Topiramate: Drug information

(For additional information see "Topiramate: Patient drug information" and see "Topiramate: Pediatric drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

Brand Names: US

Qudexy XR; Topamax; Topamax Sprinkle; Trokendi XR

Brand Names: Canada

ACH-Topiramate; AG-Topiramate; APO-Topiramate; Auro-Topiramate; DOM-Topiramate; GLN-Topiramate; JAMP-Topiramate; Mar-Topiramate; MINT-Topiramate; MYLAN-Topiramate; PMS-Topiramate; PRO-Topiramate; RAN-Topiramate [DSC]; SANDOZ Topiramate; TEVA-Topiramate; Topamax; Topamax Sprinkle

Pharmacologic Category

Anticonvulsant, Miscellaneous

Dosing: Adult

Note: The dosing recommendations in this monograph are expressed as the total daily dose (ie, per 24 hours) unless stated otherwise. The total daily oral dose is given in 1 to 2 divided doses per day depending on the type of preparation. Available preparations include: Oral immediate release (IR) (dosed twice daily) and extended release (ER) (dosed once daily).

Binge-eating disorder (alternative agent) (off-label use):

Oral: Initial: 25 mg once daily; increase dose gradually in progressively larger increments of 25 to 100 mg at intervals ≥1 week based on response and tolerability up to 400 mg/day (McElroy 2007).

Headache, cluster (prevention) (alternative agent; adjunctive therapy) (off-label use):

Note: Some experts often use in combination with verapamil (May 2020).

Oral: Initial: 25 to 50 mg once daily; increase dose gradually in 25 to 50 mg increments at intervals ≥1 week based on response and tolerability, up to a recommended dose of 100 mg/day; a further increase up to 200 mg/day may be necessary in some patients for optimal response (EFNS [May 2006]; Pascual 2007).

Headache, short-lasting unilateral neuralgiform attacks (prevention) (alternative agent) (off-label use): Based on limited data:

Oral: Initial: 15 to 25 mg once daily; may increase dose based on response and tolerability in 25 mg increments every 2 weeks up to 100 mg/day in 2 divided doses, and thereafter in 50 mg increments every few weeks up to 400 mg/day (Cohen 2007; Matharu 2019).

Migraine (prevention):

Oral: Initial: 25 mg once daily; increase dose in 25 to 50 mg increments at intervals ≥1 week based on response and tolerability up to 100 mg/day. Some patients may require up to 200 mg/day for optimal response; however, adverse effects may increase (Linde 2013).

Seizures:

Note: FDA-approved as monotherapy and adjunctive therapy for focal (partial) onset seizures and primary generalized tonic-clonic seizures, or as adjunctive therapy for Lennox-Gastaut syndrome; may be used off label for other seizure types.

Monotherapy: **Oral:** Initial: 50 mg/day; increase dose in 50 mg increments at weekly intervals based on response and tolerability up to 200 mg/day; thereafter, may further increase in 100 mg increments at weekly intervals up to 400 mg/day.

Adjunctive therapy: **Oral:** Initial: 25 to 50 mg/day; increase in 25 to 50 mg increments at weekly intervals based on response and tolerability up to 400 mg/day.

Tremor, essential (alternative agent for patients who fail preferred therapies) (off-label use):

Oral: Initial: 25 mg once or twice daily; increase dose gradually in increments of 25 to 50 mg at intervals ≥1 week based on response and tolerability up to 400 mg/day (AAN [Zesiewicz 2011]; Connor 2008; Ondo 2006).

Weight gain, antipsychotic-induced (alternative agent; adjunct to behavioral and antipsychotic modifications) (off-label use):

Oral: Initial: 50 mg/day; increase in 25 to 50 mg increments at weekly intervals based on response and tolerability up to a recommended dose of 200 mg/day (Jarskog 2019; Ko 2005; WFSBP [Hasan 2013]).

Dosing conversion:

Between IR and ER formulations: Convert using same total daily dose but adjust frequency as indicated for the IR (2 times daily) and ER (once daily) products.

Between ER formulations: Bioequivalence has not been demonstrated between Trokendi XR and Qudexy XR.

Discontinuation of therapy: In patients receiving topiramate long-term, unless safety concerns require a more rapid withdrawal, topiramate should be withdrawn gradually over a few weeks to several months to minimize the potential of seizures or other withdrawal symptoms (Schachter 2020). In clinical trials, adult doses were decreased by 50 to 100 mg each week over 2 to 8 weeks for seizure treatment, and by 25 to 50 mg each week for migraine prophylaxis.

Dosage adjustment for concomitant therapy: Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information.

Dosing: Renal Impairment: Adult

CrCl ≥70 mL/minute/1.73 m^2: There are no dosage adjustments provided in the manufacturer's labeling.

CrCl <70 mL/minute/1.73 m^2: Reduce dose to 50% of normal dose and titrate more slowly.

Hemodialysis: 50 to 100 mg twice daily; administer a supplemental dose (50 to 100 mg) post-dialysis (Israni 2006). Topiramate is cleared by hemodialysis.

Dosing: Hepatic Impairment: Adult

There are no dosage adjustments provided in the manufacturer's labeling; however, topiramate clearance may be reduced in hepatic impairment. Use with caution.

Dosing: Pediatric

(For additional information see "Topiramate: Pediatric drug information")

Note: Do not abruptly discontinue therapy; taper dosage gradually to prevent rebound effects.

Infantile spasms; monotherapy or adjunctive: Limited data available, efficacy results variable. Not first-line therapy, but may be considered in refractory cases (AAN [Go 2012]; Nelson 2015).

Infants and Children <4 years: Oral: Immediate release: Initial dose: 0.5 to 1 mg/kg/day in divided doses twice daily; may titrate based on clinical response and tolerance in 0.5 to 1 mg/kg/day increments at 5- to 7-day intervals; reported range: 2 to 40 mg/kg/day (Korinthenberg 2007; Zou 2008).

Dosing based on an open-label trial of 544 patients diagnosed with infantile spasms (349 infants; 243 patients on monotherapy); initial topiramate dose was 0.5 to 1 mg/kg/day; doses were titrated as appropriate; reported final dose range: 3.57 to 20 mg/kg/day. After 20 weeks of therapy, 460 patients (84.5%) had a >50% reduction in seizures and seizure freedom was attained in 122 (50.2%) as monotherapy and in 117 (38.9%) as add-on therapy (Zou 2008). A higher median initial dose of 1.6 mg/kg/day was reported in another trial of 100 patients (median age: 11.9 months; range: 3.6 to 45.1 months; 36 patients on monotherapy); patients were titrated to an effective final dose; reported final dose range: 2 to 40 mg/kg/day; results showed reduction in infantile spasms from a median of 40 episodes/week to a median of 15 episodes/week and 47 patients had a >50% reduction in all seizures. No difference in efficacy was observed for final dose stratifications of low dose (n=31; 2 to 8 mg/kg/day), medium dose (n=39; 9 to 17 mg/kg/day), or high dose (n=24; 18 to 40 mg/kg/day) (Korinthenberg 2007). However, other trials have reported a poor response to topiramate; in a single-center trial evaluating 31 infants and young children, 9.7% (3/31) achieved remission with topiramate (responder maximum dose range: 25 to 28 mg/kg/day), and all experienced subsequent electroclinical relapse (Weber 2015).

Migraine; prevention:

Note: Pediatric migraine efficacy trials have been observed to have a high placebo response; a meta-analysis has shown that 30% to 61% of subjects receiving placebo report decreased number of migraine attacks or decrease in headache days. Specific to topiramate therapy, trials have shown a reduction in number of headache days and migraine attacks compared to placebo; there is insufficient evidence in pediatric

subjects receiving topiramate to demonstrate a 50% reduction in headache frequency, headache day, and migraine disability compared to placebo (AAN/AHS [Oskoui 2019]).

Children 6 to <12 years; weight: ≥20 kg: Limited data available: Oral: Immediate release: Initial: 15 mg once daily for 1 week; then increase to 15 mg twice daily for 1 week; then increase to 25 mg twice daily for 7 days; continue to gradually titrate to effect up to target dose of 2 to 3 mg/kg/day divided twice daily; maximum daily dose: 200 mg/**day** has been reported; however, in older pediatric patients, a targeted daily dose of 100 mg/day is recommended (AAN/AHS [Oskoui 2019]; Winner 2005). Dosing based on a double-randomized, placebo-controlled trial of 90 pediatric patients <12 years (treatment arm: n=59; mean age: 11.3 years as part of a larger trial with a total of 108 pediatric patients receiving topiramate compared to 49 receiving placebo) which showed a mean reduction in migraine days/month with topiramate and significantly more topiramate patients experienced ≥75% reduction in mean monthly migraine days compared to placebo (32% vs 14%) for overall study population; mean maintenance dose: 2 mg/kg/day; treatment duration of maintenance dose: 12 weeks (Winner 2005).

Children ≥12 years and Adolescents:

Immediate release: Oral: Initial: 25 mg/day once daily at night for 1 week; increase at weekly intervals in 25 mg/day increments as tolerated and indicated to recommended dose of 50 mg twice daily; in a double-blind, placebo-controlled, dose-finding trial of 103 pediatric patients ≥12 years (mean age: 14.2 years), the daily dose of 100 mg/day was shown to significantly decrease frequency of migraine attacks compared to a lower dose of 50 mg/day (Lewis 2009).

