Public Assessment Report

Decentralised Procedure

TOPIRAMATE 15MG AND 25MG HARD CAPSULES

UK/H/1579 and 2407/001-2/DC
UK Licence No: PL 18909/0238-9 and 0337-8

ARROW GENERICS LIMITED
LAY SUMMARY

On 21st August 2009, the UK granted Arrow Generics Limited Marketing Authorisations (licences) for the prescription only medicinal products Topiramate 15mg and 25mg Hard Capsules (PL 18909/0238-9 and 0337-8; UK/H/1579 and 2407/001-2/DC).

Topiramate belongs to a group of medicines used to treat epilepsy (antiepileptic) and prevent migraine headaches. Topiramate affects chemicals in the brain that are involved in sending signals to the nerves.

Topiramate is used for the treatment of:
- Epilepsy, including primary generalised epilepsy and partial epilepsy with or without secondary generalisation.
- Migraine, frequently recurring migraine headaches in adults. Topiramate Capsules are not intended for the treatment of individual migraine attacks.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Topiramate 15mg and 25mg Hard Capsules outweigh the risks; hence these Marketing Authorisations have been granted.
## TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Module</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 1:</td>
<td>Information about initial procedure</td>
<td>4</td>
</tr>
<tr>
<td>Module 2:</td>
<td>Summary of Product Characteristics</td>
<td>5</td>
</tr>
<tr>
<td>Module 3:</td>
<td>Product Information Leaflets</td>
<td>19</td>
</tr>
<tr>
<td>Module 4:</td>
<td>Labelling</td>
<td>23</td>
</tr>
<tr>
<td>Module 5:</td>
<td>Scientific Discussion</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>1 Introduction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 Quality aspects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 Non-clinical aspects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 Clinical aspects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 Overall conclusions</td>
<td></td>
</tr>
<tr>
<td>Module 6:</td>
<td>Steps taken after initial procedure</td>
<td>33</td>
</tr>
</tbody>
</table>
### Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Topiramate 15mg and 25mg Hard Capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Topiramate</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Hard Capsules</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>15mg and 25mg</td>
</tr>
</tbody>
</table>
| **MA Holder** | Arrow Generics Limited  
Unit 2, Eastman Way, Stevenage, Hertfordshire, SG1 4SZ |
| **Reference Member State (RMS)** | UK |
| **CMS** | Belgium, Cyprus, the Czech Republic, Ireland, Italy, Malta, the Netherlands, Poland, Portugal, the Slovak Republic and Slovenia |
| **Procedure Number** | UK/H/1579/001-2/DC and UK/H/2407/001-2/DC |
| **End of Procedure** | Day 210 – 05/08/2009 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Topiramate 15mg Capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 15mg of topiramate.
Each capsule also contains 41.4 mg of sucrose. For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Capsule, hard (capsule).
White opaque body and white opaque cap. The body has ‘15’ printed in black and the cap has ‘>’ over ‘T’ printed in black.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Adults and adolescents aged 12 years and older: Adjunctive therapy for epileptic patients with partial onset seizures and/or generalised tonic-clonic seizures.

Adults and adolescents aged 12 years and older: Monotherapy of epileptic patients with partial onset seizures and/or generalised tonic-clonic seizures.


4.2 Posology and method of administration
General:
For optimal seizure control in both adults and adolescents and to avoid dose dependent undesirable effects, it is recommended that therapy be initiated at a low dose followed by titration to a clinically effective dose. When concomitant antiepilepsy drugs (AED) 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 is recommended.

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

Topiramate should be withdrawn gradually to minimise the potential of increased seizure frequency. In clinical trials, dosages were decreased by 50-100 mg/day at weekly intervals. In some patients, dose decrease was accelerated without complications.

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

For doses not realisable/practicable with this medicinal product other strengths of this medicinal product or other pharmaceutical forms and products are available.

Method of administration:
Topiramate Capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoon) of soft food e.g. apple sauce, mashed banana, ice cream or yoghurt. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use.

Topiramate can be taken with or without a meal with a sufficient quantity of liquid.

Adjunctive Therapy in Adults and Adolescents aged 12 years and over:

Titration should begin at 25 - 50 mg nightly for 7 days. The dosage should then be increased at 7 day or 14 day intervals by increments of 25 - 50 mg/day, administered in two divided doses. If the patient is unable to tolerate the titration regimen, smaller dose increments or longer intervals between dose increments may be used. Dose titration should be guided by clinical outcome.
The minimal effective dose as adjunctive therapy is 200 mg/day. The usual total daily dose is 200 mg to 400 mg administered in two divided doses. Some patients may achieve efficacy with a once-a-day dosing. Some patients may require higher doses. The maximum recommended daily dose is 800 mg.

**Monotherapy for adults and adolescents aged 12 years and over:**
Titration should begin at 25 mg nightly for 7 days. The dosage should then be increased at 7 or 14 day 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 dose increments or longer intervals between dose increments may be used. Dose titration should be guided by clinical outcome.

The recommended initial target dose for topiramate monotherapy in adults is 100 mg/day. The maximum recommended daily dose is 400 mg.

**Prophylaxis of Migraine in Adults:**
Titration should begin at 25 mg nightly for 7 days. The dosage should then be increased at 7 day intervals by increments of 25 mg/day. If the patient is unable to tolerate the titration regimen, longer intervals between dose adjustments may be used.

The recommended total daily dose of topiramate for prophylaxis of migraine in adults is 100 mg/day administered in two divided doses. Higher doses do not result in increased benefit.

Some patients may experience a benefit at a total daily dose of 50 mg/day. Dose and titration rate should be guided by clinical outcome.

There are no efficacy or safety data for longer than six months in the prophylactic treatment of migraine.

**Impaired renal function:**
For patients with moderate (creatinine clearance 30-69 ml/min) and severe (creatinine clearance <30 ml/min) renal dysfunction, it is recommended to start with half of the daily dose than usual and to titrate with smaller steps and at slower pace as is usual. As with all patients, the titrations schedule should be guided by clinical outcome with the knowledge that it may require longer to reach steady-state after each dose change in renally impaired patients. In patients with moderate or severe renal impairment, it may take 10 to 15 days to reach steady concentrations as compared to 4 to 8 days in patients with normal renal function.

**Impaired hepatic function:**
In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased. (see section 4.4 and 5.2).

**Patients undergoing haemodialysis:**
Topiramate is removed from plasma by haemodialysis. Therefore a supplemental dose of topiramate equal to approximately one-half of 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. As for all patients, the dose titration should be guided by clinical outcome (e.g. seizure control, avoidance of undesirable effects).

## 4.3 Contraindications

Hypersensitivity to topiramate or to any of the excipients in the medicinal product.

Treatment for prophylaxis of migraine during pregnancy, and in women of childbearing potential if not using an effective method of contraception. In pregnancy, the occurrence of seizures forms a considerable risk for mother and child. Preventing seizures by topiramate, provided given for the right indication, therefore outweighs the risk of malformations. However preventing migraine attacks does not outweigh this risk. Consequently, topiramate for the indication prophylaxis of migraine is contraindicated in pregnancy and women with child bearing potential if not using an effective method of contraception (see section 4.6).
4.4 Special warnings and precautions for use

General:
Adequate hydration while using topiramate is important. Hydration can reduce the risk of nephrolithiasis (see below). Treatment with topiramate may decrease sweating, primarily in paediatric patients. Activities such as exercise or exposure to warm temperatures while using topiramate may increase the risk of heat-related adverse events (see section 4.8).

Patients with rare hereditary problems of fructose intolerance, glucose/galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Patients on long term topiramate treatment should be regularly monitored for weight loss. A dietary supplement or increased food intake may be considered if the patient is losing weight or has inadequate weight gain while on this medication. If clinically significant weight loss occurs, discontinuation of the medication should be considered.

Topiramate should only be used for the prophylaxis of migraine and is not intended for acute treatment. There is limited experience on the use of topiramate in children aged 12 years and under.

Suicidal ideation and behaviour
Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also 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 (43 out of 7,999 treated patients) and at a 3 fold higher incidence than in those treated with placebo (0.15%; 5 out of 3,150 patients treated).

Therefore patients should be monitored for signs of suicidal ideation and behaviours 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 emerges.

Mood disturbances/Depression:
Mood disturbances and depression are common during topiramate treatment (see section 4.8). Patient should be monitored for signs of depression and referred for appropriate treatment if necessary. Rarely psychotic reactions and aggressive behaviour have been observed during the treatment with topiramate.

Renal Impairment:
Caution should be exercised when treating patients with moderate to severe renal impairment (see section 4.2) as subjects with known renal impairment may require longer to reach a steady state at each dose.

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. However, none of these risk factors reliably predict stone formation during topiramate treatment. In addition, patients taking other medication associated with nephrolithiasis (Acetazolamide, Triamteren, Vitamin C >2g/day) may be increased risk.

Such medication should be avoided. Ketogenic diets should be avoided whilst on topiramate therapy since they may create a physiological environment that increases the risk of renal stone formation.

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

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

**Metabolic Acidosis:**

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

Chronic metabolic acidosis in paediatric patients can reduce growth and may cause osteomalacia (rickets). The effect of topiramate on growth and bone-related sequelae has not been systematically investigated in paediatric or adult populations.

Measurement of serum bicarbonate levels is recommended with topiramate therapy, especially in patients with conditions or therapies that predispose to metabolic acidosis. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering).

Chronic metabolic acidosis enhances the risk of renal stone formation.

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

In an in–vitro study, topiramate was a weak inducer of CYP3A4 enzyme formation in a concentration-dependent manner. This may explain why ethinyl-estradiol (a CYP3A4 substrate) exposure was decreased after high doses of topiramate, but not after low doses of topiramate. No other clinical relevant interactions where topiramate acts as a CYP3A4 inducer are reported.

Topiramate inhibits the enzyme CYP 2C19 and influence other substances, which are metabolized via this enzyme, such as diazepam, imipramine, moclobemide, proguanil, omeprazole. However, this has not been studied in vivo.

**Effects of other antiepileptic drugs on topiramate:**

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

The addition or withdrawal of valproic acid or lamotrigine does not produce clinically significant changes in plasma concentrations of topiramate and, therefore, does not warrant dosage adjustment of topiramate. Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse event is not due to a pharmacokinetic interaction.

**Effects of topiramate on other antiepileptic drugs:**

The addition of topiramate to other antiepileptic drugs (carbamazepine, valproic acid, Phenobarbital, primidone or lamotrigine) has no clinically significant effect on their steady-state plasma concentrations. In some patients, treatment with topiramate and phenytoin may result in an increase of plasma concentrations of phenytoin. Consequently, it is advised that any patient on phenytoin should have phenytoin levels monitored.
Other Drug Interactions

Cardiovascular Drugs:

Digoxin:
In a single-dose study, serum digoxin area under plasma concentration curve (AUC) decreased by 12% due to concomitant administration of topiramate. Serum digoxin should be carefully monitored during the first weeks after starting topiramate treatment, when markedly changing the topiramate dose or when discontinuing topiramate treatment.

Diltiazem:
Topiramate at a dose of 150 mg/day reduced the exposure to diltiazem and the metabolite des acetyl diltiazem by 25% and 18% respectively, but does not change the exposure to the metabolite N-demethyl diltiazem. The effect of topiramate may be more pronounced at higher doses. Treatment with diltiazem increased the exposure of topiramate by 20%. The effect of diltiazem may be higher when topiramate is used in combination with other AEDs.

Hydrochlorothiazide (HCTZ):
HCTZ increases the topiramate exposure by approximately 30%. The clinical relevance of this change is unknown, but the addition of HCTZ to topiramate therapy may require an adjustment of the topiramate dose. The pharmacokinetics of HCTZ is not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicate a decrease in serum potassium after topiramate or HCTZ administration, which was greater when HCTZ and topiramate were administered in combination.

Oral Contraceptives:
In a pharmacokinetic interaction study with a combined oral contraceptive (1 mg norethisterone plus 35 mcg ethinyl estradiol) in healthy volunteers, topiramate monotherapy at topiramate monotherapy at doses of 50 mg/day to 200 mg/day did not affect exposure (AUC) of oral contraceptives. However, another study, exposure to ethinylestradiol was significantly decreased at topiramate doses of 200, 400 and 800 mg/day when given as adjunctive therapy in patients taking valproic acid. The levels of norethisterone exposure were not affected. The clinical significance of the changes observed is not known. The risk of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking estrogen containing contraceptive products with topiramate.

Patients who are taking oral contraceptives containing estrogen should be advised to report any change in their menstrual bleeding pattern.

Antidiabetic Drugs:

Metformin:
A drug-drug 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 was given alone and when metformin and topiramate were given simultaneously. The result of this study indicated that metformin mean Cmax and mean AUC 0-12h increased by 18% and 25%, respectively, while mean CL/F decreased 20 % when metformin was co-administered with topiramate. Topiramate did not affect metformin tmax.

The clinical significance of the effect of topiramate on metformin pharmacokinetics is unclear.

Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The extent of change in the clearance is unknown. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear. When topiramate is added or withdrawn in patients on metformin therapy, careful attention should be given to the routine monitoring for adequate control of their diabetic disease state.

Pioglitazone:
The steady state pharmacokinetics of topiramate were not significantly influenced by the concomitant administration of pioglitazone. Topiramate causes a 15% decline in pioglitazone exposure and in the exposure of the active (but less potent) hydroxy- and keto-metabolites of pioglitazone by 16 and 60%, respectively. The clinical significance of these findings is not known. When topiramate is added to pioglitazone therapy or pioglitazone is added to or withdrawn from topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.
Glibenclamide (Glyburide):
Concomitant treatment with topiramate when slowly titrated over 5 weeks and maintained at 150 mg/day for 1 week resulted in a 25% reduction in glyburide AUC24 and a modest reduction in the systemic exposure of the active metabolites, 4-trans-hydroxy-glyburide (M1) and 3-cis-hydroxyglyburide (M2). It may not be excluded that the effect of topiramate is more pronounced at higher doses. 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.

Psychoactive Drugs:
Risperidone:
When administered concomitantly with Topiramate at escalating doses of 100 to 400 mg/day for one week plus the dose titration period, there was a reduction in risperidone systemic exposure (16% and 33% for steady-state AUC at the 250 and 400 mg/day doses, respectively).

Minimal alterations in the pharmacokinetics of the total active moiety (respiridone plus 9-hydroxyrisperidone) and no alterations for 9-hydroxyrispiridone were observed. The effect may be slightly more marked during longer co-treatment and at higher Topiramate doses.

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.

Amitriptyline:
Topiramate does not change the exposure to amitriptyline. However, topiramate increases the exposure to the active amitriptyline metabolite, nortriptyline, by 20%. The clinical relevance of this is not known.

Haloperidole:
Topiramate does not change the exposure to haloperidole. However, topiramate increases the exposure to the active reduced haloperidole metabolite by 31%. The clinical relevance of this is not known.

Venlafaxine:
Venlafaxine does not affect the pharmacokinetics of topiramate. Topiramate 150 mg daily did not affect the pharmacokinetics of venlafaxine or its active metabolite. However, the effect of higher topiramate doses is unknown.

Interactions with alcohol:
Central nervous effects might increase in concomitant use with alcohol. It is recommended not to use topiramate in combination with alcohol or other CNS depressants.

