IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PPA1500/050/001
Case No: 2083758

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Profind Wholesale Ltd.

Unit 625, Kilshane Avenue, **Northwest Business Park**, **Dublin 15**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Topamax 25mg Film-coated Tablets

the particulars of which are set out in the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **28/07/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Topamax 25mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 25mg topiramate.

Excipients: contains lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Product imported from Greece:
White, embossed, round, film-coated tablets imprinted with “TOP” on one side and “25” on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Epilepsy

Topamax is indicated as monotherapy or adjunctive therapy for adults and children over 4 years of age for partial onset seizures with or without secondarily generalised seizures and primary generalised tonic-clonic seizures.

Topamax is also indicated in adults and children as adjunctive therapy for seizures associated with Lennox Gastaut Syndrome.

Migraine

Topamax is indicated in adults for the prophylaxis of migraine headaches in patients intolerant of or unresponsive to other migraine treatments.

4.2 Posology and method of administration

General

For optimal 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.

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

These dosing recommendations apply to children and 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.

When concomitant anti-epileptic drugs (AEDs) are withdrawn to achieve monotherapy with topiramate, consideration should be given to the effects this may have on seizure control.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

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

Epilepsy

(a) Monotherapy

Adults

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

Children

Treatment of children aged 4 years and above should begin at 1 to 3 mg/kg 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. 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 aged four years and above is 3 to 6 mg/kg/day. Children over 50 kg with recently diagnosed partial onset seizures have received doses of up to 500 mg/day.

(b) Adjunctive therapy of epilepsy

Adults and children over 16 years

The minimal effective dose 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 1600 mg per day which is the maximum 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 nightly for one week. Subsequently, at weekly or biweekly intervals, the dose should be increased by 25-50 mg and taken in two divided doses. Dose titration should be guided by clinical outcome. Some patients may achieve efficacy with once-a-day dosing.

Children aged 4 – 16 years

The recommended total daily dose of Topamax 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 (administrated 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.

Migraine

Adults

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. Patients have received a total daily dose up to 200 mg/day. Dose and titration rate should be guided by clinical outcome.

Children

Topamax in migraine prophylaxis has not been studied in children.

4.3 Contraindications

Hypersensitivity to any component of this product.

4.4 Special warnings and precautions for use

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

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 (ie seizure control, avoidance of side effects) with the knowledge that subjects with known renal impairment may require a longer time to reach steady-state at each dose.

Adequate hydration while using topiramate is very important. Hydration can reduce the risk of nephrolithiasis (see below).

Proper hydration prior to and during activities such as exercise or exposure to warm temperatures may reduce the risk of heat-related adverse events *(see section 4.8).*

Mood Disturbances/Depression: An increased incidence of mood disturbances and depression has been observed during topiramate treatment.

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

In the double-blind phases of clinical trials with topiramate in approved and investigational indications, suicide attempts occurred at a rate of 0.003 (13 events/3999 patient years) on topiramate versus 0 (0 events/1430 patient years) on placebo. One completed suicide was reported in a bipolar disorder double-blind trial in a patient on topiramate.

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

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

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

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 (i.e decreased serum bicarbonate below the normal reference range in the absence of respiratory alkalosis) is associated with topiramate treatment. This decrease in serum bicarbonate is due to the inhibitory effect of topiramate on renal carbonic anhydrase. Generally, the decrease in bicarbonate occurs early in treatment although it can occur at any time during treatment. These decreases are usually mild to moderate (average decrease of 4 mmol/L at doses of 100mg/day or above in adults and at approximately 6mg/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.

4.5 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 effect on their steady-state plasma concentrations, except in the occasional patient, where the addition of Topamax to phenytoin may result in an increase of plasma concentrations of phenytoin. This is possibly due to inhibition of a specific enzyme polymorphic isoform ($CYP2C_{meph}$). Consequently, any patient on phenytoin showing clinical signs or symptoms of toxicity should have phenytoin levels monitored.

