



Public Assessment Report

from the Norwegian Medicines Agency

Topiramate Teva 25 mg film-coated tablets
Topiramate Teva 50 mg film-coated tablets
Topiramate Teva 100 mg film-coated tablets
Topiramate Teva 200 mg film-coated tablets
Topiramate Teva 300 mg film-coated tablets
Topiramate Teva 400 mg film-coated tablets

MA-holder: Teva Sweden AB

MA-numbers in Norway:

25 mg: 05-3166, 50 mg: 05-3167, 100 mg: 05-3168,
200 mg: 05-3169, 300 mg: 05-3170, 400 mg: 05-3171

Date: 2008-06-05

This assessment report is published by the Norwegian Medicines Agency (NoMA) following Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier which was submitted to the NoMA and its fellow organisations in all concerned EEA member states. It reflects the scientific discussion between the NoMA and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval and issue of a marketing authorisation.

This assessment report will be updated by an addendum whenever new important information becomes available.

Module 1: Information about the initial procedure
Module 2: Summary of product Characteristics (SPC)
Module 3: Package Leaflet
Module 4: Labelling
Module 5: Scientific discussion
Module 6: Update

Module 1: Information about the initial procedure:

1. Type of application:
An abridged application according to Directive 2001/83/EC, Article 10(1), so called generic application (for the strengths 25 mg, 50 mg, 100 mg and 200 mg).
An abridged application according to Directive 2001/83/EC, Article 10(3), so called hybrid application (for the strength 300 mg and 400 mg).
2. Active substance: topiramate
3. Pharmaceutical form: Film-coated tablets
4. Strengths: 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg
5. MA holder: Teva Sweden AB, PO Box 1070, SE-25110 Helsingborg, Sweden
6. Reference Member State: Norway
7. Concerned Member States:
25, 50 and 100 mg (NO/H/136/001-003/MR): AT, BE, BG, CZ, DE, DK, EE, EL, FI, FR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SE, SI, SK, UK
200 mg (NO/H/136/004/MR): AT, BE, BG, DE, DK, EE, EL, FI, FR, HU, IE, IT, LT, LU, LV, NL, PL, PT, RO, SE, SI, SK, UK
300 and 400 mg ((NO/H/136/005-006/MR): AT, BE, BG, EL, FI, HU, IE, LU, NL, PL, SE, UK
8. Procedure-number: NO/H/136/001-006/MR
9. Timetable:
Start (Day 0):13.12.2007
End (Day 90):12.03.2008

Module 2: Summary of product Characteristics (SPC)

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Topiramate Teva 25 mg film-coated tablets
Topiramate Teva 50 mg film-coated tablets
Topiramate Teva 100 mg film-coated tablets
Topiramate Teva 200 mg film-coated tablets
Topiramate Teva 300 mg film-coated tablets
Topiramate Teva 400 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg topiramate.

Excipients

25 mg: Each film-coated tablet contains 28.5 mg lactose.

50 mg: Each film-coated tablet contains 21.14 mg lactose.

100 mg: Each film-coated tablet contains 42.28 mg lactose.

200 mg: Each film-coated tablet contains 84.55 mg lactose and 0.060 mg allura red AC lake (E129).

300 mg: Each film-coated tablet contains 126.83 mg lactose.

400 mg: Each film-coated tablet contains 169.1 mg lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

25 mg: White to off-white, film-coated, capsule-shaped tablet debossed "T25" on one side and plain on the other.

50 mg: Light yellow, film-coated, capsule-shaped tablet scored and debossed "T" and "50" on either side of the score on one side, and plain on the other side.

The tablet can be divided into equal halves.

100 mg: Yellow, film-coated, capsule-shaped tablet scored and debossed "T" and "100" on either side of the score on one side, and plain on the other side.

The tablet can be divided into equal halves.

200 mg: Salmon, film-coated, capsule-shaped tablet scored and debossed "T" and "200" on either side of the score on one side, and plain on the other side.

The tablet can be divided into equal halves.

300 mg: White to off-white, film-coated, capsule-shaped tablet scored and debossed "T" and "300" on either side of the score on one side, and plain on the other side.

The tablet can be divided into equal halves.

400 mg: White to off-white, film-coated, capsule-shaped tablet scored and debossed "T" and "400" on either side of the score on one side and plain on the other side.

The tablet can be divided into equal halves.

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 epileptic seizures and/or generalised tonic-clonic seizures.

Adults: Second line treatment for migraine prophylaxis (not intended for acute treatment)

4.2 Posology and method of administration

For optimal seizure control in both adults and adolescents aged 12 years and over, it is recommended that therapy be initiated at a low dose followed by gradual titration to an effective dose in order to avoid dose-dependent adverse events.