Extended release: Qudexy XR, Trokendi: Oral: Initial: 25 mg/day once daily at night for 1 week; increase at weekly intervals in 25 mg/day increments as tolerated and indicated to recommended dose of 100 mg/day; during titration, some patients may require longer intervals prior to dose escalation.

Seizure disorder, adjunctive therapy for partial onset seizures, primary generalized tonic-clonic seizures, or Lennox Gastaut syndrome :

Children and Adolescents 2 to 16 years:

Immediate release: Children and Adolescents 2 to 16 years: Oral: Initial: 1 to 3 mg/kg/day (maximum dose: 25 mg/dose) administered nightly for 1 week; increase at 1- to 2-week intervals in increments of 1 to 3 mg/kg/day in 2 divided doses;

titrate dose to response; usual maintenance: 5 to 9 mg/kg/day in 2 divided doses; maximum daily dose: 400 mg/**day**.

Extended release:

Qudexy XR: Children and Adolescents 2 to 16 years: Oral: Initial: 25 mg once daily (approximately 1 to 3 mg/kg/day) administered nightly for 1 week; increase at 1- to 2-week intervals in increments of 1 to 3 mg/kg/day rounded to the nearest appropriate capsule size administered once daily; titrate dose to response; usual maintenance range: 5 to 9 mg/kg/dose once daily; maximum daily dose: 400 mg/**day**.

Trokendi XR: Children and Adolescents 6 to 16 years, able to swallow capsule whole: Oral: Initial: 25 mg once daily (approximately 1 to 3 mg/kg/day) administered nightly for 1 week; increase at 1- to 2-week intervals in increments of 1 to 3 mg/kg/day rounded to the nearest appropriate capsule size administered once daily; titrate dose to response; usual maintenance: 5 to 9 mg/kg/dose once daily; maximum daily dose: 400 mg/**day**.

Adolescents ≥17 years:

Immediate release: Oral: Initial: 25 to 50 mg/day administered daily for 1 week; increase at weekly intervals by 25 to 50 mg/day; administer in 2 divided doses; titrate dose to response. Usual maintenance dose dependent on seizure type; for partial onset seizures or Lennox-Gastaut syndrome: 100 to 200 mg twice daily; usual maintenance dose for primary generalized tonic-clonic seizures 200 mg twice daily; maximum daily dose: 400 mg/**day**; **Note:** Doses above 400 mg/day have not been shown to increase efficacy in dose-response studies in adults with partial onset seizures.

Extended release: Qudexy XR, Trokendi XR: Oral: Initial: 25 to 50 mg once daily for 1 week; increase at weekly intervals by 25 to 50 mg/day once daily; titrate dose to response; longer intervals between dosage adjustment may be used; usual maintenance dose for partial onset seizures or Lennox Gastaut syndrome: 200 to 400 mg once daily; usual maintenance dose for primary generalized tonic-clonic seizures: 400 mg once daily; maximum daily dose: 400 mg/**day**; higher doses have not been studied.

Seizure disorder, monotherapy for partial onset seizures or primary generalized tonic-clonic seizures :

Immediate release:

Children 2 to <10 years: Oral: Initial: 25 mg once daily (in evening); may increase if tolerated to 25 mg twice daily in week 2; thereafter, may increase by 25 to 50 mg/day at weekly intervals over 5 to 7 weeks up to the lower end of the target daily maintenance dosing range (ie, to the minimum recommended maintenance dose); if additional seizure control is needed and therapy is tolerated, may further increase by 25 to 50 mg/day at weekly intervals up to the upper end of the target daily maintenance dosing range (ie, to the maximum recommended maintenance dose):

Target daily fixed maintenance dosing range:

≤11 kg: 150 to 250 mg/**day** in 2 divided doses.

12 to 22 kg: 200 to 300 mg/**day** in 2 divided doses.

23 to 31 kg: 200 to 350 mg/**day** in 2 divided doses.

32 to 38 kg: 250 to 350 mg/**day** in 2 divided doses.

>38 kg: 250 to 400 mg/**day** in 2 divided doses.

Children ≥10 years and Adolescents: Oral: Initial: 25 mg twice daily; increase at weekly intervals by 50 mg/day increments up to a dose of 100 mg twice daily (week 4 dose); thereafter, may further increase at weekly intervals by 100 mg/day increments up to the recommended maximum dose of 200 mg twice daily.

Extended release:

Qudexy XR:

Children 2 to 9 years: Oral: Initial: 25 mg once daily (in evening); may increase if tolerated to 50 mg once daily in week 2; thereafter, may increase by 25 to 50 mg/day at weekly intervals over 5 to 7 weeks up to the lower end of the target daily maintenance dosing range (ie, to the minimum recommended maintenance dose); if additional seizure control is needed and therapy is tolerated, may further increase by 25 to 50 mg/day at weekly intervals up to the upper end of the target daily maintenance dosing range (ie, to the maximum recommended maintenance dose); see the following table.

Monotherapy Targeted Total Daily Fixed Maintenance Doses for Patients 2 to 9 Years		
Patient Weight	**Total MINimum Daily Dose (mg/day)**	**Total MAXimum Daily Dose (mg/day)**

Monotherapy Targeted Total Daily Fixed Maintenance Doses for Patients 2 to 9 Years		
Patient Weight	**Total MINimum Daily Dose (mg/day)**	**Total MAXimum Daily Dose (mg/day)**
≤11 kg	150	250
12 to 22 kg	200	300
23 to 31 kg	200	350
32 to 38 kg	250	350
>38 kg	250	400

Children ≥10 years and Adolescents: Oral: Initial: 50 mg once daily for 1 week; increase at weekly intervals by 50 mg/day increments up to a dose of 200 mg once daily (week 4 dose); thereafter, may increase at weekly intervals by 100 mg/day increments up to the recommended dose of 400 mg once daily.

Trokendi XR:

Children 6 to 9 years able to swallow capsule whole: Oral: Initial: 25 mg once daily (in evening); may increase if tolerated to 50 mg once daily in week 2; thereafter, may increase by 25 to 50 mg/day at weekly intervals over 5 to 7 weeks up to the lower end of the target daily maintenance dosing range (ie, to the minimum recommended maintenance dose); if additional seizure control is needed and therapy is tolerated, may further increase by 25 to 50 mg/day at weekly intervals up to the upper end of the target daily maintenance dosing range (ie, to the maximum recommended maintenance dose); see the following table.

Monotherapy Targeted Total Daily Fixed Maintenance Doses for Patients 6 to 9 Years of Age		
Patient Weight	**Total MINimum Daily Dose (mg/day)**	**Total MAXimum Daily Dose (mg/day)**
≤11 kg	150	250
12 to 22 kg	200	300
23 to 31 kg	200	350
32 to 38 kg	250	350
>38 kg	250	400

Children ≥10 years and Adolescents: Oral: Initial: 50 mg once daily for 1 week; increase at weekly intervals by 50 mg/day increments up to a dose of 200 mg once daily (week 4 dose); thereafter, may increase at weekly intervals by 100 mg/day increments up to the recommended dose of 400 mg once daily.

Dosage adjustment for concomitant therapy: Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information.

Dosing: Renal Impairment: Pediatric

Altered Kidney Function:

Children ≥2 years and Adolescents: There are no pediatric-specific dosage adjustments provided in the manufacturer's labeling. Clearance is reduced in patients with CrCl of <70 mL/minute/1.73 m^2 and a dosage adjustment is recommended. Based on adult data, a 50% dosage reduction may be required in patients with a CrCl <70 mL/minute/1.73 m^2 (Manitpisitkul 2014; manufacturer's labeling).

Hemodialysis: Children ≥2 years and Adolescents: Removed by hemodialysis, supplemental dose may be required (Manitpisitkul 2014; manufacturer's labeling).

Dosing: Hepatic Impairment: Pediatric

Children and Adolescents: There are no dosage adjustments provided in the manufacturer's labeling; however, clearance may be reduced. Carefully adjust dose as plasma concentrations may be increased if normal dosing is used.

Dosing: Geriatric

Most older adults have creatinine clearances <70 mL/minute/1.73 m^2; obtain a serum creatinine and calculate creatinine clearance prior to initiation of therapy. An initial dose of 25 mg/day may be recommended, followed by incremental increases of 25 mg at weekly intervals until an effective dose is reached; refer to adult dosing for titration schedule.