A pharmacokinetic interaction study of patients with epilepsy indicated that 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:

AED Coadministered	AED Concentration	Topiramate Concentration
Phenytoin	↔**	↓
Carbamazepine (CBZ)	↔	↓
Valproic Acid	↔	↔
Lamotrigine	↔	↔
Phenobarbital	↔	NS
Primidone	↔	NS

↔ = No effect on plasma concentration (≤ 15% change)
** = Plasma concentrations increase in occasional 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.

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

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

Risperidone: Drug-drug interaction studies conducted under single and multiple dose conditions in healthy volunteers and patients with bipolar disorder yielded similar results. When administered concomitantly with topiramate at escalating doses of 100, 250 and 400mg/day there was a reduction in risperidone (administered at doses ranging from 1 to 6 mg/day) systemic exposure (16% and 33% for steady-state AUC at the 250 and 400 mg/day doses, respectively). Minimal alterations in the pharmacokinetics of the total active moiety (risperidone plus 9-hydroxyrisperidone) and no alterations for 9-hydroxyrisperidone were observed. There were no clinically significant changes in the systemic exposure of the risperidone total active moiety or of topiramate, therefore this interaction is not likely to be of clinical significance.

Hydrochlorothiazide (HCTZ): A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of HCTZ (25 mg q24h) and topiramate (96 mg q12h) when administered alone and concomitantly.

The results of this study indicate that topiramate C_{max} increased by 27% and AUC increased by 29% when HCTZ was added to topiramate. The clinical significance of this change is unknown. The addition of HCTZ to topiramate therapy may require an adjustment of the topiramate dose. The steady-state pharmacokinetics of HCTZ were not significantly influenced by the concomitant administration of topiramate. Clinical laboratory results indicated decreases in serum potassium after topiramate or HCTZ administration, which were greater when HCTZ and topiramate were administered in combination.

Metformin: A drug-drug interaction study conducted in healthy volunteers evaluated the steady-state pharmacokinetics of metformin and topiramate in plasma when metformin was given alone and when metformin and topiramate were given simultaneously. The results of this study indicated that metformin mean C_{max} and mean AUC_{0-12h} increased by 18% and 25%, respectively, while mean CL/F decreased 20% when metformin was co-administered with topiramate. Topiramate did not affect metformin t_{max}. The clinical significance of the effect of topiramate on metformin pharmacokinetics is unclear. Oral plasma clearance of topiramate appears to be reduced when administered with metformin. The extent of change in the clearance is unknown. The clinical significance of the effect of metformin on topiramate pharmacokinetics is unclear. When 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 AUCτ, ss of pioglitazone with no alteration in $C_{max'ss}$ was observed. This finding was not statistically significant. In addition, a 13% and 16% decrease in C_{max}, ss and AUCτ,ss respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in $C_{max'ss}$ and $AUC_{\tau,ss}$ of the active keto-metabolite.
The clinical significance of these findings is not known. When 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.

Glibenclamide: A drug-drug interaction study conducted in patients with type 2 diabetes evaluated the steady-state pharmacokinetics of glibenclamide (5mg/day) alone and concomitantly with topiramate (150mg/day). There was a 25% reduction in glibenclamide AUC_{24} during topiramate administration. Systemic exposure of the active metabolites, 4-*trans*-hydroxy-glibenclamide (M1) and 3-*cis*-hydroxyglibenclamide (M2), were also reduced by 13% and 15% respectively. The steady-state pharmacokinetics of topiramate were unaffected by concomitant administration of glibenclamide. When topiramate is added to glibenclamide therapy or glibenclamide is added to topiramate therapy, careful attention should be given to the routine monitoring of patients for adequate control of their diabetic disease state.

Other forms of interactions:
Agents predisposing to nephrolithiasis
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.

