PRESCRIBING INFORMATION

TOPAMAX®

NAME OF MEDICINAL PRODUCT

Trademark

TOPAMAX®

International Nonproprietary Name:

topiramate

QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets

TOPAMAX® (topiramate) is available in tablets for oral administration containing 25, 50, 100 or 200 mg of topiramate.

Sprinkle Capsules

TOPAMAX® (topiramate) is available as a sprinkle formulation contained in capsules containing 15, 25 or 50 mg of topiramate, and is intended for oral administration.

PHARMACEUTICAL FORM

Tablets

TOPAMAX® is available as engraved, round, coated tablets in the following strengths and colors: 25 mg white, 50 mg light yellow, 100 mg yellow, 200 mg salmon. The tablets are imprinted as follows:
25 mg - "TOP" on one side; "25" on the other;
50 mg - "TOP" on one side; "50" on the other;
100 mg - "TOP" on one side; "100" on the other;
200 mg - "TOP" on one side; "200" on the other.

Sprinkle Capsules

TOPAMAX® is also available as a sprinkle formulation. Finished product is provided as small, white to off-white spheres in gelatin capsules consisting of white bodies with clear natural caps.
The capsules are printed with black pharmaceutical ink as follows:
15 mg - "TOP" on the cap and "15 mg" on the capsule body;
25 mg - "TOP" on the cap and "25 mg" on the capsule body;
50 mg - "TOP" on the cap and "50 mg" on the capsule body.

CLINICAL PARTICULARS

Therapeutic Indications

TOPAMAX® is indicated as adjunctive therapy for adults and children aged 2 and above with partial onset seizures or generalized tonic-clonic seizures.

TOPAMAX® is also indicated in adults and children as adjunctive therapy for the treatment of seizures associated with Lennox Gastaut syndrome.

TOPAMAX® can be prescribed as monotherapy in patients with recently diagnosed epilepsy in adults and children aged 7 and above or for conversion to monotherapy in patient with epilepsy.

TOPAMAX® is indicated in adults for the prevention of migraines. The use of TOPAMAX® in the acute treatment of migraine has not been studied.

Posology and Method of Administration

General

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

TOPAMAX® is available in tablets and a capsule sprinkle formulation. It is recommended that tablets not be broken. The sprinkle formulation is provided for those patients who cannot swallow tablets, e.g. pediatric and the elderly.

TOPAMAX® (topiramate) Sprinkle capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoon) of soft food. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use.
It is not necessary to monitor topiramate plasma concentrations to optimize therapy with TOPAMAX®. On rare occasions, the addition of TOPAMAX® to phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcome. Addition or withdrawal of phenytoin and carbamazepine to adjunctive therapy with TOPAMAX® may require adjustment of the dose of TOPAMAX®.

TOPAMAX® Sprinkle capsules and tablets should be ingested with ample fluid.

TOPAMAX® can be taken without regard to meals.

Adjunctive Therapy Epilepsy

Adults

Therapy should begin at 25 - 50 mg nightly for one week. Subsequently, at weekly or bi-weekly intervals, the dose should be increased by 25 - 50 to 100 mg/day and taken in two divided doses. Dose titration should be guided by clinical outcome. Some patients may achieve efficacy with once-a-day dosing.

In clinical trials as adjunctive therapy, 200 mg was effective and was the lowest dosage studied. This is therefore considered the minimum effective dose. The usual daily dose is 200 - 400 mg in two divided doses. Individual patients have received doses as high as 1600 mg/day.

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

These dosing recommendations apply to all adults, including the elderly, in the absence of underlying renal disease. (See section Special Warnings and Special Precautions for Use.)

Children Aged 2 and Above

The recommended total daily dose of TOPAMAX® (topiramate) as adjunctive therapy is approximately 5 to 9 mg/kg/day in two divided doses. Titration should begin at 25 mg (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses), to achieve optimal clinical response. Dose titration should be guided by clinical outcome.

Daily doses up to 30 mg/kg/day have been studied and were generally well tolerated.

Monotherapy Epilepsy

General

When concomitant 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.

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 for topiramate monotherapy in adults is 100 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 7 years and above should begin at 0.5 to 1 mg/kg nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 0.5 to 1 mg/kg/day, administered in two divided doses. If the child is unable to tolerate the titration regimen, smaller increments or longer intervals between dose increments can be used. Dose and dose titration rate should be guided by clinical outcome.

The recommended initial target dose range for topiramate monotherapy in children aged seven years and above is 3 to 6 mg/kg/day. Children with recently diagnosed partial onset seizures have received doses of up to 500 mg/day.

Migraine

Titration should be initiated with 25 mg every night for 1 week. The dose should then be increased by 25 mg a day, at intervals of 1 week. If the patient cannot tolerate the titration schedule, longer intervals between dosage adjustments can be used.

The total daily dose of topiramate recommended for preventive treatment of migraine is 100 mg/day taken in two doses. Some patients may feel improvement with a total daily dose of 50 mg/day. Some patients take a total daily dose of 200 mg/day. The dosage rate and titration should be clinically monitored.

Contraindications

Hypersensitivity to any component of this product.

Special Warnings and Special 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 50-100 mg in adults with epilepsy and by 25-50 mg in adults receiving TOPAMAX® at doses up to 100 mg/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 (i.e., 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 Post-marketing and Other Experience.)

Oligohidrosis and Hyperthermia

Oligohidrosis (decreased sweating), infrequently resulting in hospitalization, has been reported in association with TOPAMAX® use. Decreased sweating and an elevation in body temperature above normal characterized these cases. Some of the cases were reported after exposure to elevated environmental temperatures.

The majority of the reports have been in children. Patients, especially pediatric patients, treated with TOPAMAX® should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather. Caution should be used when TOPAMAX® is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity.