Anti-migraine Drugs:
There are no pharmacokinetic interactions between topiramate and propanolol, dihydroergotamine or pizotifen.
Topiramate does not influence the pharmacokinetics of sumatriptan (oral or subcutaneous).

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

Concomitant intake of carbonic anhydrase inhibitors (e.g. sultiam, zonisamide) and topiramate has not been examined in clinical studies. Combination of these drugs may increase the side effects due to inhibition of the carbonic anhydrase.
Topiramate 100 mg daily has no effect on the pharmacokinetics of flunarazine.
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 drugs during the first trimester of the pregnancy.

Combination therapy appears to increase the risk of malformation and therefore it is important that monotherapy 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 placenta.

Epilepsy:
There are no studies using topiramate in pregnant women. Therefore topiramate should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus.

Specialist advice should be given to women who are likely to become pregnant or who are of childbearing potential. It is recommended that women of childbearing potential use adequate contraception.

In post marketing experience, cases of hypospadias in male infants exposed in utero to topiramate, with or without other anticonvulsants, have been reported. However, a causal relationship with topiramate has not been established.

In pregnancy, if seizure prophylaxis is impaired or discontinued, this may bring about a considerable risk for the mother as well as for the foetus, which probably is more severe than the risk of malformation. During pregnancy, antiepileptic drugs should consequently be prescribed with consideration of these risks.

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

Lactation:
Topiramate is excreted in the human breast milk. Limited observations suggest a plasma milk ratio of 1:1. Therefore topiramate should only be used during breastfeeding if the potential benefits for the mother outweigh the potential risks to the child.

4.7 Effects on ability to drive and use machines
Topiramate may have a major influence on the ability to drive and use machines.
Topiramate acts on the central nervous system and may produce drowsiness, dizziness and other related symptoms that may affect the ability to concentrate when sharpened attention is required. Patients should be advised to exercise caution when driving or using machines until the individual patients experience with the drug is established.

4.8 Undesirable effects
The safety profile for topiramate is based on data from subjects and patients in adjunctive therapy trials.
### Frequency of Adverse Events

<table>
<thead>
<tr>
<th>Organ System Disorder</th>
<th>Very common (≥1/10)</th>
<th>Common (≥1/100 and &lt;1/10)</th>
<th>Uncommon (≥1/1000 and &lt;1/100)</th>
<th>Rare (≥1/10000 and &lt;1/1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>Dizziness, fatigue, somnolence, nervousness, headache, nausea</td>
<td>Skeletal pain, allergic reaction, insomnia</td>
<td>Metabolic acidosis</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
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<tr>
<td>Blood and lymphatic system disorders</td>
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<tr>
<td>Psychiatric disorders</td>
<td>Difficulty with memory, anorexia, confusion and psychomotor slowing, depression, concentration disturbances, anxiety</td>
<td>Apathy, asthenia, euphoria, emotional lability, agitation, cognitive problems, decreased libido, aggressive reactions, psychosis or psychotic symptoms</td>
<td>hallucinations, personality disorders, suicidal ideation, suicidal attempts</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
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<td></td>
<td></td>
<td>Dyspnoea</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td>Constipation, abdominal pain</td>
<td>Diarrhoea, vomiting and dry mouth</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia</td>
<td>Folliculitis and pruritus</td>
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<tr>
<td>Renal and urinary disorders</td>
<td>Urinary incontinence, nephrolithiasis</td>
<td></td>
<td></td>
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<tr>
<td>Nervous system disorders</td>
<td>Ataxia, paraesthesia, speech disorders, aphasia</td>
<td>Tremor, co-ordination abnormal, abnormal gait, nystagmus, taste perversion</td>
<td>Hypokinesia, stupor</td>
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<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td>Increase in liver enzymes</td>
<td></td>
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<tr>
<td>Eye disorders</td>
<td>Diplopia, abnormal vision</td>
<td></td>
<td>Acute myopia and secondary angle closure glaucoma, eye pain</td>
<td></td>
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<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td>Menstrual disturbances</td>
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</table>

In patients treated with topiramate as adjunctive therapy, approximately 1 case of thrombo-embolic events per 100 patient years has been reported. Of these, the majority was treated for more than half a year and had more than one risk factor. No relation to topiramate could be established.

Since topiramate has most frequently been co-administered with other antiepileptic agents, it is difficult to determine which agents, if any, are associated with adverse effects.

Qualitatively, the types of adverse events observed in monotherapy trials were generally similar to those observed during adjunctive therapy trials. With the exception of paraesthesia and fatigue, these adverse events were reported at similar or lower incidence rates in monotherapy trials. In double-blind clinical trials clinically relevant adverse events occurring at an incidence greater than or equal to 10% in
the topiramate-treated adult patients included: paraesthesia, headache, fatigue, dizziness, somnolence, weight decrease, nausea, and anorexia.

From marketing use, rare reports of increase in liver enzymes, metabolic acidosis and isolated reports of hepatitis and hepatic failure have been received in patients treated with topiramate.

Clinical trial data indicates that topiramate has been associated with an average decrease of 4 mmol/l in the serum bicarbonate level (see also section 4.4). Oligohidrosis sometimes with accompanying symptoms of fever and flushing has been reported rarely with the use of topiramate. The majority of these reports have been in children. Suicide related events have been uncommonly reported (see section 4.4).

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

There have been rare reports of acute myopia and secondary angle closure glaucoma in patients treated with topiramate (see also section 4.4). Symptoms include acute onset of decreased visual acuity and/or ocular pain typically within 1 month of initiating topiramate therapy. Paediatric patients as well as adults may be affected.

From post-marketing use, very rare reports of transient blindness have been received. However, a casual relationship with the treatment has not been established.

In double-blind clinical trials for migraine, the incidence of dose related side effects were in general lower than in epilepsy trials, because lower doses were used in the migraine trials.

4.9 Overdose

Signs and symptoms:
Signs and symptoms included drowsiness, speech disturbances, blurred vision, diplopia, impaired mentation, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness, depression and seizures. The clinical consequences were generally not severe but patient 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. In acute topiramate overdose where the ingestion is recent, the gastro-intestinal tract should be emptied by gastric lavage or activated charcoal should be given to prevent the absorption of topiramate. 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 groups: Other antiepileptics
ATC-code: N03AX11

Topiramate is a novel antiepileptic agent classified as a sulphamate-substituted monosaccharide. Three pharmacological properties of topiramate have been identified that may contribute to its anticonvulsant activity.

Topiramate reduces the frequency at which action potentials are generated when neurones are subjected to a sustained depolarisation indicative of a state-dependent blockade of voltage-sensitive sodium channels.

Topiramate enhances the activity of GABA at some types of GABA receptors. Topiramate weakly antagonises the excitatory activity of kainate/AMPA subtype of glutamate receptor but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype.
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 multicenter, 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 multicenter, 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 from base period for 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. Differences were not statistically significant.

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

5.2 Pharmacokinetic properties

Absorption:
Recovery of radioactivity from the urine indicates that the mean extent of absorption of a 100 mg dose of 14C topiramate was at least 81 %. There is no clinically significant effect of food on topiramate.

Distribution:
The mean apparent volume of distribution has been measured as 0.55-0.8 l/kg for single doses up to 1200mg. There is an effect of gender on the volume of distribution, where the distribution volume in females is approximately 50% of that for males. Topiramate is known to bind to erythrocytes but the binding is likely to be saturated at 3-10 µg/ml. Generally 13-17% of topiramate is bound to plasma proteins.
After oral intake of 400 mg, Cmax is reached after approximately 2 hours. There are no data from intravenous administration. Based on data from urine, the bioavailability may be estimated to approximately 50%. The variability in the kinetics is 25-35%. There is no information concerning distribution to CSF.

Metabolism:
Topiramate is moderately metabolized (approximately 20%) in healthy volunteers. After simultaneous administration of antiepileptics with known enzyme inducing effect, the metabolism may increase up to 50%. Six metabolites have been isolated, characterised and identified from plasma, urine and faeces of humans.

Elimination:
In humans the major route of elimination of topiramate and its metabolites is via the kidney. Renal clearance is approximately 18 ml/min. This is less than expected and indicates a tubular reabsorption of topiramate. Overall, following oral administration in humans, plasma clearance is approximately 20 to 30 ml/min.

Special patient Populations:
Renal impairment:
Topiramate has linear pharmacokinetics with a dose-proportional increase of the plasma concentration in the tested dose range of 100-800 mg/day. Patients with normal renal function may take 4 to 8 days to reach steady-state plasma concentrations whilst patients with moderate to severe renal impairment may take 10 – 15 days. The mean maximal plasma concentration (Cmax) in healthy volunteers following multiple, twice daily oral doses of 100 mg was approximately 7 µg/ml. Following administration of multiple doses of 50 mg and 100 mg topiramate twice daily, the mean plasma half-life was approximately 21 hours.
The plasma and renal clearance of topiramate are decreased in patients with impaired renal function. Compared to normal renal function (creatinine clearance >70 mg/min/1.73 m²), topiramate clearance was 42% lower in patients with moderate renal impairment (creatinine clearance <30-69 ml/min) and 54% lower in patients with severe renal impairment (creatinine clearance <30 ml/min). In some patients with severe renal impairment, the reduction in clearance can be larger. In general, half of the usual daily dose is recommended in patients with moderate or severe renal impairment.

Hepatic impairment:
Plasma clearance of topiramate is reduced with 20-30% in patients with moderate to severe hepatic impairment.

Elderly Patients:
Plasma clearance of topiramate in elderly patients, in the absence of underlying renal disease, is unchanged.

Paediatric Patients:
The pharmacokinetics of topiramate in children, as in adults receiving adjunctive therapy, are linear, with clearance independent of dose and steady-state plasma concentrations increasing in proportion to dose. Children, however, have a higher clearance and shorter elimination half-life. Consequently, the plasma concentrations of topiramate for the same mg/kg dose may be lower in children compared to adults. As in adults, hepatic enzyme inducing antiepileptic drugs decrease 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 (anemia). Toxicity was evident at systemic exposures of animals which were below that expected in patients given recommended therapy. 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 that expected in patients given recommended therapy. The human risk is unknown, but cannot be excluded. Moderate inhibition of a rapid potassium channel has been demonstrated in vitro, suggesting a potential risk for QT prolongation at high doses in the presence of other arrhythmogenic factors.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sugar Spheres (which contain sucrose, maize starch)
Povidone
Opadry-II-85F18378 White: (which contain polyvinyl alcohol-part hydrolysed, titanium dioxide, macrogol, talc)
Aniseed Flavour
Saccharin Sodium (E 954)
Magnesium Stearate

Capsule Body and Cap Composition:
Titanium Dioxide (E-171)
Gelatin

Black Printing Ink:
Shellac
Ethanol
Isopropanol
Butanol
Propylene glycol
Water, purified
Strong ammonia solution
Potassium hydroxide
Black iron oxide (E172)
6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
30 months

6.4 **Special precautions for storage**
Store in the original container. Keep the container tightly closed in order to protect from moisture.

6.5 **Nature and contents of container**
High density polyethylene bottle with polypropylene induction sealed cap containing a desiccant (silica gel).

Pack sizes: 14, 20, 28, 56 and 60 capsules.
Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements.

7 **MARKETING AUTHORISATION HOLDER**
Arrow Generics Ltd
Unit 2, Eastman Way
Stevenage, Hertfordshire
SG1 4SZ
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 18909/0238

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
21/08/2009

10 **DATE OF REVISION OF THE TEXT**
21/08/2009
NAME OF THE MEDICINAL PRODUCT
Topiramate 25mg Capsules, hard

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 25mg of topiramate.
Each capsule also contains 69 mg of sucrose. For a full list of excipients, see section 6.1

PHARMACEUTICAL FORM
Capsule, hard (capsule).
White opaque body and white opaque cap. The body has ‘25’ printed in black and the cap has ‘>’ over ‘T’ printed in black.

CLINICAL PARTICULARS
Therapeutic indications
Adults and adolescents aged 12 years and older: Adjunctive therapy for epileptic patients with partial onset seizures and/or generalised tonic-clonic seizures.

Adults and adolescents aged 12 years and older: Monotherapy of epileptic patients with partial onset seizures and/or generalised tonic-clonic seizures.

Posology and method of administration
General:
For optimal seizure control in both adults and adolescents and to avoid dose dependent undesirable effects, it is recommended that therapy be initiated at a low dose followed by titration to a clinically effective dose. When concomitant antiepilepsy drugs (AED) 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 is recommended.

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

Topiramate should be withdrawn gradually to minimise the potential of increased seizure frequency. In clinical trials, dosages were decreased by 50-100 mg/day at weekly intervals. In some patients, dose decrease was accelerated without complications.

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

For doses not realisable/practicable with this medicinal product other strengths of this medicinal product or other pharmaceutical forms and products are available.

Method of administration:
Topiramate Capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoon) of soft food e.g. apple sauce, mashed banana, ice cream or yoghurt. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use.

Topiramate can be taken with or without a meal with a sufficient quantity of liquid.

Adjunctive Therapy in Adults and Adolescents aged 12 years and over:

Titration should begin at 25 - 50 mg nightly for 7 days. The dosage should then be increased at 7 day or 14 day intervals by increments of 25 - 50 mg/day, administered in two divided doses. If the patient is unable to tolerate the titration regimen, smaller dose increments or longer intervals between dose increments may be used. Dose titration should be guided by clinical outcome.

The minimal effective dose as adjunctive therapy is 200 mg/day. The usual total daily dose is 200 mg to 400 mg administered in two divided doses. Some patients may achieve efficacy with a once-a-day dosing. Some patients may require higher doses. The maximum recommended daily dose is 800 mg.
Monotherapy for adults and adolescents aged 12 years and over:
Titration should begin at 25 mg nightly for 7 days. The dosage should then be increased at 7 or 14 day 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 dose increments or longer intervals between dose increments may be used. Dose titration should be guided by clinical outcome.

The recommended initial target dose for topiramate monotherapy in adults is 100 mg/day. The maximum recommended daily dose is 400mg

Prophylaxis of Migraine in Adults:
Titration should begin at 25 mg nightly for 7 days. The dosage should then be increased at 7 day intervals by increments of 25 mg/day. If the patient is unable to tolerate the titration regimen, longer intervals between dose adjustments may be used.

The recommended total daily dose of topiramate for prophylaxis of migraine in adults is 100 mg/day administered in two divided doses. Higher doses do not result in increased benefit.

Some patients may experience a benefit at a total daily dose of 50 mg/day. Dose and titration rate should be guided by clinical outcome.

There are no efficacy or safety data for longer than six months in the prophylactic treatment of migraine.

Impaired renal function:
For patients with moderate (creatinine clearance 30-69 ml/min) and severe (creatinine clearance <30 ml/min) renal dysfunction, it is recommended to start with half of the daily dose than usual and to titrate with smaller steps and at slower pace as is usual. As with all patients, the titrations schedule should be guided by clinical outcome with the knowledge that it may require longer to reach steady-state after each dose change in renally impaired patients. In patients with moderate or severe renal impairment, it may take 10 to 15 days to reach steady concentrations as compared to 4 to 8 days in patients with normal renal function.

Impaired hepatic function:
In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased. (see section 4.4 and 5.2).

Patients undergoing haemodialysis:
Topiramate is removed from plasma by haemodialysis. Therefore a supplemental dose of topiramate equal to approximately one-half of 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. As for all patients, the dose titration should be guided by clinical outcome (e.g. seizure control, avoidance of undesirable effects).