Estimation of plasma levels is not necessary for optimisation of topiramate therapy.

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:

The tablets should not be crushed due to bitter taste. Topiramate can be taken with or without a meal with a sufficient quantity of liquid.

Monotherapy for adults and adolescents aged 12 years and older

Titration should begin at 25 mg in the evening for one 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 titration should be guided by clinical outcome.

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

When concomitant antiepileptic medicinal products are withdrawn to achieve monotherapy with topiramate, the possible effects on seizure control should be taken into account. If the safety of the patient doesn't require rapid interruption of the other concomitant epileptic therapy, a gradual discontinuation of the concomitant epileptic therapy by one third every other week is recommended.

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

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

Adjunctive therapy for adults and adolescents aged 12 years and older

Titration should begin at 25 mg to 50 mg topiramate in the evening for one week. The total daily dose should then be increased by 25 mg-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.

The minimum effective dose given in clinical studies as adjunctive therapy was 200 mg per day.

Therefore it was considered to be the minimum effective dose. The usual daily dose is 200 mg to 400 mg in two divided doses. Some patients achieve maximum efficacy with a single daily dose. Some patients may require the maximum daily dose of 800 mg.

Migraine therapy in adults:

Titration should begin at 25 mg in the evening 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. There are no efficacy or safety data for longer than six months in the prophylactic treatment of migraine.

Patients with hepatic and/or renal impairment

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 the usual daily dose and to titrate with smaller steps and at a slower pace than is usual. As with all patients, the titration 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.

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

Patients undergoing haemodialysis

Since topiramate is removed from plasma by haemodialysis, a supplemental dose of topiramate equal to approximately one half of the daily doses 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 form of dialysis and equipment being used. Like in other patients, the dose titration occurs according to the clinical outcome (e.g. seizure control, avoidance of undesirable effects).

Withdrawal

Antiepileptic agents, including 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.

4.3 Contraindications

Hypersensitivity to topiramate, 200 mg: allura red AC lake or to any of the excipients.

Treatment for prophylaxis of migraine: In 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. Preventing migraine attacks however, 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

Renal impairment

The major route of elimination of topiramate and its metabolites is *via* the kidney. Caution should be exercised in patients with moderate or severe renal impairment. Accumulation because of reduced elimination may occur and it may take longer than usual to achieve steady-state. Dose titration should occur at a lower pace than usual (see section 4.2).

Use in children

There is only limited information about the use of the medicinal product in children less than 12 years of age.

Hydration

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).

Nephrolithiasis

There is an increased risk of renal stone formation and associated signs and symptoms such as renal colic, renal pain or flank pain, especially in patients with a predisposition to nephrolithiasis. Risk factors for nephrolithiasis include prior stone formation, a family history of nephrolithiasis and hypercalciuria. None of these risk factors can reliably predict stone formation during topiramate treatment. Topiramate, when used concomitantly with other agents predisposing to nephrolithiasis (acetazolamide, triamterene, vitamin C >2g/day), may increase the risk of nephrolithiasis. While using topiramate, agents like these and ketogenic diets should be avoided since they may create a physiological environment that increases the risk of renal stone formation.

Decreased hepatic function

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

Acute myopia and secondary angle-closure syndrome

Secondary angle-closure glaucoma with acute myopia has been reported in patients receiving topiramate (see also section 4.8). Treatment includes discontinuation of topiramate as rapidly as possible in the judgement of the treating physician, and appropriate measures to reduce intraocular pressure.

Metabolic acidosis

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

Chronic metabolic acidosis enhances the risk of renal stone formation.

Chronic metabolic acidosis in paediatric patients may cause osteomalacia (rickets) and may reduce growth rates. 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 during 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).

Mood disturbances/depression

During treatment with topiramate, an increased incidence of mood disturbances (including aggression), psychotic reactions and depression has been observed (see section 4.8). Patients should be monitored for signs of depression and referred for appropriate treatment if necessary.

Suicide attempts

In the double-blind phases of clinical trials with topiramate in approved and investigational indications, suicide attempts occurred uncommonly (see section 4.8). In accordance with good clinical practice, patients with a history of depression and/or suicidal behaviour should be closely monitored, especially at the beginning of treatment. Patients (and caregivers of patients) should be advised to seek medical advice immediately if suicidal thoughts emerge.

Prophylaxis of migraine in adults

Patients on long term topiramate treatment for migraine prophylaxis should be regularly weighed and monitored for continuing weight loss. If a clinically significant weight loss occurs, the discontinuation of the medication should be considered.