Dosage Forms: US

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule ER 24 Hour Sprinkle, Oral:

Qudexy XR: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg

Generic: 25 mg, 50 mg, 100 mg, 150 mg, 200 mg

Capsule Extended Release 24 Hour, Oral:

Trokendi XR: 25 mg [contains brilliant blue fcf (fd&c blue #1), sodium benzoate]

Trokendi XR: 50 mg, 100 mg, 200 mg [contains brilliant blue fcf (fd&c blue #1), fd&c yellow #6 (sunset yellow), sodium benzoate]

Capsule Sprinkle, Oral:

Topamax Sprinkle: 15 mg, 25 mg

Generic: 15 mg, 25 mg

Tablet, Oral:

Topamax: 25 mg, 50 mg, 100 mg, 200 mg

Generic: 25 mg, 50 mg, 100 mg, 200 mg

Generic Equivalent Available: US

May be product dependent

Dosage Forms: Canada

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Capsule Sprinkle, Oral:

Topamax Sprinkle: 15 mg, 25 mg

Tablet, Oral:

Topamax: 25 mg, 100 mg, 200 mg [contains polysorbate 80]

Generic: 25 mg, 50 mg, 100 mg, 200 mg

Medication Guide and/or Vaccine Information Statement (VIS)

An FDA-approved patient medication guide, which is available with the product information and as follows, must be dispensed with this medication:

Qudexy XR: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/205122s010lbl.pdf#page=60

Topamax: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020505s061,020844s052lbl.pdf#page=52

Trokendi XR: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/201635s025lbl.pdf#page=49

Administration: Adult

Administer without regard to meals. Administer the IR formulation in divided doses. It is not recommended to crush, break, or chew immediate release tablets due to bitter taste. Swallow ER and sprinkle capsules whole. Sprinkle capsules and Qudexy XR capsules may also be opened to sprinkle the entire contents on a small amount (~1 teaspoon) of soft food; swallow immediately and do not chew. Do not store drug/food mixture for future use. Do not sprinkle Trokendi XR capsules on food, chew, or crush. Avoid alcohol use with Trokendi XR capsules within 6 hours prior to and 6 hours after administration.

Bariatric surgery: Capsule, extended release: Some institutions may have specific protocols that conflict with these recommendations; refer to institutional protocols as appropriate. IR tablet and sprinkle capsule formulations are available. If safety and efficacy can be effectively monitored, no change in formulation or administration is required after bariatric surgery; however, if swallowing is an issue after surgery, Qudexy XR formulation may be sprinkled on a small amount of soft food.

Administration: Pediatric

Oral: May be administered without regard to food.

Immediate release:

Tablets: Broken tablets have a bitter taste; tablets may be crushed, mixed with water, and administered immediately.

Sprinkle capsules: Swallow sprinkle capsules whole or open and sprinkle contents on small amount of soft food (eg, 1 teaspoonful of applesauce, oatmeal, ice cream, pudding, custard, or yogurt); swallow sprinkle/food mixture immediately; do not chew; do not store for later use; drink fluids after dose to make sure mixture is completely swallowed.

Extended release:

Qudexy XR: May be swallowed whole or may be opened and sprinkled on a small amount (~1 teaspoon) of soft food; swallow immediately and do not chew.

Trokendi XR: Swallow capsules whole; do not sprinkle capsules on food, chew, or crush. Avoid alcohol use with within 6 hours prior to and 6 hours after administration.

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 3]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

NIOSH recommends single gloving for administration of intact tablets or capsules. If manipulating tablets/capsules (eg, to prepare an oral suspension), NIOSH recommends double gloving, a protective gown, and preparation in a controlled device; if not prepared in a controlled device, respiratory and eye/face protection as well as ventilated engineering controls are recommended. NIOSH recommends double gloving, a protective gown, and (if there is a potential for vomit or spit up) eye/face protection for administration of an oral liquid/feeding tube administration (NIOSH 2016). Assess risk to determine appropriate containment strategy (USP-NF 2017).

Use: Labeled Indications

Migraine (prevention): Prophylaxis of migraine headache in patients ≥12 years of age

Seizures: Monotherapy or adjunctive therapy in patients ≥2 years of age (immediate release and Qudexy XR) or ≥6 years of age (Trokendi XR) with focal (partial) onset or primary generalized tonic-clonic seizures; adjunctive therapy in patients ≥2 years of age (immediate release and Qudexy XR) or ≥6 years of age (Trokendi XR only) with seizures associated with Lennox-Gastaut syndrome

Use: Off-Label: Adult

Antipsychotic-induced weight gain; Binge eating disorder; Headache, cluster (prevention); Headache, short-lasting unilateral neuralgiform attacks (prevention); Tremor, essential

Medication Safety Issues

Sound-alike/look-alike issues:

Topamax may be confused with Sporanox, TEGretol, TEGretol-XR, Toprol-XL

Administration issues

Bioequivalence has not been demonstrated between Trokendi XR and Qudexy XR.

Qudexy XR capsules may be swallowed whole or opened to sprinkle the entire contents on a small amount (~1 teaspoon) of soft food. Do not open and sprinkle Trokendi XR capsules on food, chew, or crush; doing so may disrupt the triphasic release properties.

Avoid alcohol use with Trokendi XR within 6 hours prior to and 6 hours after administration; concurrent use may result in dose dumping.

Adverse Reactions (Significant): Considerations

CNS effects/cognitive dysfunction

Topiramate is associated with a range of effects involving the central nervous system (CNS). Most common are dose-related sedative effects (eg, **dizziness, drowsiness, fatigue**). Additionally, topiramate has been associated with both short-term and long-term **cognitive dysfunction** in both children and adults, even at low doses (≤100 mg/day), including **disturbance in attention**, **memory impairment**, and **language problems**. Topiramate-associated cognitive dysfunction includes declines in verbal fluency, attention/concentration, processing speed, language skills, perception, working memory, reduced IQ, poor verbal fluency, abnormal thinking, and word-finding deficits (Lee 2003). Topiramate is also associated with psychiatric disturbances (eg, **aggressive behavior**, **mood disorder**, **anxiety, depression, exacerbation of depression**), particularly in patients with previous history of depression or cognitive adverse reactions. Topiramate is also associated with **paresthesia**. The numbness and tingling of topiramate paresthesia are generally self-limiting, resolving over 2 to 3 months of therapy (Minton 2011, Sedighi 2016).

Mechanism: Dose-related (sedative effects; other effects may involve multiple mechanisms). Multiple effects on receptors within the CNS including sodium channel blockade, L-type calcium channel blockade (Zhang 2000), potentiation of gamma-amino butyric acid (GABA) transmission, inhibition of glutamate neuroexcitatory pathways through AMPA and kainate receptors (Delorenzo 2000, Perucca 1997). Topiramate is also a weak inhibitor of type II and type IV carbonic anhydrase (Leiniger 2004). It has been speculated that rapid titration may increase the relative GABA effects leading to more prominent psychiatric symptoms (Mula 2003, Mula 2009).

Onset: Varied. Drowsiness and fatigue may occur early in therapy. Psychiatric effects may be delayed, with an onset up to 6 weeks after initiation of therapy (Khan 1999, Mula 2012, Pasini 2014).

Risk factors:

Sedative effects:

- Dose-related

Cognitive impairment:

- Higher initial dose and/or rapid titration (Minton 2011, Mula 2012)
- Older adults (Mula 2012)
- High working memory capacity (Barkley 2018)
- Pediatric patients (6 to 11 years of age)
- Serum drug concentrations (Mula 2012)

Psychiatric disturbances:

- Higher initial dose and/or rapid titration (Minton 2011, Mula 2012)
- History of febrile seizures (Mula 2003)
- Personal or family history of psychiatric disorder (Mula 2003)
- Previous psychotic history (for psychosis) (Adachi 2019)

Paresthesia:

- Females (Sedighi 2016)
- Higher dose (Sedighi 2016)
- Patients receiving topiramate for migraine (Sedighi 2016)

Metabolic acidosis

Topiramate is associated with **hyperchloremic metabolic acidosis** (nonanion gap). Chronic acidosis may predispose individuals to **nephrolithiasis**, **nephrocalcinosis**, and osteomalacia/osteoporosis. In children, reduced growth rates and/or reduced weight may result. Acidosis is rarely symptomatic (Sinha 2018, Takeoka 2001).

Mechanism: May be dose-related; inhibition of carbonic anhydrase with increased renal bicarbonate excretion (Sinha 2018).

Risk factors:

- May be dose-related; however, metabolic acidosis may occur at doses as low as 50 mg/day

• Conditions that predispose to acidosis (eg, hepatic, kidney, and/or respiratory impairment)

• Ketogenic diet (Takeoka 2002)

• Diarrhea

• Concurrent treatment with other drugs which may cause acidosis (eg, zonisamide, acetazolamide)

Nephrolithiasis

Topiramate increases the risk of nephrolithiasis between 2 to 4 times that of the untreated population. Kidney stones have been reported in both children and adults.

Mechanism: Dose-related; exhibits weak carbonic anhydrase inhibitory properties and may elevate the pH of the urine while decreasing urinary citrate concentrations, predisposing to calcium phosphate stone formation (Welch 2006).

Onset: Delayed; occurs after long term therapy, usually months to years (Maalouf 2011).

Risk factors:

• Concurrent medications known to cause metabolic acidosis

• Ketogenic diet (conflicting data) (Kossoff 2002)

Ocular effects

Topiramate is associated with **acute myopia with secondary angle-closure glaucoma** in children and adults. Also associated with **choroidal effusion** (Lan 2018) and **visual field defect**, **scotoma**, and **maculopathy**, which may occur without elevation of intraocular pressure (Gualtieri 2013, Haque 2016).

Mechanism: Not established; may be related to alterations in ion transfer (sodium and carbon dioxide), idiosyncratic swelling of the ciliary body, and displacement of lens and ciliary body, leading to acute angle closure and elevation of intraocular pressure (Richa 2010).

