Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

TOPAMAX® 25 mg Tablets
TOPAMAX® 50 mg Tablets
TOPAMAX® 100 mg Tablets
TOPAMAX® 200 mg Tablets

TOPAMAX® Sprinkle Capsules 15, 25 or 50 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25, 50, 100 and 200 mg of topiramate.
Topamax Sprinkle Capsules contain topiramate 15, 25 or 50 mg.

For excipients see Section 6.1.

3. PHARMACEUTICAL FORM

Topamax Tablets are available as engraved, round, film-coated tablets in the following strengths and colours: 25 mg - white, 50 mg – light - yellow, 100 mg - yellow, 200 mg - salmon. The tablets are engraved as follows:

25 mg “TOP” on one side; “25” on the other
50 mg “TOP” on one side; “50” on the other
100 mg “TOP” on one side; “100” on the other
200 mg “TOP” on one side; “200” on the other

Topamax Sprinkle Capsules are available as hard gelatin capsules containing topiramate in coated beads.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Epilepsy

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

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

The efficacy and safety of conversion from adjunctive therapy to Topamax monotherapy has not been demonstrated.
Migraine

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

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

Continuing therapy should be reviewed every six months.

The usefulness of Topamax in the acute treatment of migraine has not been studied.

4.2 Posology and method of administration

4.2.1 General

For optimal seizure control in both adults and children, it is recommended that therapy be initiated at a low dose followed by titration to an effective dose.

Tablets should not be broken. Topamax can be taken without regard to meals.

Topamax Sprinkle 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 yoghurts. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use.

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

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

Since Topamax is removed from plasma by haemodialysis, a supplemental dose of Topamax equal to approximately one-half the daily dose should be administered on haemodialysis days. The supplemental dose should be administered in divided doses at the beginning and completion of the haemodialysis procedure. The supplemental dose may differ based on the characteristics of the dialysis equipment being used.

4.2.2 Epilepsy

a) Monotherapy

Adults and children over 16 years

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

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

**Children aged 6-16 years**

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

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

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

b) **Adjunctive Therapy**

**Adults and children over 16 years**

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

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

**Children aged 2 - 16 years**

The recommended total daily dose of Topamax (topiramate) as adjunctive therapy is approximately 5 to 9 mg/kg/day in two divided doses. Titration should begin at 25 mg nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses), to achieve optimal clinical response. Dose titration should be guided by clinical outcome.
Daily doses up to 30 mg/kg/day have been studied and were generally well tolerated.

4.2.3 Migraine

Adults and children over 16 years

Titration should begin at 25 mg nightly for 1 week. The dosage should then be increased in increments of 25 mg/day administered at 1-week intervals. If the patient is unable to tolerate the titration regimen, longer intervals between dose adjustments can be used.

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

Children

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

4.3 Contraindications

Hypersensitivity to any component of this product.

4.4 Special warnings and special precautions for use

4.4.1 General

Antiepileptic drugs, including Topamax, should be withdrawn gradually to minimise the potential of increased seizure frequency. In clinical trials, dosages were decreased by 100 mg/day at weekly intervals. In some patients, withdrawal was accelerated without complications.

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

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

Some patients, especially those with a predisposition to nephrolithiasis, may be at increased risk for renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain. Adequate hydration whilst using topiramate is very important as it can reduce the risk of developing renal stones. In addition, it
may reduce the risk of heat-related adverse events during exercise and exposure to particularly warm environments (see section 4.8).

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

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

Depression and mood alterations have been reported in patients treated with topiramate. In double blind clinical trials, suicide related events (SREs) (suicidal ideation, suicide attempts and suicide) occurred at a frequency of 0.5% in topiramate treated patients (43 out of 7,999 patients treated) and at a 3 fold higher incidence than in those treated with placebo (0.15%; 5 out of 3,150 patients treated).

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

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

Acute myopia with secondary angle-closure glaucoma has been reported rarely in both children and adults receiving Topamax. 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 Topamax as rapidly as is clinically feasible and appropriate measures to reduce intraocular pressure. These measures generally result in a decrease in intraocular pressure. If increased intraocular pressure is suspected, immediate specialist advice should be sought.

**Metabolic Acidosis:** Hyperchloraemic, non-anion gap, metabolic acidosis (ie decreased serum bicarbonate below the normal reference range in the absence of respiratory alkalosis) is associated with topiramate treatment. This decrease in serum bicarbonate is due to the inhibitory effect of topiramate on renal carbonic anhydrase. Generally, the decrease in bicarbonate occurs early in treatment although it can occur at any time during treatment. These decreases are usually mild to moderate (average decrease of 4 mmol/L at doses of 100 mg/day or above in adults and at approximately 6 mg/kg/day in paediatric patients). Rarely, patients have experienced decreases to values below 10 mmol/L. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhoea, surgery, ketogenic diet, or certain drugs) may be additive to the bicarbonate lowering effects of topiramate.
Chronic metabolic acidosis in paediatric patients can reduce growth rates. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated in paediatric or adult populations.