Weight loss

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

Excipients

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

200 mg: This medicinal product contains allura red AC lake (E129) and may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of topiramate on other antiepileptic agents

The addition of topiramate to carbamazepine, valproic acid or lamotrigine has little or no effect on their steady-state plasma concentrations. In occasional patients, treatment with topiramate and phenytoin may result in an increase in plasma concentrations of phenytoin. Therefore plasma concentrations of phenytoin should be monitored in patients with symptoms of phenytoin toxicity.

Effects of other antiepileptic agents on topiramate

During simultaneous treatment with phenytoin or carbamazepine the plasma concentration of topiramate decreases, probably due to induced metabolism. The addition or withdrawal of phenytoin or carbamazepine to topiramate therapy may require an adjustment in dosage of the latter. This should be done by titrating to clinical effect.

The addition or withdrawal of valproic acid or lamotrigine does not produce clinically significant changes in plasma concentrations of topiramate. Rare reports of encephalopathy with or without hyperammonaemia have been received for patients treated with topiramate while also taking valproate or other antiepileptic agents.

Other interactions with medicinal products

Digoxin:

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

Contraceptives:

In a pharmacokinetic interaction study in healthy volunteers topiramate monotherapy at doses of 50 mg/day to 200 mg/day did not affect exposure (AUC) of combination oral contraceptives (containing 1 mg norethisterone plus 35 micrograms ethinyloestradiol). However, in another study, exposure to ethinyloestradiol was significantly decreased at topiramate doses of 200, 400 and 800 mg/day (18%, 21% and 30%, respectively) when given as adjunctive therapy in patients taking valproic acid, while norethisterone exposure was 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 oestrogen-containing contraceptive products with topiramate containing . Patients who are taking oral contraceptives containing oestrogen should be asked to report any change in their bleeding pattern to their treating physician.

Hydrochlorothiazide (HCTZ):

HCTZ increases 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 decreases in serum potassium after topiramate or HCTZ administration, which were greater when HCTZ and topiramate were administered in combination.

Metformin:

An interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin 500 mg twice daily and topiramate 100 mg twice daily in plasma when metformin and topiramate were given simultaneously. The results of this study indicated that metformin mean C_{max} and mean AUC_{0-12h} increased by 18% and 25%, respectively, while mean CL/F decreased by 20% when metformin was co-administered with topiramate. The clinical significance of the effect of topiramate on metformin pharmacokinetics is unclear. The oral plasma clearance of topiramate appears to be reduced when administered with metformin. The extent of the change in clearance is unknown. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear. When topiramate is added or withdrawn in patients on metformin therapy, careful attention should be given to the routine monitoring for adequate control of their diabetic disease state.

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.

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 or withdrawn from pioglitazone 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.

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.

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 AUC_{24} and a modest reduction in the systemic exposure of the active metabolites, 4-trans-hydroxyglyburide (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.

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.

Additional pharmacokinetic interaction studies:

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.

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

There are no pharmacokinetic interactions between topiramate and propranolol, dihydroergotamine or pizotifen.

Topiramate does not affect the pharmacokinetics of sumatriptan (oral or subcutaneous).

Potential interactions which have not been studied

Topiramate inhibits the enzyme CYP2C19 and may influence other active substances which are metabolized *via* this enzyme, such as diazepam, imipramine, moclobemide, proguanil, omeprazole. However, this has not been studied.

Simultaneous intake of carbonic anhydrase inhibitors (e.g. sultiame, zonisamide) and topiramate has not been examined in clinical studies. Combination of these agents may increase the adverse events due to inhibition of carbonic anhydrase.

4.6 Pregnancy and lactation

Pregnancy

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

Combination treatment appears to increase the risk of malformation and therefore it is important that 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 placental barrier.

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

Epilepsy:

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

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

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

Migraine prophylaxis:

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

Lactation

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

4.7 Effects on ability to drive and use machines

Topiramate has 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 and therefore may decrease attention to demanding motor activities. This has to be taken into account for e.g. driving a car or using machines.

4.8 Undesirable effects

very common ($\geq 1/10$);
 common ($\geq 1/100$ to $< 1/10$);
 uncommon ($\geq 1/1,000$ to $< 1/100$);
 rare ($\geq 1/10,000$ to $< 1/1,000$);
 very rare ($< 1/10,000$)
 not known (cannot be estimated from the available data).

The undesirable effect profile of topiramate is based on data from 1,800 subjects in clinical studies.

