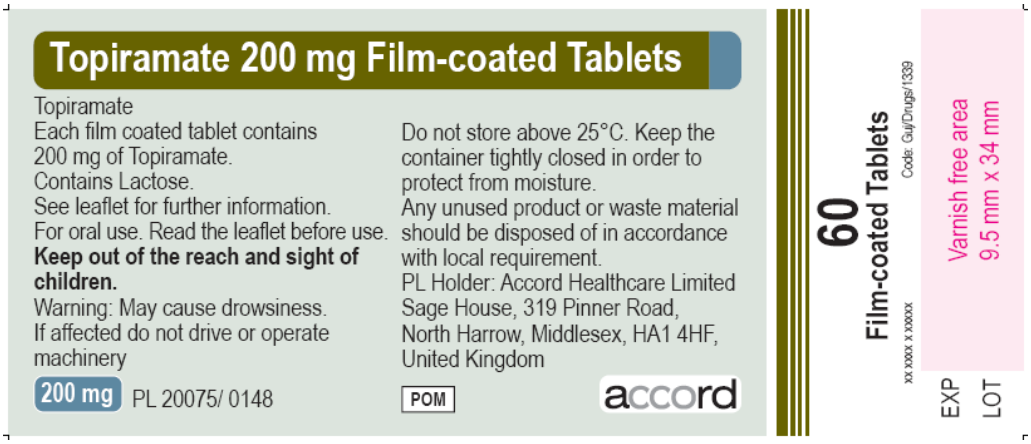


Bottle label



Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Accord Healthcare Limited Marketing Authorisations for the medicinal products Topiramate 25mg, 50mg, 100mg, and 200mg film-coated tablets (PL 20075/0145-0148, UK/H/1438/01-04/DC) on 20th October 2009. The products are prescription-only medicines.

These are abridged applications for Topiramate 25mg, 50mg, 100mg, and 200mg film-coated tablets, four strengths of topiramate, submitted under Article 10.1 of 2001/83 EC, as amended. The applications refer to the reference products, Topamax Tablets 25mg, 50mg, 100mg, and 200mg (PL 00242/0301-0304 respectively), authorised to Janssen-Cilag Limited on 18th July 1995. These are the innovator products. The innovator products have been authorised in the UK for more than 10 years, so the period of data exclusivity has expired.

Topiramate film-coated tablets are indicated as 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. The tablets are also indicated as 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 film-coated tablets are also indicated in adults for the prophylaxis of migraine headache after careful evaluation of possible alternative treatment options. Topiramate is not intended for acute treatment. Therapy is initiated at a low dose followed by gradual titration to an effective dose. Dose and titration rate should be guided by clinical response.

Topiramate belongs to the pharmacotherapeutic group, anti-epileptics (ATC code N03A X11) and 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 sustained depolarisation, indicative of 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 the 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. In addition, topiramate inhibits some isoenzymes of carbonic anhydrase. This effect is not thought to be a major component of the antiepileptic activity of topiramate.

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.

No new preclinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

The applications are supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product, Topiramate 200mg film-coated

tablets, to that of the reference product, Topamax Tablets 200mg (PL 00242/0304, Janssen-Cilag Limited). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that 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.

The marketing authorisation holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. The marketing authorisation holder has provided adequate justification for not submitting a Risk Management Plan (RMP).

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Topiramate 25mg film-coated tablets Topiramate 50mg film-coated tablets Topiramate 100mg film-coated tablets Topiramate 200mg film-coated tablets
Name(s) of the active substance(s) (INN)	Topiramate
Pharmacotherapeutic classification (ATC code)	Other anti-epileptics (N03A X11)
Pharmaceutical form and strength(s)	Film-coated tablets 25mg, 50mg, 100mg, & 200mg
Reference numbers for the Mutual Recognition Procedure	UK/H/1438/01-04/DC
Reference Member State	United Kingdom
Member States concerned	BG, DE, ES, IT, LT, NL, PL, and PT
Marketing Authorisation Number(s)	PL 20075/0145-0148
Name and address of the authorisation holder	Accord Healthcare Limited Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF, United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

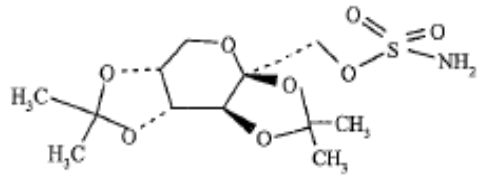
ACTIVE SUBSTANCE

Topiramate

Nomenclature:

INN:	Topiramate
Chemical name:	- 2,3:4,5-Bis-O-(1-methylethylidene)-ß-D-fructopyranose sulfamate - 2,3:4,5-di-O-isopropylidene-ß-D-fructopyranose sulfamate

Structure:



Molecular formula:	$C_{12}H_{21}NO_8S$
Molecular weight:	339.36 g/mol
CAS No:	97240-79-4
Physical form:	White or off white crystalline powder
Solubility:	Soluble in methanol, acetone, dimethyl formamide, 0.1N aqueous sodium hydroxide solution and slightly soluble in water

The active substance, topiramate, is not the subject of a European Pharmacopeia (Ph. Eur.) 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 specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

An appropriate specification has been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. It is packed in HDPE drums lined with double polythene bags. Specifications and Certificates of Analysis have been provided for the packaging materials used. The polyethylene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in containers representative of the proposed commercial packaging. These data demonstrate the stability of the active substance and support a retest period of 24 months.