Mood Disturbances/Depression

An increased incidence of mood disturbances and depression has been observed during topiramate treatment.

Suicide Attempt

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 trial in a patient on topiramate.

Nephrolithiasis

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.

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 Glaucoma

A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving TOPAMAX®. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness) and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within 1 month of initiating TOPAMAX® therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in pediatric patients as well as adults. The primary treatment to reverse symptoms is discontinuation of TOPAMAX® as rapidly as possible, according to the judgment of the treating physician. Other measures, in conjunction with discontinuation of TOPAMAX®, may be helpful. These measures generally result in a decrease in intraocular pressure.

Metabolic Acidosis

Hyperchloremic, non-anion gap, metabolic acidosis (i.e., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with topiramate treatment. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of topiramate on carbonic anhydrase. Such electrolyte imbalance has been observed with the use of topiramate in placebo-controlled clinical trials and in the post-marketing period. Generally, topiramate-induced metabolic acidosis occurs early in treatment although cases can occur at any time during treatment.

Bicarbonate decrements are usually mild-moderate (average decrease of 4 mEq/L at daily doses of 100 mg in adults and at approximately 6 mg/kg/day in pediatric patients); rarely, patients can experience severe decrements to values below 10 mEq/L. Conditions or therapies that predispose to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, or drugs) may be additive to the bicarbonate lowering effects of topiramate.

Some manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fractures. Chronic metabolic acidosis in pediatric patients may also reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated.

Safety and effectiveness in patients below the age of 2 years have not been established. Topiramate is associated with metabolic acidosis. Chronic untreated metabolic acidosis in pediatric patients may cause osteomalacia (rickets) and may reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated.

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).

Nutritional supplementation

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

Interactions with Other Medicinal Products and Other Forms of Interaction

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

Effects of TOPAMAX® on Other Antiepileptic Drugs

The addition of TOPAMAX® to other antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no clinically relevant 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 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 TOPAMAX®. 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 TOPAMAX®.

The results of these interactions are summarized below:

AED Coadministered	AED Concentration	TOPAMAX® Concentration
Phenytoin	↔**	↓
Carbamazepine (CBZ)	↔	↓
Valproic acid	↔	↔
Lamotrigine	↔	↔
Phenobarbital	↔	NS
Primidone	↔	NS

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

Other Drug Interactions

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

CNS Depressants: Concomitant administration of TOPAMAX® and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. It is recommended that TOPAMAX® not be used concomitantly with alcohol or other CNS depressant drugs.

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 effect 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 estrogen containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding.

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

Risperidone: Drug-drug interaction studies conducted under single 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 400 mg/day there was a reduction in risperidone (administered at doses ranging from 1 to 6 mg/day) systemic exposure (16% and 33% for steady-state AUC at the 250 and 400 mg/day doses, respectively). 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 $AUC_{0\text{-}12h}$ 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 $AUC_{t,ss}$ 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 $AUC_{t,ss}$ respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in $C_{max,ss}$ and $AUC_{t,ss}$ 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.

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

Others forms of interaction:

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 opiramate 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.

Laboratory Tests
Clinical trial data indicate that topiramate has been associated with an average decrease of 4 mmol/L in the serum bicarbonate level (see section Special Warnings and Special Precautions for Use).

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.

Use During Lactation
TOPAMAX® should not be used during breastfeeding.

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

In post-marketing experience, cases of hypospadias have 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.

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. These otherwise mild or moderate 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.

Undesirable Effects

Reported adverse events were classified using a modified WHO-ART dictionary. The majority of the most common adverse events in clinical trials were mild-moderate in severity and dose-related. These dose-related adverse events typically began in the titration phase and often persisted into the maintenance phase but infrequently began in the maintenance phase. Rapid titration rate and higher initial dose were associated with higher incidences of adverse events leading to discontinuation.

Adjunctive Therapy Clinical Trials
Since TOPAMAX® has most frequently been co-administered with other antiepileptic agents, it is not possible to determine which agents, if any, are associated with adverse events.

Adults
In double-blind clinical trials, some of which included a rapid titration period, adverse events which occurred with a frequency greater than or equal to 5% and with a higher incidence in the topiramate-treated adult patients than in the placebo group included: somnolence, dizziness, nervousness, ataxia, fatigue, speech disorders/related speech problems, psychomotor slowing, abnormal vision, difficulty with memory NOS*, confusion, paraesthesia, diplopia, anorexia, nystagmus, nausea, weight decrease, language problems, difficulty with concentration/attention, depression, abdominal pain, asthenia, and mood problems.

Adverse events that occurred less frequently but were considered potentially medically relevant included: taste perversion, agitation, cognitive problems NOS*, emotional lability, coordination problems, abnormal gait, apathy, psychosis/psychotic symptoms, aggressive reaction/behavior, leucopenia, and nephrolithiasis. Isolated cases of thromboembolic events have also been reported, although a causal association with the drug has not been established.

Children
In double-blind clinical trials, adverse events which occurred at a frequency greater than or equal to 5% and with a higher incidence in the topiramate-treated pediatric patients than in the placebo group included: somnolence, anorexia, fatigue, nervousness, personality disorder, difficulty with concentration/attention, aggressive reaction, weight decrease, abnormal gait, mood problems, ataxia, saliva increased, nausea, difficulty with memory NOS*, hyperkinesia, dizziness, speech disorders/related speech problems, and paraesthesia.

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

Monotherapy Epilepsy Clinical Trials
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.

Adults
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.

Children
In double-blind clinical trials clinically relevant adverse events occurring at an incidence greater than or equal to 10% in the topiramate-treated pediatric patients included: headache, fatigue, anorexia, and somnolence.