<i>System organ class</i>	<i>Very common</i>	<i>Common</i>	<i>Uncommon</i>	<i>Rare</i>
Blood and lymphatic system disorders		Anaemia, epistaxis, purpura, leucopenia, thrombocytopenia		Neutropenia
Nervous system disorders	Ataxia, paraesthesia, speech disorders, aphasia	Tremor, coordination abnormal, abnormal gait, nystagmus, taste perversion	Hypokinesia, stupor	
Eye disorders	Diplopia, abnormal vision			Acute myopia and secondary angle closure glaucoma, eye pain
Respiratory, thoracic and mediastinal disorders			Dyspnoea	
Gastrointestinal disorders		Constipation, abdominal pain	Diarrhoea, vomiting and dry mouth	
Renal and urinary disorders		Urinary incontinence, nephrolithiasis		
Skin and subcutaneous tissue disorders		Alopecia	Folliculitis and pruritus	
Metabolism and nutrition disorders	Weight loss	Metabolic acidosis		
General disorders and administration site conditions	Dizziness, fatigue, somnolence, nervousness, headache, nausea	Skeletal pain, allergic reaction, insomnia		

Hepatobiliary disorders				Increase in liver enzymes
Reproductive system and breast disorders		Menstrual disturbances, impotence		
Psychiatric disorders	Difficulty with memory, anorexia, confusion and psychomotor slowing, depression, concentration disturbances, anxiety	Apathy, asthenia, euphoria, emotional lability, agitation, cognitive problems, decreased libido, aggressive reactions, psychosis or psychotic symptoms	Hallucinations, personality disorders, suicidal ideation, suicidal attempts	

In patients treated with topiramate as add-on 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 settled. 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, as well as convulsion after withdrawal of topiramate (even in patients with no history of epilepsy) 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). Oligohydrosis 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 agents 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 have been 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

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

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

Treatment

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antiepileptics

ATC code: N03A X11

Topiramate is classified as a sulphamate-substituted monosaccharide. Three pharmacological properties of topiramate have been identified that may contribute to its anticonvulsant activity. Topiramate reduces the frequency at which action potentials are generated when neurones are subjected to sustained depolarisation, indicative of state-dependent blockade of voltage-sensitive sodium channels.

Topiramate enhances the activity of GABA at some types of GABA receptors. Topiramate weakly antagonises the excitatory activity of the kainate/AMPA subtype of glutamate receptor, but has no apparent effect on the activity of *N*-methyl-*D*-aspartate (NMDA) at the NMDA receptor subtype. In addition, topiramate inhibits some isoenzymes of carbonic anhydrase. This effect is not thought to be a major component of the antiepileptic activity of topiramate.

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

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

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

5.2 Pharmacokinetic properties

Absorption

Topiramate is rapidly absorbed. After oral intake of 400 mg, C_{max} is reached after approximately 2 hours. Topiramate has linear pharmacokinetics with a dose-proportional increase of the plasma concentration in the tested dose range of 200-800 mg/day.

There are no data from intravenous administration. 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%. Based on data from urine, the bioavailability may be estimated to approximately 50%. There is no clinically significant effect of food on topiramate. The variability in the kinetics is 25-35%. The maximal plasma concentration (C_{max}) in healthy volunteers seen after repeated dosage of 100 mg twice daily is approximately 7 $\mu g/ml$.

Distribution

The mean apparent volume of distribution has been measured as 0.55-0.8 l/kg. 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 binds to erythrocytes, but the binding is probably saturated at 3-10 $\mu g/ml$. The plasma protein binding rate is 13-17%. There is no information concerning distribution to cerebrospinal fluid.

Metabolism

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

Elimination

Renal clearance is approximately 18 ml/min. This is far less than expected, which indicates tubular reabsorption of topiramate. Overall, plasma clearance is approximately 20-30 ml/min following oral administration. The most important route of elimination for topiramate and its metabolites is *via* the kidneys.

Following administration of repeated doses of 50 mg and 100 mg topiramate twice daily, the mean half-life was ca. 21 hours. Patients with normal renal function may take 4-8 days to reach steady-state plasma concentrations, while patients with moderate to severe renal impairment may need 10-15 days of treatment. The plasma and renal clearance of topiramate are decreased in patients with impaired renal function.

