# TOPAMAX®
topiramate

**TOPAMAX***
Tablets (Topiramate)

**Therapeutic Classification: Anti-epileptic**

## CLINICAL PHARMACOLOGY

### Pharmacodynamics

**TOPAMAX** (topiramate) is a novel antiepileptic agent classified as a sulphamate substituted monosaccharide. Three pharmacological properties of topiramate are believed to contribute to its anticonvulsant activity. First, topiramate reduces the frequency at which action potentials are generated when neurons are subjected to a sustained depolarization indicative of a state-dependent blockade of voltage-sensitive sodium channels. Second, topiramate markedly enhances the activity of GABA at some types of GABA 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. Third, topiramate antagonizes the ability of kainate to activate the kainate/AMPA subtype of excitatory amino acid (glutamate) receptors but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype.

In addition, topiramate inhibits some isoenzymes of carbonic anhydrase. This 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.

## PHARMACOKINETICS

### Absorption and Distribution

Topiramate is rapidly and well-absorbed. Following oral administration of 100 mg topiramate to healthy subjects, a mean peak plasma concentration (Cmax) of 1.5 µg/mL was achieved within 2 to 3 hours (Tmax). The mean extent of absorption from a 100 mg oral dose of $^{14}$C-topiramate was at least 81% based on the recovery of radioactivity from the urine.

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 Cmax following multiple, twice-a-day oral doses of 100 mg to healthy subjects was 6.76 µg/mL. The mean plasma elimination half-lives from multiple 50 mg and 100 mg q12h doses of topiramate were approximately 21 hours. The elimination half-life did not significantly change when switching from single dose to multiple dose.

Concomitant multiple-dose administration of topiramate, 100 to 400 mg q12h, with phenytoin or carbamazepine shows dose proportional increases in plasma concentrations of topiramate.

There was no clinically significant effect of food on the bioavailability of topiramate.

Approximately 13% to 17% of topiramate is bound to plasma proteins. A low capacity binding site for topiramate in/on erythrocytes that is saturable above plasma concentrations of 4 µg/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.

### Metabolism and Excretion

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 pharmacological 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 4 days. The mean renal clearance for 50 mg and 100 mg of topiramate, following q12h dosing, was approximately 18 mL/min and 17 mL/min, respectively. Evidence exists for renal tubular reabsorption of topiramate. This is supported by studies in rats where topiramate was co-administered with probenecid, and a significant increase in renal clearance of topiramate was observed. This interaction has not been evaluated in humans. Overall, plasma clearance is approximately 20 to 30 mL/min in humans following oral administration.

### Special Populations

***Renal Impairment:***

The plasma and renal clearance of topiramate are decreased in patients with impaired renal function (CLCR ≤ 60 mL/min), and the plasma clearance is decreased in patients with end-stage renal disease. As a result, higher steady-state topiramate plasma concentrations are expected for a given dose in renally-impaired patients as compared to those with normal renal function. Plasma clearance of topiramate is unchanged in elderly subjects in the absence of underlying renal disease.

***Hemodialysis:***

Topiramate is effectively removed from plasma by hemodialysis. (See DOSAGE AND ADMINISTRATION.)

***Hepatic Impairment:***

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

***Age and Gender:***

Age (18-67) and gender appear to have no effect on the plasma clearance of topiramate.

In well-controlled add-on trials, no correlation has been demonstrated between trough plasma concentrations and its clinical efficacy.

No evidence of tolerance requiring increased dosage has been demonstrated in man during 4 years of use.

### Pediatric Pharmacokinetics

Pharmacokinetics of topiramate were evaluated in patients ages 4 to 17 years receiving one or two other antiepileptic drugs. Pharmacokinetic profiles were obtained after one week at doses of 1, 3, and 9 mg/kg/day. As in adults, topiramate pharmacokinetics were linear with clearance independent of dose and steady-state plasma concentrations increasing in proportion to dose. Compared with adult epileptic patients, mean topiramate clearance is approximately 50% higher in pediatric patients. Steady-state plasma topiramate concentrations for the same mg/kg dose are expected to be approximately 33% lower in children compared to adults. As with adults, hepatic enzyme-inducing antiepileptic drugs (AEDs) decrease the plasma concentration of topiramate.

