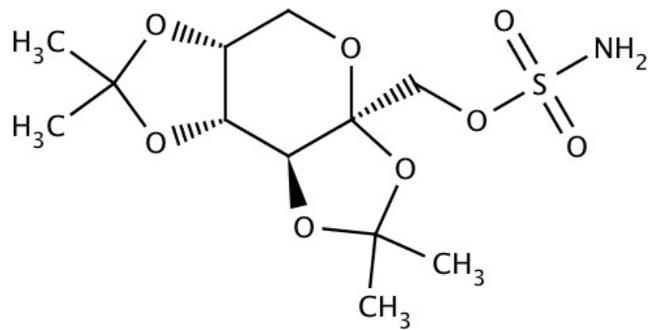


# CINAPS COMPOUND DOSSIER

## Topiramate



9/7/2010

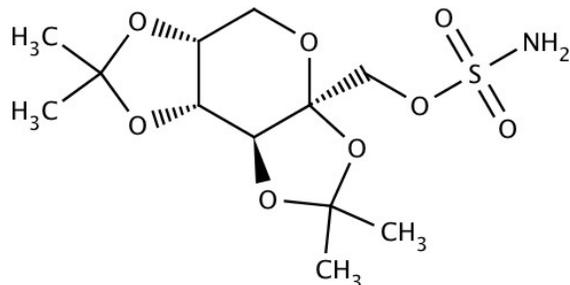
## Table of Contents

I. Compound Information.....	3
II. Rationale.....	4
IIa. Scientific Rationale / Mechanism.....	4
IIb. Consistency.....	4
III. Efficacy (Animal Models of Parkinson’s Disease).....	6
IIIa. Animal Models: Rodent.....	6
IIIb. Animal Models: Non-human Primates.....	6
IV. Efficacy (Clinical and Epidemiological Evidence).....	7
IVa. Clinical Studies.....	7
IVb. Epidemiological Evidence.....	7
V. Relevance to Other Neurodegenerative Diseases.....	8
VI. Pharmacokinetics.....	9
VIa. General ADME.....	9
VIb. CNS Penetration.....	9
VIc. Calculated $\log([\text{brain}]/[\text{blood}])$ .....	9
VII. Safety, Tolerability, and Drug Interaction Potential.....	10
VIIa. Safety and Tolerability.....	10
VIIb. Drug Interaction Potential.....	16
VIII. Bibliography.....	17

## I. Compound Information

**Common name:** Topiramate

**Structure:**



**Pubchem ID:** 5284627 **Mol. Formula:** C<sub>12</sub>H<sub>21</sub>NO<sub>8</sub>S **FW:** 339.36

**CASRN:** 97240-79-4 **Polar surface area:** 116 **logP:** -0.8

**IUPAC name:** [(3a*S*,5a*R*,8a*R*,8b*S*)-2,2,7,7-Tetramethyltetrahydro-3aH-bis[1,3]dioxolo[4,5-b:4',5'-d]pyran-3a-yl]methyl sulfamate

**Other names:** Topamax®

**Drug class:** Anitconvulsant; sodium channel blocker; carbonic anhydrase inhibitor

**Medicinal chemistry development potential:** High

## **II. Rationale**

### **IIa. Scientific Rationale / Mechanism**

Topiramate is an approved, marketed, and now generic, medication used in the treatment of epilepsy. Topiramate has multiple pharmacologic effects on the CNS. The anti-convulsant activity of topiramate is considered due to blockade of sodium channels,<sup>1-2</sup> a modulatory effect on GABAA receptors,<sup>3-4</sup> and inhibition of the non-NMDA glutamate ionotropic receptors.<sup>4-5</sup> Further to these effects, topiramate inhibits some isozymes of carbonic anhydrase<sup>6</sup> and increases energy metabolism in rats by mechanisms that have not been fully elucidated although inhibition of the mitochondrial permeability transition pore plays a role.<sup>7</sup>

As discussed below, there is no direct evidence that topiramate prevents the onset of symptoms in animal models of Parkinson's disease (PD). Nevertheless, data from models of cerebral ischemia and status-epilepticus suggest the potential for neuroprotective activity (see Section V). Thus, the concept that topiramate has potential as a neuroprotectant agent in Parkinson's Disease rests primarily on this generalized evidence of neuroprotective effect attributed to increased energy metabolism and inhibition of the mitochondrial permeability transition pore.<sup>7</sup>