Special patient groups

Renal impairment:

Compared to normal renal function (creatinine clearance > 70 ml/min), 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 by 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 agents 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 (anaemia). Toxicity was evident in animals at systemic exposures which were those expected in patients given recommended doses. The clinical relevance of these findings is unknown, but cannot be excluded.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core: Lactose monohydrate
Starch, pregelatinised (maize)
Cellulose, microcrystalline
Sodium starch glycolate (type A)
Silica, colloidal anhydrous
Magnesium stearate

Coating:
Titanium dioxide (E171)

25, 300 and 400 mg:
Macrogol 4000
Polydextrose
Hypromellose

50 mg: Macrogol 3350
Polyvinyl alcohol
Talc
Yellow iron oxide (E172)

100 mg: Macrogol 4000
Polydextrose
Hypromellose
Yellow iron oxide (E172)
Black iron oxide (E172)

200 mg: Macrogol 4000
Polydextrose
Hypromellose
Red iron oxide (E172)
Allura red AC lake (E129)

Indigo carmine lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years (25, 50, 100, 200 and 300 mg tablets)

27 months (400 mg tablets)

6.4 Special precautions for storage

Store below 30°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Blisters: OPA/Al/PVC-Aluminium blisters

Bottles: White HDPE bottles with white PP child-resistant closures and silica gel as desiccant.

Pack sizes:

25 mg

Blisters: 10, 20, 28, 30, 50, 56, 60, 100 and 120 film-coated tablets.

Bottles: 60 film-coated tablets.

50 mg

Blisters: 10, 20, 28, 30, 50, 56, 60, 100, 120 and 200 film-coated tablets.

Bottles: 60 film-coated tablets.

100 mg

Blisters: 10, 20, 28, 30, 50, 56, 60, 100, 120 and 200 film-coated tablets.

Bottles: 60 film-coated tablets.

200 mg

Blisters: 10, 20, 28, 30, 50, 56, 60, 100, 120 and 200 film-coated tablets.

Bottles: 60 film-coated tablets.

300 mg

Blisters: 10, 28, 30, 50, 60, 100, 120 and 200 film-coated tablets.

Bottles: 60 film-coated tablets.

400 mg

Blisters: 10, 28, 30, 50, 60, 100, 120 and 200 film-coated tablets.

Bottles: 60 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Teva Sweden AB, Helsingborg, Sweden

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2007-06-08

10. DATE OF REVISION OF THE TEXT

2008-03-12

Module 3: Package Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Topiramate Teva 25 mg film-coated tablets
Topiramate Teva 50 mg film-coated tablets
Topiramate Teva 100 mg film-coated tablets
Topiramate Teva 200 mg film-coated tablets
Topiramate Teva 300 mg film-coated tablets
Topiramate Teva 400 mg film-coated tablets
Topiramate

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

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

In this leaflet:

1. What Topiramate Teva is and what it is used for
2. Before you take Topiramate Teva
3. How to take Topiramate Teva
4. Possible side effects
5. How to store Topiramate Teva
6. Further information

1. WHAT TOPIRAMATE TEVA IS AND WHAT IT IS USED FOR

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

Epilepsy:

Topiramate 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 antiepileptic medicines to treat adults and adolescents over 12 years of age.

Migraine:

Topiramate can be used to treat frequently recurring migraine headaches in adults. It is not intended for the treatment of individual migraine attacks.

2. BEFORE YOU TAKE TOPIRAMATE TEVA

Do NOT take Topiramate Teva

- if you are allergic (hypersensitive) to topiramate, 200 mg: allura red AC lake, or any of

the other ingredients of Topiramate Teva (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 Teva

You should tell your doctor if any of the following apply to you:

- if you have been prescribed topiramate for epilepsy and are pregnant, planning to become pregnant or are breast-feeding - see the section 'Pregnancy and breast-feeding' below 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 near-sightedness (myopia) and/or pain in the eyes. Contact your doctor immediately as this medicine can cause sudden glaucoma in a minority of patients.
- if you notice any changes in your mood, feel depressed or have thoughts of harming yourself, you should contact your doctor straightaway.

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.

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 tablets 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
- 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
- pioglitazone (for diabetes), as topiramate can reduce its effect
- amitriptyline (for depression), as topiramate can increase its effect
- haloperidol (for mental illnesses), as topiramate can increase its effect
- diltiazem (for high blood pressure), as topiramate can reduce its effect and it may increase the effect of topiramate
- glibenclamide (for diabetes), as topiramate can reduce its effect
- lithium (for depression), as topiramate can alter 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 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 Teva with food and drink

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

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

Pregnancy and breast-feeding

Epilepsy:

If you plan to become pregnant or find out that you are pregnant while taking these tablets, 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, think you may be pregnant or are of child-bearing age and not using an effective method of contraception you must not take topiramate 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 can 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 Teva

This medicinal product contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

200 mg: This medicinal product contains allura red AC lake and may cause allergic reactions.