Monotherapy (all patients)
In double-blind studies comparing low topiramate doses (25-100 mg daily) to relatively high topiramate doses (200-1000 mg daily), the following ADRs occurred in both treatment groups at a frequency of >10%: paresthesia, headaches, dizziness, fatigue, weight loss, nausea and diarrhea. These ADRs are similar to those occurring in TOPAMAX® adjunct therapy.

Migraine Clinical Trials
Clinically relevant adverse events that occurred in double-blind clinical trials at a frequency equal to or greater than 5% with a higher incidence in patients treated with topiramate than in the placebo group included: fatigue, paresthesia, dizziness, hypoesthesia, speech disorders, nausea, diarrhea, dyspepsia, dry mouth, weight reduction, anorexia, drowsiness, difficulty with memory NOS (not otherwise specified), difficulty with concentration/attention, insomnia, anxiety, altered mood, depression, altered taste and altered vision.

Patients treated with topiramate experienced moderate dose-dependent alterations in their weight. These alterations were not found in the placebo group. Moderate alterations of 0.0, -2.3%, -3.2% and -3.8% were determined in the placebo group, and the 50, 100 and 200 topiramate groups, respectively.

Post-marketing and Other Experience
Reports of increases in liver function tests in patients taking TOPAMAX® with and without other medications have been received. Isolated reports have been received of hepatitis and hepatic failure occurring in patients taking multiple medications while being treated with TOPAMAX®. Metabolic acidosis has been reported rarely (see section Special Warnings and Special Precautions for Use).

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

Oligohydrosis has been reported rarely with the use of topiramate. The majority of these reports have been in children.

Post-marketing reports of adverse drug reactions

Blood and Lymphatic System Disorders	Very rare: leucopenia and neutropenia, thrombocytopenia
Metabolism and Nutrition Disorders	Rare: anorexia Very rare: metabolic acidosis (see section Special Warnings and Special Precautions for Use); decreased appetite, hyperammonemia (see section Interactions with Other Medicinal Products and Other Forms of Interaction)
Psychiatric Disorders	Rare: depression (see section Special Warnings and Special Precautions for Use); agitation; somnolence Very rare: insomnia, confusional state, psychotic disorder, aggression, hallucination, suicidal ideation, attempts, and suicide (see section Special Warnings and Special Precautions for Use); expressive language disorder
Nervous System Disorders	Rare: paresthesia, convulsion, headache Very rare: speech disorder, dysgeusia, amnesia, memory impairment, drug withdrawal convulsion (see section Special Warnings and Special Precautions for Use)
Eye Disorders	Rare: visual disturbance, vision blurred Very rare: myopia, angle closure glaucoma (see section Special Warnings and Special Precautions for Use), eye pain
Gastrointestinal Disorders	Rare: nausea Very rare: diarrhea, abdominal pain, vomiting
Skin and Subcutaneous Tissue Disorders	Rare: alopecia Very rare: rash
Renal and Urinary Disorders	Rare: nephrolithiasis (see section Special Warnings and Special Precautions for Use)
General Disorders and Administration Site Conditions	Rare: fatigue Very rare: pyrexia, feeling abnormal, asthenia
Investigations	Rare: weight decreased

Table 1: Incidence of Treatment-Emergent Adverse Events in Adults in Placebo-Controlled, Add-On Epilepsy Trials[a,b]
(>10% in the recommended dosage range for topiramate)

Body System/ Adverse Event	TOPAMAX® Dosage (mg/day) Placebo (N=291)	200-400 (N=183)	600-1,000 (N=414)
Body as a Whole- General Disorders			
Fatigue	13.4	14.8	29.7
Central & Peripheral Nervous System Disorders			
Dizziness	15.1	24.6	32.1
Ataxia	6.5	15.8	14.5
Speech Disorders/related speech problems	2.1	13.1	11.4
Paraesthesia	3.8	10.9	19.1
Psychiatric Disorders			
Somnolence	12.0	29.0	27.8
Nervousness	6.2	16.4	19.3
Psychomotor Slowing	2.4	12.6	20.8
Difficulty with Memory NOS	3.1	12.0	14.5
Confusion	5.2	11.5	13.8
Anorexia	4.5	10.4	12.3
Vision Disorders			
Vision Abnormal	2.4	12.6	10.1
Diplopia	5.5	10.4	10.4

a Patients in these add-on trials were receiving 1 to 2 concomitant antiepileptic drugs in addition of TOPAMAX® or placebo.
b Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

Table 2: Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Epilepsy Trials in Adults[a,b]
(≥1% and ≤10% in the recommended dosage range for topiramate)

Body System/ Adverse Event	TOPAMAX® Dosage (mg/day) Placebo (N=291)	200-400 (N=183)	600-1,000 (N=414)
Body as a Whole - General Disorders			
Asthenia	1.0	6.0	3.1
Back Pain	4.1	5.5	2.9
Chest Pain	3.4	3.8	2.4
Influenza-Like Symptoms	2.4	3.3	3.6
Leg Pain	1.7	2.2	3.6
Allergy	1.0	1.6	2.9
Edema	1.4	1.6	1.0
Hot Flushes	1.4	1.6	0.7
Body Odor	0.0	1.1	0.0
Rigors	0.0	1.1	0.5
Central & Peripheral Nervous System Disorders			
Nystagmus	6.9	9.8	11.1
Language Problems	1.0	6.0	10.4
Tremor	6.2	8.7	8.9
Coordination Abnormal	1.7	3.8	3.6
Gait Abnormal	1.4	2.7	2.2
Hypoaesthesia	0.7	2.2	1.2
Muscle Contractions Involuntary	1.0	2.2	2.2
Stupor	0.0	1.6	1.2
Vertigo	1.0	1.1	1.7
Gastrointestinal System Disorders			
Nausea	8.2	9.8	12.1
Dyspepsia	6.2	7.1	6.3
Abdominal Pain	3.8	6.0	7.0
Constipation	2.4	3.8	3.4
Gastroenteritis	1.4	2.2	1.0
Mouth Dry	0.7	1.6	3.9
Gastrointestinal Disorder NOS	0.3	1.1	0.0
Gingivitis	0.3	1.1	1.2
Hearing and Vestibular Disorders			
Hearing Decreased	0.7	1.6	1.2
Metabolic and Nutritional Disorders			
Weight Decrease	3.1	9.3	12.8