4.3 Contraindications
Hypersensitivity to topiramate or to any of the excipients in the medicinal product.

Treatment for prophylaxis of migraine during pregnancy, and in women of childbearing potential if not using an effective method of contraception. In pregnancy, the occurrence of seizures forms a considerable risk for mother and child. Preventing seizures by topiramate, provided given for the right indication, therefore outweighs the risk of malformations. However preventing migraine attacks does not outweigh this risk. Consequently, topiramate for the indication prophylaxis of migraine is contraindicated in pregnancy and women with child bearing potential if not using an effective method of contraception (see section 4.6).

4.4 Special warnings and precautions for use
General:
Adequate hydration while using topiramate is important. Hydration can reduce the risk of nephrolithiasis (see below). Treatment with topiramate may decrease sweating, primarily in paediatric
patients. Activities such as exercise or exposure to warm temperatures while using topiramate may increase the risk of heat-related adverse events (see section 4.8).

Patients with rare hereditary problems of fructose intolerance, glucose/galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Patients on long term topiramate treatment should be regularly monitored for weight loss. A dietary supplement or increased food intake may be considered if the patient is losing weight or has inadequate weight gain while on this medication. If clinically significant weight loss occurs, discontinuation of the medication should be considered.

Topiramate should only be used for the prophylaxis of migraine and is not intended for acute treatment. There is limited experience on the use of topiramate in children aged 12 years and under.

Suicidal ideation and behaviour
Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also 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 (43 out of 7,999 treated patients) and at a 3 fold higher incidence than in those treated with placebo (0.15%; 5 out of 3,150 patients treated).

Therefore patients should be monitored for signs of suicidal ideation and behaviours 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 emerges.

Mood disturbances/Depression:
Mood disturbances and depression are common during topiramate treatment (see section 4.8). Patient should be monitored for signs of depression and referred for appropriate treatment if necessary. Rarely psychotic reactions and aggressive behaviour have been observed during the treatment with topiramate.

Renal Impairment:
Caution should be exercised when treating patients with moderate to severe renal impairment (see section 4.2) as subjects with known renal impairment may require longer to reach a steady state at each dose.

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. However, none of these risk factors reliably predict stone formation during topiramate treatment. In addition, patients taking other medication associated with nephrolithiasis (Acetazolamide, Triamteren, Vitamin C >2g/day) may be increased risk.

Such medication should be avoided. Ketogenic diets should be avoided whilst on topiramate therapy since they may create a physiological environment that increases the risk of renal stone formation.

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

Acute myopia and secondary angle closure formation:
Acute myopia associated with secondary angle-closure glaucoma has been reported in both adults and children receiving topiramate.

Symptoms typically occur within 1 month of the start of treatment and include decreased visual acuity and/or ocular pain. Ophthalmological findings include bilateral myopia, anterior chamber shallowing, hyperaemia and increased intra-ocular pressure with or without mydriasis. There may be supraciliary effusion resulting in anterior displacement of the lens and iris. Treatment includes discontinuation of
topiramate as rapidly as is clinically feasible and appropriate measures to reduce intraocular pressure. If increased intra-ocular pressure is suspected, immediate specialist advice should be sought.

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

Chronic metabolic acidosis in paediatric patients can reduce growth and may cause osteomalacia (rickets). The effect of topiramate on growth and bone-related sequelae has not been systematically investigated in paediatric or adult populations. Measurement of serum bicarbonate levels is recommended with topiramate therapy, especially in patients with conditions or therapies that predispose to metabolic acidosis. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering).

Chronic metabolic acidosis enhances the risk of renal stone formation.

4.5 Interaction with other medicinal products and other forms of interaction

In an in–vitro study, topiramate was a weak inducer of CYP3A4 enzyme formation in a concentration-dependent manner. This may explain why ethinyl-estradiol (a CYP3A4 substrate) exposure was decreased after high doses of topiramate, but not after low doses of topiramate. No other clinical relevant interactions where topiramate acts as a CYP3A4 inducer are reported.

Topiramate inhibits the enzyme CYP 2C19 and influence other substances, which are metabolized via this enzyme, such as diazepam, imipramine, moclobemide, proguanil, omeprazole. However, this has not been studied in vivo.

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

The addition or withdrawal of valproic acid or lamotrigine does not produce clinically significant changes in plasma concentrations of topiramate and, therefore, does not warrant dosage adjustment of topiramate. Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse event is not due to a pharmacokinetic interaction.

Effects of topiramate on other antiepileptic drugs:
The addition of topiramate to other antiepileptic drugs (carbamazepine, valproic acid, Phenobarbital, primidone or lamotrign) has no clinically significant effect on their steady-state plasma concentrations. In some patients, treatment with topiramate and phenytoin may result in an increase of plasma concentrations of phenytoin. Consequently, it is advised that any patient on phenytoin should have phenytoin levels monitored.

Other Drug Interactions
Cardiovascular Drugs:
Digoxin:
In a single-dose study, serum digoxin area under plasma concentration curve (AUC) decreased by 12% due to concomitant administration of topiramate. Serum digoxin should be carefully monitored during the first weeks after starting topiramate treatment, when markedly changing the topiramate dose or when discontinuing topiramate treatment.
Diltiazem:
Topiramate at a dose of 150 mg/day reduced the exposure to diltiazem and the metabolite des acetyl diltiazem by 25% and 18% respectively, but does not change the exposure to the metabolite N-demethyl diltiazem. The effect of topiramate may be more pronounced at higher doses. Treatment with diltiazem increased the exposure of topiramate by 20%. The effect of diltiazem may be higher when topiramate is used in combination with other AEDs.

Hydrochlorothiazide (HCTZ):
HCTZ increases the topiramate exposure by approximately 30%. The clinical relevance of this change is unknown, but the addition of HCTZ to topiramate therapy may require an adjustment of the topiramate dose. The pharmacokinetics of HCTZ is not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicate a decrease in serum potassium after topiramate or HCTZ administration, which was greater when HCTZ and topiramate were administered in combination.

Oral Contraceptives:
In a pharmacokinetic interaction study with a combined oral contraceptive (1 mg norethisterone plus 35 mcg ethinyl estradiol) in healthy volunteers, topiramate monotherapy at topiramate monotherapy at doses of 50 mg/day to 200 mg/day did not affect exposure (AUC) of oral contraceptives. However, in another study, exposure to ethinylestradiol was significantly decreased at topiramate doses of 200, 400 and 800 mg/day when given as adjunctive therapy in patients taking valproic acid. The levels of norethisterone exposure were not affected. The clinical significance of the changes observed is not known. The risk of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking estrogen containing contraceptive products with topiramate.

Patients who are taking oral contraceptives containing estrogen should be advised to report any change in their menstrual bleeding pattern.

Antidiabetic Drugs:
Metformin:
A drug-drug 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 was given alone and when metformin and topiramate were given simultaneously. The result of this study indicated that metformin mean Cmax and mean AUC 0-12h increased by 18% and 25%, respectively, while mean CL/F decreased 20 % when metformin was co-administered with topiramate. Topiramate did not affect metformin tmax.

The clinical significance of the effect of topiramate on metformin pharmacokinetics is unclear. Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The extent of change in the clearance is unknown. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear. When topiramate is added or withdrawn in patients on metformin therapy, careful attention should be given to the routine monitoring for adequate control of their diabetic disease state.

Pioglitazone:
The steady state pharmacokinetics of topiramate were not significantly influenced by the concomitant administration of pioglitazone. Topiramate causes a 15% decline in pioglitazone exposure and in the exposure of the active (but less potent) hydroxy- and keto-metabolites of pioglitazone by 16 and 60%, respectively. The clinical significance of these findings is not known. When topiramate is added to pioglitazone therapy or pioglitazone is added to or withdrawn from topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Glibenclamide (Glyburide):
Concomitant treatment with topiramate when slowly titrated over 5 weeks and maintained at 150 mg/day for 1 week resulted in a 25% reduction in glyburide AUC24 and a modest reduction in the systemic exposure of the active metabolites, 4-trans-hydroxy-glyburide (M1) and 3-cis-hydroxyglyburide (M2). It may not be excluded that the effect of topiramate is more pronounced at higher doses. 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.

Psychoactive Drugs:

Risperidone:
When administered concomitantly with Topiramate at escalating doses of 100 to 400 mg/day for one week plus the dose titration period, there was a reduction in risperidone systemic exposure (16% and 33% for steady-state AUC at the 250 and 400 mg/day doses, respectively).

Minimal alterations in the pharmacokinetics of the total active moiety (respiidone plus 9-hydroxyrisperidone) and no alterations for 9-hydroxyrisperidone were observed. The effect may be slightly more marked during longer co-treatment and at higher Topiramate doses.

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.

Amitriptyline:
Topiramate does not change the exposure to amitriptyline. However, topiramate increases the exposure to the active amitriptyline metabolite, nortriptyline, by 20%. The clinical relevance of this is not known.

Haloperidole:
Topiramate does not change the exposure to haloperidole. However, topiramate increases the exposure to the active reduced haloperidole metabolite by 31%. The clinical relevance of this is not known.

Venlafaxine:
Venlafaxine does not affect the pharmacokinetics of topiramate. Topiramate 150 mg daily did not affect the pharmacokinetics of venlafaxine or its active metabolite. However, the effect of higher topiramate doses is unknown.

Interactions with alcohol:
Central nervous effects might increase in concomitant use with alcohol. It is recommended not to use topiramate in combination with alcohol or other CNS depressants.

Anti-migraine Drugs:
There are no pharmacokinetic interactions between topiramate and propanolol, dihydroergotamine or pizotifen.
Topiramate does not influence the pharmacokinetics of sumatriptan (oral or subcutaneous).

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

Concomitant intake of carbonic anhydrase inhibitors (e.g. sulfiame, zonisamide) and topiramate has not been examined in clinical studies. Combination of these drugs may increase the side effects due to inhibition of the carbonic anhydrase.
Topiramate 100 mg daily has no effect on the pharmacokinetics of flunarazine.

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 drugs during the first trimester of the pregnancy.
Combination therapy appears to increase the risk of malformation and therefore it is important that monotherapy 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 placenta.

**Epilepsy:**
There are no studies using topiramate in pregnant women. Therefore topiramate should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus.

Specialist advice should be given to women who are likely to become pregnant or who are of childbearing potential. It is recommended that women of childbearing potential use adequate contraception.

In post marketing experience, cases of hypospadias in male infants exposed in utero to topiramate, with or without other anticonvulsants, have been reported. However, a causal relationship with topiramate has not been established.

In pregnancy, if seizure prophylaxis is impaired or discontinued, this may bring about a considerable risk for the mother as well as for the foetus, which probably is more severe than the risk of malformation. During pregnancy, antiepileptic drugs should consequently be prescribed with consideration of these risks.

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

**Lactation:**
Topiramate is excreted in the human breast milk. Limited observations suggest a plasma milk ratio of 1:1. Therefore topiramate should only be used during breastfeeding if the potential benefits for the mother outweigh the potential risks to the child.

### 4.7 Effects on ability to drive and use machines
Topiramate may have a major influence on the ability to drive and use machines.
Topiramate acts on the central nervous system and may produce drowsiness, dizziness and other related symptoms that may affect the ability to concentrate when sharpened attention is required. Patients should be advised to exercise caution when driving or using machines until the individual patients experience with the drug is established.

### 4.8 Undesirable effects
The safety profile for topiramate is based on data from subjects and patients in adjunctive therapy trials.
<table>
<thead>
<tr>
<th>Organ System Disorder</th>
<th>Very common (≥1/10)</th>
<th>Common (≥1/100 and &lt;1/10)</th>
<th>Uncommon (≥1/1000 and &lt;1/100)</th>
<th>Rare (≥1/10000 and &lt;1/1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>Dizziness, fatigue, somnolence, nervousness, headache, nausea</td>
<td>Skeletal pain, allergic reaction, insomnia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Weight loss</td>
<td>Metabolic acidosis</td>
<td></td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td>Anaemia, epistaxis, purpura, leucopenia, thrombocytopenia</td>
<td></td>
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<tr>
<td>Psychiatric disorders</td>
<td>Difficulty with memory, anorexia, confusion and psychomotor slowing, depression, concentration disturbances, anxiety</td>
<td>Apathy, asthena, euphoria, emotional lability, agitation, cognitive problems, decreased libido, aggressive reactions, psychosis or psychotic symptoms</td>
<td></td>
<td>Hallucinations, personality disorders, suicidal ideation, suicidal attempts</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td>Diapnoea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Constipation, abdominal pain</td>
<td>Diarrhoea, vomiting and dry mouth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia</td>
<td>Folliculitis and pruritus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Urinary incontinence, nephrolithiasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Ataxia, paraesthesia, speech disorders, aphasia</td>
<td>Tremor, co-ordination abnormal, abnormal gait, nystagmus, taste perversion</td>
<td></td>
<td>Hypokinesia, stupor</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td>Increase in liver enzymes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Diplopia, abnormal vision</td>
<td>Acute myopia and secondary angle closure glaucoma, eye pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Menstrual disturbances</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

In patients treated with topiramate as adjunctive therapy, approximately 1 case of thrombo-embolic events per 100 patient years has been reported. Of these, the majority was treated for more than half a year and had more than one risk factor. No relation to topiramate could be established. Since topiramate has most frequently been co-administered with other antiepileptic agents, it is difficult to determine which agents, if any, are associated with adverse effects.

Qualitatively, the types of adverse events observed in monotherapy trials were generally similar to those observed during adjunctive therapy trials. With the exception of paraesthesia and fatigue, these adverse events were reported at similar or lower incidence rates in monotherapy trials. In double-blind clinical trials clinically relevant adverse events occurring at an incidence greater than or equal to 10% in
the topiramate-treated adult patients included: paraesthesia, headache, fatigue, dizziness, somnolence, weight decrease, nausea, and anorexia.

From marketing use, rare reports of increase in liver enzymes, metabolic acidosis and isolated reports of hepatitis and hepatic failure have been received in patients treated with topiramate.

Clinical trial data indicates that topiramate has been associated with an average decrease of 4 mmol/l in the serum bicarbonate level (see also section 4.4). Oligohidrosis sometimes with accompanying symptoms of fever and flushing has been reported rarely with the use of topiramate. The majority of these reports have been in children. Suicide related events have been uncommonly reported (see section 4.4).

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

There have been rare reports of acute myopia and secondary angle closure glaucoma in patients treated with topiramate (see also section 4.4). Symptoms include acute onset of decreased visual acuity and/or ocular pain typically within 1 month of initiating topiramate therapy. Paediatric patients as well as adults may be affected.

From post-marketing use, very rare reports of transient blindness have been received. However, a casual relationship with the treatment has not been established.

In double-blind clinical trials for migraine, the incidence of dose related side effects were in general lower than in epilepsy trials, because lower doses were used in the migraine trials.

### 4.9 Overdose

**Signs and symptoms:**
Signs and symptoms included drowsiness, speech disturbances, blurred vision, diplopia, impaired mentation, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness, depression and seizures. The clinical consequences were generally not severe but patient 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. In acute topiramate overdose where the ingestion is recent, the gastro-intestinal tract should be emptied by gastric lavage or activated charcoal should be given to prevent the absorption of topiramate. 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 groups: Other antiepileptics
ATC-code: N03AX11

Topiramate is a novel antiepileptic agent classified as a sulphamate-substituted monosaccharide. Three pharmacological properties of topiramate have been identified that may contribute to its anticonvulsant activity.