Onset: Varied; typically within 1 month of initiation but has occurred as early as 9 days after initiation (2 days after dose increase) (Sierra-Rodrigues 2019).

Oligohidrosis/hyperthermia

Topiramate is associated with decreased sweat production (**hypohidrosis**) and symptoms of heat intolerance including facial flushing, lethargy, itching sensation, and irritability with **hyperthermia**. Some episodes may be severe, requiring hospitalization and/or resulting in long-term sequelae (ataxia and tremor) (Galicia 2005).

Mechanism: Dose-related; inhibition of carbonic anhydrase leading to a reduction in sweat production without peripheral nervous system involvement (Ben-Zeev 2003, Margari 2008).

Onset: Varied; from within 2 weeks to 2 months after initiation (Ben-Zeev 2003, Fung 2006).

Risk factors:

- Exercise and higher environmental temperature (Ben-Zeev 2003)
- Pediatric patients (Ben-Zeev 2003)
- Concurrent use of other drugs which may inhibit carbonic anhydrase or drugs with anticholinergic activity

Suicidal ideation/tendencies

Antiepileptic drugs (AEDs) have been associated with **suicidal ideation** and **suicidal tendencies**. However, the FDA meta-analysis has been criticized due to several limitations (Hesdorffer 2009, Mula 2013). The risk of suicide is increased in epilepsy (Bell 2009), but the occurrence of suicidal ideation/tendencies in epilepsy is multifactorial. While some AEDs (but not all) have been associated with treatment-emergent psychiatric effects such as anxiety and depression, other factors such as postictal suicidal behavior and pertinent patient history must also be evaluated to provide an accurate assessment of risk for any individual drug (Mula 2013). In one case report, the onset of topiramate-associated suicidal ideation corresponded to an increase in topiramate dose followed by the appearance of depressive symptoms. The patient was described as euthymic with the resolution of this symptom within a week of discontinuation (Abraham 2003).

Mechanism: Not established; associated with depression and anxiety, which may potentially be related to suicidal ideation and tendencies (Abraham 2003, Kanner 2011).

Onset: Varied; peak incidence of suicidality across AEDs (not specific to individual agents) has been noted to occur between 1 and 12 weeks of therapy (Bellivier 2017). A review of clinical trials noted that risk extended from 1 week to 24 weeks of therapy, corresponding to the duration of most trials.

Risk factors:

• May correspond to dose increases (Abraham 2003)

• History of depression (Arana 2010)

• Use in conditions other than epilepsy, depression, or bipolar disorder (Arana 2010)

• Higher initial dose and/or rapid titration may increase risk for psychiatric disturbances (Mula 2003)

• Family and personal psychiatric history (Mula 2003)

• Family history of epilepsy (Mula 2003)

• History of febrile seizures (Mula 2003)

Weight loss/anorexia

Weight loss was originally observed as an adverse reaction in several trials for various indications with topiramate. More recently, topiramate has been explored therapeutically to promote weight loss (Verotti 2011). Weight loss may be significant. In a typical series of adult patients with epilepsy, a loss of 3 kg was reported in the first 3 months of therapy, which increased to 5.9 kg after 1 year (Ben-Menacham 2003). The exacerbation and development of **eating disorder**, including **anorexia** and bulimia, has been reported in adolescents receiving topiramate for migraines or chronic headaches and an adult receiving topiramate for epilepsy (Lebow 2015, Rosenow 2002). Of interest, topiramate has been used to successfully decrease binge eating frequency in binge eating disorder (Brownley 2016).

Mechanism: Not established; reduced caloric intake has been observed, while additional proposed mechanisms include hormonal influences on energy production (via leptin, adiponectin, and insulin resistance) and changes in glucose and lipid metabolism via carbonic anhydrase inhibition (Ben-Menacham 2003, Verrotti 2011).

Onset: Varied; typically reported during the first 4 to 6 months of therapy and may continue for at least a year, then trend toward baseline levels (Verrotti 2011).

Risk factors:

Weight loss:

• Duration of treatment and high baseline body mass index (Verrotti 2011)

• Daily dose and sex (inconsistent associations) (Verrotti 2011)

Development of eating disorders:

• History of eating disorder (Lebow 2015)

• Dieting (Lebow 2015)

• Cognitive symptoms of eating disorders (eg, body image distortion, fear of gaining weight, drive for thinness) (Lebow 2015)

• Patients with migraine (Lebow 2015)

Adverse Reactions

The following adverse drug reactions and incidences are derived from product labeling unless otherwise specified. Adverse reactions are reported for adult and pediatric patients for various indications and regimens. A wide range of dosages were studied. Incidence of adverse reactions was frequently lower in the pediatric population studied, unless otherwise specified.

>10%:

Endocrine & metabolic: Decreased serum bicarbonate (children and adolescents: 67% [placebo: 10%]; >5 mEq/L to <17 mEq/L: 11% [placebo: ≤2]), hyperammonemia (adolescents: 14% to 26% [placebo: 9%]), weight loss (4% to 17% [placebo: 1% to 3%])

Gastrointestinal: Abdominal pain (adolescents and adults: 6% to 15%), anorexia (adolescents and adults: 4% to 15% [placebo: 4% to 6%]), diarrhea (2% to 11%), dysgeusia (adolescents and adults: 3% to 15%), nausea (adolescents and adults: 8% to 13%)

Nervous system: Dizziness (dose-related) (adolescents and adults: 6% to 14% [placebo: 4%]), drowsiness (dose-related) (adolescents and adults: 6% to 15% [placebo: 2% to 5%]), fatigue (dose-related) (8% to 15% [placebo: 7% to 11%]), memory impairment (1% to 11% [placebo: 2%]), paresthesia (adolescents and adults: 19% to 51% [placebo: 6% to 7%]; children and adolescents: 3% to 12% [placebo: 0%])

Respiratory: Upper respiratory tract infection (13% to 26%)

Miscellaneous: Fever (1% to 12%)

1% to 10%:

Cardiovascular: Chest pain (adults: 1% to 2%), flushing (children and adolescents: ≤5%)

Dermatologic: Acne vulgaris (adults: 2% to 3%), alopecia (1% to 4%), pruritus (adolescents and adults: 1% to 4%), skin rash (1% to 4%)

Endocrine & metabolic: Increased gamma-glutamyl transferase (adults: 1% to 3%), increased thirst (adolescents and adults: 2%), intermenstrual bleeding (children and adolescents: ≤3%), menstrual disease (adolescents and adults: 3%)

Gastrointestinal: Ageusia (adolescents and adults: 1%), constipation (adolescents and adults: 1% to 4%), dyspepsia (adolescents and adults: 4% to 5%), gastritis (adults: ≤3%), gastroenteritis (adolescents and adults: 3%), gastroesophageal reflux disease (adults: 1% to 2%), xerostomia (adolescents and adults: 1% to 3%)

Genitourinary: Cystitis (adults: 1% to 3%), decreased libido (adults: ≤3%), dysuria (adults: ≤2%), premature ejaculation (adolescents and adults: 3%), urinary frequency (≤3%), urinary incontinence (children and adolescents: 1% to 3%), urinary tract infection (adolescents and adults: 1% to 4%), vaginal hemorrhage (adults: ≤3%)

Hematologic & oncologic: Anemia (children and adolescents: 1% to 3%), hemorrhage (4% to 5%), neoplasm (adolescents and adults: 2%)

Hypersensitivity: Hypersensitivity reaction (adolescents and adults: 2% to 4%)

Infection: Infection (2% to 8%), viral infection (3% to 8%)

Nervous system: Agitation (adolescents and adults: 2%), anxiety (adolescents and adults: 4% to 6% [placebo: 3%]), ataxia (adolescents and adults: 1% to 4%), behavioral problems (children and adolescents: ≤3%), cognitive dysfunction (1% to 6%) (literature suggests higher incidence; Lee 2006; Mula 2012), confusion (≤3%), depression (adults: 7% to 9%; children and adolescents: ≤3%), disturbance in attention, headache (children and adolescents: 4%), hypertonia (adults: ≤3%), hypoesthesia (adolescents and adults: 4% to 7%), insomnia (adolescents and adults: 6% to 9%), lack of concentration, mood disorder (1% to 8% [placebo: 2%]), nervousness (adolescents and adults: 4%), psychomotor impairment (adolescents and adults: 2% to 5% [placebo: 1%]) (literature suggests higher incidence) (Javed 2015), speech disturbance (adolescents and adults: 1%), vertigo (children and adolescents: ≤3%)

Neuromuscular & skeletal: Arthralgia (adolescents and adults: 3% to 7%), asthenia (≤6%), lower extremity pain (adolescents and adults: 2% to 3%), muscle spasm (≤3%)

Ophthalmic: Blurred vision (adolescents and adults: 4%), conjunctivitis (adolescents and adults: 2% to 7%), visual disturbance (adolescents and adults: 1% to 2%)

Otic: Otitis media (adolescents and adults: 1% to 2%)

Renal: Nephrolithiasis (adolescents and adults: 7%) (literature suggests higher incidence) (Giannapoulou 2015; Maalouf 2011)