Musculoskeletal System Disorders			
Myalgia	0.7	1.6	1.7
Skeletal Pain	0.0	1.1	0.0
Platelet, Bleeding, & Clotting Disorders			
Epistaxis	1.4	2.2	0.7
Purpura	0.7	1.1	0.0
Psychiatric Disorders			
Difficulty with Concentration/Attention	1.7	6.0	14.5
Depression	4.8	5.5	13.0
Mood Problems	2.1	3.8	9.2
Agitation	2.1	3.3	3.4
Aggressive Reaction	1.7	2.7	2.9
Emotional Lability	1.4	2.7	2.7
Cognitive Problems NOS	1.0	2.7	2.9
Libido Decreased	0.7	1.6	0.2
Apathy	0.7	1.1	3.1
Depersonalization	0.7	1.1	2.2
Red Blood Cell Disorders			
Anaemia	1.0	1.1	0.5
Reproductive Disorders, Female	(N=93)	(N=57)	(N=128)
Breast Pain	2.2	3.5	0.0
Amenorrhea	1.1	1.8	1.6
Menorrhagia	0.0	1.8	0.8
Menstrual Disorder	1.1	1.8	0.8
Reproductive Disorders, Male	(N=198)	(N=126)	(N=286)
Prostatic Disorder	0.5	2.4	0.0
Resistance Mechanism Disorders			
Infection	1.0	1.6	0.7
Infection Viral	1.4	1.6	0.5
Moniliasis	0.3	1.1	0.0
Respiratory System Disorders			
Rhinitis	5.8	6.6	6.3
Pharyngitis	2.1	6.0	3.1
Sinusitis	4.1	4.9	5.6
Dyspnea	1.0	1.1	2.4
Skin and Appendages Disorders			
Skin Disorder	0.3	1.6	0.7
Rash Erythematous	0.3	1.1	0.2
Sweating Increased	0.3	1.1	0.5
Special Sense Other, Disorders			
Taste Perversion	0.0	1.6	3.9
Urinary System Disorders			
Urinary Tract Infection	0.7	2.2	2.9
Haematuria	0.7	1.6	0.5
Urinary Incontinence	0.3	1.6	1.4
Micturition Frequency	0.7	1.1	2.4
Urine Abnormal	0.0	1.1	0.5
White Cell and RES Disorders			
Leucopenia	0.7	1.6	1.2

a Patients in these add-on trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX® or placebo.

b Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

Table 3: Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Epilepsy Trials in Children (< 16 years of age) [a,b] (>10% in the topiramate-treated group)

Body System/ Adverse Event	Placebo (N=101)	Topiramate (N=98)
Body as a Whole – General Disorders		
Fatigue	5.0	16.3
Injury	12.9	14.3
Psychiatric Disorders		
Somnolence	15.8	25.5
Anorexia	14.9	24.5
Nervousness	6.9	14.3
Personality Disorder (Behavior Problems)	8.9	11.2
Difficulty with Concentration/Attention	2.0	10.2
Respiratory System Disorders		
Upper Respiratory Tract Infection	36.6	36.7

Table 4: Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Epilepsy Trials in Children (< 16 years of age) [a,b] (≥1% and ≤10% in the recommended dosage range for topiramate)

Body System/ Adverse Event	Placebo (N=101)	Topiramate (N=98)
Body as a Whole - General Disorders		
Allergic Reaction	1.0	2.0
Back Pain	0.0	1.0
Pallor	0.0	1.0
Cardiovascular Disorders – General		
Hypertension	0.0	1.0
Central & Peripheral Nervous System Disorders		
Gait Abnormal	5.0	8.2
Ataxia	2.0	6.1
Hyperkinesia	4.0	5.1
Dizziness	2.0	4.1
Speech Disorders/ speech-related problems	2.0	4.1
Convulsions Aggravated	3.0	3.1
Hyporeflexia	0.0	2.0
Convulsions Grand Mal	0.0	1.0
Fecal Incontinence	0.0	1.0
Paraesthesia	0.0	1.0
Gastrointestinal System Disorders		
Nausea	5.0	6.1
Saliva Increased	4.0	6.1
Constipation	4.0	5.1
Gastroenteritis	2.0	3.1
Dysphagia	0.0	1.0
Flatulence	0.0	1.0
Gastroesophageal Reflux	0.0	1.0
Glossitis	0.0	1.0
Gum Hyperplasia	0.0	1.0
Heart Rate and Rhythm Disorders		
Bradycardia	0.0	1.0
Metabolic and Nutritional Disorders		
Weight Decrease	1.0	9.2
Thirst	1.0	2.0
Hypoglycaemia	0.0	1.0
Weight Increase	0.0	1.0
Platelet, Bleeding, & Clotting Disorders		
Purpura	4.0	8.2
Epistaxis	1.0	4.1
Haematoma	0.0	1.0
Prothrombin Increased	0.0	1.0
Thrombocytopenia	0.0	1.0
Psychiatric Disorders		
Aggressive Reaction	4.0	9.2
Insomnia	6.9	8.2
Mood Problems	6.9	7.1
Difficulty with Memory NOS	0.0	5.1