Topiramate reduces the frequency at which action potentials are generated when neurones are subjected to a sustained depolarisation indicative of a state-dependent blockade of voltage-sensitive sodium channels.

Topiramate enhances the activity of GABA at some types of GABA receptors. Topiramate weakly antagonises the excitatory activity of kainate/AMPA subtype of glutamate receptor but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype.
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 multicenter, 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 multicenter, 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 from base period for 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. Differences were not statistically significant.

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

5.2 Pharmacokinetic properties

Absorption:
Recovery of radioactivity from the urine indicates that the mean extent of absorption of a 100 mg dose of 14C topiramate was at least 81%. There is no clinically significant effect of food on topiramate.

Distribution:
The mean apparent volume of distribution has been measured as 0.55-0.8 l/kg for single doses up to 1200mg. There is an effect of gender on the volume of distribution, where the distribution volume in females is approximately 50% of that for males. Topiramate is known to bind to erythrocytes but the binding is likely to be saturated at 3-10 µg/ml. Generally 13-17% of topiramate is bound to plasma proteins.
After oral intake of 400 mg, Cmax is reached after approximately 2 hours. There are no data from intravenous administration. Based on data from urine, the bioavailability may be estimated to approximately 50%. The variability in the kinetics is 25-35%. There is no information concerning distribution to CSF.

Metabolism:
Topiramate is moderately metabolized (approximately 20%) in healthy volunteers. After simultaneous administration of antiepileptics with known enzyme inducing effect, the metabolism may increase up to 50%. Six metabolites have been isolated, characterised and identified from plasma, urine and faeces of humans.

Elimination:
In humans the major route of elimination of topiramate and its metabolites is via the kidney. Renal clearance is approximately 18 ml/min. This is less than expected and indicates a tubular reabsorption of topiramate. Overall, following oral administration in humans, plasma clearance is approximately 20 to 30 ml/min.

Special patient Populations:
Renal impairment:
Topiramate has linear pharmacokinetics with a dose-proportional increase of the plasma concentration in the tested dose range of 100-800 mg/day. Patients with normal renal function may take 4 to 8 days to reach steady-state plasma concentrations whilst patients with moderate to severe renal impairment may take 10 – 15 days. The mean maximal plasma concentration (Cmax) in healthy volunteers following multiple, twice daily oral doses of 100 mg was approximately 7 µg/ml. Following administration of multiple doses of 50 mg and 100 mg topiramate twice daily, the mean plasma half-life was approximately 21 hours.
The plasma and renal clearance of topiramate are decreased in patients with impaired renal function. Compared to normal renal function (creatinine clearance >70 mg/min/1.73 m²), topiramate clearance was 42% lower in patients with moderate renal impairment (creatinine clearance <30-69 ml/min) and 54% lower in patients with severe renal impairment (creatinine clearance <30 ml/min). In some patients with severe renal impairment, the reduction in clearance can be larger. In general, half of the usual daily dose is recommended in patients with moderate or severe renal impairment.

**Hepatic impairment:**
Plasma clearance of topiramate is reduced with 20-30% in patients with moderate to severe hepatic impairment.

**Elderly Patients:**
Plasma clearance of topiramate in elderly patients, in the absence of underlying renal disease, is unchanged.

**Paediatric Patients:**
The pharmacokinetics of topiramate in children, as in adults receiving adjunctive therapy, are linear, with clearance independent of dose and steady-state plasma concentrations increasing in proportion to dose. Children, however, have a higher clearance and shorter elimination half-life. Consequently, the plasma concentrations of topiramate for the same mg/kg dose may be lower in children compared to adults. As in adults, hepatic enzyme inducing antiepileptic drugs decrease 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 (anemia). Toxicity was evident at systemic exposures of animals which were below that expected in patients given recommended therapy. 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 that expected in patients given recommended therapy. The human risk is unknown, but cannot be excluded. Moderate inhibition of a rapid potassium channel has been demonstrated in vitro, suggesting a potential risk for QT prolongation at high doses in the presence of other arrhythmogenic factors.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients
Sugar Spheres (which contain sucrose, maize starch)
Povidone
Opadry-II-85F18378 White: (which contain polyvinyl alcohol-part hydrolysed, titanium dioxide, macrogol, talc)
Aniseed Flavour
Saccharin Sodium (E 954)
Magnesium Stearate

**Capsule Body and Cap Composition:**
Titanium Dioxide (E-171)
Gelatin

**Black Printing Ink:**
Shellac
Ethanol
Isopropanol
Butanol
Propylene glycol
Water, purified
Strong ammonia solution
Potassium hydroxide
Black iron oxide (E172)
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
30 months

6.4 Special precautions for storage
Store in the original container. Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container
High density polyethylene bottle with polypropylene induction sealed cap containing a desiccant (silica gel).

Pack sizes: 14, 20, 28, 56 and 60 capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Arrow Generics Ltd
Unit 2, Eastman Way
Stevenage, Hertfordshire
SG1 4SZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 18909/0239

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/08/2009

10 DATE OF REVISION OF THE TEXT
21/08/2009
1 NAME OF THE MEDICINAL PRODUCT
Topiramate 15mg Capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 15mg of topiramate.
Each capsule also contains 41.4 mg of sucrose. For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Capsule, hard (capsule).
White opaque body and white opaque cap. The body has ‘15’ printed in black and the cap has ‘>’ over ‘Ti’ printed in black.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Adults and adolescents aged 12 years and older: Adjunctive therapy for epileptic patients with partial onset seizures and/or generalised tonic-clonic seizures.

Adults and adolescents aged 12 years and older: Monotherapy of epileptic patients with partial onset seizures and/or generalised tonic-clonic seizures.


4.2 Posology and method of administration
General:
For optimal seizure control in both adults and adolescents and to avoid dose dependent undesirable effects, it is recommended that therapy be initiated at a low dose followed by -titration to a clinically effective dose. When concomitant antiepilepsy drugs (AED) 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 is recommended.

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

Topiramate should be withdrawn gradually to minimise the potential of increased seizure frequency. In clinical trials, dosages were decreased by 50-100 mg/day at weekly intervals. In some patients, dose decrease was accelerated without complications.

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

For doses not realisable/practicable with this medicinal product other strengths of this medicinal product or other pharmaceutical forms and products are available.

Method of administration:
Topiramate Capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoon) of soft food e.g. apple sauce, mashed banana, ice cream or yoghurt. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use.

Topiramate can be taken with or without a meal with a sufficient quantity of liquid.

Adjunctive Therapy in Adults and Adolescents aged 12 years and over:

Titration should begin at 25 - 50 mg nightly for 7 days. The dosage should then be increased at 7 day or 14 day intervals by increments of 25 - 50 mg/day, administered in two divided doses. If the patient is unable to tolerate the titration regimen, smaller dose increments or longer intervals between dose increments may be used. Dose titration should be guided by clinical outcome.

The minimal effective dose as adjunctive therapy is 200 mg/day. The usual total daily dose is 200 mg to 400 mg administered in two divided doses. Some patients may achieve efficacy with a once-a-day dosing. Some patients may require higher doses. The maximum recommended daily dose is 800 mg.
Monotherapy for adults and adolescents aged 12 years and over:
Titration should begin at 25 mg nightly for 7 days. The dosage should then be increased at 7 or 14 day 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 dose increments or longer intervals between dose increments may be used. Dose titration should be guided by clinical outcome.

The recommended initial target dose for topiramate monotherapy in adults is 100 mg/day. The maximum recommended daily dose is 400mg

Prophylaxis of Migraine in Adults:
Titration should begin at 25 mg nightly for 7 days. The dosage should then be increased at 7 day intervals by increments of 25 mg/day. If the patient is unable to tolerate the titration regimen, longer intervals between dose adjustments may be used.

The recommended total daily dose of topiramate for prophylaxis of migraine in adults is 100 mg/day administered in two divided doses. Higher doses do not result in increased benefit.

Some patients may experience a benefit at a total daily dose of 50 mg/day. Dose and titration rate should be guided by clinical outcome.

There are no efficacy or safety data for longer than six months in the prophylactic treatment of migraine.

Impaired renal function:
For patients with moderate (creatinine clearance 30-69 ml/min) and severe (creatinine clearance <30 ml/min) renal dysfunction, it is recommended to start with half of the daily dose than usual and to titrate with smaller steps and at slower pace as is usual. As with all patients, the titrations schedule should be guided by clinical outcome with the knowledge that it may require longer to reach steady-state after each dose change in renally impaired patients. In patients with moderate or severe renal impairment, it may take 10 to 15 days to reach steady concentrations as compared to 4 to 8 days in patients with normal renal function.

Impaired hepatic function:
In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased. (see section 4.4 and 5.2).

Patients undergoing haemodialysis:
Topiramate is removed from plasma by haemodialysis. Therefore a supplemental dose of topiramate equal to approximately one-half of 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. As for all patients, the dose titration should be guided by clinical outcome (e.g. seizure control, avoidance of undesirable effects).

4.3 Contraindications
Hypersensitivity to topiramate or to any of the excipients in the medicinal product.

Treatment for prophylaxis of migraine during pregnancy, and in women of childbearing potential if not using an effective method of contraception. In pregnancy, the occurrence of seizures forms a considerable risk for mother and child. Preventing seizures by topiramate, provided given for the right indication, therefore outweighs the risk of malformations. However preventing migraine attacks does not outweigh this risk. Consequently, topiramate for the indication prophylaxis of migraine is contraindicated in pregnancy and women with child bearing potential if not using an effective method of contraception (see section 4.6).

4.4 Special warnings and precautions for use
General:
Adequate hydration while using topiramate is important. Hydration can reduce the risk of nephrolithiasis (see below). Treatment with topiramate may decrease sweating, primarily in paediatric
patients. Activities such as exercise or exposure to warm temperatures while using topiramate may increase the risk of heat-related adverse events (see section 4.8).

Patients with rare hereditary problems of fructose intolerance, glucose/galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Patients on long term topiramate treatment should be regularly monitored for weight loss. A dietary supplement or increased food intake may be considered if the patient is losing weight or has inadequate weight gain while on this medication. If clinically significant weight loss occurs, discontinuation of the medication should be considered.

Topiramate should only be used for the prophylaxis of migraine and is not intended for acute treatment. There is limited experience on the use of topiramate in children aged 12 years and under.

**Suicidal ideation and behaviour**

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also 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 (43 out of 7,999 treated patients) and at a 3 fold higher incidence than in those treated with placebo (0.15%; 5 out of 3,150 patients treated).

Therefore patients should be monitored for signs of suicidal ideation and behaviours 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 emerges.

**Mood disturbances/Depression:**

Mood disturbances and depression are common during topiramate treatment (see section 4.8). Patient should be monitored for signs of depression and referred for appropriate treatment if necessary. Rarely psychotic reactions and aggressive behaviour have been observed during the treatment with topiramate.

**Renal Impairment:**

Caution should be exercised when treating patients with moderate to severe renal impairment (see section 4.2) as subjects with known renal impairment may require longer to reach a steady state at each dose.

**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. However, none of these risk factors reliably predict stone formation during topiramate treatment. In addition, patients taking other medication associated with nephrolithiasis (Acetazolamide, Triamteren, Vitamin C >2g/day) may be increased risk. Such medication should be avoided. Ketogenic diets should be avoided whilst on topiramate therapy since they may create a physiological environment that increases the risk of renal stone formation.

**Hepatic Impairment:**

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

**Acute myopia and secondary angle closure formation:**

Acute myopia associated with secondary angle-closure glaucoma has been reported in both adults and children receiving topiramate.

Symptoms typically occur within 1 month of the start of treatment and include decreased visual acuity and/or ocular pain. Ophthalmological findings include bilateral myopia, anterior chamber shallowing, hyperaemia and increased intra-ocular pressure with or without mydriasis. There may be supraciliary effusion resulting in anterior displacement of the lens and iris. Treatment includes discontinuation of
topiramate as rapidly as is clinically feasible and appropriate measures to reduce intraocular pressure. If increased intra-ocular pressure is suspected, immediate specialist advice should be sought.

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

Chronic metabolic acidosis in paediatric patients can reduce growth and may cause osteomalacia (rickets). The effect of topiramate on growth and bone-related sequelae has not been systematically investigated in paediatric or adult populations. Measurement of serum bicarbonate levels is recommended with topiramate therapy, especially in patients with conditions or therapies that predispose to metabolic acidosis. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering).

Chronic metabolic acidosis enhances the risk of renal stone formation.

4.5 Interaction with other medicinal products and other forms of interaction

In an in–vitro study, topiramate was a weak inducer of CYP3A4 enzyme formation in a concentration-dependent manner. This may explain why ethinyl-estradiol (a CYP3A4 substrate) exposure was decreased after high doses of topiramate, but not after low doses of topiramate. No other clinical relevant interactions where topiramate acts as a CYP3A4 inducer are reported.

Topiramate inhibits the enzyme CYP 2C19 and influence other substances, which are metabolized via this enzyme, such as diazepam, imipramine, moclobemide, proguanil, omeprazole. However, this has not been studied in vivo.

**Effects of other antiepileptic drugs on topiramate:**
Phenytoin and carbamazepine decrease the plasma concentration of topiramate. The addition or withdrawal of phenytoin or carbamazepine to topiramate therapy may require an adjustment in dosage of topiramate. This should be done by titrating to clinical effect.

The addition or withdrawal of valproic acid or lamotrigine does not produce clinically significant changes in plasma concentrations of topiramate and, therefore, does not warrant dosage adjustment of topiramate. Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse event is not due to a pharmacokinetic interaction.

**Effects of topiramate on other antiepileptic drugs:**
The addition of topiramate to other antiepileptic drugs (carbamazepine, valproic acid, Phenobarbital, primidone or lamotrigine) has no clinically significant effect on their steady-state plasma concentrations. In some patients, treatment with topiramate and phenytoin may result in an increase of plasma concentrations of phenytoin. Consequently, it is advised that any patient on phenytoin should have phenytoin levels monitored.

**Other Drug Interactions**

**Cardiovascular Drugs:**

**Digoxin:**
In a single-dose study, serum digoxin area under plasma concentration curve (AUC) decreased by 12% due to concomitant administration of topiramate. Serum digoxin should be carefully monitored during the first weeks after starting topiramate treatment, when markedly changing the topiramate dose or when discontinuing topiramate treatment.
Diltiazem:
Topiramate at a dose of 150 mg/day reduced the exposure to diltiazem and the metabolite des acetyl diltiazem by 25% and 18% respectively, but does not change the exposure to the metabolite N-demethyl diltiazem. The effect of topiramate may be more pronounced at higher doses. Treatment with diltiazem increased the exposure of topiramate by 20%. The effect of diltiazem may be higher when topiramate is used in combination with other AEDs.

Hydrochlorothiazide (HCTZ):
HCTZ increases the topiramate exposure by approximately 30%. The clinical relevance of this change is unknown, but the addition of HCTZ to topiramate therapy may require an adjustment of the topiramate dose. The pharmacokinetics of HCTZ is not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicate a decrease in serum potassium after topiramate or HCTZ administration, which was greater when HCTZ and topiramate were administered in combination.