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

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

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

### 4.4.2 Migraine Prophylaxis

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

#### Weight loss

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

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

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

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

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

#### Effects of Topamax on Other Antiepileptic Drugs

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

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

**Effects of Other Antiepileptic Drugs on Topamax**

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

The addition or withdrawal of valproic acid does not produce clinically significant changes in plasma concentrations of topiramate and, therefore, does not warrant dosage adjustment of Topamax.

The results of these interactions are summarised in the following table:

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

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

**Other Drug Interactions**

Digoxin: In a single-dose study, serum digoxin area under plasma concentration curve (AUC) decreased 12% due to concomitant administration of Topamax. The clinical relevance of this observation has not been established. When Topamax is added or withdrawn in patients on digoxin therapy, careful attention should be given to the routine monitoring of serum digoxin.

**CNS Depressants:** Concomitant administration of Topamax and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, topiramate should be used with caution if used in combination with alcohol and other CNS depressants.
Oral Contraceptives: In an interaction study with a combined oral contraceptive, Topamax increased plasma clearance of the oestrogenic component significantly. Consequently, and bearing in mind the potential risk of teratogenicity, patients should receive a preparation containing not less than 50 µg of oestrogen or use some alternative non-hormonal method of contraception. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns.

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

Metformin: A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin 500mg bd and topiramate 100mg bd in plasma when metformin was given alone and when metformin and topiramate were given simultaneously. The results of this study indicated that metformin mean $C_{\text{max}}$ and mean AUC$_{0-12\text{h}}$ increased by 18% and 25%, respectively, while mean CL/F decreased 20% when metformin was co-administered with topiramate. Topiramate did not affect metformin $t_{\text{max}}$. The clinical significance of the effect of topiramate on metformin pharmacokinetics is unclear. Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The extent of change in the clearance is unknown. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear. When Topamax is added or withdrawn in patients on metformin therapy, careful attention should be given to the routine monitoring for adequate control of their diabetic disease state.

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

Others: Topamax, when used concomitantly with other agents predisposing to nephrolithiasis, may increase the risk of nephrolithiasis. While using Topamax, agents like these should be avoided since they may create a physiological environment that increases the risk of renal stone formation. The interaction with benzodiazepines has not been studied.
**Additional Pharmacokinetic Drug Interaction Studies:** Clinical studies have been conducted to assess the potential pharmacokinetic drug interaction between topiramate and other agents. The changes in C\text{max} or AUC as a result of the interactions are summarized below. The second column (concomitant drug concentration) describes what happens to the concentration of the concomitant drug listed in the first column when topiramate is added. The third column (topiramate concentration) describes how the coadministration of a drug listed in the first column modifies the concentration of topiramate.

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>Concomitant Drug Concentration(^a)</th>
<th>Topiramate Concentration(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>↔</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>20% increase in C\text{max} and AUC of nortriptyline metabolite</td>
<td></td>
</tr>
<tr>
<td>Dihydroergotamine (Oral and Subcutaneous)</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>↔</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>31% increase in AUC of the reduced metabolite</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>↔</td>
<td>16% increase in C\text{max}, 17% increase in AUC (80 mg propranolol q12h)</td>
</tr>
<tr>
<td></td>
<td>17% increase in C\text{max} for 4-OH propranolol (TPM 50 mg q12h)</td>
<td></td>
</tr>
<tr>
<td>Sumatriptan (Oral and Subcutaneous)</td>
<td>↔</td>
<td>NS</td>
</tr>
<tr>
<td>Pizotifen</td>
<td>↔</td>
<td>↔</td>
</tr>
</tbody>
</table>

\(^a\) % values are the changes in treatment mean C\text{max} or AUC with respect to monotherapy

\(↔\) = No effect on C\text{max} and AUC (\(\leq 15\%\) change) of the parent compound

NS = Not studied

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

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

**4.6 Pregnancy and lactation**
Topiramate was teratogenic in mice, rats and rabbits. In rats, topiramate crosses the placental barrier.
There are no studies using Topamax in pregnant women. However, Topamax should not be used during pregnancy unless, in the opinion of the physician, the potential benefit outweighs the potential risk to the foetus.