### Clinical Experience

The results of clinical trials established the efficacy of **TOPAMAX** as adjunctive therapy in patients with refractory partial onset seizures with or without secondarily generalized seizures. Six multicentre, outpatient, randomized, double-blind, placebo controlled trials were completed. Patients in all six studies were permitted a maximum of two antiepileptic drugs (AEDS) in addition to **TOPAMAX** therapy (target doses of 200, 400, 600, 800, or 1,000 mg/day) or placebo.

In all six add-on trials, the primary efficacy measurement was reduction in seizure rate from baseline during the entire double-blind phase; responder rate (fraction of patients with a 50% reduction) was also measured. The median percent reductions in seizure rates and the responder rates by treatment group for each study are shown in Table 1.

**Table 1**
Median Percent Seizure Rate Reduction and Percent Responders in Six Double-Blind, Placebo-Controlled, Add-On Trials

| | | Target Topiramate Dosage (mg/day) | | | | | |
|---|---|---|---|---|---|---|---|
| Protocol | Efficacy Results | Placebo | 200 | 400 | 600 | 800 | 1,000 |
| YD | N | 45 | 45 | 45 | 46 | – | – |
| | Median % Reduction | 13.1 | 29.6[a] | 47.8[c] | 44.7[d] | – | – |
| | % Responders | 18 | 27 | 47[b] | 46[b] | – | – |
| YE | N | 47 | – | – | 48 | 48 | 47 |
| | Median % Reduction | 1.2 | – | – | 40.7[d] | 41.0[d] | 37.5[d] |
| | % Responders | 9 | – | – | 44[d] | 40[c] | 38[c] |
| Y1 | N | 24 | – | 23 | – | – | – |
| | Median % Reduction | 1.1 | – | 40.7[†] | – | – | – |
| | % Responders | 8 | – | 35[b] | – | – | – |
| Y2 | N | 30 | – | – | 30 | – | – |
| | Median % Reduction | -12.2 | – | – | 46.4[c] | – | – |
| | % Responders | 10 | – | – | 47[c] | – | – |
| Y3 | N | 28 | – | – | – | 28 | – |
| | Median % Reduction | -17.8 | – | – | – | 35.8[c] | – |
| | % Responders | 0 | – | – | – | 43[c] | – |
| YF/YG | N | 42 | – | – | – | – | 167 |
| | Median % Reduction | 1.2 | – | – | – | – | 50.8[d] |
| | % Responders | 19 | – | – | – | – | 52[c] |

Comparisons with placebo: * p = 0.051; [b] p < 0.05; [c] p ≤ 0.01; [d] p ≤ 0.001; [a] p = 0.053; [†] p = 0.065

Across the six efficacy trials, 232 of the 527 topiramate patients (44%) responded to treatment with at least a 50% seizure reduction during the double-blind phase; by comparison, only 25 of the 216 placebo-treated patients (12%) showed the same level of treatment response. When the treatment response was defined more rigorously as a 75% or greater decrease from baseline in seizure rate during double-blind treatment, 111 of the 527 topiramate patients (21%) in the 200 to 1,000 mg/day groups, but only 8 of the 216 placebo patients (4%), demonstrated this level of efficacy. At target dosages of 400 mg/day and higher, the percent of treatment responders was statistically greater for topiramate-treated than placebo-treated patients.

Pooled analyses of secondarily generalized seizure rates for all patients who had this seizure type during the studies show statistically significant percent reductions in the **TOPAMAX** groups when compared with placebo. The median percent reduction in the rate of generalized seizures was 57% for topiramate-treated patients compared with -4% for placebo-treated patients. Among topiramate-treated patients, 109 (55%) of 198 had at least a 50% reduction in generalized seizure rate compared with 24 (27%) of 88 placebo-treated patients.