Emotional Lability	5.0	5.1
Confusion	3.0	4.1
Psychomotor Slowing	2.0	3.1
Appetite Increased	0.0	1.0
Neurosis	0.0	1.0
Reproductive Disorders, Female		
Leukorrhoea	0.0	2.3
Resistance Mechanism Disorders		
Infection Viral	3.0	7.1
Infection	3.0	3.1
Respiratory System Disorders		
Pneumonia	1.0	5.1
Respiratory Disorder	0.0	1.0
Skin and Appendages Disorders		
Skin Disorder	2.0	3.1
Alopecia	1.0	2.0
Dermatitis	0.0	2.0
Hypertrichosis	1.0	2.0
Rash Erythematous	0.0	2.0
Eczema	0.0	1.0
Seborrhoea	0.0	1.0
Skin Discolouration	0.0	1.0
Urinary System Disorders		
Urinary Incontinence	2.0	4.1
Nocturia	0.0	1.0
Vision Disorders		
Eye Abnormality	1.0	2.0
Vision Abnormal	1.0	2.0
Diplopia	0.0	1.0
Lacrimation Abnormal	0.0	1.0
Myopia	0.0	1.0
White Cell and RES Disorders		
Leucopenia	0.0	2.0

a Patients in these add-on trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX® or placebo.

b Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

Suicidal ideations, attempts and suicide have been reported very rarely (see section Special Warnings and Special Precautions for Use).

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 coordination, 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 (see section Special Warnings and Special Precautions for Use).

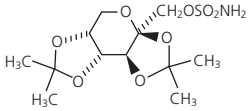
A patient who ingested a dose calculated to be between 96 and 110 g topiramate was admitted to hospital with coma lasting 20-24 hours followed by full recovery after 3 to 4 days.

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. Hemodialysis has been shown to be an effective means of removing topiramate from the body. The patient should be well hydrated.

PHARMACOLOGICAL PROPERTIES

Topiramate is a novel antiepileptic compound and is designated chemically as 2,3:4,5-bis-*O*-(1-methylethylidene)-β-D-fructopyranose sulfamate. The empirical formula is $C_{12}H_{21}NO_8S$. The molecular weight is 339.36. The structural formula is:



Topiramate is a white crystalline powder having a bitter taste. Topiramate is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and having a pH of 9 to 10. It is freely soluble in acetone, chloroform, dimethylsulfoxide and ethanol. The solubility in water is 9.8 mg/mL. Its saturated solution has a pH of 6.3.

Pharmacodynamic Properties

Topiramate is a novel antiepileptic agent classified as a sulfamate-substituted monosaccharide. The precise mechanism by which topiramate exerts its antiseizure and migraine prophylaxis effects are unknown. Electrophysiological and biochemical studies on cultured neurons have identified three properties that may contribute to the antiepileptic efficacy of topiramate.

Action potentials elicited repetitively by a sustained depolarization of the neurons were blocked by topiramate in a time-dependent manner, suggestive of a state-dependent sodium channel blocking action. Topiramate increased the frequency at which γ-aminobutyrate (GABA) activated $GABA_A$ receptors, and enhanced the ability of GABA to induce a flux of chloride ions into neurons, suggesting that topiramate potentiates the activity of this inhibitory neurotransmitter.

This effect was not blocked by flumazenil, a benzodiazepine antagonist, nor did topiramate increase the duration of the channel open time, differentiating topiramate from barbiturates that modulate $GABA_A$ receptors.

Because the antiepileptic profile of topiramate differs markedly from that of the benzodiazepines, it may modulate a benzodiazepine-insensitive subtype of $GABA_A$ receptor. Topiramate antagonized the ability of kainate to activate the kainate/AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) subtype of excitatory amino acid (glutamate) receptor, but had no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype. These effects of topiramate were concentration-dependent over a range of 1 mcM to 200 mcM, with minimum activity observed at 1 mcM to 10 mcM.

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.

In animal studies, topiramate exhibits anticonvulsant activity in rat and mouse maximal electroshock seizure (MES) tests and is effective in rodent models of epilepsy, which include tonic and absence-like seizures in the spontaneous epileptic rat (SER) and tonic and clonic seizures induced in rats by kindling of the amygdala or by global ischemia. Topiramate is only weakly effective in blocking clonic seizures induced by the $GABA_A$ receptor antagonist, pentylenetetrazole.

Studies in mice receiving concomitant administration of topiramate and carbamazepine or phenobarbital showed synergistic anticonvulsant activity, while combination with phenytoin showed additive anticonvulsant activity. In well-controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations of topiramate and its clinical efficacy. No evidence of tolerance has been demonstrated in man.

Epilepsy Clinical Trials

The results of controlled clinical trials established the efficacy of TOPAMAX® (topiramate) Tablets and TOPAMAX® (topiramate capsules) Sprinkle Capsules as monotherapy for adults and children (ages 6 and older) with epilepsy, adjunctive therapy in adults and pediatric patients ages 2-16 years with partial onset seizures or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome.