Oral Contraceptives:
In a pharmacokinetic interaction study with a combined oral contraceptive (1 mg norethisterone plus 35 mcg ethinyl estradiol) in healthy volunteers, topiramate monotherapy at doses of 50 mg/day to 200 mg/day did not affect exposure (AUC) of oral contraceptives. However, in another study, exposure to ethinylestradiol was significantly decreased at topiramate doses of 200, 400 and 800 mg/day when given as adjunctive therapy in patients taking valproic acid. The levels of norethisterone exposure were not affected. The clinical significance of the changes observed is not known. The risk of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking estrogen containing contraceptive products with topiramate.

Patients who are taking oral contraceptives containing estrogen should be advised to report any change in their menstrual bleeding pattern.

Antidiabetic Drugs:
Metformin:
A drug-drug 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 was given alone and when metformin and topiramate were given simultaneously. The result of this study indicated that metformin mean Cmax and mean AUC 0-12h increased by 18% and 25%, respectively, while mean CL/F decreased 20 % when metformin was co-administered with topiramate. Topiramate did not affect metformin tmax.

The clinical significance of the effect of topiramate on metformin pharmacokinetics is unclear.

Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The extent of change in the clearance is unknown. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear. When topiramate is added or withdrawn in patients on metformin therapy, careful attention should be given to the routine monitoring for adequate control of their diabetic disease state.

Pioglitazone:
The steady state pharmacokinetics of topiramate were not significantly influenced by the concomitant administration of pioglitazone. Topiramate causes a 15% decline in pioglitazone exposure and in the exposure of the active (but less potent) hydroxy- and keto-metabolites of pioglitazone by 16 and 60%, respectively. The clinical significance of these findings is not known. When topiramate is added to pioglitazone therapy or pioglitazone is added to or withdrawn from topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Glibenclamide (Glyburide):
Concomitant treatment with topiramate when slowly titrated over 5 weeks and maintained at 150 mg/day for 1 week resulted in a 25% reduction in glyburide AUC24 and a modest reduction in the systemic exposure of the active metabolites, 4-trans-hydroxy-glyburide (M1) and 3-cis-hydroxyglyburide (M2). It may not be excluded that the effect of topiramate is more pronounced at higher doses. 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.

**Psychoactive Drugs:**

**Risperidone:**
When administered concomitantly with Topiramate at escalating doses of 100 to 400 mg/day for one week plus the dose titration period, there was a reduction in risperidone systemic exposure (16% and 33% for steady-state AUC at the 250 and 400 mg/day doses, respectively).

Minimal alterations in the pharmacokinetics of the total active moiety (respiidone plus 9-hydroxyrisperidone) and no alterations for 9-hydroxyrespiridone were observed. The effect may be slightly more marked during longer co-treatment and at higher Topiramate doses.

**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.

**Amitriptyline:**
Topiramate does not change the exposure to amitriptyline. However, topiramate increases the exposure to the active amitriptyline metabolite, nortriptyline, by 20%. The clinical relevance of this is not known.

**Haloperidole:**
Topiramate does not change the exposure to haloperidole. However, topiramate increases the exposure to the active reduced haloperidole metabolite by 31%. The clinical relevance of this is not known.

**Venlafaxine:**
Venlafaxine does not affect the pharmacokinetics of topiramate. Topiramate 150 mg daily did not affect the pharmacokinetics of venlafaxine or its active metabolite. However, the effect of higher topiramate doses is unknown.

**Interactions with alcohol:**
Central nervous effects might increase in concomitant use with alcohol. It is recommended not to use topiramate in combination with alcohol or other CNS depressants.

**Anti-migraine Drugs:**
There are no pharmacokinetic interactions between topiramate and propanolol, dihydroergotamine or pizotifen.
Topiramate does not influence the pharmacokinetics of sumatriptan (oral or subcutaneous).

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

Concomitant intake of carbonic anhydrase inhibitors (e.g. sulfaime, zonisamide) and topiramate has not been examined in clinical studies. Combination of these drugs may increase the side effects due to inhibition of the carbonic anhydrase.
Topiramate 100 mg daily has no effect on the pharmacokinetics of flunarazine.

### 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 drugs during the first trimester of the pregnancy.
Combination therapy appears to increase the risk of malformation and therefore it is important that monotherapy 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 placenta.

**Epilepsy:**
There are no studies using topiramate in pregnant women. Therefore topiramate should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus.

Specialist advice should be given to women who are likely to become pregnant or who are of childbearing potential. It is recommended that women of childbearing potential use adequate contraception.

In post marketing experience, cases of hypospadias in male infants exposed in utero to topiramate, with or without other anticonvulsants, have been reported. However, a causal relationship with topiramate has not been established.

In pregnancy, if seizure prophylaxis is impaired or discontinued, this may bring about a considerable risk for the mother as well as for the foetus, which probably is more severe than the risk of malformation. During pregnancy, antiepileptic drugs should consequently be prescribed with consideration of these risks.

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

**Lactation:**
Topiramate is excreted in the human breast milk. Limited observations suggest a plasma milk ratio of 1:1. Therefore topiramate should only be used during breastfeeding if the potential benefits for the mother outweigh the potential risks to the child.

**4.7 Effects on ability to drive and use machines**
Topiramate may have a major influence on the ability to drive and use machines.
Topiramate acts on the central nervous system and may produce drowsiness, dizziness and other related symptoms that may affect the ability to concentrate when sharpened attention is required. Patients should be advised to exercise caution when driving or using machines until the individual patients experience with the drug is established.

**4.8 Undesirable effects**
The safety profile for topiramate is based on data from subjects and patients in adjunctive therapy trials.
## Frequency of Adverse Events

<table>
<thead>
<tr>
<th>Organ System Disorder</th>
<th>Very common (≥1/10)</th>
<th>Common (≥1/100 and &lt;1/10)</th>
<th>Uncommon (≥1/1000 and &lt;1/100)</th>
<th>Rare (≥1/10000 and &lt;1/1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>Dizziness, fatigue, somnolence, nervousness, headache, nausea</td>
<td>Skeletal pain, allergic reaction, insomnia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Weight loss</td>
<td>Metabolic acidosis</td>
<td></td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td>Anaemia, epistaxis, purpura, leucopenia, thrombocytopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Difficulty with memory, anorexia, confusion and psychomotor slowing, depression, concentration disturbances, anxiety</td>
<td>Apathy, asthenia, euphoria, emotional lability, agitation, cognitive problems, decreased libido, aggressive reactions, psychosis or psychotic symptoms</td>
<td>Hallucinations, personality disorders, suicidal ideation, suicidal attempts</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td>Dyspnœa</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td>Constipation, abdominal pain</td>
<td>Diarrhoea, vomiting and dry mouth</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Alopecia</td>
<td>Folliculitis and pruritus</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td>Urinary incontinence, nephrolithiasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Ataxia, paraesthesia, speech disorders, aphasia</td>
<td>Tremor, co-ordination abnormal, abnormal gait, nystagmus, taste perversion</td>
<td>Hypokinesia, stupor</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td>Increase in liver enzymes</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Diplopia, abnormal vision</td>
<td></td>
<td>Acute myopia and secondary angle closure glaucoma, eye pain</td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td>Menstrual disturbances</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In patients treated with topiramate as adjunctive therapy, approximately 1 case of thrombo-embolic events per 100 patient years has been reported. Of these, the majority was treated for more than half a year and had more than one risk factor. No relation to topiramate could be established.

Since topiramate has most frequently been co-administered with other antiepileptic agents, it is difficult to determine which agents, if any, are associated with adverse effects.

Qualitatively, the types of adverse events observed in monotherapy trials were generally similar to those observed during adjunctive therapy trials. With the exception of paraesthesia and fatigue, these adverse events were reported at similar or lower incidence rates in monotherapy trials. In double-blind clinical trials clinically relevant adverse events occurring at an incidence greater than or equal to 10% in
the topiramate-treated adult patients included: paraesthesia, headache, fatigue, dizziness, somnolence, weight decrease, nausea, and anorexia.

From marketing use, rare reports of increase in liver enzymes, metabolic acidosis and isolated reports of hepatitis and hepatic failure have been received in patients treated with topiramate.

Clinical trial data indicates that topiramate has been associated with an average decrease of 4 mmol/l in the serum bicarbonate level (see also section 4.4). Oligohidrosis sometimes with accompanying symptoms of fever and flushing has been reported rarely with the use of topiramate. The majority of these reports have been in children. Suicide related events have been uncommonly reported (see section 4.4).

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

There have been rare reports of acute myopia and secondary angle closure glaucoma in patients treated with topiramate (see also section 4.4). Symptoms include acute onset of decreased visual acuity and/or ocular pain typically within 1 month of initiating topiramate therapy. Paediatric patients as well as adults may be affected.

From post-marketing use, very rare reports of transient blindness have been received. However, a casual relationship with the treatment has not been established. In double-blind clinical trials for migraine, the incidence of dose related side effects were in general lower than in epilepsy trials, because lower doses were used in the migraine trials.

### 4.9 Overdose

**Signs and symptoms:**
Signs and symptoms included drowsiness, speech disturbances, blurred vision, diplopia, impaired mentation, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness, depression and seizures. The clinical consequences were generally not severe but patient 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. In acute topiramate overdose where the ingestion is recent, the gastro-intestinal tract should be emptied by gastric lavage or activated charcoal should be given to prevent the absorption of topiramate. 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 groups: Other antiepileptics
ATC-code: N03AX11

Topiramate is a novel antiepileptic agent classified as a sulphamate-substituted monosaccharide. Three pharmacological properties of topiramate have been identified that may contribute to its anticonvulsant activity.

Topiramate reduces the frequency at which action potentials are generated when neurones are subjected to a sustained depolarisation indicative of a state-dependent blockade of voltage-sensitive sodium channels.

Topiramate enhances the activity of GABA at some types of GABA receptors. Topiramate weakly antagonises the excitatory activity of kainate/AMPA subtype of glutamate receptor but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype.
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 multicenter, 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 multicenter, 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 from base period for 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. Differences were not statistically significant.

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

5.2 Pharmacokinetic properties

Absorption:
Recovery of radioactivity from the urine indicates that the mean extent of absorption of a 100 mg dose of 14C topiramate was at least 81%. There is no clinically significant effect of food on topiramate.

Distribution:
The mean apparent volume of distribution has been measured as 0.55-0.8 l/kg for single doses up to 1200mg. There is an effect of gender on the volume of distribution, where the distribution volume in females is approximately 50% of that for males. Topiramate is known to bind to erythrocytes but the binding is likely to be saturated at 3-10 µg/ml. Generally 13-17% of topiramate is bound to plasma proteins.

After oral intake of 400 mg, Cmax is reached after approximately 2 hours. There are no data from intravenous administration. Based on data from urine, the bioavailability may be estimated to approximately 50%. The variability in the kinetics is 25-35%. There is no information concerning distribution to CSF.

Metabolism:
Topiramate is moderately metabolized (approximately 20%) in healthy volunteers. After simultaneous administration of antiepileptics with known enzyme inducing effect, the metabolism may increase up to 50%. Six metabolites have been isolated, characterised and identified from plasma, urine and faeces of humans.

Elimination:
In humans the major route of elimination of topiramate and its metabolites is via the kidney. Renal clearance is approximately 18 ml/min. This is less than expected and indicates a tubular reabsorption of topiramate. Overall, following oral administration in humans, plasma clearance is approximately 20 to 30 ml/min.

Special patient Populations:
Renal impairment:
Topiramate has linear pharmacokinetics with a dose-proportional increase of the plasma concentration in the tested dose range of 100-800 mg/day. Patients with normal renal function may take 4 to 8 days to reach steady-state plasma concentrations whilst patients with moderate to severe renal impairment may take 10 – 15 days. The mean maximal plasma concentration (Cmax) in healthy volunteers following multiple, twice daily oral doses of 100 mg was approximately 7 µg/ml. Following administration of multiple doses of 50 mg and 100 mg topiramate twice daily, the mean plasma half-life was approximately 21 hours.
The plasma and renal clearance of topiramate are decreased in patients with impaired renal function. Compared to normal renal function (creatinine clearance >70 mg/min/1.73 m²), topiramate clearance was 42% lower in patients with moderate renal impairment (creatinine clearance <30-69 ml/min) and 54% lower in patients with severe renal impairment (creatinine clearance <30 ml/min). In some patients with severe renal impairment, the reduction in clearance can be larger. In general, half of the usual daily dose is recommended in patients with moderate or severe renal impairment.

Hepatic impairment:
Plasma clearance of topiramate is reduced with 20-30% in patients with moderate to severe hepatic impairment.

Elderly Patients:
Plasma clearance of topiramate in elderly patients, in the absence of underlying renal disease, is unchanged.

Paediatric Patients:
The pharmacokinetics of topiramate in children, as in adults receiving adjunctive therapy, are linear, with clearance independent of dose and steady-state plasma concentrations increasing in proportion to dose. Children, however, have a higher clearance and shorter elimination half-life. Consequently, the plasma concentrations of topiramate for the same mg/kg dose may be lower in children compared to adults. As in adults, hepatic enzyme inducing antiepileptic drugs decrease 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 (anemia). Toxicity was evident at systemic exposures of animals which were below that expected in patients given recommended therapy. 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 that expected in patients given recommended therapy. The human risk is unknown, but cannot be excluded. Moderate inhibition of a rapid potassium channel has been demonstrated in vitro, suggesting a potential risk for QT prolongation at high doses in the presence of other arrhythmogenic factors.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sugar Spheres (which contain sucrose, maize starch)
Povidone
Opadry-II-85F18378 White: (which contain polyvinyl alcohol-part hydrolysed, titanium dioxide, macrogol, talc)
Aniseed Flavour
Saccharin Sodium (E 954)
Magnesium Stearate
Titanium Dioxide (E-171)
Gelatin

Capsule Body and Cap Composition:
Titanium Dioxide (E-171)
Gelatin

Black Printing Ink:
Shellac
Ethanol
Isopropanol
Butanol
Propylene glycol
Water, purified
Strong ammonia solution
Potassium hydroxide
Black iron oxide (E172)
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
30 months

6.4 Special precautions for storage
Store in the original container. Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container
High density polyethylene bottle with polypropylene induction sealed cap containing a desiccant (silica gel).

Pack sizes: 14, 20, 28, 56 and 60 capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Arrow Generics Ltd
Unit 2, Eastman Way
Stevenage, Hertfordshire
SG1 4SZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 18909/0337

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/08/2009

10 DATE OF REVISION OF THE TEXT
21/08/2009
1 NAME OF THE MEDICINAL PRODUCT
Topiramate 25mg Capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 25mg of topiramate.
Each capsule also contains 69 mg of sucrose. For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Capsule, hard (capsule).
White opaque body and white opaque cap. The body has ‘25’ printed in black and the cap has ‘>’ over ‘Ti’ printed in black.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Adults and adolescents aged 12 years and older: Adjunctive therapy for epileptic patients with partial onset seizures and/or generalised tonic-clonic seizures.

Adults and adolescents aged 12 years and older: Monotherapy of epileptic patients with partial onset seizures and/or generalised tonic-clonic seizures.


4.2 Posology and method of administration
General:
For optimal seizure control in both adults and adolescents and to avoid dose dependent undesirable effects, it is recommended that therapy be initiated at a low dose followed by titration to a clinically effective dose. When concomitant antiepilepsy drugs (AED) 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 is recommended.

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

Topiramate should be withdrawn gradually to minimise the potential of increased seizure frequency. In clinical trials, dosages were decreased by 50-100 mg/day at weekly intervals. In some patients, dose decrease was accelerated without complications.