The dose titration in the original clinical trials was 100 mg/day the first week, 100 mg bid/day the second week, and 200 mg bid/day the third week. In a 12-week, double-blind trial, this titration rate was compared to a less rapid rate beginning at 50 mg/day. There were significantly fewer adverse experiences leading to discontinuation and/or dosage adjustment in the group titrated at the less rapid rate. Seizure rate reductions were comparable between the groups at all time points measured.

## INDICATIONS AND CLINICAL USE

**TOPAMAX** (topiramate) is indicated as adjunctive therapy for the management of patients with epilepsy who are not satisfactorily controlled with conventional therapy. There is limited information on the use of topiramate in monotherapy at this time.

## CONTRAINDICATIONS

**TOPAMAX** (topiramate) is contraindicated in patients with a history of hypersensitivity to any components of this product.

## WARNINGS

Antiepileptic drugs, including **TOPAMAX** (topiramate), should be withdrawn gradually to minimize the potential of increased seizure frequency. In clinical trials, dosages were decreased by 100 mg/day at weekly intervals.

### Central Nervous System Effects

Adverse events most often associated with the use of **TOPAMAX** (topiramate) were central nervous system-related. The most significant of these can be classified into two general categories: i) psychomotor slowing: difficulty with concentration, and speech or language problems, in particular, word-finding difficulties and ii) somnolence or fatigue.

Additional nonspecific CNS effects occasionally observed with topiramate as add-on therapy include dizziness or imbalance, confusion, memory problems, and exacerbation of mood disturbances (e.g., irritability and depression).

These events were generally mild to moderate, and generally occurred early in therapy. While the incidence of psychomotor slowing does not appear to be dose-related, both language problems and difficulty with concentration or attention increased in frequency with increasing dosage in the six double-blind trials suggesting that these events are dose-related (see ADVERSE REACTIONS).

## PRECAUTIONS

### Effects Related to Carbonic Anhydrase Inhibition

***Kidney Stones***

A total of 32/1,715 (1.5%) of patients exposed to topiramate during its development reported the occurrence of kidney stones, an incidence about 10 times that expected in a similar, untreated population (M/F ratio; 27/1092 male; 5/623 female). In the general population, risk factors for kidney stone formation include gender (male), ages between 20-50 years, prior stone formation, family history of nephrolithiasis, and hypercalciuria. Based on logistic regression analysis of the clinical trial data, no correlation between mean topiramate dosage, duration of topiramate therapy, or age and the occurrence of kidney stones was established; of the risk factors evaluated, only gender (male) showed a correlation with the occurrence of kidney stones.

Carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. Concomitant use of **TOPAMAX**, a weak carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided.

Patients, especially those with a predisposition to nephrolithiasis, may have an increased risk of renal stone formation. Increased fluid intake increases the urinary output lowering the concentration of substances involved in stone formation. Therefore, adequate hydration is recommended to reduce this risk. None of the risk factors for nephrolithiasis can reliably predict stone formation during **TOPAMAX** treatment.

***Paresthesia***

Paresthesia, an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of **TOPAMAX**. These events were usually intermittent and mild and not necessarily related to the dosage of topiramate.

### Adjustment of Dose in Renal Failure

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 impaired renal function (CLCR ≤ 60 mL/min) or with end-stage renal disease receiving hemodialysis treatments 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 patients with known renal impairment may require a longer time to reach steady state at each dose. (See DOSAGE AND ADMINISTRATION).

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**Decreased Hepatic Function**

In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate was decreased compared with normal subjects.

**Information for Patients**

***Adequate Hydration***

Patients, especially those with predisposing factors, should be instructed to maintain an adequate fluid intake in order to minimize the risk of renal stone formation.