3. HOW TO TAKE TOPIRAMATE TEVA

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

For doses not realisable/practicable with this strength other strengths of this medicinal product are available.

Epilepsy

Adults and adolescents (aged 12 years and older):

If you are only taking topiramate to control your epilepsy, the usual dose is 100 mg per day. This can be taken as 100 mg a day or 50 mg 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 together with other anti-epileptic medicines, the usual dose of topiramate is between 100-200 mg taken twice a day. However your doctor may tell you to use a higher or lower

dose.

When you first start taking Topiramate Teva 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 Teva is not recommended for use in children under 12 years old.

Migraine

The usual dose for the treatment of migraine is 50 mg 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 your doctor will prescribe a much lower dose and slowly increase it, usually at one week intervals.

Your treatment will then normally be reviewed every six months.

This medicinal product is not recommended for the prevention of migraine headaches in adolescents and children under 16 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.

Method of administration

Your tablets should be swallowed with a glass of water. Do not crush them. The tablets are normally taken twice a day (e.g. in the morning and evening) and can be taken before, during or after meals.

If you take more Topiramate Teva 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 tablets with you.

If you forget to take Topiramate Teva

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.

If you stop taking Topiramate Teva

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

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

4. POSSIBLE SIDE EFFECTS

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

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

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

The 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
- confusion
- depression
- anorexia
- memory problems and slowing of thoughts
- problems with concentrating
- anxiety
- 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)
- bleeding into the skin from small vessels (purpura)
- a decrease in the number of certain blood cells (leucopenia, anaemia and thrombocytopenia)
- nosebleeds
- apathy
- lack of energy
- mood swings including a feeling of euphoria
- feeling agitated or aggressive
- co-ordination problems
- problems with thinking
- loss of sexual desire
- changes in thoughts
- stomach pain
- constipation
- hair loss
- incontinence
- kidney stones (which may present as blood in the urine or pain in the lower back or genital area)
- shaking (tremor)
- abnormal walking
- involuntary movement of the eyes (nystagmus)
- taste changes
- disruption in the menstrual cycle
- impotence.

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

- personality disorders (changes in thoughts, feelings and behaviour)
- hallucinations
- difficulty in breathing
- diarrhoea
- vomiting
- dry mouth
- itching
- inflammation of the scalp
- stupor
- reduction in mobility (hypokinesia).

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)
- acute shortsightedness
- eye pain
- 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 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. 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 gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE TOPIRAMATE TEVA

Keep out of the reach and sight of children.

Do not use Topiramate Teva after the expiry date which is stated on the carton and bottle or blister after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C. Store in the original package in order to protect from moisture.

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

6. FURTHER INFORMATION

What Topiramate Teva contains

The active substance is topiramate.

25 mg: Each film-coated tablet contains 25 mg topiramate.

50 mg: Each film-coated tablet contains 50 mg topiramate.

100 mg: Each film-coated tablet contains 100 mg topiramate.

200 mg: Each film-coated tablet contains 200 mg topiramate.

300 mg: Each film-coated tablet contains 300 mg topiramate.

400 mg: Each film-coated tablet contains 400 mg topiramate.

The other ingredients are lactose monohydrate, pregelatinised maize starch, microcrystalline cellulose, sodium starch glycolate (type A), colloidal anhydrous silica, magnesium stearate, titanium dioxide (E171),

25, 300 and 400 mg: macrogol 4000, polydextrose and hypromellose

50 mg: macrogol 3350, polyvinyl alcohol, talc and yellow iron oxide (E172)

100 mg: macrogol 4000, polydextrose, hypromellose, yellow iron oxide (E172), black iron oxide (E172)

200 mg: macrogol 4000, polydextrose, hypromellose, red iron oxide (E172), allura red AC lake (E129) and indigo carmine lake (E132)

What Topiramate Teva looks like and contents of the pack

Film-coated tablet

25 mg: White to off-white, film-coated, capsule-shaped tablet debossed "T25" on one side and plain on the other.

50 mg: Light yellow, film-coated, capsule-shaped tablet scored and debossed "T" and "50" on either side of the score on one side, and plain on the other side. The tablet can be divided into equal halves.

100 mg: Yellow, film-coated, capsule-shaped tablet scored and debossed "T" and "100" on either side of the score on one side, and plain on the other side. The tablet can be divided into equal halves.

200 mg: Salmon, film-coated, capsule-shaped tablet scored and debossed "T" and "200" on either side of the score on one side, and plain on the other side. The tablet can be divided into equal halves.

300 mg: White to off-white, film-coated, capsule-shaped tablet scored and debossed "T" and "300" on either side of the score on one side, and plain on the other side. The tablet can be divided into equal halves.