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

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

Summary of Results from Additional Clinical Pharmacokinetic Drug Interaction Studies

Concomitant Drug	Concomitant Drug Concentration[a]	Topiramate Concentration[a]
Amitriptyline	↔ 20% increase in C_{max} and AUC of nortriptyline metabolite	NS
Dihydroergotamine (Oral and Subcutaneous)	↔	↔
Haloperidol	↔ 31% increase in AUC of the reduced metabolite	NS
Propranolol	↔ 17% increase in C_{max} for 4-OH propranolol (TPM 50 mg q12h)	16% increase in C_{max}, 17% increase in AUC (80 mg propranolol q12h)
Sumatriptan (Oral and Subcutaneous)	↔	NS
Pizotifen	↔	↔
Diltiazem	25% decrease in AUC of diltiazem and 18% decrease in DEA, and ↔ for DEM*	20% increase in AUC
Venlafaxine	↔	↔
Flunarizine	16% increase in AUC (TPM 50 mg q12h)[b]	↔

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

↔	=	No effect on C_{max} and AUC (≤ 15% change) of the parent compound
NS	=	Not studied
*DEA	=	Des acetyl diltiazem, DEM = N-demethyl diltiazem
[b]	=	Flunarizine AUC increased 14% in subjects taking flunarizine alone. Increase in exposure may be attributed to accumulation during achievement of steady state.

4.6 Pregnancy and lactation

Use During Pregnancy
As with other antiepileptic drugs, 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 be used during pregnancy only if the potential benefit outweighs the potential risk to the foetus.

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.

Use during lactation:
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 suggest an extensive excretion of topiramate into breast milk. Since many drugs are excreted in human milk, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

As with all antiepileptic drugs, Topamax acts on the central nervous system and may produce drowsiness, dizziness or other related symptoms. It may also cause visual disturbances and/or blurred vision. These adverse 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

The safety of TOPAMAX® was evaluated from a clinical trial database consisting of 4111 patients (3182 on TOPAMAX® and 929 on placebo) who participated in 20 double-blind trials and 2847 patients who participated in 34 open-label trials, respectively, for the treatment of primary generalized tonic-clonic seizures, partial onset seizures, seizures associated with Lennox-Gastaut syndrome, newly or recently diagnosed epilepsy or migraine. The information presented in this section was derived from pooled data.
The majority of adverse drug reactions (ADRs) were mild to moderate in severity.

Table 1 lists all the ADRs derived from clinical trials and post marketing experience irrespective of indication or population. The frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000, including isolated reports

Table 1 Clinical trial and post marketing adverse drug reactions

System Organ Class	Adverse Drug Reaction				
	Frequency				
	Very common	Common	Uncommon	Rare	Not known
Infections and Infestations	Nasopharyngitis				
Blood and Lymphatic System Disorders		Anaemia	Eosinophilia, leucopoenia, lymphadenopathy, thrombocytopenia	Neutropenia	
Metabolism and Nutrition Disorders		Anorexia, decreased appetite	Hypocalcaemia, increased appetite, metabolic acidosis, polydipsia	Acidosis hyperchloraemic	

Psychiatric Disorders	Depression	Abnormal behaviour, aggression, agitation, anger, anxiety, bradyphrenia, confusional state, depressed mood, disorientation, expressive language disorder, insomnia, mood altered, mood swings	Affect lability, apathy, crying, distractibility, dysphemia, early morning awakening, elevated mood, euphoric mood, flat, affect, hallucination, hallucination, auditory, hallucination, visual, initial insomnia, lack of spontaneous speech, libido decreased, listless, loss of libido, middle insomnia, panic attack, panic reaction, paranoia, perseveration, psychotic disorder, reading disorder, restlessness, sleep disorder, suicidal ideation, suicide attempt, tearfulness, thinking abnormal	Anorgasmia, disturbance in sexual arousal, feeling of despair, hypomania, , mania, orgasm abnormal, orgasmic sensation decreased, panic disorder	
Nervous System Disorders	Dizziness, parathesia, somnolence	Amnesia, balance disorder, cognitive disorder, convulsion, coordination abnormal, disturbance in attention, dysarthria, dysgeusia, hypoaesthesia, intention tremor, lethargy, memory impairment, mental impairment, nystagmus, psychomotor skills impaired, sedation, tremor	Ageusia, aphasia, aura, burning sensation, cerebellar syndrome, clumsiness, complex partial seizures, depressed level of consciousness, dizziness postural, drooling, dysaesthesia, dysgraphia, dyskinesia, dysphasia, dystonia, formication, grand mal convulsion, hypersomnia, hypogeusia, hypokinesia, neuropathy peripheral, parosmia, poor quality sleep, presyncope, psychomotor hyperactivity, repetitive speech,	Akinesia, anosmia, apraxia, circadian rhythm sleep disorder, essential tremor, hyperaesthesia, hyposmia, unresponsive to stimuli	