***Effects on Ability to Drive and Use Machines***

Patients should be warned about the potential for somnolence, dizziness, confusion, and difficulty concentrating and advised not to drive or operate machinery until they have gained sufficient experience on topiramate to gauge whether it adversely affects their mental and/or motor performance.

**Drug Interactions**

***Anti-epileptic Drugs***

*Potential interactions between topiramate and standard AEDS were measured in controlled clinical pharmacokinetic* studies in patients with epilepsy. The effect of these interactions on plasma concentrations are summarized in Table 2:

**Table 2**

Drug Interactions with TOPAMAX Therapy

| AED Co-administered | AED Concentration | **TOPAMAX** Concentration |
|---|---|---|
| Phenytoin | ⇔** | ⇓59% |
| Carbamazepine (CBZ) | ⇔ | ⇓40% |
| CBZ epoxide* | ⇔ | NS |
| Valproic acid | ⇓11% | ⇓14% |
| Phenobarbital | ⇔ | NS |
| Primidone | ⇔ | NS |

* Is not administered but is an active metabolite of carbamazepine

⇔ No effect on plasma concentration

** Plasma concentrations increased 25% in some patients, generally those on a b.i.d. dosing regimen of phenytoin

⇓ Plasma concentrations decrease in individual patients

NS Not studied

AED Antiepileptic drug

The effect of topiramate on steady-state pharmacokinetics of phenytoin may be related to the frequency of phenytoin dosing. A slight increase in steady-state phenytoin plasma concentrations was observed, primarily in patients receiving phenytoin in two divided doses. The slight increase may be due to the saturable nature of phenytoin pharmacokinetics and inhibition of phenytoin metabolism.

The addition of **TOPAMAX** therapy to phenytoin should be guided by clinical outcome. In general, as evidenced in clinical trials, patients do not require dose adjustments. However, any patient on phenytoin showing clinical signs or symptoms of toxicity should have phenytoin levels monitored.

***Other Drug Interactions***

*Digoxin:*

In a single-dose study, serum digoxin AUC decreased 12% due to concomitant **TOPAMAX** administration. Multiple dose studies have not been performed. 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 an interaction study with oral contraceptives using a combination product containing norethindrone plus ethinyl estradiol, **TOPAMAX** did not significantly affect the oral clearance of norethindrone. The serum levels of the estrogenic component decreased by 18%, 21%, and 30% at daily doses of 200, 400 and 800 mg, respectively. Consequently, the efficacy of low dose (e.g., 20 µg) oral contraceptives may be reduced in this situation. Patients taking oral contraceptives should receive a preparation containing not less than 50 µg of estrogen. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns.

*Others:*

Concomitant use of **TOPAMAX**, a weak carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors, e.g., acetazolamide or dichlorphenamide, may create a physiological environment that increases the risk of renal stone formation, and should therefore be avoided if possible.

**Laboratory Tests**

There are no known interactions of **TOPAMAX** with commonly used laboratory tests.

**Use in Pregnancy and Lactation**

Like 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** therapy should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Topiramate is excreted in the milk of lactating rats. It is not known if topiramate is excreted in human milk. Since many drugs are excreted in human milk, and because the potential for serious adverse reactions in nursing infants to **TOPAMAX** exists, the prescriber should decide whether to discontinue nursing or discontinue the drug, taking into account the risk benefit ratio of the importance of the drug to the mother and the risks to the infant.

The effect of **TOPAMAX** on labor and delivery in humans is unknown.

**Pediatric Use**

Safety and effectiveness in children under 18 years of age have not been established.

**Geriatric Use**

There is limited information in patients over 65 years of age. The possibility of age-associated renal function abnormalities should be considered when using **TOPAMAX**.

**Race and Gender Effects**

Although direct comparison studies of pharmacokinetics have not been conducted, analysis of plasma concentration data from clinical efficacy trials have shown that race and gender appear to have no effect on the plasma clearance of topiramate. In addition, based on pooled analyses, race and gender appear to have no effect on the efficacy of topiramate.