Respiratory: Bronchitis (1% to 5%), cough (adolescents and adults: 2% to 7%), dyspnea (adolescents and adults: 1% to 3%), epistaxis (children and adolescents: ≤4%), pharyngitis (adolescents and adults: 5% to 6%), rhinitis (2% to 7%), sinusitis (1% to 10%)

Miscellaneous: Accidental injury (adolescents and adults: 9%), language problems (adolescents and adults: 6% to 7% [placebo: 2%])

<1%: Hematologic & oncologic: Major hemorrhage (children)

Frequency not defined:

Cardiovascular: Hypotension, orthostatic hypotension, syncope

Endocrine & metabolic: Hyperchloremia, increased serum total protein, increased uric acid

Gastrointestinal: Gingival hemorrhage

Genitourinary: Hematuria

Hematologic & oncologic: Abnormal serum phosphorus level (decreased), decreased neutrophils, decreased white blood cell count, eosinophilia, quantitative disorders of platelets (increased)

Neuromuscular & skeletal: Myalgia

Ophthalmic: Myopia, scotoma

Postmarketing:

Dermatologic: Bullous rash, erythema multiforme, hypohidrosis (more common in pediatric patients) (Ben-Zeev 2003), pemphigus (Alkhalifa 2017), Stevens-Johnson syndrome, toxic epidermal necrolysis

Endocrine & metabolic: Hyperammonemic encephalopathy (usually in combination with valproate) (Tantikittichaikul 2015; Yamamoto 2013), hyperchloremic metabolic

acidosis (nonanion gap) (Sinha 2018; Ture 2016)

Gastrointestinal: Pancreatitis

Hepatic: Hepatic failure (Tsien 2016), hepatitis

Nervous system: Aggressive behavior (more frequent: ≥4% to <10%) (Hansen 2018), anorgasmia (Chen 2017), eating disorder (Lebow 2015), hallucination (Register 2017), hyperthermia (more common in pediatric patients) (Galecia 2005), mania (Duan 2019), psychosis (Mula 2003), suicidal ideation (Abraham 2003), suicidal tendencies

Ophthalmic: Acute myopia with secondary angle-closure glaucoma (Sierra-Rodrigues 2019), choroidal effusion (Lau 2018), maculopathy (Gualtieri 2013), visual field defect (Gualtieri 2013)

Renal: Nephrocalcinosis (Barnett 2018)

Contraindications

Extended release: Recent alcohol use (ie, within 6 hours prior to and 6 hours after administration) (Trokendi XR only); patients with metabolic acidosis who are taking concomitant metformin (Qudexy XR only).

Immediate release: There are no contraindications listed in the manufacturer's labeling.

Canadian labeling: Hypersensitivity to topiramate or any component of the formulation or container; pregnancy and women in childbearing years not using effective contraception (migraine prophylaxis only).

Warnings/Precautions

Concerns related to adverse effects:

• CNS effects: Cognitive dysfunction (confusion, psychomotor slowing, difficulty with concentration/attention, difficulty with memory, speech or language problems), psychiatric disturbances (depression or mood disorders), and sedation (somnolence or fatigue) may occur with use; incidence may be related to rapid titration and higher doses; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). May also cause paresthesia, dizziness, and ataxia.

• Dermatologic reactions: Cases of severe skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported. Discontinue treatment

at the first appearance of skin rash and consider alternative therapy.

• Hyperammonemia/encephalopathy: Hyperammonemia with or without encephalopathy may occur with monotherapy or in combination with valproic acid and has been documented in patients who have tolerated each drug alone; incidence may be dose-related. Risk may be increased in patients with inborn errors of metabolism or decreased hepatic mitochondrial activity. May be asymptomatic; monitor for lethargy, vomiting, or unexplained changes in mental status.

• Metabolic acidosis: May be associated with hyperchloremic nonanion gap metabolic acidosis due to inhibition of carbonic anhydrase and increased renal bicarbonate loss. Decreases in serum bicarbonate are relatively common (up to 67% of epilepsy patients and 77% of migraine patients) but usually mild-to-moderate (average decrease of 4 mEq/L at dose of 400 mg/day in adults and 6 mg/kg/day in children). However, risk may be increased in patients with a predisposing condition (renal, respiratory and/or hepatic impairment), diarrhea, ketogenic diet, status epilepticus, or concurrent treatment with other drugs which may cause acidosis. Metabolic acidosis may occur at dosages as low as 50 mg/day. Serum bicarbonate should be monitored, as well as potential complications of chronic acidosis (nephrolithiasis, nephrocalcinosis, osteomalacia/osteoporosis, and reduced growth rates and/or reduced weight in children). Dose reduction or discontinuation (by tapering dose) should be considered in patients with persistent or severe metabolic acidosis. If treatment is continued, alkali supplementation should be considered.

• Oligohidrosis/hyperthermia: May be associated with oligohidrosis and hyperthermia, most frequently in children; use caution and monitor closely during strenuous exercise, during exposure to high environmental temperature, or in patients receiving other carbonic anhydrase inhibitors and drugs with anticholinergic activity.

• Ophthalmic effects: Has been associated with acute myopia and secondary angle-closure glaucoma in adults and children, typically within 1 month of initiation; discontinue in patients with acute onset of decreased visual acuity and/or ocular pain.

• Renal calculus: Topiramate exhibits weak carbonic anhydrase inhibitory properties and may increase the risk of kidney stones about 2 to 4 times that of the untreated population. Kidney stones have been reported in children and adults (incidence higher in males). Consider avoiding use in patients on a ketogenic diet. The risk of kidney stones may be reduced by increasing fluid intake.

• Suicidal ideation: Pooled analysis of trials involving various antiepileptics (regardless of indication) showed an increased risk of suicidal thoughts/behavior (incidence rate: 0.43% treated patients compared to 0.24% of patients receiving placebo); risk observed as early as 1 week after initiation and continued through duration of trials (most trials ≤24 weeks). Monitor all patients for notable changes in behavior that might indicate suicidal thoughts or depression; notify healthcare provider immediately if symptoms occur.

• Visual field defects: Has been reported independent of increased intraocular pressure; generally reversible upon discontinuation. Consider discontinuation if visual problems occur at any time during treatment.

Disease-related concerns:

• Depression: Use with caution in patients with depression or suicidal tendencies.

• Eating disorders: The exacerbation and development of eating disorders, including anorexia nervosa and bulimia, has been reported in case reports of adolescents receiving topiramate for migraines or chronic headaches and an adult receiving topiramate for epilepsy. Prior to initiation of topiramate screen for a history of eating disorder symptoms, eating disorder risk factors (eg, history of dieting behavior), cognitive symptoms of eating disorders (eg, weight or shape concerns, fear of gaining weight, drive for thinness), and any recent changes in social functioning including increased withdrawal or isolation. Inquire whether the patient has unrealistic or unhealthy weight goals. Evaluate exercise habits (eg, look for over-exercising or compulsive exercising above that of similarly athletic peers) and dietary intake; assess rigid patterns or avoidance of specific categories of foods and preoccupation with maintaining a “healthy diet” or experimentation with fad diets. In adolescents assess developmental weight history with growth curves. Monitor eating behaviors and weight closely in patients receiving topiramate who have eating disorder symptoms or risk factors (Lebow 2015; Rosenow 2002).

• Hepatic impairment: Use caution with hepatic impairment; clearance may be reduced. Dosage adjustment may be required.

• Renal impairment: Use caution with renal impairment; clearance may be reduced. Dosage adjustment may be required.

Special populations:

• Elderly: Use with caution; dosage adjustment may be necessary. Weight loss, cognitive impairment, sedation, and gait/balance disturbances may be more pronounced in the older adult cohort (Sommer 2010).

Other warnings/precautions:

• Withdrawal: Do not discontinue abruptly because of the possibility of increasing seizure frequency; therapy should be withdrawn gradually to minimize the potential of increased seizure frequency, unless safety concerns require a more rapid withdrawal. Doses were also gradually withdrawn in migraine prophylaxis studies (decreased in weekly intervals by 25-50 mg/day).

Warnings: Additional Pediatric Considerations

Necrotizing enterocolitis (NEC) has been reported in neonates; a case series of 10 preterm neonates (GA: 23 to 36 weeks; birthweight: 440 to 2,100 g) who received topiramate at a dose of 10 mg/kg on day 1, followed by 5 mg/kg/dose once daily for treatment of neonatal seizures reported the development of NEC within 1 to 7 days following topiramate administration in 4 of 10 (40%) of preterm neonates; one patient even developed symptoms suggesting a recurrence of NEC following reintroduction of topiramate. No causal relationship can be determined; monitor closely (Courchia 2018).