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

For doses not realisable/practicable with this medicinal product other strengths of this medicinal product or other pharmaceutical forms and products are available.

Method of administration:
Topiramate Capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoon) of soft food e.g. apple sauce, mashed banana, ice cream or yoghurt. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use.

Topiramate can be taken with or without a meal with a sufficient quantity of liquid.

Adjunctive Therapy in Adults and Adolescents aged 12 years and over:

Titration should begin at 25 - 50 mg nightly for 7 days. The dosage should then be increased at 7 day or 14 day intervals by increments of 25 - 50 mg/day, administered in two divided doses. If the patient is unable to tolerate the titration regimen, smaller dose increments or longer intervals between dose increments may be used. Dose titration should be guided by clinical outcome.

The minimal effective dose as adjunctive therapy is 200 mg/day. The usual total daily dose is 200 mg to 400 mg administered in two divided doses. Some patients may achieve efficacy with a once-a-day dosing. Some patients may require higher doses. The maximum recommended daily dose is 800 mg.
Monotherapy for adults and adolescents aged 12 years and over:
Titration should begin at 25 mg nightly for 7 days. The dosage should then be increased at 7 or 14 day 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 dose increments or longer intervals between dose increments may be used. Dose titration should be guided by clinical outcome.

The recommended initial target dose for topiramate monotherapy in adults is 100 mg/day. The maximum recommended daily dose is 400mg

Prophylaxis of Migraine in Adults:
Titration should begin at 25 mg nightly for 7 days. The dosage should then be increased at 7 day intervals by increments of 25 mg/day. If the patient is unable to tolerate the titration regimen, longer intervals between dose adjustments may be used.

The recommended total daily dose of topiramate for prophylaxis of migraine in adults is 100 mg/day administered in two divided doses. Higher doses do not result in increased benefit.

Some patients may experience a benefit at a total daily dose of 50 mg/day. Dose and titration rate should be guided by clinical outcome.

There are no efficacy or safety data for longer than six months in the prophylactic treatment of migraine.

Impaired renal function:
For patients with moderate (creatinine clearance 30-69 ml/min) and severe (creatinine clearance <30 ml/min) renal dysfunction, it is recommended to start with half of the daily dose than usual and to titrate with smaller steps and at slower pace as is usual. As with all patients, the titrations schedule should be guided by clinical outcome with the knowledge that it may require longer to reach steady-state after each dose change in renally impaired patients. In patients with moderate or severe renal impairment, it may take 10 to 15 days to reach steady concentrations as compared to 4 to 8 days in patients with normal renal function.

Impaired hepatic function:
In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate may be decreased. (see section 4.4 and 5.2).

Patients undergoing haemodialysis:
Topiramate is removed from plasma by haemodialysis. Therefore a supplemental dose of topiramate equal to approximately one-half of 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. As for all patients, the dose titration should be guided by clinical outcome (e.g. seizure control, avoidance of undesirable effects).

4.3 Contraindications
Hypersensitivity to topiramate or to any of the excipients in the medicinal product.

Treatment for prophylaxis of migraine during pregnancy, and in women of childbearing potential if not using an effective method of contraception. In pregnancy, the occurrence of seizures forms a considerable risk for mother and child. Preventing seizures by topiramate, provided given for the right indication, therefore outweighs the risk of malformations. However preventing migraine attacks does not outweigh this risk. Consequently, topiramate for the indication prophylaxis of migraine is contraindicated in pregnancy and women with child bearing potential if not using an effective method of contraception (see section 4.6).

4.4 Special warnings and precautions for use
General:
Adequate hydration while using topiramate is important. Hydration can reduce the risk of nephrolithiasis (see below). Treatment with topiramate may decrease sweating, primarily in paediatric
patients. Activities such as exercise or exposure to warm temperatures while using topiramate may increase the risk of heat-related adverse events (see section 4.8).

Patients with rare hereditary problems of fructose intolerance, glucose/galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Patients on long term topiramate treatment should be regularly monitored for weight loss. A dietary supplement or increased food intake may be considered if the patient is losing weight or has inadequate weight gain while on this medication. If clinically significant weight loss occurs, discontinuation of the medication should be considered.

Topiramate should only be used for the prophylaxis of migraine and is not intended for acute treatment. There is limited experience on the use of topiramate in children aged 12 years and under.

Suicidal ideation and behaviour
Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also 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 (43 out of 7,999 treated patients) and at a 3 fold higher incidence than in those treated with placebo (0.15%; 5 out of 3,150 patients treated).

Therefore patients should be monitored for signs of suicidal ideation and behaviours 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 emerges.

Mood disturbances/Depression:
Mood disturbances and depression are common during topiramate treatment (see section 4.8). Patient should be monitored for signs of depression and referred for appropriate treatment if necessary. Rarely psychotic reactions and aggressive behaviour have been observed during the treatment with topiramate.

Renal Impairment:
Caution should be exercised when treating patients with moderate to severe renal impairment (see section 4.2) as subjects with known renal impairment may require longer to reach a steady state at each dose.

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. However, none of these risk factors reliably predict stone formation during topiramate treatment. In addition, patients taking other medication associated with nephrolithiasis (Acetazolamide, Triamteren, Vitamin C >2g/day) may be increased risk.

Such medication should be avoided. Ketogenic diets should be avoided whilst on topiramate therapy since they may create a physiological environment that increases the risk of renal stone formation.

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

Acute myopia and secondary angle closure formation:
Acute myopia associated with secondary angle-closure glaucoma has been reported in both adults and children receiving topiramate.

Symptoms typically occur within 1 month of the start of treatment and include decreased visual acuity and/or ocular pain. Ophthalmological findings include bilateral myopia, anterior chamber shallowing, hyperaemia and increased intra-ocular pressure with or without mydriasis. There may be suprachoroidal effusion resulting in anterior displacement of the lens and iris. Treatment includes discontinuation of
topiramate as rapidly as is clinically feasible and appropriate measures to reduce intraocular pressure. If increased intra-ocular pressure is suspected, immediate specialist advice should be sought.

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

Chronic metabolic acidosis in paediatric patients can reduce growth and may cause osteomalacia (rickets). The effect of topiramate on growth and bone-related sequelae has not been systematically investigated in paediatric or adult populations. Measurement of serum bicarbonate levels is recommended with topiramate therapy, especially in patients with conditions or therapies that predispose to metabolic acidosis. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering).

Chronic metabolic acidosis enhances the risk of renal stone formation.

**4.5 Interaction with other medicinal products and other forms of interaction**
In an in–vitro study, topiramate was a weak inducer of CYP3A4 enzyme formation in a concentration-dependent manner. This may explain why ethinyl-estradiol (a CYP3A4 substrate) exposure was decreased after high doses of topiramate, but not after low doses of topiramate. No other clinical relevant interactions where topiramate acts as a CYP3A4 inducer are reported.

Topiramate inhibits the enzyme CYP 2C19 and influence other substances, which are metabolized via this enzyme, such as diazepam, imipramine, moclobemide, proguanil, omeprazole. However, this has not been studied in vivo.

**Effects of other antiepileptic drugs on topiramate:**
Phenytoin and carbamazepine decrease the plasma concentration of topiramate. The addition or withdrawal of phenytoin or carbamazepine to topiramate therapy may require an adjustment in dosage of topiramate. This should be done by titrating to clinical effect.

The addition or withdrawal of valproic acid or lamotrigine does not produce clinically significant changes in plasma concentrations of topiramate and, therefore, does not warrant dosage adjustment of topiramate. Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse event is not due to a pharmacokinetic interaction.

**Effects of topiramate on other antiepileptic drugs:**
The addition of topiramate to other antiepileptic drugs (carbamazepine, valproic acid, Phenobarbital, primidone or lamotrigine) has no clinically significant effect on their steady-state plasma concentrations. In some patients, treatment with topiramate and phenytoin may result in an increase of plasma concentrations of phenytoin. Consequently, it is advised that any patient on phenytoin should have phenytoin levels monitored.

**Other Drug Interactions**
**Cardiovascular Drugs:**
**Digoxin:**
In a single-dose study, serum digoxin area under plasma concentration curve (AUC) decreased by 12% due to concomitant administration of topiramate. Serum digoxin should be carefully monitored during the first weeks after starting topiramate treatment, when markedly changing the topiramate dose or when discontinuing topiramate treatment.
Diltiazem:
Topiramate at a dose of 150 mg/day reduced the exposure to diltiazem and the metabolite des acetyl diltiazem by 25% and 18%, respectively, but does not change the exposure to the metabolite N-demethyl diltiazem. The effect of topiramate may be more pronounced at higher doses. Treatment with diltiazem increased the exposure of topiramate by 20%. The effect of diltiazem may be higher when topiramate is used in combination with other AEDs.

Hydrochlorothiazide (HCTZ):
HCTZ increases the topiramate exposure by approximately 30%. The clinical relevance of this change is unknown, but the addition of HCTZ to topiramate therapy may require an adjustment of the topiramate dose. The pharmacokinetics of HCTZ is not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicate a decrease in serum potassium after topiramate or HCTZ administration, which was greater when HCTZ and topiramate were administered in combination.

Oral Contraceptives:
In a pharmacokinetic interaction study with a combined oral contraceptive (1 mg norethisterone plus 35 mcg ethinyl estradiol) in healthy volunteers, topiramate monotherapy at topiramate monotherapy at doses of 50 mg/day to 200 mg/day did not affect exposure (AUC) of oral contraceptives. However, in another study, exposure to ethinylestradiol was significantly decreased at topiramate doses of 200, 400 and 800 mg/day when given as adjunctive therapy in patients taking valproic acid. The levels of norethisterone exposure were not affected. The clinical significance of the changes observed is not known. The risk of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking estrogen containing contraceptive products with topiramate.

Patients who are taking oral contraceptives containing estrogen should be advised to report any change in their menstrual bleeding pattern.

Antidiabetic Drugs:
Metformin:
A drug-drug 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 was given alone and when metformin and topiramate were given simultaneously. The result of this study indicated that metformin mean Cmax and mean AUC 0-12h increased by 18% and 25%, respectively, while mean CL/F decreased 20% when metformin was co-administered with topiramate. Topiramate did not affect metformin tmax.

The clinical significance of the effect of topiramate on metformin pharmacokinetics is unclear.

Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The extent of change in the clearance is unknown. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear. When topiramate is added or withdrawn in patients on metformin therapy, careful attention should be given to the routine monitoring for adequate control of their diabetic disease state.

Pioglitazone:
The steady state pharmacokinetics of topiramate were not significantly influenced by the concomitant administration of pioglitazone. Topiramate causes a 15% decline in pioglitazone exposure and in the exposure of the active (but less potent) hydroxy- and keto-metabolites of pioglitazone by 16 and 60%, respectively. The clinical significance of these findings is not known. When topiramate is added to pioglitazone therapy or pioglitazone is added to or withdrawn from topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Glibenclamide (Glyburide):
Concomitant treatment with topiramate when slowly titrated over 5 weeks and maintained at 150 mg/day for 1 week resulted in a 25% reduction in glyburide AUC24 and a modest reduction in the systemic exposure of the active metabolites, 4-trans-hydroxy-glyburide (M1) and 3-cis-hydroxyglyburide (M2). It may not be excluded that the effect of topiramate is more pronounced at higher doses. The steady-state pharmacokinetics of topiramate were unaffected by concomitant administration.
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.

**Psychoactive Drugs:**

**Risperidone:**
When administered concomitantly with Topiramate at escalating doses of 100 to 400 mg/day for one week plus the dose titration period, there was a reduction in risperidone systemic exposure (16% and 33% for steady-state AUC at the 250 and 400 mg/day doses, respectively).

Minimal alterations in the pharmacokinetics of the total active moiety (risperidone plus 9-hydroxyrisperidone) and no alterations for 9-hydroxyrisperidone were observed. The effect may be slightly more marked during longer co-treatment and at higher Topiramate doses.

**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.

**Amitriptyline:**
Topiramate does not change the exposure to amitriptyline. However, topiramate increases the exposure to the active amitriptyline metabolite, nortriptyline, by 20%. The clinical relevance of this is not known.

**Haloperidol:**
Topiramate does not change the exposure to haloperidol. However, topiramate increases the exposure to the active reduced haloperidol metabolite by 31%. The clinical relevance of this is not known.

**Venlafaxine:**
Venlafaxine does not affect the pharmacokinetics of topiramate. Topiramate 150 mg daily did not affect the pharmacokinetics of venlafaxine or its active metabolite. However, the effect of higher topiramate doses is unknown.

**Interactions with alcohol:**
Central nervous effects might increase in concomitant use with alcohol. It is recommended not to use topiramate in combination with alcohol or other CNS depressants.

**Anti-migraine Drugs:**
There are no pharmacokinetic interactions between topiramate and propranolol, dihydroergotamine or pizotifen.
Topiramate does not influence the pharmacokinetics of sumatriptan (oral or subcutaneous).

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

Concomitant intake of carbonic anhydrase inhibitors (e.g. sulthiame, zonisamide) and topiramate has not been examined in clinical studies. Combination of these drugs may increase the side effects due to inhibition of the carbonic anhydrase.

Topiramate 100 mg daily has no effect on the pharmacokinetics of flunarazine.

**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 drugs during the first trimester of the pregnancy.
Combination therapy appears to increase the risk of malformation and therefore it is important that monotherapy 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 placenta.

**Epilepsy:**
There are no studies using topiramate in pregnant women. Therefore topiramate should be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus.

Specialist advice should be given to women who are likely to become pregnant or who are of childbearing potential. It is recommended that women of childbearing potential use adequate contraception.

In post marketing experience, cases of hypospadias in male infants exposed in utero to topiramate, with or without other anticonvulsants, have been reported. However, a causal relationship with topiramate has not been established.

In pregnancy, if seizure prophylaxis is impaired or discontinued, this may bring about a considerable risk for the mother as well as for the foetus, which probably is more severe than the risk of malformation. During pregnancy, antiepileptic drugs should consequently be prescribed with consideration of these risks.

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

**Lactation:**
Topiramate is excreted in the human breast milk. Limited observations suggest a plasma milk ratio of 1:1. Therefore topiramate should only be used during breastfeeding if the potential benefits for the mother outweigh the potential risks to the child.

4.7 **Effects on ability to drive and use machines**
Topiramate may have a major influence on the ability to drive and use machines.
Topiramate acts on the central nervous system and may produce drowsiness, dizziness and other related symptoms that may affect the ability to concentrate when sharpened attention is required. Patients should be advised to exercise caution when driving or using machines until the individual patients experience with the drug is established.