Monotherapy

The effectiveness of topiramate as monotherapy in adults and children 6 years of age and older with newly diagnosed epilepsy was established in 4 randomized, double-blind, parallel-group trials. Study EPMN-106 was conducted in 487 patients (6 to 83 years of age) who had a new diagnosis of epilepsy (partial onset or generalized) or a diagnosis of recurrent epilepsy while not taking antiepileptic drugs (AEDs). Patients were randomized to receive topiramate 50 mg/day or topiramate 400 mg/day. Patients remained in the double-blind phase until they experienced a first partial onset or generalized tonic-clonic seizure, until termination of the double-blind phase 6 months after randomization of the last subject, or until withdrawal for protocol-specified reasons. The primary efficacy assessment was based on the comparison between topiramate dose groups with respect to time to first partial onset or generalized tonic-clonic seizure during the double-blind phase. Comparison of the Kaplan-Meier survival curves of time to first seizure favored topiramate 400 mg/day over topiramate 50 mg/day (p=0.0002, log rank test). The separation between the groups in favor of the higher dose group occurred early in the titration phase and was statistically significant as early as 2 weeks post randomization (p = 0.046), when, by following the weekly titration schedule, the subjects in the higher dose group had achieved a maximum topiramate dose of 100 mg/day. The higher dose group was also superior to the lower dose group with respect to the proportion of subjects who remained seizure-free, based on the Kaplan-Meier estimates, for a minimum of 6 months of therapy (82.9% vs. 71.4%; p = 0.005), and for a minimum of 1 year of therapy (75.7% vs. 58.8%; p = 0.001). The ratio of hazard rates for time to first seizure was 0.516 (95% confidence interval, 0.364 to 0.733). The treatment effects with respect to time to first seizure were consistent across various subject subgroups defined by age, sex, geographic region, baseline body weight, baseline seizure type, time since diagnosis, and baseline AED use.

In study YI, a single center study, patients ages 15-63 with refractory partial onset seizures (n=48) were converted from their existing treatment to TOPAMAX® 100 mg/day or 1000 mg/day as monotherapy. The high dose group was statistically superior to the low dose group for efficacy variables. 54% of high dose patients achieved monotherapy compared with 17% in the low dose group with the difference between the doses being statistically significant (p=0.005). The mean time to exit was significantly greater in the high dose group (p=0.002). The investigator and subject global evaluations of clinical response statistically favoured the high dose group (≤0.002).

In study EPMN-104, adult and paediatric patients (ages 6-85) with recently diagnosed epilepsy (n=252) were randomised into the low dose (25 or 50 mg/day) or the high dose group (200 or 500 mg/day) based on their body weight. Overall, 54% of high dose patients and 39% of low dose patients were reported to be seizure free during the double-blind phase (p=0.022). The high dose group was also superior to the low dose group with respect to seizure frequency distribution (p=0.008) and the difference in time to first seizure across three plasma topiramate concentration strata (p=0.015).

In study EPMN-105, patients aged 6-84 with newly diagnosed epilepsy (n=613) were randomised to receive either 100 or 200 mg/day of TOPAMAX® or standard anti-epileptic treatment (carbamazepine or valproate). TOPAMAX® was at least as efficacious as carbamazepine or valproate in reducing seizures in these patients; the 95% confidence intervals for the difference between the two treatment groups were narrow and included zero, indicating that there were no statistically significant between-group

difference. The two treatment groups were also comparable with respect to all clinical utility and efficacy endpoints including time to exit, proportion of seizure-free subjects and time to first seizure.

Patients (n=207; 32 were aged ≤ 16 years) who completed the double-blind phase of study YI and EPMN-104 were enrolled in long term extension studies with the majority of patients receiving TOPAMAX® for 2 to 5 years. In these studies, sustained efficacy was demonstrated with long term administration of TOPAMAX® as monotherapy. There was no significant change in dosage during the extension period and no indication that effectiveness of TOPAMAX® monotherapy diminished with continued exposure.

Adjunctive Therapy

Controlled Trials in Patients With Partial Onset Seizures

Adults With Partial Onset Seizures

The effectiveness of topiramate as an adjunctive treatment for adults with partial onset seizures was established in six multicenter, randomized, double-blind, placebo-controlled trials, two comparing several dosages of topiramate and placebo and four comparing a single dosage with placebo, in patients with a history of partial onset seizures, with or without secondarily generalized seizures. Patients in these studies were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® Tablets or placebo. In each study, patients were stabilized on optimum dosages of their concomitant AEDs during baseline phase lasting between 4 and 12 weeks. Patients who experienced a prespecified minimum number of partial onset seizures, with or without secondary generalization, during the baseline phase (12 seizures for 12-week baseline, 8 for 8-week baseline, or 3 for 4-week baseline) were randomly assigned to placebo or a specified dose of TOPAMAX® Tablets in addition to their other AEDs.

Following randomization, patients began the double-blind phase of treatment. In five of the six studies, patients received active drug beginning at 100 mg per day; the dose was then increased by 100 mg or 200 mg/day increments weekly or every other week until the assigned dose was reached, unless intolerance prevented increases. In the sixth study (119), the 25 or 50 mg/day initial doses of topiramate were followed by respective weekly increments of 25 or 50 mg/day until the target dose of 200 mg/day was reached. After titration, patients entered a 4, 8, or 12-week stabilization period. The numbers of patients randomized to each dose, and the actual mean and median doses in the stabilization period are shown in Table 1.

Pediatric Patients Ages 2 - 16 Years With Partial Onset Seizures

The effectiveness of topiramate as an adjunctive treatment for pediatric patients ages 2 - 16 years with partial onset seizures was established in a multicenter, randomized, double-blind, placebo-controlled trial, comparing topiramate and placebo in patients with a history of partial onset seizures, with or without secondarily generalized seizures.

Patients in this study were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® Tablets or placebo. In this study, patients were stabilized on optimum dosages of their concomitant AEDs during an 8-week baseline phase. Patients who experienced at least six partial onset seizures, with or without secondarily generalized seizures, during the baseline phase were randomly assigned to placebo or TOPAMAX® Tablets in addition to their other AEDs.

Following randomization, patients began the double-blind phase of treatment. Patients received active drug beginning at 25 or 50 mg per day; the dose was then increased by 25 mg to 150 mg/day increments every other week until the assigned dosage of 125, 175, 225, or 400 mg/day based on patients' weight to approximate a dosage of 6 mg/kg per day was reached, unless intolerance prevented increases. After titration, patients entered an 8-week stabilization period.