In pediatric clinical trials for adjunctive treatment of seizures, persistent decreases in serum bicarbonate occurred in 67% of patients receiving topiramate (versus 10% of those receiving placebo). Markedly low serum bicarbonate values were reported in 11% of pediatric patients receiving topiramate (versus 0% of those receiving placebo). In pediatric monotherapy trials, persistent decreases in serum bicarbonate occurred in 9% of patients receiving 50 mg/day and 25% of patients receiving 400 mg/day. Markedly low serum bicarbonate values were reported in 1% to 6% of pediatric patients receiving topiramate monotherapy. The risk of topiramate-induced metabolic acidosis may be increased in patients with predisposing conditions (eg, diarrhea, status epilepticus, hepatic impairment, renal dysfunction, severe respiratory disorders, ketogenic diet, surgery) or concurrent treatment with other drugs that may cause acidosis. Metabolic acidosis may be more common and more severe in infants and children <2 years of age with up to 45% of patients receiving 25 mg/kg/day developing metabolic acidosis in clinical trials. Monitor for potential complications of chronic acidosis including nephrolithiasis, nephrocalcinosis, osteomalacia/osteoporosis, and reduction in growth rates (including weight). Reductions in Z scores (from baseline) for length, weight, and head circumference were observed in infants and toddlers who received long-term topiramate (for up to 1 year) for intractable partial epilepsy; reductions in Z scores for length and weight

correlated to the severity of metabolic acidosis. Serum bicarbonate should be monitored at baseline and periodically during topiramate therapy. The most common adverse effects of topiramate observed in children include the following: Anorexia, cognitive problems, dizziness, fatigue, fever, flushing, headache, mood problems, paresthesia, somnolence, and weight loss; neuropsychiatric and cognitive adverse effects were reported with a lower incidence in children than adults. Pediatric patients <24 months of age may be at increased risk for topiramate-associated hyperammonemia, especially when used concurrently with valproic acid; monitor closely for lethargy, vomiting, or unexplained changes in mental status.

Risk of nephrolithiasis (kidney stones) is higher in children; reported incidence in adults: 1.5%; in pediatric patients <24 months with long-term use (up to 1 year): 7% (kidney or bladder stones); one retrospective study evaluating long-term use (1 year) in children with epilepsy (n=96; mean age: 6.9 ± 3.8 years) reported an incidence of 5.2% (Mahmoud 2011); risk may be increased with ketogenic diet or concomitant drugs that produce metabolic acidosis; avoid use while on topiramate therapy; maintain adequate hydration during therapy; monitor for signs or symptoms of kidney or bladder or kidney stone development.

Metabolism/Transport Effects

None known.

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Alcohol (Ethyl): May enhance the CNS depressant effect of Topiramate. Alcohol (Ethyl) may increase the serum concentration of Topiramate. This applies specifically to use with the extended-release topiramate capsules (Trokendi XR). Also, topiramate concentrations may be subtherapeutic in the later portion of the dosage interval. Management: Concurrent use of alcohol within 6 hours of ingestion of extended-release topiramate (Trokendi XR) is contraindicated. Any use of alcohol with topiramate should be avoided when possible and should only be undertaken with extreme caution. *Risk X: Avoid combination*

Alizapride: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Alpha-/Beta-Agonists (Indirect-Acting): Carbonic Anhydrase Inhibitors may increase the serum concentration of Alpha-/Beta-Agonists (Indirect-Acting). *Risk C: Monitor therapy*

Amantadine: Carbonic Anhydrase Inhibitors may increase the serum concentration of Amantadine. *Risk C: Monitor therapy*

Amitriptyline: Topiramate may enhance the CNS depressant effect of Amitriptyline. Topiramate may increase serum concentrations of the active metabolite(s) of Amitriptyline. Topiramate may increase the serum concentration of Amitriptyline. *Risk C: Monitor therapy*

Amphetamines: Carbonic Anhydrase Inhibitors may decrease the excretion of Amphetamines. *Risk C: Monitor therapy*

Anticholinergic Agents: May enhance the adverse/toxic effect of Topiramate. *Risk C: Monitor therapy*

Azelastine (Nasal): May enhance the CNS depressant effect of CNS Depressants. *Risk X: Avoid combination*

Blonanserin: CNS Depressants may enhance the CNS depressant effect of Blonanserin. Management: Use caution if coadministering blonanserin and CNS depressants; dose reduction of the other CNS depressant may be required. Strong CNS depressants should not be coadministered with blonanserin. *Risk D: Consider therapy modification*

Brexanolone: CNS Depressants may enhance the CNS depressant effect of Brexanolone. *Risk C: Monitor therapy*

Brimonidine (Topical): May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Bromopride: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Bromperidol: May enhance the CNS depressant effect of CNS Depressants. *Risk X: Avoid combination*

Buprenorphine: CNS Depressants may enhance the CNS depressant effect of Buprenorphine. Management: Consider reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-injection. Initiate buprenorphine at lower doses in patients already receiving CNS depressants. *Risk D: Consider therapy modification*

Cannabidiol: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Cannabis: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

CarBAMazepine: May decrease the serum concentration of Topiramate. *Risk C: Monitor therapy*

Carbonic Anhydrase Inhibitors: May enhance the adverse/toxic effect of other Carbonic Anhydrase Inhibitors. The development of acid-base disorders with concurrent use of ophthalmic and oral carbonic anhydrase inhibitors has been reported. Management: Avoid concurrent use of different carbonic anhydrase inhibitors if possible. Monitor patients closely for the occurrence of kidney stones and with regards to severity of metabolic acidosis. *Risk X: Avoid combination*

Chlormethiazole: May enhance the CNS depressant effect of CNS Depressants. Management: Monitor closely for evidence of excessive CNS depression. The chlormethiazole labeling states that an appropriately reduced dose should be used if such a combination must be used. *Risk D: Consider therapy modification*

Chlorphenesin Carbamate: May enhance the adverse/toxic effect of CNS Depressants. *Risk C: Monitor therapy*

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*

Dimethindene (Topical): May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Doxylamine: May enhance the CNS depressant effect of CNS Depressants. Management: The manufacturer of Diclegis (doxylamine/pyridoxine), intended for use in pregnancy, specifically states that use with other CNS depressants is not recommended. *Risk C: Monitor therapy*

Dronabinol: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Droperidol: May enhance the CNS depressant effect of CNS Depressants. Management: Consider dose reductions of droperidol or of other CNS agents (eg, opioids, barbiturates) with concomitant use. *Risk D: Consider therapy modification*

Esketamine: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Estrogen Derivatives (Contraceptive): Topiramate may decrease the serum concentration of Estrogen Derivatives (Contraceptive). Contraceptive failure is possible. Management: Risk of contraceptive failure appears greatest for higher topiramate doses (200 mg/day or

greater). May consider using at least 50 mcg/day of ethinyl estradiol, but the effectiveness of this is unclear. Consider a nonhormonal form of contraception. *Risk D: Consider therapy modification*

Flecainide: Carbonic Anhydrase Inhibitors may increase the serum concentration of Flecainide. *Risk C: Monitor therapy*

Flunitrazepam: CNS Depressants may enhance the CNS depressant effect of Flunitrazepam. Management: Reduce the dose of CNS depressants when combined with flunitrazepam and monitor patients for evidence of CNS depression (eg, sedation, respiratory depression). Use non-CNS depressant alternatives when available. *Risk D: Consider therapy modification*

Fosphenytoin: May decrease the serum concentration of Topiramate. Topiramate may increase the serum concentration of Fosphenytoin. *Risk C: Monitor therapy*

HydrOXYzine: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Kava Kava: May enhance the adverse/toxic effect of CNS Depressants. *Risk C: Monitor therapy*

Lacosamide: Antiepileptic Agents (Sodium Channel Blockers) may enhance the adverse/toxic effect of Lacosamide. Specifically the risk for bradycardia, ventricular tachyarrhythmias, or a prolonged PR interval may be increased. *Risk C: Monitor therapy*

Lemborexant: May enhance the CNS depressant effect of CNS Depressants. Management: Dosage adjustments of lemborexant and of concomitant CNS depressants may be necessary when administered together because of potentially additive CNS depressant effects. Close monitoring for CNS depressant effects is necessary. *Risk D: Consider therapy modification*

Lisuride: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Lithium: Topiramate may increase the serum concentration of Lithium. *Risk C: Monitor therapy*

Lofexidine: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Loop Diuretics: May enhance the hypokalemic effect of Topiramate. *Risk C: Monitor therapy*

Magnesium Sulfate: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Mefloquine: May diminish the therapeutic effect of Anticonvulsants. Mefloquine may decrease the serum concentration of Anticonvulsants. Management: Mefloquine is contraindicated for malaria prophylaxis in persons with a history of convulsions. If anticonvulsants are being used for another indication, monitor anticonvulsant concentrations and treatment response closely with concurrent use. *Risk D: Consider therapy modification*

Memantine: Carbonic Anhydrase Inhibitors may increase the serum concentration of Memantine. *Risk C: Monitor therapy*

MetFORMIN: Topiramate may enhance the adverse/toxic effect of MetFORMIN. *Risk C: Monitor therapy*

Methenamine: Carbonic Anhydrase Inhibitors may diminish the therapeutic effect of Methenamine. Management: Consider avoiding this combination. Monitor for decreased therapeutic effects of methenamine if used concomitant with a carbonic anhydrase inhibitor. *Risk D: Consider therapy modification*

Methotrimeprazine: CNS Depressants may enhance the CNS depressant effect of Methotrimeprazine. Methotrimeprazine may enhance the CNS depressant effect of CNS Depressants. Management: Reduce the usual dose of CNS depressants by 50% if starting methotrimeprazine until the dose of methotrimeprazine is stable. Monitor patient closely for evidence of CNS depression. *Risk D: Consider therapy modification*

Metoclopramide: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

MetyroSINE: CNS Depressants may enhance the sedative effect of MetyroSINE. *Risk C: Monitor therapy*