### **IIb. Consistency**

n/a

### **III. Efficacy (Animal Models of Parkinson's Disease)**

#### **IIIa. Animal Models: Rodent**

There is no direct evidence of topiramate efficacy in rodent models of Parkinson's disease. One study indicated that topiramate was not neuroprotective in the mouse MPTP model, even though other antiepileptics with a similar putative mechanism of action were protective.<sup>8</sup>

#### **IIIb. Animal Models: Non-human Primates**

Topiramate (two 20 mg/kg doses, p.o.) attenuates L-DOPA-induced dyskinesia in MPTP-lesioned marmosets, possibly through a dampening of AMPA-receptor mediated transmission.<sup>9</sup>

#### **IV. Efficacy (Clinical and Epidemiological Evidence)**

##### **IVa. Clinical Studies**

There are no clinical reports of topiramate providing neuroprotective effects or attenuation of the onset of Parkinsonian symptoms.

##### **IVb. Epidemiological Evidence**

There is no epidemiological evidence for a neuroprotective effect of topiramate in Parkinson's disease or any other neurodegenerative disorder.

## **V. Relevance to Other Neurodegenerative Diseases**

The relevance of topiramate to other neurodegenerative disorders is unclear. There is no data available in disorders where neurodegeneration is considered the primary pathology. However, several studies have highlighted a potential neuroprotective role for topiramate in hypoxic ischemia,<sup>10-12</sup> and epilepsy/tremor.<sup>7, 13-15</sup>

## **VI. Pharmacokinetics**

### **Via. General ADME**

Topiramate pharmacokinetics have been described in study involving 11 epilepsy patients. Mono-therapy kinetics of topiramate gave a C<sub>max</sub> of 16.24 ± 6.24 mg/L, t<sub>max</sub> of 1.46 ± 0.63 h and an AUC at steady state of 154.7 ± 64.2 mg-h/L.<sup>16</sup>

### **Vib. CNS Penetration**

In human subjects the median cerebrospinal fluid (CSF)/plasma concentration ratio of topiramate has been found to be 0.85 with the concentration of topiramate in CSF equal to the unbound proportion of topiramate in plasma.<sup>17</sup>

### **Vic. Calculated log([brain]/[blood])**

-1.70 (Clark Model<sup>18</sup>)

## **VII. Safety, Tolerability, and Drug Interaction Potential**

### **VIIa. Safety and Tolerability**

The safety and tolerability of topiramate are summarized by the package insert from the currently available clinical form from Johnson and Johnson: Topamax® (DailyMed Website: <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=7412>).

In brief, the main side effects listed for Topamax® include: numbness, burning, or tingling in the hands or feet, slowed reactions, difficulty concentrating, speech problems, especially difficulty thinking of specific words, memory problems, lack of coordination, confusion, nervousness, aggressive behavior, irritability, mood swings, depression, headache, drowsiness, weakness, excessive movement, uncontrollable shaking of a part of the body, uncontrollable eye movements, extreme thirst, weight loss, constipation, diarrhea, gas, heartburn, change in ability to taste food, swelling of the tongue, overgrowth of the gums, dry mouth, increased saliva, trouble swallowing, nosebleed, teary or dry eyes, back, muscle, or bone pain, missed menstrual periods, excessive menstrual bleeding, skin problems or changes in skin color, dandruff, hair loss, growth of hair in unusual places, ringing in the ears, difficulty falling or staying asleep, swelling of the hands, arms, feet, ankles, or lower legs, difficulty urinating or pain urinating.

### **VIIb. Drug Interaction Potential**

The drug interaction potential for topiramate is described in full in the package insert for the currently available Johnson and Johnson product. The drug interaction potential includes the following from this package insert (<http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=7412>):

#### **Digoxin**

In a single-dose study, serum digoxin AUC was decreased by 12% with concomitant TOPAMAX® administration. The clinical relevance of this observation has not been established.

#### **CNS Depressants**

Concomitant administration of TOPAMAX® and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. Because of the potential of topiramate to cause CNS depression, as well as other cognitive and/or neuropsychiatric adverse events, topiramate should be used with extreme caution if used in combination with alcohol and other CNS depressants.