Controlled Trials in Patients With Primary Generalized Tonic-Clonic Seizures

The effectiveness of topiramate as an adjunctive treatment for primary generalized tonic-clonic seizures in patients 2 years old and older was established in a multicenter, randomized, double-blind, placebo-controlled trial, comparing a single dosage of topiramate and placebo.

Patients in this study were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® or placebo. Patients were stabilized on optimum dosages of their concomitant AEDs during an 8-week baseline phase. Patients who experienced at least three primary generalized tonic-clonic seizures during the baseline phase were randomly assigned to placebo or TOPAMAX® in addition to their other AEDs.

Following randomization, patients began the double-blind phase of treatment. Patients received active drug beginning at 50 mg per day for four weeks; the dose was then increased by 50 mg to 150 mg/day increments every other week until the assigned dose of 175, 225, or 400 mg/day based on patients' body weight to approximate a dosage of 6 mg/kg per day was reached, unless intolerance prevented increases. After titration, patients entered a 12-week stabilization period

Controlled Trial in Patients with Lennox-Gastaut Syndrome

The effectiveness of topiramate as an adjunctive treatment for seizures associated with Lennox-Gastaut syndrome was established in a multicenter, randomized, double-blind, placebo-controlled trial comparing a single dosage of topiramate with placebo in patients 2 years of age and older.

Patients in this study were permitted a maximum of two antiepileptic drugs (AEDs) in addition to TOPAMAX® or placebo. Patients who were experiencing at least 60 seizures per month before study entry were stabilized on optimum dosages of their concomitant AEDs during a four week baseline phase. Following baseline, patients were randomly assigned to placebo or TOPAMAX® in addition to their other AEDs. Active drug was titrated beginning at 1 mg/kg per day for a week; the dose was then increased to 3 mg/kg per day for one week then to 6 mg/kg per day. After titration, patients entered an 8-week stabilization period. The primary measures of effectiveness were the percent reduction in drop attacks and a parental global rating of seizure severity.

In all add-on trials, the reduction in seizure rate from baseline during the entire double-blind phase was measured. The median percent reductions in seizure rates and the responder rates (fraction of patients with at least a 50% reduction) by treatment group for each study are shown below in Table 5. As described above, a global improvement in seizure severity was also assessed in the Lennox-Gastaut trial.

Table 5: Efficacy Results in Double-Blind, Placebo-Controlled, Add-On Epilepsy Trials

		Target Topiramate Dosage (mg/day)						
Protocol	**Efficacy Results**	**Placebo**	**200**	**400**	**600**	**800**	**1,000**	**≈6 mg/kg/day***
Partial Onset Seizures								
Studies in Adults								
YD	N	45	45	45	46	--	--	--
	Median % Reduction	11.6	27.2[a]	47.5[b]	44.7[c]	--	--	--
	% Responders	18	24	44[d]	46[d]	--	--	--
YE	N	47	--	--	48	48	47	--
	Median % Reduction	1.7	--	--	40.8[c]	41.0[c]	36.0[c]	--
	% Responders	9	--	--	40[c]	41[c]	36[d]	--
Y1	N	24	--	23	--	--	--	--
	Median % Reduction	1.1	--	40.7[e]	--	--	--	--
	% Responders	8	--	35[d]	--	--	--	--
Y2	N	30	--	--	30	--	--	--
	Median % Reduction	-12.2	--	--	46.4[f]	--	--	--
	% Responders	10	--	--	47[c]	--	--	--
Y3	N	28	--	--	--	28	--	--
	Median % Reduction	-20.6	--	--	--	24.3[c]	--	--
	% Responders	0	--	--	--	43[c]	--	--
119	N	91	168	--	--	--	--	--
	Median % Reduction	20.0	44.2[c]	--	--	--	--	--
	% Responders	24	45[c]	--	--	--	--	--
Studies in Pediatric Patients								
YP	N	45	--	--	--	--	--	41
	Median % Reduction	10.5	--	--	--	--	--	33.1[d]
	% Responders	20	--	--	--	--	--	39
Primary Generalized Tonic Clonic[h]								
YTC	N	40	--	--	--	--	--	39
	Median % Reduction	9.0	--	--	--	--	--	56.7[d]
	% Responders	20	--	--	--	--	--	56[c]
Lennox-Gastaut Syndrome[i]								
YL	N	49	--	--	--	--	--	46
	Median % Reduction	-5.1	--	--	--	--	--	14.8[d]
	% Responders	14	--	--	--	--	--	28[g]
	Improvement in Seizure Severity[j]	28	--	--	--	--	--	52[d]

Comparisons with placebo: [a] p=0.080; [b] p≤0.010; [c] p≤0.001; [d] p≤0.050; e p=0.065; [f] p≤0.005; [g] p=0.071;
[h] Median % reduction and % responders are reported for PGTC seizures;
[i] Median % reduction and % responders for drop attacks, i.e., tonic or atonic seizures;
[j] Percent of subjects who were minimally, much, or very much improved from baseline

* For Protocols YP and YTC, protocol-specified target dosages (<9.3 mg/kg/day) were assigned based on subject's weight to approximate a dosage of 6 mg/kg per day; these dosages corresponded to mg/day dosages of 125, 175, 225, and 400 mg/day.

Subset analyses of the antiepileptic efficacy of TOPAMAX® Tablets in these studies showed no differences as a function of gender, race, age, baseline seizure rate, or concomitant AED.