Mianserin: May diminish the therapeutic effect of Anticonvulsants. *Risk C: Monitor therapy*

Minocycline (Systemic): May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Nabilone: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Opioid Agonists: CNS Depressants may enhance the CNS depressant effect of Opioid Agonists. Management: Avoid concomitant use of opioid agonists and benzodiazepines or other CNS depressants when possible. These agents should only be combined if alternative treatment options are inadequate. If combined, limit the dosages and duration of each drug. *Risk D: Consider therapy modification*

Orlistat: May decrease the serum concentration of Anticonvulsants. *Risk C: Monitor therapy*

Orphenadrine: CNS Depressants may enhance the CNS depressant effect of Orphenadrine. *Risk X: Avoid combination*

Oxomemazine: May enhance the CNS depressant effect of CNS Depressants. *Risk X: Avoid combination*

Oxybate Salt Products: CNS Depressants may enhance the CNS depressant effect of Oxybate Salt Products. Management: Consider alternatives to this combination when possible. If combined, dose reduction or discontinuation of one or more CNS depressants (including the oxybate salt product) should be considered. Interrupt oxybate salt treatment during short-term opioid use *Risk D: Consider therapy modification*

OxyCODONE: CNS Depressants may enhance the CNS depressant effect of OxyCODONE. Management: Avoid concomitant use of oxycodone and benzodiazepines or other CNS depressants when possible. These agents should only be combined if alternative treatment options are inadequate. If combined, limit the dosages and duration of each drug. *Risk D: Consider therapy modification*

Paraldehyde: CNS Depressants may enhance the CNS depressant effect of Paraldehyde. *Risk X: Avoid combination*

Perampanel: May enhance the CNS depressant effect of CNS Depressants. Management: Patients taking perampanel with any other drug that has CNS depressant activities should avoid complex and high-risk activities, particularly those such as driving that require alertness and coordination, until they have experience using the combination. *Risk D: Consider therapy modification*

Phenytoin: Topiramate may increase the serum concentration of Phenytoin. Phenytoin may decrease the serum concentration of Topiramate. *Risk C: Monitor therapy*

Pioglitazone: Topiramate may decrease the serum concentration of Pioglitazone. *Risk C: Monitor therapy*

Piribedil: CNS Depressants may enhance the CNS depressant effect of Piribedil. *Risk C: Monitor therapy*

Pramipexole: CNS Depressants may enhance the sedative effect of Pramipexole. *Risk C: Monitor therapy*

Primidone: Carbonic Anhydrase Inhibitors may enhance the adverse/toxic effect of Primidone. Specifically, osteomalacia and rickets. Carbonic Anhydrase Inhibitors may decrease the serum concentration of Primidone. *Risk C: Monitor therapy*

Progestins (Contraceptive): Topiramate may decrease the serum concentration of Progestins (Contraceptive). Management: Caution patients that this combination may be associated with reduced contraceptive effectiveness. Consider adding an additional (non-hormonal) contraceptive method. *Risk D: Consider therapy modification*

QuiNIDine: Carbonic Anhydrase Inhibitors may decrease the excretion of QuiNIDine. *Risk C: Monitor therapy*

ROPINIRole: CNS Depressants may enhance the sedative effect of ROPINIRole. *Risk C: Monitor therapy*

Rotigotine: CNS Depressants may enhance the sedative effect of Rotigotine. *Risk C: Monitor therapy*

Rufinamide: May enhance the adverse/toxic effect of CNS Depressants. Specifically, sleepiness and dizziness may be enhanced. *Risk C: Monitor therapy*

Salicylates: May enhance the adverse/toxic effect of Carbonic Anhydrase Inhibitors. Salicylate toxicity might be enhanced by this same combination. Management: Avoid these combinations when possible.Dichlorphenamide use with high-dose aspirin as contraindicated. If another combination is used, monitor patients closely for adverse effects. Tachypnea, anorexia, lethargy, and coma have been reported. *Risk D: Consider therapy modification*

Suvorexant: CNS Depressants may enhance the CNS depressant effect of Suvorexant. Management: Dose reduction of suvorexant and/or any other CNS depressant may be necessary. Use of suvorexant with alcohol is not recommended, and the use of suvorexant with any other drug to treat insomnia is not recommended. *Risk D: Consider therapy modification*

Tetrahydrocannabinol: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Tetrahydrocannabinol and Cannabidiol: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Thalidomide: CNS Depressants may enhance the CNS depressant effect of Thalidomide. *Risk X: Avoid combination*

Thiazide and Thiazide-Like Diuretics: May enhance the hypokalemic effect of Topiramate. Thiazide and Thiazide-Like Diuretics may increase the serum concentration of Topiramate. Management: Monitor for increased topiramate levels/adverse effects (eg, hypokalemia) with initiation/dose increase of a thiazide diuretic. Closely monitor serum potassium concentrations with concomitant therapy. Topiramate dose reductions may be necessary. *Risk D: Consider therapy modification*

Trimeprazine: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

Ulipristal: Topiramate may decrease the serum concentration of Ulipristal. *Risk X: Avoid combination*

Valproate Products: Topiramate may enhance the adverse/toxic effect of Valproate Products. *Risk C: Monitor therapy*

Zolpidem: CNS Depressants may enhance the CNS depressant effect of Zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem adult dose to 1.75 mg for men who are also receiving other CNS depressants. No such dose change is recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol. *Risk D: Consider therapy modification*

Food Interactions

Ketogenic diet may increase the possibility of acidosis and/or kidney stones. Management: Monitor for symptoms of acidosis or kidney stones.

Reproductive Considerations

Effective contraception should be used in females of reproductive potential who are not planning a pregnancy; consider use of alternative medications in women who wish to become pregnant.

Pregnancy Considerations

Based on limited data (n=5), topiramate was found to cross the placenta and could be detected in neonatal serum (Ohman 2002).

Topiramate may cause fetal harm if administered to a pregnant woman. An increased risk of oral clefts (cleft lip and/or palate) and for being small for gestational age (SGA) has been observed following in utero exposure. Data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry reported that the prevalence of oral clefts was 1.1% for infants exposed to topiramate during the first trimester of pregnancy, versus 0.36% for infants exposed to a reference antiepileptic drug, and 0.12% for infants with no exposure born to mothers without epilepsy; the relative risk of oral clefts in infants exposed to topiramate was calculated to be 9.6 (95% CI: 4 to 23). Data from the NAAED Pregnancy Registry reported that the prevalence of small for gestational age newborns was 19.7% for newborns exposed to topiramate in utero, versus 7.9% for newborns exposed to a reference antiepileptic drug, and 5.4% for newborns with no exposure born to mothers without epilepsy. Although not evaluated during pregnancy, metabolic acidosis may be induced by topiramate. Metabolic acidosis during pregnancy may result in adverse effects and fetal death. Pregnant women and their newborns should be monitored for metabolic acidosis. In general, maternal polytherapy with antiepileptic drugs may increase the risk of congenital malformations; monotherapy with the lowest effective dose is recommended. Newborns of women taking antiepileptic medications may be at an increased risk of a 1 minute Apgar score <7 (Harden 2009).

Maternal serum concentrations may decrease during the second and third trimesters of pregnancy; therefore, therapeutic drug monitoring should be considered during pregnancy and postpartum in patients who require therapy (Ohman 2009; Westin 2009).

Data collection to monitor pregnancy and infant outcomes following exposure to topiramate is ongoing. Patients may enroll themselves into the NAAED Pregnancy Registry by calling 1-888-233-2334. Additional information is available at www.aedpregnancyregistry.org.

Breast-Feeding Considerations

Topiramate is present in breast milk.

The relative infant dose (RID) of topiramate is ~3% to 23% when calculated using a range of breast milk concentrations obtained from three lactating women and compared to a weight-adjusted maternal dose of 150 to 200 mg/day (Ohman 2002).

In general, breastfeeding is considered acceptable when the RID of a medication is <10%; when the RID is >25% breastfeeding should generally be avoided (Anderson 2016; Ito 2000).

The RID of topiramate was calculated using a range of milk concentrations of 1.6 to 14.6 micromolar, providing an estimated daily infant dose via breast milk of ~0.1 to 0.7 mg/kg/day. These milk concentrations were obtained following maternal administration of

oral topiramate 150 to 200 mg/day in three women 2 weeks' to 3 months' postpartum; concomitant medications included carbamazepine or valproic acid, both of which may have had an impact on maternal serum concentrations. Topiramate was detected in the plasma of the breastfed infants at ~10% to 20% of the maternal plasma concentration (Ohman 2002).

Diarrhea and somnolence have been reported in breastfed infants. In 1 infant, resolution of diarrhea occurred 2 days after breastfeeding was stopped (Westergren 2014).

According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.