#### **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® (50 to 200 mg/day) given in the absence of other medications 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 when coadministered with TOPAMAX® doses of 200, 400, and 800 mg/day (18%, 21%, and 30%, respectively) given as an adjunctive therapy in patients taking valproic acid. In both studies, TOPAMAX® (50 mg/day to 800 mg/day) did not significantly affect exposure to NET. Although there was a dose dependent decrease in EE exposure for TOPAMAX® 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.

### **Hydrochlorothiazide (HCTZ)**

A drug-drug interaction study 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 the topiramate C<sub>max</sub> increased by 27% and AUC increased by 29% when HCTZ was given concomitantly. 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 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<sub>max</sub> and mean AUC<sub>0-12h</sub> 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<sub>max</sub>. 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 in healthy volunteers evaluated the steady-state

pharmacokinetics of topiramate and pioglitazone when administered alone and concomitantly. A 15% decrease in the AUC<sub>T,ss</sub> of pioglitazone with no alteration in C<sub>max,ss</sub> was observed. This finding was not statistically significant. In addition, a 13% and 16% decrease in C<sub>max,ss</sub> and AUC<sub>T,ss</sub> respectively, of the active hydroxy-metabolite was noted as well as a 60% decrease in C<sub>max,ss</sub> and AUC<sub>T,ss</sub> 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.

### **Lithium**

Multiple dosing of topiramate 100 mg every 12 hrs decreased the AUC and C<sub>max</sub> of lithium (300 mg every 8 hrs) by 20% (N=12, 6 M, 6 F).

### **Haloperidol**

The pharmacokinetics of a single dose of haloperidol (5 mg) were not affected following multiple dosing of topiramate (100 mg every 12 hr) in 13 healthy adults (6 M, 7 F).

### **Amitriptyline**

There was a 12% increase in AUC and C<sub>max</sub> for amitriptyline (25 mg per day) in 18 normal subjects (9 M, 9 F) receiving 200 mg/day of topiramate. Some subjects may experience a large increase in amitriptyline concentration in the presence of topiramate and any adjustments in amitriptyline dose should be made according to the patient's clinical response and not on the basis of plasma levels.

### **Sumatriptan**

Multiple dosing of topiramate (100 mg every 12 hrs) in 24 healthy volunteers (14 M, 10 F) did not affect the pharmacokinetics of single dose sumatriptan either orally (100 mg) or subcutaneously (6 mg).

### **Risperidone**

There was a 25% decrease in exposure to risperidone (2 mg single dose) in 12 healthy volunteers (6 M, 6 F) receiving 200 mg/day of topiramate. Therefore, patients receiving risperidone in combination with topiramate should be closely monitored for clinical response.

### **Propranolol**

Multiple dosing of topiramate (200 mg/day) in 34 healthy volunteers (17 M, 17 F) did not affect the pharmacokinetics of propranolol following daily 160 mg doses. Propranolol doses of 160 mg/day in 39 volunteers (27 M, 12 F) had no effect on the exposure to topiramate at a dose of 200 mg/day of topiramate.

### **Dihydroergotamine**

Multiple dosing of topiramate (200 mg/day) in 24 healthy volunteers (12 M, 12 F) did not affect the pharmacokinetics of a 1 mg subcutaneous dose of dihydroergotamine. Similarly, a 1 mg subcutaneous dose of dihydroergotamine did not affect the pharmacokinetics of a 200 mg/day dose of topiramate in the same study.

### **Others**

Concomitant use of TOPAMAX®, a 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.