**ADVERSE REACTIONS**

The most commonly observed adverse events associated with the adjunctive use of **TOPAMAX** (topiramate) at dosages of 200 to 400 mg/day in controlled trials that were seen at greater frequency in topiramate-treated patients and did not appear to be dose-related within this dosage range were: somnolence, dizziness, ataxia, speech disorders and related speech problems, psychomotor slowing, nystagmus, and paresthesia (see Table 3). The most common dose-related adverse events at dosages of 200 to 1,000 mg/day were: nervousness, difficulty with concentration or attention, confusion, depression, anorexia, language problems, and mood problems (see Table 4).

**Table 3**

Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials [a,b]

(Events that occurred in ≥ 2% of topiramate-treated patients and occurred more frequently in topiramate-treated than placebo-treated patients)

| | **TOPAMAX**® Dosage (mg/day) | | |
|---|---|---|---|
| **Body System/** Adverse Event | **Placebo** (N=216) | **200-400** (N=113) | **600-1,000** (N=414) |
| **Body as a Whole** | | | |
| Asthenia | 1.4 | 8.0 | 3.1 |
| Back Pain | 4.2 | 6.2 | 2.9 |
| Chest Pain | 2.8 | 4.4 | 2.4 |
| Influenza-Like Symptoms | 3.2 | 3.5 | 3.6 |
| Leg Pain | 2.3 | 3.5 | 3.6 |
| Hot Flushes | 1.9 | 2.7 | 0.7 |
| **Nervous System** | | | |
| Dizziness | 15.3 | 28.3 | 32.1 |
| Ataxia | 6.9 | 21.2 | 14.5 |
| Speech Disorders/Related Speech Problems | 2.3 | 16.8 | 11.4 |
| Nystagmus | 9.3 | 15.0 | 11.1 |
| Paresthesia | 4.6 | 15.0 | 19.1 |
| Tremor | 6.0 | 10.6 | 8.9 |
| Language Problems | 0.5 | 6.2 | 10.4 |
| Coordination Abnormal | 1.9 | 5.3 | 3.6 |
| Hypoaesthesia | 0.9 | 2.7 | 1.2 |
| Abnormal Gait | 1.4 | 1.8 | 2.2 |
| **Gastrointestinal System** | | | |
| Nausea | 7.4 | 11.5 | 12.1 |
| Dyspepsia | 6.5 | 8.0 | 6.3 |
| Abdominal Pain | 3.7 | 5.3 | 7.0 |
| Constipation | 2.3 | 5.3 | 3.4 |
| Dry Mouth | 0.9 | 2.7 | 3.9 |
| **Metabolic and Nutritional** | | | |
| Weight Decrease | 2.8 | 7.1 | 12.8 |
| **Neuropsychiatric** | | | |
| Somnolence | 9.7 | 30.1 | 27.8 |
| Psychomotor Slowing | 2.3 | 16.8 | 20.8 |
| Nervousness | 7.4 | 15.9 | 19.3 |
| *Difficulty with Memory* | 3.2 | 12.4 | 14.5 |
| Confusion | 4.2 | 9.7 | 13.8 |
| Depression | 5.6 | 8.0 | 13.0 |
| Difficulty with Concentration/Attention | 1.4 | 8.0 | 14.5 |
| Anorexia | 3.7 | 5.3 | 12.3 |
| Agitation | 1.4 | 4.4 | 3.4 |
| Mood Problems | 1.9 | 3.5 | 9.2 |
| Aggressive Reaction | 0.5 | 2.7 | 2.9 |
| Apathy | 0 | 1.8 | 3.1 |
| Depersonalization | 0.9 | 1.8 | 2.2 |
| Emotional Lability | 0.9 | 1.8 | 2.7 |
| **Reproductive, Female** | (N=59) | (N=24) | (N=128) |
| Breast Pain, Female | 1.7 | 8.3 | 0 |
| Dysmenorrhea | 6.8 | 8.3 | 3.1 |
| Menstrual Disorder | 0 | 4.2 | 0.8 |
| **Reproductive, Male** | (N=157) | (N=89) | (N=286) |
| Prostatic Disorder | 0.6 | 2.2 | 0 |
| **Respiratory System** | | | |
| Pharyngitis | 2.3 | 7.1 | 3.1 |
| Rhinitis | 6.9 | 7.1 | 6.3 |
| Sinusitis | 4.2 | 4.4 | 5.6 |
| Dyspnea | 0.9 | 1.8 | 2.4 |
| **Skin and Appendages** | | | |
| Pruritus | 1.4 | 1.8 | 3.1 |
| **Vision** | | | |
| Diplopia | 5.6 | 14.2 | 10.4 |
| Vision Abnormal | 2.8 | 14.2 | 10.1 |
| **White Cell and RES** | | | |
| Leukopenia | 0.5 | 2.7 | 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 4**