400 mg: White to off-white, film-coated, capsule-shaped tablet scored and debossed "T" and "400" on either side of the score on one side and plain on the other side. The tablet can be divided into equal halves.

Pack sizes:

Topiramate Teva 25 mg film-coated tablets

Blisters: 10, 20, 28, 30, 50, 56, 60, 100 and 120 film-coated tablets.

Bottles: 60 film-coated tablets.

Topiramate Teva 50 mg/100 mg/ 200 mg film-coated tablets

Blisters: 10, 20, 28, 30, 50, 56, 60, 100, 120 and 200 film-coated tablets.

Bottles: 60 film-coated tablets.

Topiramate Teva 300 mg/400 mg film-coated tablets

Blisters: 10, 28, 30, 50, 60, 100, 120 and 200 film-coated tablets.

Bottles: 60 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

AT: TEVA Pharma B.V.
BE: Teva Pharma Belgium N.V.
BG: Teva Pharmaceuticals Bulgaria EOOD
CZ: Teva Pharmaceuticals CR, s.r.o
DE: TEVA Generics GmbH
DK: Teva Denmark A/S
EE: TEVA Pharma B.V.
EL: TEVA Pharma B.V.
FI: TEVA Sweden AB
FR: Teva Classics S.A.
HU: TEVA Magyarország Zrt
IE: TEVA Pharma B.V.
IT: Teva Italia S.R.L.
LT: TEVA Pharma B.V.
LU: Teva Pharma Belgium N.V.
LV: TEVA Pharma B.V.
MT: TEVA Pharma B.V.
NL: Pharmachemie B.V.
NO: Teva Sweden AB
PL: Teva Pharmaceuticals Polska Sp. z o.o.
PT: TEVA Pharma – Produtos Farmacêuticos, Lda
RO: Teva Pharmaceuticals S.R.L.
SE: TEVA Sweden AB
SI: Teva Pharma B.V.
SK: TEVA Pharmaceuticals Slovakia s.r.o
UK: TEVA UK Limited

Manufacturer:

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Brampton Road, Hampden Park, Eastbourne
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Swensweg 5, Postbus 552
2003 RN Haarlem
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TEVA Santé SA
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Headquarters address: Immeuble Palatin 1, 1Cour du Triangle
92936 Paris La Défense Cedex
France

TEVA Pharmaceutical Works Private Limited Company
Pallagi út 13, 4042 Debrecen
Hungary

This medicinal product is authorised in the Member States of the EEA under the following names:

AT: Topiramat Teva 25, 50, 100, 200, 300 & 400 mg Filmtabletten
BE: Topiramate TEVA 25, 50, 100, 200, 300 & 400 mg filmomhulde tabletten
BG: Topiramate Teva 25, 50, 100, 200, 300 & 400 mg Филмирани таблетки
CZ: Topiramat - Teva 25, 50 & 100 mg

DE: Topiramate-TEVA ® 25, 50, 100 & 200 mg Filmtabletten
DK: Topiramate Teva 25, 50, 100 & 200 mg filmovertrukne tabletter
EE: Topiramate Teva
EL: Topiramate Teva 25, 50, 100, 200, 300 & 400 mg επικαλυμμένα με λεπτό υμένιο δισκία
FI: Topiramate Teva 25, 50, 100, 200, 300 & 400 mg tabletti, kalvopäällysteinen
FR: Topiramate TEVA 25, 50, 100 & 200 mg, comprimé pelliculé
HU: Topiramate-Teva 25, 50, 100, 200, 300 & 400 mg filmtablettta
IE: Topiramate Teva 25, 50, 100, 200, 300 & 400 mg Film-coated Tablets
IT: Topiramato Teva 25, 50, 100 & 200 mg compresse rivestite con film
LT: Topiramate Teva 25, 50, 100 & 200 mg plėvele dengtos tabletės
LU: Topiramate TEVA 25, 50, 100, 200, 300 & 400 mg comprimés pelliculés
LV: Topiramate Teva
MT: Topiramate Teva 25, 50 & 100 mg Film-coated Tablets
NL: Topiramaat 25, 50, 100, 200, 300 & 400 mg PCH, filmomhulde tabletten
NO: Topiramate Teva 25, 50, 100, 200, 300 & 400 mg Tabletter, filmdrasjert
PL: RAMATOP
PT: Topiramato Teva
RO: Topiramate Teva 25, 50, 100 & 200 mg, Comprimat filmate
SE: Topiramate Teva 25, 50, 100, 200, 300 & 400 mg filmdragerad tablett
SI: Topiramate Teva 25, 50, 100 & 200 mg filmsko obložene tablete
SK: Topiramate - Teva 25, 50, 100 & 200 mg filmom obalené tablety
UK: Topiramate 25, 50, 100, 200, 300 & 400 mg Film-coated Tablets

This leaflet was last approved in 2008-03-12

Module 4: Labelling

Not included

Module 5: Scientific discussion

This module reflects the scientific discussion for the approval of Topiramate Teva 25, 50, 100, 200, 300 and 400 mg film-coated tablets. The procedure was finalised at 2008-03-12 (on Day 90). For information on changes after this date please refer to the module 'Update'.