### **Drug/Laboratory Test Interactions**

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

## VIII. Bibliography

1. Zona, C.; Ciotti, M. T.; Avoli, M., Topiramate attenuates voltage-gated sodium currents in rat cerebellar granule cells. *Neurosci Lett* **1997**, *231* (3), 123-6.
2. DeLorenzo, R. J.; Sombati, S.; Coulter, D. A., Effects of topiramate on sustained repetitive firing and spontaneous recurrent seizure discharges in cultured hippocampal neurons. *Epilepsia* **2000**, *41 Suppl 1*, S40-4.
3. White, H. S.; Brown, S. D.; Woodhead, J. H.; Skeen, G. A.; Wolf, H. H., Topiramate enhances GABA-mediated chloride flux and GABA-evoked chloride currents in murine brain neurons and increases seizure threshold. *Epilepsy Res* **1997**, *28* (3), 167-79.
4. White, H. S.; Brown, S. D.; Woodhead, J. H.; Skeen, G. A.; Wolf, H. H., Topiramate modulates GABA-evoked currents in murine cortical neurons by a nonbenzodiazepine mechanism. *Epilepsia* **2000**, *41 Suppl 1*, S17-20.
5. Skradski, S.; White, H. S., Topiramate blocks kainate-evoked cobalt influx into cultured neurons. *Epilepsia* **2000**, *41 Suppl 1*, S45-7.
6. Dodgson, S. J.; Shank, R. P.; Maryanoff, B. E., Topiramate as an inhibitor of carbonic anhydrase isoenzymes. *Epilepsia* **2000**, *41 Suppl 1*, S35-9.
7. Kudin, A. P.; Debska-Vielhaber, G.; Vielhaber, S.; Elger, C. E.; Kunz, W. S., The mechanism of neuroprotection by topiramate in an animal model of epilepsy. *Epilepsia* **2004**, *45* (12), 1478-87.
8. Lagrue, E.; Chalon, S.; Bodard, S.; Saliba, E.; Gressens, P.; Castelnaud, P., Lamotrigine is neuroprotective in the energy deficiency model of MPTP intoxicated mice. *Pediatr Res* **2007**, *62* (1), 14-9.
9. Silverdale, M. A.; Nicholson, S. L.; Crossman, A. R.; Brotchie, J. M., Topiramate reduces levodopa-induced dyskinesia in the MPTP-lesioned marmoset model of Parkinson's disease. *Mov Disord* **2005**, *20* (4), 403-9.
10. Schubert, S.; Brandl, U.; Brodhun, M.; Ulrich, C.; Spaltmann, J.; Fiedler, N.; Bauer, R., Neuroprotective effects of topiramate after hypoxia-ischemia in newborn piglets. *Brain Res* **2005**, *1058* (1-2), 129-36.
11. Costa, C.; Martella, G.; Picconi, B.; Prosperetti, C.; Pisani, A.; Di Filippo, M.; Pisani, F.;

Bernardi, G.; Calabresi, P., Multiple mechanisms underlying the neuroprotective effects of antiepileptic drugs against in vitro ischemia. *Stroke* **2006**, 37 (5), 1319-26.

12. Kurul, S. H.; Yis, U.; Kumral, A.; Tugyan, K.; Cilaker, S.; Kolatan, E.; Yilmaz, O.; Genc, S., Protective effects of topiramate against hyperoxic brain injury in the developing brain. *Neuropediatrics* **2009**, 40 (1), 22-7.
13. Frisch, C.; Kudin, A. P.; Elger, C. E.; Kunz, W. S.; Helmstaedter, C., Amelioration of water maze performance deficits by topiramate applied during pilocarpine-induced status epilepticus is negatively dose-dependent. *Epilepsy Res* **2007**, 73 (2), 173-80.
14. Francois, J.; Koning, E.; Ferrandon, A.; Nehlig, A., The combination of topiramate and diazepam is partially neuroprotective in the hippocampus but not antiepileptogenic in the lithium-pilocarpine model of temporal lobe epilepsy. *Epilepsy Res* **2006**, 72 (2-3), 147-63.
15. Rigoulot, M. A.; Koning, E.; Ferrandon, A.; Nehlig, A., Neuroprotective properties of topiramate in the lithium-pilocarpine model of epilepsy. *J Pharmacol Exp Ther* **2004**, 308 (2), 787-95.
16. Dose, D. R.; Brodie, M. J.; Wilson, E. A.; Chadwick, D.; Oxbury, J.; Berry, D. J.; Schwabe, S.; Bialer, M., Topiramate and lamotrigine pharmacokinetics during repetitive monotherapy and combination therapy in epilepsy patients. *Epilepsia* **2003**, 44 (7), 917-22.
17. Christensen, J.; Hojskov, C. S.; Dam, M.; Poulsen, J. H., Plasma concentration of topiramate correlates with cerebrospinal fluid concentration. *Ther Drug Monit* **2001**, 23 (5), 529-35.
18. Clark, D. E.; Pickett, S. D., Computational methods for the prediction of 'drug-likeness'. *Drug Discov Today* **2000**, 5 (2), 49-58.