			sensory disturbance, sensory loss, speech disorder, stupor, syncope, visual field defect		
Eye Disorders		Diplopia, vision blurred, visual disturbance	Blepharospasm, dry eye, lacrimation increased, mydriasis, myopia, photophobia, photopsia, scotoma, visual acuity reduced	Accommodation disorder, altered visual depth perception, amblyopia, blindness transient, blindness unilateral, eyelid oedema, glaucoma, night blindness, presbyopia, scintillating scotoma	Abnormal sensation in eye, angle closure glaucoma, eye movement disorder
Ear and Labyrinth Disorders		Ear pain, tinnitus, vertigo	Deafness, deafness neurosensory, deafness unilateral, ear discomfort, hearing impaired		
Cardiac Disorders			Bradycardia, palpitations, sinus bradycardia		
Vascular Disorders			Flushing, hot flush, hypotension, orthostatic hypotension	Raynaud's phenomenon	
Respiratory, Thoracic and Mediastinal Disorders		Dyspnoea, epistaxis, nasal congestion, rhinorrhoea	Dysphonia, dyspnoea exertional, paranasal sinus hypersecretion		
Gastrointes-tinal Disorders	Diarrhoea, nausea	Abdominal discomfort, abdominal pain, abdominal pain upper, constipation, dry mouth, dyspepsia, gastritis, paraesthesia, oral, stomach discomfort, vomiting	Abdominal distension, abdominal pain lower, abdominal tenderness, breath odour, epigastric discomfort, flatulence, gastrooesophageal reflux disease, gingival bleeding, glossodynia, hypoaesthesia oral, oral pain, pancreatitis, salivary hypersecretion		

Renal and Urinary Disorders		Dysuria, nephrolithiasis, pollakiuria	Calculus urinary, haematuria, incontinence, micturition urgency, renal colic, renal pain, urinary incontinence	Calculus ureteric, renal tubular acidosis	
Reproductive System and Breast Disorders			Erectile dysfunction, sexual dysfunction		
Skin and Subcutaneous Tissue Disorders		Alopecia, pruritus, rash	Anhidrosis, dermatitis allergic, erythema, hypoaesthesia facial, pruritus generalised, rash macular, skin discolouration, swelling face, urticaria	Skin odour abnormal, urticaria localised	Erythema multiforme, periorbital oedema, Stevens Johnson syndrome, toxic epidermal necrolysis
Musculoskele-tal, Connective Tissue and Bone Disorders		Arthralgia, muscle spasms, muscle twitching, muscular weakness, musculoskeletal chest pain, myalgia	Flank pain, joint swelling, muscle fatigue, musculoskeletal stiffness	Limb discomfort	
Immune System Disorders		Hypersensitivity			Allergic oedema, conjunctival oedema
General Disorders and Administration Site Conditions	Fatigue	Asthenia, feeling abnormal, gait disturbance, irritability, malaise, pyrexia	Feeling drunk, feeling jittery, hyperthermia, influenza like illness, peripheral coldness, sluggishness, thirst	Calcinosis, face oedema	
Investigations	Weight decreased	Weight increased	Crystal urine present, tandem gait test abnormal, white blood cell count decreased	Blood bicarbonate decreased	
Social Circumstances			Learning disability		