Dose-Related Adverse Events From Six Placebo-Controlled, Add-On Trials

| Adverse Event | **TOPAMAX**® Dosage (mg/day) | | | |
|---|---|---|---|---|
| | Placebo (N = 216) | 200 (N = 45) | 400 (N = 68) | 600 - 1,000 (N = 414) |
| Fatigue | 13.4 | 11.1 | 11.8 | 29.7 |
| Nervousness | 7.4 | 13.3 | 17.6 | 19.3 |
| Difficulty with Concentration/Attention | 1.4 | 6.7 | 8.8 | 14.5 |
| Confusion | 4.2 | 8.9 | 10.3 | 13.8 |
| Depression | 5.6 | 8.9 | 7.4 | 13.0 |
| Anorexia | 3.7 | 4.4 | 5.9 | 12.3 |
| Language problems | 0.5 | 2.2 | 8.8 | 10.1 |
| Anxiety | 6.0 | 2.2 | 2.9 | 10.4 |
| Mood problems | 1.9 | 0.0 | 5.9 | 9.2 |

In double-blind clinical trials, 10.6% of subjects (N=113) assigned to a topiramate dosage of 200 to 400 mg/day in addition to their standard AED therapy discontinued due to adverse events compared to 5.8% of subjects (N=69) receiving placebo. The percentage of subjects discontinuing due to adverse events appeared to increase at dosages above 400 mg/day. Overall, approximately 17% of all subjects (N=527) who received topiramate in the double-blind trials, discontinued due to adverse events compared to 4% of the subjects (N=216) receiving placebo.

Nephrolithiasis was reported rarely. Isolated cases of thromboembolic events have also been reported, a causal association with the drug has not been established.

When the safety experience of patients receiving **TOPAMAX** as adjunctive therapy in both double-blind and open-label trials (n=1,446) was analyzed, a similar pattern of adverse events emerged.

**SYMPTOMS AND TREATMENT OF OVERDOSAGE**

In acute **TOPAMAX** (topiramate) overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has not been shown to adsorb topiramate *in vitro*.

Therefore, its use in overdosage is not recommended. Treatment should be appropriately supportive.

Hemodialysis is an effective means of removing topiramate from the body. However, in the few cases of acute overdosage reported, including doses of over 20 g in one individual, hemodialysis has not been necessary.

**DOSAGE AND ADMINISTRATION**

**Adults**

The recommended total daily dose of **TOPAMAX** (topiramate) as adjunctive therapy is 200-400 mg/day in two divided doses. It is recommended that therapy be initiated at 50 mg/day, followed by titration to an effective dose. Doses above 400 mg/day have not been shown to improve responses and have been associated with a greater incidence of adverse events. The maximum recommended dose is 800 mg/day. Daily doses above 1,600 mg have not been studied.

Titration should begin at 50 mg/day. At weekly intervals, the dose should be increased by 50 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.