I INTRODUCTION

Based on the review of the submitted data, the Member States have granted a marketing authorisation (MA) for Topiramate Teva 25, 50, 100, 200, 300 and 400 mg film-coated tablets. The first date of authorisation in Norway was 8. June 2007. The product is approved for the following 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 epileptic seizures and/or generalised tonic-clonic seizures.

Adults: Second line treatment for migraine prophylaxis (not intended for acute treatment).

A comprehensive description of the indications and the posology is given in the SPC (see Module 3).

The MA in Norway is granted according to Directive 2001/83/EC as amended, Article 10(1) generic application for the strengths 25, 50, 100 and 200 mg and Article 10(3) hybrid application for the strengths 300 and 400 mg.

This concerns a generic application claiming essential similarity to the innovator product Topimax "Janssen-Cilag". Topimax have been marketed in Norway since 6. March 1997. This type of application refers to information which is contained in the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the original authorised medicinal product, which is legally permitted once the data protection time of the dossier of the reference product and the patent rights have expired. Usually, it is necessary to demonstrate that the generic product has the same pharmacokinetic profile as the originator. This has been demonstrated for Topiramate Teva. No new pre-clinical or further clinical studies were conducted, which is acceptable for this generic application.

II. QUALITY ASPECTS

II.1 Introduction

Topiramate Teva film-coated tablets 25, 50, 100, 200, 300, 400 mg contain topiramate, an antiepileptic drug, as the active substance in an immediate release formulation. The film coated tablets are packaged in oriented polyamide (OPA)/aluminium/PVC-aluminium blisters or white HDPE bottles with white PP child-resistant closures and silica gel as desiccant.

II.2 Drug Substance

Topiramate is a white to off-white powder. Topiramate possesses four stereogenic carbon atoms and is optically active. There is no Ph.Eur. monograph for topiramate. The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The

analytical methods applied are sufficiently described and validated. Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period when packaged in the commercial packaging material.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained. The manufacturing process has been sufficiently described and critical steps identified. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed for two 25 mg batches, two 50 mg batches, one 100 mg batch, one 200 mg batch, one 300 mg batch and two 400 mg batches. The batch analysis results show that the finished products meet the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. Data presented support the shelf life claimed in the SPC.

III. NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of topiramate are well known. As topiramate is a widely used, well-known active substance, the applicant has not provided additional non-clinical studies and further studies are not required.

IV. CLINICAL ASPECTS

The pharmacodynamic properties and clinical efficacy and safety of topiramate are well known. As topiramate is a widely used, well-known active substance, the applicant has not provided additional clinical studies and further studies are not required. The clinical overview based on literature review is, thus, appropriate.

The submitted bioequivalence studies show that Topiramate Teva film-coated tablets 25 mg and 50 mg are bioequivalent to Topamax "Janssen-Cilag" film-coated tablets 25 mg and 50 mg, respectively, with respect to both rate and extent of absorption of topiramate. The results of the submitted bioequivalence studies with the 25 mg and 50 mg formulation can be extrapolated to the 100 mg, 200 mg, 300 mg and 400 mg strengths, according to conditions in *Note for Guidance on the Investigation of Bioavailability and Bioequivalence* CPMP/EWP/QWP/1401/98, section 5.4.

An adequate review of published clinical data and the bioequivalence has been shown.

The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Topimax, marketed by Janssen-Cilag and with other SPCs accepted during previous MRPs concerning topiramate.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Satisfactory chemical pharmaceutical documentation has been provided assuring consistent quality of the product.

Topiramate Teva film-coated tablets 25 mg and 50 mg is a generic medicinal product to Topimax "Janssen-Cilag". Topimax is a well-known medicinal product with an established efficacy and safety profile.

The risk/benefit ratio is considered positive and Topiramate Teva film-coated tablet 25 mg, 50 mg, 100 mg, 200 mg, 300 mg and 400 mg are recommended for approval.

Module 6: Update