4.8 **Undesirable effects**
The safety profile for topiramate is based on data from subjects and patients in adjunctive therapy trials.
### Frequency of Adverse Events

<table>
<thead>
<tr>
<th>Organ System Disorder</th>
<th>Very common (≥1/10)</th>
<th>Common (≥1/100 and &lt;1/10)</th>
<th>Uncommon (≥1/1000 and &lt;1/100)</th>
<th>Rare (≥1/10000 and &lt;1/1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>Dizziness, fatigue, somnolence, nervousness, headache, nausea</td>
<td>Skeletal pain, allergic reaction, insomnia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Weight loss</td>
<td>Metabolic acidosis</td>
<td></td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td>Anaemia, epistaxis, purpura, leucopenia, thrombocytopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Difficulty with memory, anorexia, confusion and psychomotor slowing, depression, concentration disturbances, anxiety</td>
<td>Apathy, asthena, euphoria, emotional lability, agitation, cognitive problems, decreased libido, aggressive reactions, psychosis or psychotic symptoms</td>
<td>hallucinations, personality disorders, suicidal ideation, suicidal attempts</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td>Dyspnoea</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Constipation, abdominal pain</td>
<td></td>
<td>Diarrhoea, vomiting and dry mouth</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia</td>
<td></td>
<td>Folliculitis and pruritus</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Urinary incontinence, nephrolithiasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Ataxia, paraesthesia, speech disorders, aphasia</td>
<td>Tremor, co-ordination abnormal, abnormal gait, nystagmus, taste perversion</td>
<td></td>
<td>Hypokinesia, stupor</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td>Increase in liver enzymes</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Diplopia, abnormal vision</td>
<td></td>
<td>Acute myopia and secondary angle closure glaucoma, eye pain</td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td>Menstrual disturbances</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In patients treated with topiramate as adjunctive therapy, approximately 1 case of thrombo-embolic events per 100 patient years has been reported. Of these, the majority was treated for more than half a year and had more than one risk factor. No relation to topiramate could be established. Since topiramate has most frequently been co-administered with other antiepileptic agents, it is difficult to determine which agents, if any, are associated with adverse effects.

Qualitatively, the types of adverse events observed in monotherapy trials were generally similar to those observed during adjunctive therapy trials. With the exception of paraesthesia and fatigue, these adverse events were reported at similar or lower incidence rates in monotherapy trials. In double-blind clinical trials clinically relevant adverse events occurring at an incidence greater than or equal to 10% in
the topiramate-treated adult patients included: paraesthesia, headache, fatigue, dizziness, somnolence, weight decrease, nausea, and anorexia.

From marketing use, rare reports of increase in liver enzymes, metabolic acidosis and isolated reports of hepatitis and hepatic failure have been received in patients treated with topiramate.

Clinical trial data indicates that topiramate has been associated with an average decrease of 4 mmol/l in the serum bicarbonate level (see also section 4.4). Oligohidrosis sometimes with accompanying symptoms of fever and flushing has been reported rarely with the use of topiramate. The majority of these reports have been in children. Suicide related events have been uncommonly reported (see section 4.4).

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

There have been rare reports of acute myopia and secondary angle closure glaucoma in patients treated with topiramate (see also section 4.4). Symptoms include acute onset of decreased visual acuity and/or ocular pain typically within 1 month of initiating topiramate therapy. Paediatric patients as well as adults may be affected.

From post-marketing use, very rare reports of transient blindness have been received. However, a casual relationship with the treatment has not been established.

In double-blind clinical trials for migraine, the incidence of dose related side effects were in general lower than in epilepsy trials, because lower doses were used in the migraine trials.

4.9 Overdose

Signs and symptoms:
Signs and symptoms included drowsiness, speech disturbances, blurred vision, diplopia, impaired mentation, lethargy, abnormal coordination, stupor, hypotension, abdominal pain, agitation, dizziness, depression and seizures. The clinical consequences were generally not severe but patient 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. In acute topiramate overdose where the ingestion is recent, the gastro-intestinal tract should be emptied by gastric lavage or activated charcoal should be given to prevent the absorption of topiramate. 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 groups: Other antiepileptics
ATC-code: N03AX11

Topiramate is a novel antiepileptic agent classified as a sulphamate-substituted monosaccharide. Three pharmacological properties of topiramate have been identified that may contribute to its anticonvulsant activity.

Topiramate reduces the frequency at which action potentials are generated when neurones are subjected to a sustained depolarisation indicative of a state-dependent blockade of voltage-sensitive sodium channels.

Topiramate enhances the activity of GABA at some types of GABA receptors. Topiramate weakly antagonises the excitatory activity of kainate/AMPA subtype of glutamate receptor but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype.
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 multicenter, 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 multicenter, 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 from base period for 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. Differences were not statistically significant.

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

5.2 Pharmacokinetic properties

Absorption:
Recovery of radioactivity from the urine indicates that the mean extent of absorption of a 100 mg dose of 14C topiramate was at least 81 %. There is no clinically significant effect of food on topiramate.

Distribution:
The mean apparent volume of distribution has been measured as 0.55-0.8 l/kg for single doses up to 1200mg. There is an effect of gender on the volume of distribution, where the distribution volume in females is approximately 50% of that for males. Topiramate is known to bind to erythrocytes but the binding is likely to be saturated at 3-10 µg/ml. Generally 13-17% of topiramate is bound to plasma proteins. After oral intake of 400 mg, Cmax is reached after approximately 2 hours. There are no data from intravenous administration. Based on data from urine, the bioavailability may be estimated to approximately 50%. The variability in the kinetics is 25-35%. There is no information concerning distribution to CSF.

Metabolism:
Topiramate is moderately metabolized (approximately 20%) in healthy volunteers. After simultaneous administration of antiepileptics with known enzyme inducing effect, the metabolism may increase up to 50%. Six metabolites have been isolated, characterised and identified from plasma, urine and faeces of humans.

Elimination:
In humans the major route of elimination of topiramate and its metabolites is via the kidney. Renal clearance is approximately 18 ml/min. This is less than expected and indicates a tubular reabsorption of topiramate. Overall, following oral administration in humans, plasma clearance is approximately 20 to 30 ml/min.

Special patient Populations:
Renal impairment:
Topiramate has linear pharmacokinetics with a dose-proportional increase of the plasma concentration in the tested dose range of 100-800 mg/day. Patients with normal renal function may take 4 to 8 days to reach steady-state plasma concentrations whilst patients with moderate to severe renal impairment may take 10 – 15 days. The mean maximal plasma concentration (Cmax) in healthy volunteers following multiple, twice daily oral doses of 100 mg was approximately 7 µg/ml. Following administration of multiple doses of 50 mg and 100 mg topiramate twice daily, the mean plasma half-life was approximately 21 hours.
The plasma and renal clearance of topiramate are decreased in patients with impaired renal function. Compared to normal renal function (creatinine clearance >70 mg/min/1.73 m²), topiramate clearance was 42% lower in patients with moderate renal impairment (creatinine clearance <30-69 ml/min) and 54% lower in patients with severe renal impairment (creatinine clearance <30 ml/min). In some patients with severe renal impairment, the reduction in clearance can be larger. In general, half of the usual daily dose is recommended in patients with moderate or severe renal impairment.

**Hepatic impairment:**
Plasma clearance of topiramate is reduced with 20-30% in patients with moderate to severe hepatic impairment.

**Elderly Patients:**
Plasma clearance of topiramate in elderly patients, in the absence of underlying renal disease, is unchanged.

**Paediatric Patients:**
The pharmacokinetics of topiramate in children, as in adults receiving adjunctive therapy, are linear, with clearance independent of dose and steady-state plasma concentrations increasing in proportion to dose. Children, however, have a higher clearance and shorter elimination half-life. Consequently, the plasma concentrations of topiramate for the same mg/kg dose may be lower in children compared to adults. As in adults, hepatic enzyme inducing antiepileptic drugs decrease 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 (anemia). Toxicity was evident at systemic exposures of animals which were below that expected in patients given recommended therapy. 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 that expected in patients given recommended therapy. The human risk is unknown, but cannot be excluded. Moderate inhibition of a rapid potassium channel has been demonstrated in vitro, suggesting a potential risk for QT prolongation at high doses in the presence of other arrhythmogenic factors.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients
Sugar Spheres (which contain sucrose, maize starch)
Povidone
Opadry-II-85F18378 White: (which contain polyvinyl alcohol-part hydrolysed, titanium dioxide, macrogol, talc)
Aniseed Flavour
Saccharin Sodium (E 954)
Magnesium Stearate

**Capsule Body and Cap Composition:**
Titanium Dioxide (E-171)
Gelatin

**Black Printing Ink:**
Shellac
Ethanol
Isopropanol
Butanol
Propylene glycol
Water, purified
Strong ammonia solution
Potassium hydroxide
Black iron oxide (E172)
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
30 months

6.4 Special precautions for storage
Store in the original container. Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container
High density polyethylene bottle with polypropylene induction sealed cap containing a desiccant (silica gel).

Pack sizes: 14, 20, 28, 56 and 60 capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Arrow Generics Ltd
Unit 2, Eastman Way
Stevenage, Hertfordshire
SG1 4SZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 18909/0338

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/08/2009

10 DATE OF REVISION OF THE TEXT
21/08/2009
Module 3
Product Information Leaflet

Topiramate 15mg and 25mg Capsules, hard
(Topiramate)

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

1. WHAT TOPIRAMATE CAPSULES ARE AND WHAT THEY ARE USED FOR

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

Epilepsy:
Topiramate Capsules can be used for the treatment of epilepsy, including primary generalised epilepsy and partial epilepsy with or without secondary generalisation.
Topiramate can be used on its own or in combination with other anti-epileptic medicines to treat adults and adolescents over 12 years of age.

Migraine:
Topiramate Capsules can be used to treat frequently recurring migraine headaches in adults. Topiramate Capsules are not intended for the treatment of individual migraine attacks.

2. BEFORE YOU TAKE TOPIRAMATE CAPSULES

Do not take Topiramate Capsules:
- if you are allergic (hypersensitive) to topiramate
- if you are allergic to any of the other ingredients of Topiramate Capsules (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.

Take special care with Topiramate Capsules:
You should tell your doctor if any of the following apply to you:
- if you have been prescribed Topiramate Capsules for epilepsy and you are pregnant, planning to become pregnant or are breast-feeding – see the section ‘Pregnancy and breast-feeding’ for more information.
- if you have or have previously had a kidney or liver disease
- if you have had a kidney stone in the past or there is a history of kidney stones in your family. If so, you should drink plenty of liquid and avoid eating fatty foods with a low carbohydrate content since these may increase the risk of having a kidney stone.
- if you suffer from sudden short-sightedness (myopia) and/or pain in the eyes. Contact your doctor immediately as this medicine can cause sudden glaucoma in a minority of patients.

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

You may experience weight loss (or absence of weight gain) whilst taking topiramate. It is therefore normal for your doctor to want to monitor you or your child’s weight on a regular basis and if necessary advise on a change in diet.
- pioglitazone (for diabetes), as topiramate can reduce its effect
- amitryptiline (for depression), as topiramate can increase its effect
- haloperidol (for mental illnesses), as topiramate can increase its effect
- diltiazem (for hypertension), as topiramate can reduce its effect and it may increase the effect of topiramate
- glibenclamide (for diabetes), as topiramate can reduce its effect
- risperidone (for mental illnesses), as topiramate can reduce its effect
- lithium (for depression), as topiramate can reduce its effect.

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

Taking Topiramate Capsules and Oral Contraceptives
If you are already taking, or plan to start taking a hormonal contraceptive (‘the pill’), it is important that you discuss this with your doctor as:
- Topiramate may reduce the effectiveness of ‘the pill’. You should tell your doctor as soon as possible if you notice any changes in menstrual pattern, such as breakthrough bleeding or spotting. You may wish to consider other forms of contraception
- It is preferable to choose a continuous oral contraceptive (one without a ‘pill-free week’).

Taking Topiramate Capsules with food and drink
It is recommended not to drink alcohol whilst you are taking Topiramate Capsules as this can increase the risk of side effects.
It is important to drink plenty of water whilst you are taking Topiramate Capsules especially if you are taking exercise or the weather is hot.

Pregnancy and breast-feeding
Epilepsy:
If you plan to become pregnant or find out that you are pregnant while taking these capsules, you should contact your doctor as soon as possible. It may be possible for you to continue to take Topiramate during pregnancy so that your epilepsy is kept under control. Your doctor will need to review your treatment and monitor your topiramate levels before, during and after pregnancy.
You must not breast-feed whilst taking topiramate without having first discussed this with your doctor.

Migraine:
If you are pregnant or think you may be pregnant or are of child bearing age and not using an effective method of contraception you must not take Topiramate Capsules to prevent migraine headaches.
You must not breast-feed whilst taking topiramate without having first discussed this with your doctor.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
This medicine may make you feel dizzy or drowsy and affect your judgement and concentration. You should talk to your doctor before driving or using machines.

Important information about some of the ingredients of Topiramate Capsules:
This medicinal product contains sucrrose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.
PAR Topiramate 15mg and 25mg Hard Capsules

Blood tests have sometimes shown a slight increase in acidity caused by a lowering of bicarbonate levels in the blood in patients taking topiramate. If necessary, your doctor will monitor this and may adjust the amount of topiramate that you are taking.

Treatment with topiramate may cause you to sweat less causing your body temperature to rise especially during exercise or when the weather is hot. This is more common in children. It is important to drink plenty of water while you are taking these capsules to avoid or reduce any side effects related to an increase in body temperature.

Taking other medicines
Tell your doctor if you are already taking any of the following as they may interact with your medicine. Your doctor may therefore need to adjust your dose of topiramate or the other medicine:

- phenytoin or carbamazepine (for epilepsy), as they can reduce the effect of topiramate and topiramate can increase the effect of phenytoin
- valproic acid (for epilepsy) as administration with topiramate can sometimes cause unwanted side effects
- digoxin (for heart failure), as topiramate can reduce its effect
- hydrochlorothiazide (for high blood pressure), as it can increase the effect of topiramate
- metformin (for diabetes), as it can alter the effectiveness of topiramate

When you first start taking Topiramate Capsules your doctor will prescribe a much lower dose and slowly increase it, usually at one or two week intervals. You should always follow your doctor’s instructions carefully and ask them if you are unsure of anything.

Topiramate is not recommended for use in children under 12 years old.

- **Migraine:**
  The usual dose for the treatment of migraine is 50mg of topiramate taken twice a day. However, your doctor may tell you to use a lower dose and you should follow their instructions.

When you first start taking Topiramate Capsules your doctor will prescribe a much lower dose and slowly increase it, usually at one week intervals.

Your treatment will then be reviewed every six months.

This medicinal product is not recommended for the prevention of migraine headaches in adolescents and children under 12 years of age.

**General:**
- If you or your child suffers from liver or kidney disease your doctor may prescribe a lower dose.
- If you or your child is undergoing haemodialysis, your doctor may increase your dose of topiramate on days when you are having haemodialysis.

Ask your doctor if you are unsure of anything and always follow their instructions carefully.

If you take more Topiramate Capsules than you should, you may feel dizzy, agitated, depressed or drowsy and have a headache, blurred or double vision, slurred speech, problems with co-ordination or stomach pain. You should contact your doctor immediately or go to the nearest casualty department. Remember to take the pack and any remaining capsules with you.

If you forget to take Topiramate Capsules, 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. Do not take a double dose to make up for the one you missed.

### 3. HOW TO TAKE TOPIRAMATE CAPSULES

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

Your capsules may be swallowed whole with a glass of water or can be administered by carefully opening the capsule and sprinkling the entire contents onto a small amount (teaspoon) of soft food, such as mashed banana, ice cream or yoghurt. This food should then be swallowed immediately and not chewed. It should not be kept for later use.

The capsules are normally taken twice a day (e.g., in the morning and evening) and can be taken before, during or after meals.

- **Epilepsy:**
  Adults and adolescents (children aged 12 years and older):
  If you are only taking Topiramate Capsules to control your epilepsy, the usual dose is 100mg per day. This can be taken as 100mg once a day or 50mg twice a day. Your doctor may increase or decrease your daily dose depending on how well your epilepsy is controlled.