DRUG PRODUCT

Description and Composition

The drug products are presented as round, biconvex film-coated tablets with bevelled edges, each containing 25mg, 50mg, 100mg, or 200mg of the active ingredient topiramate. Full descriptions of the colours and markings of the individual tablets may be found by referring to the SmPCs / patient information leaflet.

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, croscarmellose sodium, pregelatinised starch, lactose monohydrate, and magnesium stearate making up the tablet core. The film-coating comprises hypromellose, titanium dioxide (E171), and macrogol 6000 for the 25mg strength (white) tablets. For the 50mg (light yellow) and 100mg (dark yellow) strength tablets, the film-coat is made up of Opadry yellow 03F52057 and Opadry yellow 03F52056 respectively. Both Opadry yellow 03F52057 and Opadry yellow 03F52056 consist of hypromellose, macrogol 6000, titanium dioxide (E171), and iron oxide yellow (E172). For the 200mg strength (red) tablets, the film-coat is made up of Opadry pink 03F54045, which consists of hypromellose, macrogol 6000, titanium dioxide (E171), and iron oxide red (E172). Appropriate justification for the inclusion of each excipient has been provided.

The excipients are all controlled to the requirements of the current European Pharmacopoeia. The coating dispersions are not compendial but the individual components comply with the requirements of the European Pharmacopoeia. Copies of the routine tests and specifications are provided. Satisfactory Certificates of Analysis have been provided for all excipients.

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

There were no novel excipients used and no overages.

Dissolution and impurity profiles

Comparative dissolution data were provided for each strength of the generic topiramate tablets and appropriate reference tablet formulations. The dissolution profiles were found to be similar.

Comparative impurity data were also provided for the test and appropriate reference products. The impurity profiles were comparable and all impurities were within the specification limits.

Pharmaceutical development

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

Manufacture

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies were conducted on two production scale batches for each of the strengths.

Finished product specification

The finished product specifications include tests and criteria to apply for both release and end of shelf life testing and are satisfactory; they provide an assurance of the quality and consistency of the finished products. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided for two production scale batches of each of the strengths and they comply with the release specifications. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The finished products are licensed for marketing in aluminium / aluminium foil blister strips, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The tablets are packaged in pack sizes of 10, 14, 20, 28, 30, 50, 56, 60, 100, 120 and 200 film-coated. The tablets are also marketed in high density polyethylene (HDPE) bottles fitted with a white opaque polypropylene child resistant closure, supplied in cardboard cartons in pack sizes of 14, 30, 60, 100 and 200 film-coated tablets. The MA Holder has stated that not all pack sizes may be marketed.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

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, which is satisfactory. Storage conditions are ‘Do not store above 25°C’. Additional instructions of ‘Keep in the original pack in order to protect from moisture’ and ‘Keep the container tightly closed in order to protect from moisture’ are applied to the packaging for the blister pack and HDPE bottle pack respectively.

Bioequivalence Study

A bioequivalence study was presented comparing the test product, Topiramate 200mg film-coated tablets, to the reference product, Topamax Tablets 200mg (PL 00242/0304, Janssen-Cilag Limited).

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

Expert Report

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

Product Information

The approved SmPCs, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling have been provided. The labelling fulfils the statutory requirements for Braille.

Conclusion

The drug products correspond to the current EU definition of a generic medicinal product because they comply with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis, and

considering the bioequivalence data provided, the applicant's claim that Topiramate 200mg film-coated tablets is a generic medicinal product of Topamax Tablets 200mg (PL 00242/0304, Janssen-Cilag Limited) appears justified.

Topiramate demonstrates linear pharmacokinetics over the therapeutic dose range of 100 mg to 400 mg. As the test products, Topiramate 25mg, 50mg, 100mg, and 200mg 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 200mg strength were extrapolated to the 25mg, 50mg, and 100mg strength tablets.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. Marketing Authorisations were, therefore, granted.

III.2 PRE-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable for these applications for generic versions of products that have been licensed for over 10 years. The non-clinical overview provides a satisfactory review of the pharmacological and toxicological properties of topiramate, which is a widely used and well-known active substance.

