

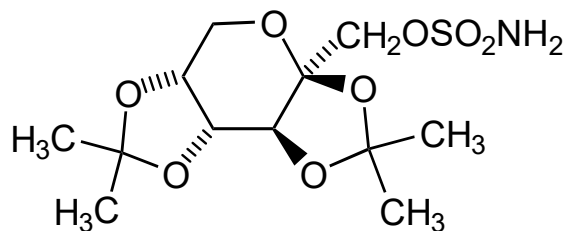
**TOPAMAX<sup>®</sup>**  
**(topiramate)**  
**Tablets**  
**TOPAMAX<sup>®</sup>**  
**(topiramate capsules)**  
**Sprinkle Capsules**

**Rx only**

**DESCRIPTION**

Topiramate is a sulfamate-substituted monosaccharide. TOPAMAX<sup>®</sup> (topiramate) Tablets are available as 25 mg, 50 mg, 100 mg, and 200 mg round tablets for oral administration. TOPAMAX<sup>®</sup> (topiramate capsules) Sprinkle Capsules are available as 15 mg and 25 mg sprinkle capsules for oral administration as whole capsules or opened and sprinkled onto soft food.

Topiramate is a white crystalline powder with 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. Topiramate has the molecular formula C<sub>12</sub>H<sub>21</sub>NO<sub>8</sub>S and a molecular weight of 339.37. Topiramate is designated chemically as 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate and has the following structural formula:



TOPAMAX<sup>®</sup> (topiramate) Tablets contain the following inactive ingredients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hypromellose, titanium dioxide, polyethylene glycol, synthetic iron oxide (50, 100, and 200 mg tablets) and polysorbate 80.

TOPAMAX<sup>®</sup> (topiramate capsules) Sprinkle Capsules contain topiramate coated beads in a hard gelatin capsule. The inactive ingredients are: sugar spheres (sucrose and starch), povidone, cellulose acetate, gelatin, silicone dioxide, sodium lauryl sulfate, titanium dioxide, and black pharmaceutical ink.

## **CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

The precise mechanisms by which topiramate exerts its anticonvulsant and migraine prophylaxis effects are unknown; however, preclinical studies have revealed four properties that may contribute to topiramate's efficacy for epilepsy and migraine prophylaxis. Electrophysiological and biochemical evidence suggests that topiramate, at pharmacologically relevant concentrations, blocks voltage-dependent sodium channels, augments the activity of the neurotransmitter gamma-aminobutyrate at some subtypes of the GABA-A receptor, antagonizes the AMPA/kainate subtype of the glutamate receptor, and inhibits the carbonic anhydrase enzyme, particularly isozymes II and IV.

### **Pharmacodynamics**

Topiramate has anticonvulsant activity in rat and mouse maximal electroshock seizure (MES) tests. Topiramate is only weakly effective in blocking clonic seizures induced by the GABA<sub>A</sub> receptor antagonist, pentylenetetrazole. Topiramate is also 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.

### **Pharmacokinetics**

The sprinkle formulation is bioequivalent to the immediate release tablet formulation and, therefore, may be substituted as a therapeutic equivalent.

Absorption of topiramate is rapid, with peak plasma concentrations occurring at approximately 2 hours following a 400 mg oral dose. The relative bioavailability of topiramate from the tablet formulation is about 80% compared to a solution. The bioavailability of topiramate is not affected by food.

The pharmacokinetics of topiramate are linear with dose proportional increases in plasma concentration over the dose range studied (200 to 800 mg/day). The mean plasma elimination half-life is 21 hours after single or multiple doses. Steady state is thus reached in about 4 days in patients with normal renal function. Topiramate is 15-41% bound to human plasma proteins over the blood concentration range of 0.5 -250 µg/mL. The fraction bound decreased as blood concentration increased.

Carbamazepine and phenytoin do not alter the binding of topiramate. Sodium valproate, at 500 µg/mL (a concentration 5-10 times higher than considered therapeutic for valproate) decreased the protein binding of topiramate from 23% to 13%. Topiramate does not influence the binding of sodium valproate.

## Metabolism and Excretion

Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine (approximately 70% of an administered dose). Six metabolites have been identified in humans, none of which constitutes more than 5% of an administered dose. The metabolites are formed via hydroxylation, hydrolysis, and glucuronidation. There is evidence of renal tubular reabsorption of topiramate. In rats, given probenecid to inhibit tubular reabsorption, along with topiramate, a significant increase in renal clearance of topiramate was observed. This interaction has not been evaluated in humans. Overall, oral plasma clearance (CL/F) is approximately 20 to 30 mL/min in humans following oral administration.

## Pharmacokinetic Interactions (see also [Drug Interactions](#))

### Antiepileptic Drugs

Potential interactions between topiramate and standard AEDs were assessed in controlled clinical pharmacokinetic studies in patients with epilepsy. The effect of these interactions on mean plasma AUCs are summarized under [PRECAUTIONS \(Table 3\)](#).

## Special Populations

### Renal Impairment

The clearance of topiramate was reduced by 42% in moderately renally impaired (creatinine clearance 30-69 mL/min/1.73m<sup>2</sup>) and by 54% in severely renally impaired subjects (creatinine clearance <30 mL/min/1.73m<sup>2</sup>) compared to normal renal function subjects (creatinine clearance >70 mL/min/1.73m<sup>2</sup>). Since topiramate is presumed to undergo significant tubular reabsorption, it is uncertain whether this experience can be generalized to all situations of renal impairment. It is conceivable that some forms of renal disease could differentially affect glomerular filtration rate and tubular reabsorption resulting in a clearance of topiramate not predicted by creatinine clearance. In general, however, use of one-half the usual starting and maintenance dose is recommended in patients with moderate or severe renal impairment (see [PRECAUTIONS: Adjustment of Dose in Renal Failure](#) and [DOSAGE AND ADMINISTRATION](#)).