  If you are taking Topiramate Capsules together with other anti-epileptic medicines, the usual dose of topiramate is 100-200mg taken twice a day. However, your doctor may tell you to use a higher or lower dose.

Uncommon (probably affecting fewer than 1 in 100 people):

- personality disorders (changes in thoughts, feelings and behaviour)
- diarrhoea
- difficulty in breathing
- dry mouth
- stupor
- vomiting

Rare (probably affecting fewer than 1 in 1,000 people):

- neutropenia (a reduction in neutrophils – a type of white blood cell)
- glaucoma (increased pressure in the eye)
- eye pain

- itching including of the hair
- reduction in mobility
- hallucinations
- acute short-sightedness
- increases in liver enzymes

Rarely, sudden blurring of vision and/or pain and redness of the eyes has occurred, in both adults and children, typically during the first month of starting treatment with topiramate. This can indicate raised pressure within the eye (glaucoma). If you develop any eye symptoms, particularly in the first few weeks of treatment, you should tell your doctor immediately. If your doctor thinks you have raised pressure within the eye, he/she will advise you on how to stop taking Topiramate Capsules and may refer you for specific eye treatment. You may also need to revisit your specialist to ensure your epilepsy is kept under control.

You may experience significant and continuing weight loss whilst taking Topiramate Capsules. It is therefore normal for your doctor to want to monitor you or your child’s weight on a regular basis and if necessary advise on a change in diet.

Blood tests have sometimes shown a slight increase in acidity. If necessary, your doctor will monitor this and may adjust the amount of topiramate that you are taking.

Very rarely hepatitis and hepatic failure, as well as convulsions following withdrawal of topiramate, have been reported.

If any of the side effects listed above gets serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
PAR Topiramate 15mg and 25mg Hard Capsules

If you stop taking Topiramate Capsules, you may have more fits or sudden worsening of your headaches. It is important that you keep taking your capsules 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 Capsules 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 have a high temperature, you should stop taking Topiramate Capsules and contact your doctor immediately.

Rarely, patients taking Topiramate Capsules 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 following side effects have been reported:

**Very common** (probably affecting more than 1 in 10 people):
- dizziness
- tiredness
- nervousness
- headache
- nausea (feeling sick)
- weight loss
- memory problems
- confusion
- depression
- anorexia
- anxiety
- problems with concentrating
- pins and needles
- speech impairment
- ataxia (problems in controlling muscles)
- abnormal or double vision.

**Common** (probably affecting fewer than 1 in 10 people):
- skeletal pain
- allergic reactions
- insomnia (trouble sleeping)
- metabolic acidosis (increase in acidity in the body)
- nosebleeds
- a decrease in the number of certain blood cells (leucopenia, anaemia and thrombocytopenia)
- apathy
- lack of energy
- loss of emotional feeling and mood swings
- feeling agitated or aggressive
- co-ordination problems
- loss of sexual desire
- stomach pain
- constipation
- hair loss
- urinary incontinence
- kidney stones (which may present as blood in the urine or pain in the lower back or genital area)
- shaking
- abnormal walking
- rolling of the eyes
- taste changes
- disruption in the menstrual cycle.

5. HOW TO STORE TOPIRAMATE CAPSULES

Keep out of the reach and sight of children.

Store in the original container.

Keep the container tightly closed in order to protect from moisture.

Do not use Topiramate Capsules after the expiry date which is stated on the carton and bottle after EXP. The expiry date refers to the last day of

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 Capsules contain:**
The active substance is topiramate (each capsule contains 15mg or 25mg of topiramate).

The other ingredients are sugar spheres (which contain sucrose, maize starch), povidone, aniseed flavour, saccharin sodium (E-954), magnesium stearate, gelatin, titanium dioxide (E-171) and Opadry II-85F18378 White (which contains polyvinyl alcohol-part hydrolysed, macrogol, talc and titanium dioxide).

The black printing ink contains shellac, ethanol, isopropanol, butanol, propylene glycol, purified water, strong ammonia solution, potassium hydroxide and black iron oxide (E-172).

**What Topiramate Capsules look like and contents of the pack:**
Your medicine is in the form of hard gelatin capsules.

The 15mg capsules are white with '15' printed in black on the body and '> ' over 'T' on the cap.

The 25mg capsules are white with '25' printed in black on the body and '> ' over 'T' on the cap.

Topiramate Capsules are available in HDPE bottles containing 14, 20, 28, 56 and 60 capsules.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**
Arrow Generics Limited, Unit 2, Eastman Way, Stevenage, Hertfordshire, SG1 4SZ, U.K.

**Manufacturer:**
Arrow Pharm (Malta) Limited, 62 Hal Far Industrial Estate, Birzebbugia, BBG3000, Malta.

This leaflet was last approved in 06/2009.
Module 4
Labelling

**Topiramate 15mg Capsules**
Keep out of the reach and sight of children.
60 capsules
LBL0100AA

**Topiramate 25mg Capsules**
Keep out of the reach and sight of children.
60 capsules
LBL0200AA

**Topiramate 15mg Capsules**
Keep out of the reach and sight of children.
60 capsules
LBL0300AA

**Topiramate 25mg Capsules**
Keep out of the reach and sight of children.
60 capsules
LBL0400AA

**For oral use.** Each capsule contains 10mg of topiramate. These capsules contain sucrose. See leaflet for further information.

**Store in the original container.** Keep the container tightly closed in order to protect from moisture.

**Read the package leaflet before use.**

**MA Holder:** Arrow Generics Limited, Unit 2, Eastman Way, Stevenage, Herts, SG1 4SZ, U.K. PL 18909/0238

**BN:**

**Exp:**
For oral use.
These capsules contain sucrose. See leaflet for further information.

Store in the original container. Keep the container tightly closed in order to protect from moisture.

Read the package leaflet before use.

Keep out of the reach and sight of children.
PAR Topiramate 15mg and 25mg Hard Capsules

Topiramate 25mg Capsules
(topiramate)
60 capsules

Each capsule contains 25mg of topiramate.

Topiramate 25mg Capsules
(topiramate)
60 capsules

Each capsule contains 25mg of topiramate.

For oral use.
These capsules contain sucrose. See leaflet for further information.

Store in the original container.
Keep the container tightly closed in order to protect from moisture.

Read the package leaflet before use.
Keep out of the reach and sight of children.

Batch/Expiry details will be printed/embossed in the space highlighted.
Topiramate 15mg Capsules (topiramate) 60 capsules

Each capsule contains 15mg of topiramate.

For oral use. These capsules contain sacrose. See leaflet for further information.

Store in the original container. Keep the container tightly closed in order to protect from moisture.

Read the package leaflet before use.

Keep out of the reach and sight of children.

PAR Topiramate 15mg and 25mg Hard Capsules

PL 18995/2037

Marketing Authorisation Holder:
Arrow Generics Limited,
Unit 2, Eastman Way,
Stevenage, Herts,
SG1 4SZ, U.K.
PAR Topiramate 15mg and 25mg Hard Capsules

Topiramate 25mg Capsules (topiramate) 60 capsules
Each capsule contains 25mg of topiramate.

Topiramate 25mg Capsules (topiramate) 60 capsules
Each capsule contains 25mg of topiramate.

For oral use. These capsules contain sucrose. See leaflet for further information.
Store in the original container. Keep the container tightly closed in order to protect from moisture. Read the package leaflet before use. Keep out of the reach and sight of children.

Marketing Authorisation Holder: Arrow Generics Limited, Unit 2, Eastman Way, Stevenage, Herts, SG1 4SZ, U.K.

PL 18989/0338

Batch/Expiry Details will be printed/embossed in the space highlighted.
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, Belgium, Cyprus, the Czech Republic, Ireland, Italy, Malta, the Netherlands, Poland, Portugal, the Slovak Republic, Slovenia and the UK considered that the applications for Topiramate 15mg and 25mg Hard Capsules could be approved. These products are prescription only medicines (POM) and used for the following indications:

- Adjunctive or monotherapy for epileptic patients (adults and adolescents aged 12 years and older), with partial onset seizures and/or generalised tonic-clonic seizures.

These applications for Topiramate 15mg and 25mg Hard Capsules are submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to Topamax 25mg Tablets, first authorised in the UK to Janssen-Cilag Limited in July 1995.

The products contain the active substance topiramate, which is classified as a sulphamate-substituted monosaccharide. Topiramate reduces the frequency at which action potentials are generated when neurones are subjected to a sustained depolarisation indicative of a state-dependent blockade of voltage-sensitive sodium channels.

Topiramate enhances the activity of GABA at some types of GABA receptors. Topiramate weakly antagonises the excitatory activity of kainate/AMPA subtype of glutamate receptor but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype.

No new preclinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies with the exception of the bioequivalence study have been performed and none are required for these applications as the pharmacology of topiramate is well-established.

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.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Topiramate 15mg and 25mg Hard Capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Topiramate</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Other antiepileptics (N03AX11)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>15mg and 25mg Hard Capsules</td>
</tr>
</tbody>
</table>
| Reference numbers for the Decentralised Procedure | UK/H/1579/001-2/DC  
                 |                                       | UK/H/2407/001-2/DC                    |
| Reference Member State                         | United Kingdom                        |
| Member States concerned                       | Belgium, Cyprus, the Czech Republic,  |
|                                               | Ireland, Italy, Malta, the Netherlands,|
|                                               | Poland, Portugal, the Slovak Republic |  |
|                                               | and Slovenia                           |
| Marketing Authorisation Number(s)              | PL 18909/0238-9                      |
|                                               | PL 18909/0337-8                      |
| Name and address of the authorisation holder   | Arrow Generics Limited               |
|                                               | Unit 2, Eastman Way, Stevenage,      |
|                                               | Hertfordshire,                        |
|                                               | SG1 4SZ                               |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Topiramate
Chemical name: 2,3:4,5-Bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate

Structural formula:

![Structural formula image]

Molecular formula: C_{12}H_{21}NO_8S

Appearance: White to off-white powder.
Solubility: Freely soluble in dichloromethane, acetone, dimethylsulphoxide

Molecular weight: 339.37

Topiramate complies with in-house specifications.

An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the active substance topiramate.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance topiramate, with suitable test methods and limits. 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 specifications and certificates of analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.
P. Medicinal Product

Other Ingredients

Other ingredients consist of pharmaceutical excipients povidone, opadry-II-85F18378 white (which contains polyvinyl alcohol-part hydrolysed, titanium dioxide, macrogol, talc), aniseed flavour, saccharin sodium (E 954), magnesium stearate and sugar spheres (which contain sucrose and maize starch).

The capsule body and cap consist of titanium dioxide (E-171) and gelatin. The black printing ink consists of shellac, ethanol, isopropanol, butanol, propylene glycol, purified water, strong ammonia solution, potassium hydroxide and black iron oxide (E172).

All excipients comply with their relevant European Pharmacopoeia monographs with the exception of opadry-II-85F18378 white, aniseed flavour, maize starch and sucrose (composition of sugar spheres) and black iron oxide (E172). All of these excipients with the exception of black iron oxide (E172) comply with in-house specifications. Black iron oxide (E172) complies with the National Formulary.

None of the excipients used contain material of animal or human origin with the exception of gelatin. Valid European Pharmacopoeia Certificates of suitability for TSE have been provided for gelatine.

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

The magnesium stearate contained in this product is sourced from vegetable origin and therefore no European Pharmacopoeia Certificates of suitability for TSE is required.

Pharmaceutical Development

The objective of the development programme was to produce products that could be considered generic medicinal products of Topamax 25mg Tablets (Janssen-Cilag Limited).

With the exception of the excipients, the reference product used in the bioequivalence study is qualitatively and quantitatively identical to the UK reference product.

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished products versus the reference products of Topamax 25mg Capsules (Janssen-Cilag Limited).

Comparative in vitro dissolution profiles and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on two pilot scale batches per strength have been provided. The applicant has committed to perform process validation on future production-scale batches.

Finished Product Specification
The finished product specification proposed for the products is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for any working standards used.

**Container-Closure System**
These products are packaged in high density polyethylene bottles with a polypropylene induction sealed cap containing a desiccant (silica gel).
The product comes in pack sizes of 14, 20, 28, 56 and 60 capsules.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary product packaging complies with EU legislation regarding contact with food.

**Stability of the product**
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 30 months with the storage instructions, ‘Store in the original container,’ and ‘Keep the container tightly closed in order to protect from moisture.’

**Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels**
The SPCs, PILs and labelling are pharmaceutically acceptable.

User testing results have been submitted for typical PILs for these products. The results indicate that the PILs are 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 they contain.

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

**Expert report**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**
It is recommended that Marketing Authorisations are granted for these applications.
III.2 PRE-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of topiramate are well-known. As topiramate is a widely used, well-known active substance, the applicant has not provided any additional studies and none are required.

The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.
III.3 CLINICAL ASPECTS
1. Introduction
This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier. For more details, the reader should refer to the company’s clinical overview and summary and to the clinical file.

The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

2. Clinical study reports
To support these applications, the marketing authorisation holder has submitted one single dose bioequivalence study.

A two-way crossover, open-label, single dose, fasting, bioequivalence study of Topiramate 25mg Capsules versus Topamax 25mg Sprinkle Capsules in normal, healthy, non-smoking male and female subjects.

All subjects were in a fasted state before dosing. Blood sampling was performed pre- and up to 144 hours post dose in each treatment period. The washout period between phases was 21 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (ng/ml/h)</th>
<th>AUC_{0-∞} (ng/ml/h)</th>
<th>C_{max} (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topiramate:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>13329.75</td>
<td>17609.87</td>
<td>264.01</td>
</tr>
<tr>
<td></td>
<td>13540.41±2476.10</td>
<td>17822.07±2881.30</td>
<td>273.45±75.32</td>
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<tr>
<td>Reference</td>
<td>13597.45</td>
<td>17968.64</td>
<td>252.79</td>
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<tr>
<td></td>
<td>13779.27±2288.80</td>
<td>18072.15±2069.65</td>
<td>263.91±83.82</td>
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<tr>
<td>Ratio (90% CI)</td>
<td>98.35</td>
<td>100.07</td>
<td>104.71</td>
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<tr>
<td></td>
<td>95.55-101.22</td>
<td>94.60-105.86</td>
<td>99.40-110.31</td>
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</table>

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-t} and C_{max} for topiramate lie within 80-125% boundaries. Thus, bioequivalence has been shown between the test and reference products in this study.

As 15mg and 25mg strength products meet all the criteria as 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 25mg strength qualify for an extrapolation, can be extrapolated to 15mg strength capsules also.

3. Post marketing experience
Topiramate has a well-recognised efficacy and an acceptable level of safety in the indications approved for Topamax 25mg Tablets and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the marketing authorisations is supported.

4. Benefit-Risk assessment
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s products and
the innovator products are interchangeable. Extensive clinical experience with topiramate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

5. Conclusions
The grant of marketing authorisations for Topiramate 15mg and 25mg Hard Capsules is recommended from a clinical viewpoint.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Topiramate 15mg and 25mg Hard Capsules 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 an application of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Topiramate 15mg and 25mg Hard Capsules and the originator products Topamax 25mg Sprinkle Capsules (Janssen-Cilag Limited).

No new or unexpected safety concerns arise from these applications.

The SPCs, PILs and labelling are satisfactory and consistent with that for the innovator products.

RISK-BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with topiramate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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