A satisfactory non-clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

III.3 CLINICAL ASPECTS

INDICATIONS

Topiramate film-coated tablets are indicated as 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. The tablets are also indicated as 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 film-coated tablets are also indicated in adults for the prophylaxis of migraine headache after careful evaluation of possible alternative treatment options. Topiramate is not intended for acute treatment. Therapy is initiated at a low dose followed by gradual titration to an effective dose. Dose and titration rate should be guided by clinical response.

The indications are consistent with those for the reference products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY

No new data have been submitted and none are required for these types of application.

CLINICAL PHARMACOLOGY

The clinical pharmacology of topiramate is well known. No novel pharmacodynamic data are supplied or required for this application.

Pharmacokinetics – bioequivalence study

The application is supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profiles of Topiramate 200mg film-coated tablets (test) and Topamax Tablets 200mg - PL 00242/0304, Janssen-Cilag Limited (reference). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). The use of the 200mg strength only for the bioequivalence study has been adequately justified.

This was a randomised, two-treatment, two-period, two sequence, single dose crossover bioavailability and bioequivalence study conducted in 26 (24 + 2 alternates) healthy adult male human subjects under fasting conditions. A single dose of the investigational products was administered orally to each subject in each period. A satisfactory washout period of 17 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 144.0 hours after administration of test or reference product. The drug concentration levels in plasma were determined by a validated LC/MS/MS 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 product was concluded if the 90% CI fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.

Results:

Twenty-five subjects completed the study and 24 were used in the statistical analysis. There were no deaths or serious adverse events.

The summary of the results of the bioequivalence study are tabulated below:

Pharmacokinetic results for a randomised, two-treatment, two-period, single dose crossover study between the test and reference products. n=24 healthy subjects, dosed fasted; t=144 hours. Wash-out period: 17 days

Parameters (Units)	Geometric Least Squares Mean			90% Confidence Interval (Parametric)
	Reference Product-A	Test Product-B	Ratio (B / A)%	
C_{max} (ng/ml)	5163.077	5130.845	99.4%	95.90-102.98%
AUC_{0-t} (ng.h/ml)	179193.662	177215.978	98.9%	96.69-101.15%
$AUC_{0-\infty}$ (ng.h/ml)	186692.315	185359.908	99.3%	97.04-101.59%

Conclusion on Bioequivalence

The results of the bioequivalence study show that the test product and reference product are bioequivalent, under fasting conditions, as the confidence intervals for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ fall within the acceptance criteria ranges of 80-125% in line with current CHMP guidelines.

Satisfactory justification is provided for a bio-waiver for Topiramate 25mg, 50mg, and 100mg film-coated tablets. Topiramate demonstrates linear pharmacokinetics over the therapeutic dose range of 100 mg to 400 mg. As Topiramate 25mg, 50mg, 100mg, and 200mg 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 200mg strength were extrapolated to the 25mg, 50mg, and 100mg strength products.

Clinical efficacy

No new data have been submitted and none are required. Efficacy is reviewed in the clinical overview. The efficacy of topiramate is well-established from its extensive use in clinical practice.

Clinical safety

No new data have been submitted and none are required for applications of this type. 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

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

Labelling

The labelling is satisfactory.

Expert report

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

CONCLUSIONS

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and demonstrates the bioequivalence of the test (Topiramate 200mg film-coated tablets, Accord Healthcare Limited) and reference (Topamax Tablets 200mg; PL 00242/0304, Janssen-Cilag Limited) products within acceptance limits. Topiramate demonstrates linear pharmacokinetics over the therapeutic dose range of 100 mg to 400 mg. The results and conclusions of the bioequivalence study on the 200mg strength were extrapolated to the 25mg, 50mg, and 100mg strength products.

Sufficient clinical information has been submitted to support these applications. Marketing Authorisations were, therefore, granted on medical grounds.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

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

PRECLINICAL

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

EFFICACY

Bioequivalence has been demonstrated between the applicant's Topiramate 200mg film-coated tablets, and the reference product, Topamax Tablets 200mg (PL 00242/0304, Janssen-Cilag Limited).

Topiramate demonstrates linear pharmacokinetics over the therapeutic dose range of 100 mg to 400 mg. As Topiramate 25mg, 50mg, 100mg, and 200mg film-coated tablets were deemed to 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 200mg strength were extrapolated to the 25mg, 50mg, and 100mg strength products, and omission of further bioequivalence studies on the other strengths can be accepted.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

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. 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 the leaflet contains.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant's products and their respective reference products are interchangeable. Extensive clinical experience with topiramate is considered to have demonstrated the therapeutic value of the active substance. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

There have been no variation applications submitted after approval of the initial procedure.

Date submitted	Application type	Scope	Outcome