Monitoring Parameters

Seizure frequency, hydration status; electrolytes (recommended monitoring includes serum bicarbonate at baseline and periodically during treatment), serum creatinine; monitor for symptoms of acute acidosis and complications of long-term acidosis (nephrolithiasis, nephrocalcinosis, osteomalacia/osteoporosis, and reduced growth rates and/or weight in children); ammonia level in patients with unexplained lethargy, vomiting, or mental status changes; intraocular pressure, symptoms of secondary angle closure glaucoma; suicidality (eg, suicidal thoughts, depression, behavioral changes); weight and eating behaviors in patients with eating disorder symptoms or risk factors; sedation

Mechanism of Action

Anticonvulsant activity may be due to a combination of potential mechanisms: Blocks neuronal voltage-dependent sodium channels, enhances GABA(A) activity, antagonizes AMPA/kainate glutamate receptors, and weakly inhibits carbonic anhydrase.

Pharmacodynamics and Pharmacokinetics

Note: Immediate-release preparations are bioequivalent (sprinkle capsule and tablet); extended-release capsules (Trokendi XR) administered once daily is bioequivalent to twice daily administration of immediate-release formulations; however, bioequivalence has not been established between Trokendi XR and Qudexy XR.

Absorption: Good, rapid; immediate release formulation is unaffected by food. A single Trokendi XR dose with a high-fat meal increased the C_{max} by 37% and shortened the T_{max} to approximately 8 hours; this effect is significantly reduced following repeat administrations. A single Qudexy XR dose with a high-fat meal delayed the T_{max} by 4 hours.

Distribution: $V_{d:}$ 0.6 to 0.8 L/kg.

Protein binding: 15% to 41% (inversely related to plasma concentrations).

Metabolism: Not extensively metabolized. Minor amounts metabolized in liver via hydroxylation, hydrolysis, and glucuronidation; there is evidence of renal tubular reabsorption; percentage of dose metabolized in liver and clearance are increased in patients receiving enzyme inducers (eg, carbamazepine, phenytoin).

Bioavailability: ~80% (immediate release).

Half-life elimination:

Immediate release:

Not receiving concomitant enzyme inducers or valproic acid:

Neonates (full-term) with hypothermia: ~43 hours (Filippi 2009).

Infants and Children 9 months to <4 years: 10.4 hours (range: 8.5 to 15.3 hours) (Mikaeloff 2004).

Children 4 to 7 years: Mean range: 7.7 to 8 hours (Rosenfeld 1999).

Children 8 to 11 years: Mean range: 11.3 to 11.7 hours (Rosenfeld 1999).

Children and Adolescents 12 to 17 years: Mean range: 12.3 to 12.8 hours (Rosenfeld 1999).

Receiving concomitant enzyme inducers (eg, carbamazepine, phenytoin, phenobarbital):

Neonates (full-term) with hypothermia: 26.5 hours (Filippi 2009).

Infants and Children 9 months to <4 years: 6.5 hours (range: 3.75 to 10.2 hours) (Mikaeloff 2004).

Children and Adolescents 4 to 17 years: 7.5 hours (Rosenfeld 1999).

Receiving valproic acid: Infants and Children 9 months to 4 years: 9.2 hours (range: 7.23 to 12 hours) (Mikaeloff 2004).

Adults: 19 to 23 hours (mean: 21 hours).

Adults with renal impairment: 59 ± 11 hours.

Extended release: Qudexy XR: ~56 hours; Trokendi XR: ~31 hours.

Time to peak, serum:

Immediate release:

Neonates (full-term) with hypothermia: 3.8 hours (Filippi 2009).

Infants and Children 9 months to <4 years: 3.7 hours (range: 1.5 to 10.2 hours) (Mikaeloff 2004).

Children 4 to 17 years: Mean range: 1 to 2.8 hours (Rosenfeld 1999).

Adults: 2 hours; range: 1.4 to 4.3 hours.

Extended release: Qudexy XR: ~20 hours; Trokendi XR: ~24 hours.

Excretion: Urine (~70% as unchanged drug); may undergo renal tubular reabsorption.

Clearance:

Not receiving concomitant enzyme inducers or valproic acid:

Neonates (full-term) with hypothermia: 13.4 mL/kg/hour (Filippi 2009).

Infants and Children 9 months to <4 years: 46.5 mL/kg/hour (range: 30.5 to 70.9 mL/kg/hour) (Mikaeloff 2004).

Children 4 to 17 years: 27.6 mL/kg/hour (Rosenfeld 1999).

Receiving concomitant enzyme inducers:

Neonates (full-term) with hypothermia: 17.9 mL/kg/hour (Filippi 2009).

Infants and Children 9 months to <4 years: 85.4 mL/kg/hour (range: 46.2 to 135 mL/kg/hour) (Mikaeloff 2004).

Children and Adolescents 4 to 17 years: 60.6 mL/kg/hour (Rosenfeld 1999).

Receiving valproic acid: Infants and Children 9 months to <4 years: 49.6 mL/kg/hour (range: 26.6 to 60.2 mL/kg/h) (Mikaeloff 2004).

Adults: 20 to 30 mL/minute.

Pharmacodynamics and Pharmacokinetics: Additional Considerations

Renal function impairment: Clearance is reduced 42% in moderately impaired (creatinine clearance [CrCl] 30 to 69 mL/minute/1.73 m^2) and 54% in severely impaired (CrCl <30

mL/minute/1.73 m^2) patients. Significantly hemodialyzed; dialysis clearance is 120 mL/minute (4-6 times higher than in adults with normal renal function).

Hepatic function impairment: Clearance is reduced by a mean of 26% in patients with moderate to severe hepatic impairment.

Geriatric: Half-life elimination is longer. Plasma and renal clearance were reduced 21% and 19%, respectively. Reduced clearance resulted in slightly higher C_{max} (23% for immediate release; 30% for Trokendi XR) and AUC (25% for immediate release; 44% for Trokendi XR). Topiramate clearance is decreased only to the extent that renal function is reduced. T_{max} for Trokendi XR is shorter (16 hours).

Pricing: US

Capsule ER 24 Hour Sprinkle (Qudexy XR Oral)

25 mg (per each): $10.76

50 mg (per each): $14.01

100 mg (per each): $27.76

150 mg (per each): $34.15

200 mg (per each): $37.98

Capsule ER 24 Hour Sprinkle (Topiramate ER Oral)

25 mg (per each): $9.37 - $9.93

50 mg (per each): $12.21 - $12.94

100 mg (per each): $24.18 - $25.63

150 mg (per each): $29.75 - $31.53

200 mg (per each): $33.08 - $35.07

Capsule ER 24 Hour Therapy Pack (Trokendi XR Oral)

25 mg (per each): $13.13

50 mg (per each): $17.11

100 mg (per each): $33.89

200 mg (per each): $46.36

Capsule, sprinkles (Topamax Sprinkle Oral)

15 mg (per each): $7.15

25 mg (per each): $8.64

Capsule, sprinkles (Topiramate Oral)

15 mg (per each): $2.42

25 mg (per each): $2.92

Tablets (Topamax Oral)

25 mg (per each): $7.56

50 mg (per each): $15.09

100 mg (per each): $20.60

200 mg (per each): $24.12

Tablets (Topiramate Oral)

25 mg (per each): $0.09 - $2.55

50 mg (per each): $0.14 - $5.10

100 mg (per each): $0.21 - $6.96

200 mg (per each): $0.34 - $8.15

Disclaimer: A representative AWP (Average Wholesale Price) price or price range is provided as reference price only. A range is provided when more than one manufacturer's AWP price is available and uses the low and high price reported by the manufacturers to determine the range. The pricing data should be used for benchmarking purposes only, and as such should not be used alone to set or adjudicate any prices for reimbursement or purchasing functions or considered to be an exact price for a single product and/or manufacturer. Medi-Span expressly disclaims all warranties of any kind or nature, whether express or implied, and assumes no liability with respect to accuracy of price or price range data published in its solutions. In no event shall Medi-Span be liable for special, indirect, incidental, or consequential damages arising from use of price or price range data. Pricing data is updated monthly.

Brand Names: International

Acomicil (ES); Conviban (EG); Epilramate (TW); Epimate (BH, EG, LK, PH, ZW); Epiramat (UA); Epitomax (FI, FR); Epitop (PH); Etopira (BD); Fagodol (ES); Gabatopa (KR); Ipramax (BH, LB); Moramax (TH); Piramed (BD); Pitomate (TH); Pradox (TH); Seziril (LK); Tamate (AU); Tiramate (NZ); Topagan (LB); Topamac (AR, CO, EC, IN, PE, PY, UY); Topamax (AE, AT, AU, BB, BE, BG, BH, BR, CH, CL, CN, CR, CY, CZ, DE, DO, EE, EG, ES, FI, GB, GT, HK, HN, HR, IE, IL, IQ, IR, IT, JM, JO, KR, KW, LB, LK, LT, LU, LV, LY, MT, MX, MY, NI, NL, NZ, OM, PA, PH, PK, PL, PT, QA, RO, RU, SA, SG, SI, SK, SV, SY, TH, TR, TW, VE, VN, YE, ZA); Topamax Sprinkle (AE, BB, CY, HK, KR, KW, NZ, SA); Topictal (EC, PY); Topilepsin (UA); Topimax (DK, IS, NO, SE); Topina (JP); Topinmate (TW); Topirol (PH); Topiromax (UA); Topiron (KR); Topirva (BD); Topitrim (IL); Topmate (BD, KR); Topnotch (EG); Topomac (GR); Topvex (PH); Toramat (LB); Toramate (TW)

For country abbreviations used in Lexicomp (show table)

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