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

In post-marketing experience, hypospadias has been reported in male infants exposed in-utero to topiramate, with or without other anticonvulsants; however, a causal relationship with topiramate has not been established.

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

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

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

As with all antiepileptic drugs, Topamax may produce central nervous system related adverse events. Drowsiness is likely and Topamax may be more sedating than other antiepileptic drugs. These adverse events could potentially be dangerous in patients driving a vehicle or operating machinery, particularly until such time as the individual patient's experience with the drug is established.

### 4.8 Undesirable effects

#### 4.8.1 Epilepsy

**a) Monotherapy**

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

**Adults:**

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

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

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

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

b) Adjunctive Therapy

Adults:

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

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

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

Children

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

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

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

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

Children

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

4.8.3 General

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

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

Acute myopia associated with secondary acute angle closure glaucoma has been reported rarely. (See section 4.4)

Metabolic acidosis has been reported rarely (see Section 4.4 Special warnings and special precautions for use).

Suicidal ideation or attempts have been reported uncommonly (see Section 4.4. special warnings and special precautions for use).

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

4.9 Overdosage
Signs and Symptoms

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

Topiramate overdose can result in severe metabolic acidosis.

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

Treatment

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

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

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

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

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

In humans, the major route of elimination of unchanged topiramate and its metabolites is via the kidney. Overall, plasma clearance is approximately 20 to 30 mL/min in humans following oral administration.

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

The plasma and renal clearance of topiramate are decreased in patients with impaired renal function (CLCR ≤ 60 mL/min), and the plasma clearance is decreased in patients with end-stage renal disease.

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

Plasma clearance of topiramate is decreased in patients with moderate to severe hepatic impairment.

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

### 5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity.

As with other antiepileptic drugs, topiramate was teratogenic in mice, rats and rabbits. Overall numbers of foetal malformations in mice were increased for all drug-treated groups, but no significant differences or dosage-response relationships were observed for overall or specific malformations, suggesting that other factors such as maternal toxicity may be involved.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Topamax contains the following inactive ingredients:

- Lactose monohydrate
- Pregelatinized starch
- Carnauba wax
- Microcrystalline cellulose
- Sodium starch glycolate
- Magnesium stearate
- OPADRY White, Yellow, Pink, Red (depending on the colour, contains hydroxypropyl methylcellulose, titanium dioxide (E171), polyethylene glycol, synthetic iron oxide and polysorbate 80).

Topamax Sprinkle Capsules contain the following inactive ingredients:

- Sugar spheres
- Povidone
- Cellulose Acetate

**Capsule Composition**
- Gelatin
- Titanium dioxide (E171)
- Silicon dioxide
- Sodium lauryl sulphate

**Ink Composition**
- OPACODE contains synthetic iron oxide, pharmaceutical glaze, n-butyl alcohol, alcohol, hydroxypropyl methyl cellulose, propylene glycol, ammonium hydroxide, simethicone and distilled water.

6.2 Incompatibilities

None known

6.3 Shelf life

- Topamax Tablets: 36 months.
- Topamax Sprinkle Capsules: 24 months.
6.4 **Special precautions for storage**

Topamax Tablets: Do not store above 25°C. Keep container tightly closed.
Topamax Sprinkle Capsules: Do not store above 25°C. Keep container tightly closed.

6.5 **Nature and contents of container**

Topamax Tablets: Available in high density polyethylene (HDPE) bottles with low density polyethylene (LDPE) tamper-evident closures containing 60 tablets. Each bottle contains a desiccant sachet.

Topamax Sprinkle Capsules: Available in opaque HDPE containers with tamper evident closures containing 60 capsules. The closures consist of either an HDPE outer shell and polypropylene inner shell or polypropylene outer shell and LDPE inner shell.

6.6 **Instructions for use/handling (and disposal)**

Not applicable.

7. **MARKETING AUTHORISATION HOLDER**

Janssen-Cilag Limited
Saunderton
High Wycombe
Buckinghamshire
HP14 4HJ
UK

8. **MARKETING AUTHORISATION NUMBER**

Topamax 25 mg Tablets PL 00242/0301
Topamax 50 mg Tablets PL 00242/0302
Topamax 100 mg Tablets PL 00242/0303
Topamax 200 mg Tablets PL 00242/0304
Topamax Sprinkle Capsules 15 mg PL 00242/0348
Topamax Sprinkle Capsules 25 mg PL 00242/0349
Topamax Sprinkle Capsules 50 mg PL 00242/0350

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Topamax Tablets: 18 July 1995 / 30 March 2005
Topamax Sprinkle Capsules: 17 February 1999 / 30 March 2005

10. **DATE OF REVISION OF THE TEXT**