**THE RECOMMENDED TITRATION RATE IS:**

| | AM Dose | PM Dose |
|---|---|---|
| Week 1 | none | 50 mg |
| Week 2 | 50 mg | 50 mg |
| Week 3 | 50 mg | 100 mg |
| Week 4 | 100 mg | 100 mg |
| Week 5 | 100 mg | 150 mg |
| Week 6 | 150 mg | 150 mg |
| Week 7 | 150 mg | 200 mg |
| Week 8 | 200 mg | 200 mg |

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

**Geriatrics**

See PRECAUTIONS section.

**Pediatrics**

As yet there is limited experience on the use of **TOPAMAX** (topiramate) in children aged 18 years and under and dosing recommendations cannot be made for this patient population.

**Patients with Renal Impairment**

In renally impaired subjects (creatinine clearance less than 70 mL/min/1.73m$^2$), one half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.

**Patients Undergoing Hemodialysis**

Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than a normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an anti-seizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis a supplemental dose of topiramate may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed.

**Patients with Hepatic Disease**

In hepatically impaired patients topiramate plasma concentrations are increased approximately 30%. This moderate increase is not considered to warrant adjustment of the topiramate dosing regimen. Initiate topiramate therapy with the same dose and regimen as for patients with normal hepatic function. The dose titration in these patients should be guided by clinical outcome, i.e., seizure control and avoidance of adverse effects. Such patients will require a longer time to reach steady-state at each dose.

**PHARMACEUTICAL INFORMATION**

**i) Drug Substance**

Proper Name: topiramate

Chemical Name: 2,3:4,5-bis-O-(1-methylethylidene)-ß-D-fructopyranose sulfamate

Molecular Formula: $C_{12}H_{21}NO_8S$

Molecular Weight: 339.36

Description: Topiramate is a white crystalline powder having a bitter taste. Topiramate is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate with 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.

**ii) Composition**

**TOPAMAX** (topiramate) contains the following inactive ingredients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, polysorbate 80 and may contain synthetic iron oxide.

**iii) Stability and Storage Recommendations**

**TOPAMAX** Tablets should be stored in tightly closed containers at controlled room temperature (15 to 30°C). Protect from moisture.

**AVAILABILITY OF DOSAGE FORMS**

**TOPAMAX** (topiramate) is available as embossed tablets in the following strengths as described below:

| | |
|---|---|
| 25 mg: | white, round, coated tablets containing 25 mg topiramate. |
| 100 mg: | yellow, round, coated tablets containing 100 mg topiramate. |
| 200 mg: | salmon-coloured, round, coated tablets containing 200 mg topiramate. |
| Supplied: | Bottles of 60 tablets with desiccant. |

Product Monograph available on request

**REFERENCES:**

**1.** Faught E et al. Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosages. *Neurology* 1996; 46:1684-90. **2.** TOPAMAX (topiramate) Product Monograph. Janssen-Ortho Inc., 1997. **3.** Walker MC and Sander JWAS. Topiramate: a new antiepileptic drug for refractory epilepsy. *Seizure* 1996; 5: 199-203. **4.** Shorvan SD. Safety of topiramate: adverse events and relationships to dosing. *Epilepsia* 1996; 37(Suppl) 2): S18-22.



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TOPAMAX® topiramate

See pages xi, vii, xxii, xxiii

**Table 3: Percentage of patients with headache relief at 2 hours**

| Study | Placebo (n) | 5 mg (n) | 10 mg (n) | 20 mg (n) |
|---|---|---|---|---|
| Study 6* | 35% (100) | – | 54%$^{\vee}$ (106) | 63%$^{\vee}$ (202) |
| Study 7* | 29% (112) | – | 43% (109) | 62%$^{\vee}$ (215) |
| Total | 208/695 | 232/494 | 482/985 | 722/1195 |
| **Weighted Average** | **30%** | **47%** | **49%** | **60%** |
| **Range** | **25-42%** | **44-67%** | **43-67%** | **55-78%** |