Migraine Clinical Trials

The clinical development program to evaluate the efficacy of TOPAMAX® in prophylaxis of migraine included two multicenter, randomized, double-blind placebo-controlled, parallel group pivotal trials conducted in North America (MIGR-001 and MIGR-002). The primary efficacy endpoint was the reduction in migraine headache frequency, as measured by the change in 4-week migraine rate from the baseline phase to the double-blind treatment phase in each TOPAMAX® treatment group compared to placebo in the intent to treat (ITT) population.The pooled results of the two pivotal trials evaluating TOPAMAX® doses of 50 (N=233), 100 (N=244) and 200 mg/day (N=228) found a median percent reduction in 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 of TOPAMAX® were statistically better than placebo. Notably, 27% of patients administered TOPAMAX® 100 mg/day achieved at least a 75% reduction in migraine frequency, whilst 52% achieved at least a 50% reduction. An additional supportive study, MIGR-003, demonstrated that TOPAMAX® 100 mg/day was comparable in terms of efficacy to propranolol 160 mg/day. There was no statistically significant difference between the two groups in the primary efficacy endpoint.

Pharmacokinetic Properties

The tablet and sprinkle formulations are bioequivalent.

The pharmacokinetic profile of topiramate compared to other antiepileptic drugs shows a long plasma half-life, linear pharmacokinetics, predominantly renal clearance, absence of significant protein binding, and lack of clinically relevant active metabolites.

Topiramate is not a potent inducer of drug metabolizing enzymes, can be administered without regard to meals, and routine monitoring of plasma topiramate concentrations is not necessary. In clinical studies, there was no consistent relationship between plasma concentrations and efficacy or adverse events.

Topiramate is rapidly and well absorbed. Following oral administration of 100 mg topiramate to healthy subjects, a mean peak plasma concentration (C_{max}) of 1.5 mcg/mL was achieved within 2 to 3 hours (T_{max}). Based on the recovery of radioactivity from the urine the mean extent of absorption of a 100 mg oral dose of ^{14}C-topiramate was at least 81%. There was no clinically

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

Topiramate is not extensively metabolized (~20%) in healthy volunteers. It is metabolized up to 50% in patients receiving concomitant antiepileptic therapy with known inducers of drug metabolizing enzymes. Six metabolites, formed through hydroxylation, hydrolysis and glucuronidation, have been isolated, characterized and identified from plasma, urine and feces of humans. Each metabolite represents less than 3% of the total radioactivity excreted following administration of ^{14}C-topiramate. 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 (at least 81% of the dose). Approximately 66% of a dose of ^{14}C-topiramate was excreted unchanged in the urine within four days. Following twice a day dosing with 50 mg and 100 mg of topiramate the mean renal clearance was approximately 18 mL/min and 17 mL/min, respectively. There is evidence of renal tubular reabsorption of topiramate. This is supported by studies in rats where topiramate was coadministered with probenecid, and a significant increase in renal clearance of topiramate was observed. Overall, plasma clearance is approximately 20 to 30 mL/min in humans following oral administration.

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

Concomitant multiple-dose administration of topiramate, 100 to 400 mg twice a day, with phenytoin or carbamazepine shows dose proportional increases in plasma concentrations of topiramate.

The plasma and renal clearance of topiramate are decreased in patients with impaired renal function (CL_{CR} < 60 mL/min), and the plasma clearance is decreased in patients with end-stage renal disease. As a result, higher steady-state topiramate plasma concentrations are expected for a given dose in renal-impaired patients as compared to those with normal renal function. Topiramate is effectively removed from plasma by hemodialysis.

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

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

Pediatric pharmacokinetics up to 12 years of age: The pharmacokinetics of topiramate in children, as in adults receiving add- on therapy, are linear, with clearance independent of dose and steady-state plasma concentrations increasing in proportion to dose. Children, however, have a higher clearance and a shorter elimination half-life. Consequently, the plasma concentrations of topiramate for the same mg/kg dose may be lower in children compared to adults. As in adults, hepatic enzyme inducing antiepileptic drugs decrease the steady-state plasma concentrations.

Preclinical Safety Data

Acute and long-term exposure of mice, rats, dogs and rabbits to topiramate was well tolerated. Hyperplasia of the gastric epithelial cells was observed only in rodents and in rats was reversible after 9 weeks without treatment. Tumors of smooth muscle origin in the urinary bladder were seen only in mice (oral dosages up to 300 mg/kg for 21 months) and appear to be unique to the species. Since no human counterpart exists, they were not considered clinically relevant. No such findings occurred in the rat carcinogenicity study (oral dosages up to 120 mg/kg/day for 24 months). Other toxicologic and pathologic effects of topiramate observed in these studies may be related to the weak induction of drug metabolizing enzymes or weak carbonic anhydrase inhibition. Despite maternal and paternal toxicity as low as 8 mg/kg/day, no effects on fertility were observed, in male or female rats with up to 100 mg/kg/day.

As with other antiepileptic drugs, topiramate was teratogenic in mice, rats and rabbits. In mice, fetal weights and skeletal ossification were reduced at 500 mg/kg/day in conjunction with maternal toxicity. Overall numbers of fetal malformations in mice were increased for all drug-treated groups (20, 100 and 500 mg/kg/day), 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.

In rats, dosage-related maternal and embryo/fetal toxicity (reduced fetal weights and/or skeletal ossification) were observed down to 20 mg/kg/day with teratogenic effects (limb and digit defects) at 400 mg/kg/day and above. In rabbits, dosage-related maternal toxicity was noted down to 10 mg/kg/day with embryo/fetal toxicity (increased lethality) down to 35 mg/kg/day, and teratogenic effects (rib and vertebral malformations) at 120 mg/kg/day.

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. Effects on growth were also indicated by lower weights at birth and during lactation for pups from female rats treated with 20 or 100 mg/kg/day during gestation and lactation. In rats, topiramate crosses the placental barrier.

In a battery of *in vitro* and *in vivo* mutagenicity assays, topiramate did not show genotoxic potential.

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