ADRs identified from the clinical trial database that occurred in the paediatric population at a frequency of at least 1% and twice the frequency of the rate in adults in descending order include: decreased appetite, lethargy, disturbance in attention, aggression, abnormal behaviour, gait disturbance, mood altered, abdominal discomfort, diplopia, increased appetite, poor quality sleep, feeling abnormal, lacrimation increased, and sinus bradycardia.
In addition, the following ADRs regardless of frequency were reported in the paediatric population but not in adults: eosinophilia, vertigo, vomiting, hyperthermia, pyrexia, psychomotor hyperactivity, and learning disability.

ADRs reported in each of the three therapy areas (monotherapy, adjunctive therapy and epilepsy) are detailed below.

Epilepsy

(a) Monotherapy

Adults
In double-blind, placebo-controlled monotherapy epilepsy trials, ADRs that had an incidence >5% at the recommended dose (400 mg/day) in descending order of frequency included paraesthesia, weight decreased, fatigue, anorexia, depression, memory impairment, anxiety, diarrhoea, asthenia, dysguesia, and hypoesthesia.

Children
In double-blind, placebo-controlled monotherapy epilepsy trials, ADRs that had an incidence >5% at the recommended dose (400 mg/day) in descending order of frequency included weight decreased, paraesthesia, diarrhoea, disturbance in attention, pyrexia, and alopecia.

(b) Adjunctive therapy of epilepsy

Adults
In double-blind, placebo-controlled adjunctive epilepsy trials, ADRs that had an incidence >5% in the recommended dose range (200 to 400 mg/day) in descending order of frequency included somnolence, dizziness, fatigue, irritability, weight decreased, bradyphrenia, paresthesias, diplopia, coordination abnormal, nausea, nystgamus, lethargy, anorexia, dysarthria, vision blurred, decreased appetite, memory impairment and diarrhoea.

Children
In double-blind, placebo-controlled adjunctive epilepsy trials, ADRs that had an incidence >5% in the recommended dose range (5 to 9 mg/kg/day) in descending order of frequency included decreased appetite, fatigue, somnolence, lethargy irritability, disturbance in attention, weight decreased, aggression, rash, abnormal behaviour, anorexia, balance disorder, and constipation.

Migraine

Adults
In double-blind, placebo-controlled migraine prophylaxis trials, ADRs that had an incidence >5% at the recommended dose (100 mg/day) in descending order of frequency included paraesthesia, fatigue, nausea, diarrhoea, weight decreased, dysguesia, anorexia, decreased appetite, insomnia, hypoesthesia, disturbance in attention, anxiety, somnolence, and expressive language disorder.

4.9 Overdose

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 bioavailability of 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_{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 ($CL_{CR\leq}$ 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

Acute and long-term exposure of mice, rats, dogs and rabbits to topiramate was well-tolerated.

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.

The teratogenic effects seen in rats and rabbits were similar to those seen with carbonic anhydrase inhibitors, which have not been associated with malformations in humans.
In a battery of *in vitro* and *in vivo* mutagenicity assays, topiramate did not show genotoxic potential.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Topamax tablets contain the following inactive ingredients:
Lactose monohydrate
Pregelatinised starch
Carnauba wax
Microcrystalline cellulose (E460)
Sodium starch glycollate (Type A)
Magesium stearate
OPADRY White YS-1-7706-G:

Contains: Hypromellose
Titanium dioxide (E171)
Macrogol
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the bottle and outer carton of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25˚ c.
Keep the bottle tightly closed.

6.5 Nature and contents of container

High density polyethylene bottle (HDPE) bottle with polypropylene (PP) child resistant closure, with a dessicant inserted into the cap. Each bottle contains 60 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 PARALLEL PRODUCT AUTHORISATION HOLDER

Profind Wholesale Ltd
Unit 625, Kilshane Avenue
Northwest Business Park
Dublin 15
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1500/50/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th February 2010

10 DATE OF REVISION OF THE TEXT

July 2010