### Hemodialysis

Topiramate is cleared by hemodialysis. Using a high efficiency, counterflow, single pass-dialysate hemodialysis procedure, topiramate dialysis clearance was 120 mL/min with blood flow through the dialyzer at 400 mL/min. This high clearance (compared to 20-30 mL/min total oral clearance in healthy adults) will remove a clinically significant amount of topiramate from the patient over the hemodialysis

treatment period. Therefore, a supplemental dose may be required (see [DOSAGE AND ADMINISTRATION](#)).

### Hepatic Impairment

In hepatically impaired subjects, the clearance of topiramate may be decreased; the mechanism underlying the decrease is not well understood.

### Age, Gender, and Race

The pharmacokinetics of topiramate in elderly subjects (65-85 years of age, N=16) were evaluated in a controlled clinical study. The elderly subject population had reduced renal function [creatinine clearance (-20%)] compared to young adults. Following a single oral 100 mg dose, maximum plasma concentration for elderly and young adults was achieved at approximately 1-2 hours. Reflecting the primary renal elimination of topiramate, topiramate plasma and renal clearance were reduced 21% and 19%, respectively, in elderly subjects, compared to young adults. Similarly, topiramate half-life was longer (13%) in the elderly. Reduced topiramate clearance resulted in slightly higher maximum plasma concentration (23%) and AUC (25%) in elderly subjects than observed in young adults. Topiramate clearance is decreased in the elderly only to the extent that renal function is reduced. As recommended for all patients, dosage adjustment may be indicated in the elderly patient when impaired renal function (creatinine clearance rate  $\leq 70$  mL/min/1.73 m<sup>2</sup>) is evident. It may be useful to monitor renal function in the elderly patient (see [Special Populations: Renal Impairment](#), [PRECAUTIONS: Adjustment of Dose in Renal Failure](#) and [DOSAGE AND ADMINISTRATION](#)).

Clearance of topiramate in adults was not affected by gender or race.

### 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. Clearance was independent of dose.

Pediatric patients have a 50% higher clearance and consequently shorter elimination half-life than adults. Consequently, the plasma concentration for the same mg/kg dose may be lower in pediatric patients compared to adults. As in adults, hepatic enzyme-inducing antiepileptic drugs decrease the steady state plasma concentrations of topiramate.

## CLINICAL STUDIES

The studies described in the following sections were conducted using TOPAMAX<sup>®</sup> (topiramate) Tablets.

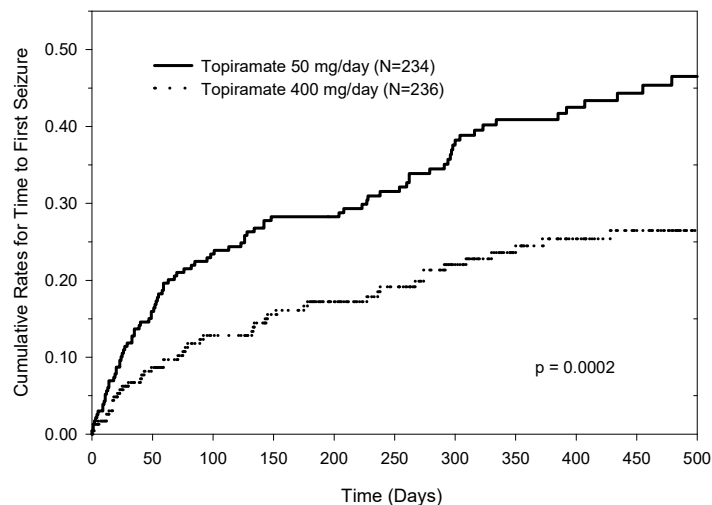
### Epilepsy

#### Monotherapy Controlled Trial

The effectiveness of topiramate as initial monotherapy in adults and children 10 years of age and older with partial onset or primary generalized seizures was established in a multicenter, randomized, double-blind, parallel-group trial.

The trial was conducted in 487 patients diagnosed with epilepsy (6 to 83 years of age) who had 1 or 2 well-documented seizures during the 3-month retrospective baseline phase who then entered the study and received topiramate 25 mg/day for 7 days in an open-label fashion. Forty-nine percent of subjects had no prior AED treatment and 17% had a diagnosis of epilepsy for greater than 24 months. Any AED therapy used for temporary or emergency purposes was discontinued prior to randomization. In the double-blind phase, 470 patients were randomized to titrate up to 50 mg/day or 400 mg/day. If the target dose could not be achieved, patients were maintained on the maximum tolerated dose. Fifty eight percent of patients achieved the maximal dose of 400 mg/day for  $\geq 2$  weeks, and patients who did not tolerate 150 mg/day were discontinued. The primary efficacy assessment was a between group comparison of time to first seizure during the double-blind phase. Comparison of the Kaplan-Meier survival curves of time to first seizure favored the topiramate 400 mg/day group over the topiramate 50 mg/day group ( $p=0.0002$ , log rank test; [Figure 1](#)). The treatment effects with respect to time to first seizure were consistent across various patient subgroups defined by age, sex, geographic region, baseline body weight, baseline seizure type, time since diagnosis, and baseline AED use.

**Figure 1:** Kaplan-Meier Estimates of Cumulative Rates for Time to First Seizure



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