Headache relief was defined as a decrease in headache severity from severe or moderate to mild or none. n = total number of patients who received treatment. *comparisons between sumatriptan doses not conducted $^{\vee}$ $p \leq 0.05$ versus placebo $^{\uparrow}$ $p \leq 0.05$ versus lower sumatriptan doses ▲ $p \leq 0.05$ vs 5 mg – not evaluated

As shown in the table above, optimal rates of headache relief were seen with the 20 mg dose. Single doses above 20 mg should not be used due to limited safety data and lack of increased efficacy relative to the 20 mg single dose.

Within the range of 5-20 mg, an increase in dose was not associated with any significant increase in the incidence or severity of adverse events other than taste disturbance (See Adverse Reactions).

The nasal spray should be administered into one nostril **only**. The device is a ready to use single dose unit and **must not** be primed before administration. Patients should be advised to read the patient instruction leaflet regarding the use of the nasal spray device before administration.

**STABILITY AND STORAGE RECOMMENDATIONS** IMITREX Tablets should be stored at 2°C to 30°C. IMITREX Injection and Nasal Spray should be stored between 2°C to 30°C and protected from light.

**COMPOSITION** IMITREX TABLETS contain 100 mg or 50 mg sumatriptan (base) as the succinate salt. Imitrex Tablets also contain lactose, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

IMITREX INJECTION contains 6 mg sumatriptan (base) as the succinate salt in an isotonic sodium chloride solution.

IMITREX Nasal Spray contains 5 mg, 10 mg or 20 mg of sumatriptan base (as the hemisulphate salt formed *in situ*) in an aqueous buffered solution containing monobasic potassium phosphate, anhydrous dibasic sodium phosphate, sulphuric acid, sodium hydroxide, and purified water.

**AVAILABILITY OF DOSAGE FORMS** IMITREX TABLETS 100 mg are pink film-coated tablets available in blister packs containing 6 tablets, packed in a cardboard carton.

IMITREX TABLETS 50 mg are white film-coated tablets available in blister packs containing 6 tablets.

Each tablet contains 100 mg or 50 mg sumatriptan (base) as the succinate salt.

IMITREX INJECTION is available in pre-filled syringes containing 6 mg of sumatriptan base, as the succinate salt, in an isotonic solution (total volume = 0.5 mL). Syringes are placed in a tamper-evident carrying/disposal case. Two pre-filled syringes plus an autoinjector are packed in a patient starter kit. A refill pack is available containing 2 x 2 pre-filled syringes in a carton.

IMITREX INJECTION is also available to physicians or hospitals in a single dose vial (total volume = 0.5 mL) containing 6 mg of sumatriptan base, as the succinate salt.

IMITREX Nasal Spray 5 mg and 20 mg are each supplied in boxes of 6 nasal spray devices (3 X 2 devices). Each unit dose spray supplies 5 and 20 mg, respectively, of sumatriptan (base) as the hemisulphate salt.

Product Monograph available to physicians and pharmacists upon request. Please contact Glaxo Wellcome Inc., 7333 Mississauga Road N, Mississauga, Ontario, L5N 6L4.



**REFERENCES:**

1. Product Monograph of IMITREX®, Glaxo Wellcome Inc., 1996. 2. Ryan R et al. The efficacy and tolerability of sumatriptan 5, 10 and 20 mg nasal sprays in the acute treatment of repeated attacks of migraine. Presented at the 7th International Headache Congress. Sept. 16-20, 1995. Toronto, Canada. 3. Becker WJ et al. A placebo-controlled, dose-defining study of sumatriptan nasal spray in the acute treatment of migraine. Presented at the 7th International Headache Congress. Sept. 16-20, 1995. Toronto, Canada.

PAAB CCPP GlaxoWellcome

℞IMITREX®
SUMATRIPTAN NASAL SPRAY

See pages xiv, xv.