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PERSONALIZED MEDICINE

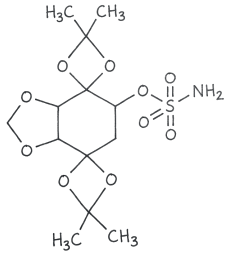
CLINICAL MONOGRAPH · METABOLIC & WEIGHT

Topiramate

Anticonvulsant used off-label in metabolic contexts

Topiramate is an oral anticonvulsant that has been FDA-approved since 1996 for epilepsy and since 2004 for migraine prevention [brandes2004; margulis2012]. The brand name is Topamax, and generic topiramate has been available for many years [fda_label_topamax]. A combination capsule of phentermine and topiramate, Qsymia, was approved in 2012 for chronic weight management [fda_label_qsymia; gadde2011].

Doctors also use topiramate off-label for alcohol use disorder, binge eating disorder, idiopathic intracranial hypertension, essential tremor, and post-traumatic stress disorder. Common side effects include tingling in the hands and feet (paresthesias), trouble finding words, fatigue, and weight loss. Topiramate can cause kidney stones, lower the body's bicarbonate (metabolic acidosis), and reduce sweating in children. Taken in early pregnancy it raises the risk of cleft lip and cleft palate [hernandezdiaz2018].



EVIDENCE POSTURE FDA APPROVED WELL STUDIED REVIEWED **2026-05-11**

State-licensed 503A | Pharmacist reviewed | Doctor led | Cold-chain ready | Patient choice preserved

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FOR CLINICIANS

Topiramate is an oral sulfamate-substituted monosaccharide with broad-spectrum anticonvulsant activity. It was FDA-approved in 1996 (Topamax) as adjunctive therapy for partial-onset and primary generalized tonic-clonic seizures in adults [faught1996], with subsequent approvals for monotherapy in patients with epilepsy [sachdeo1997], for Lennox-Gastaut syndrome adjunctive therapy [sachdeo1999], for migraine prophylaxis in adults (2004) [brandes2004, silberstein2004], and as the phentermine/topiramate fixed-dose combination Qsymia for chronic weight management (2012) [gadde2011, allison2012, garvey2012] [fda_label_topamax; fda_label_qsymia]. Mechanism is multimodal: state-dependent sodium-channel blockade, potentiation of GABA-A receptor activity at a non-benzodiazepine site, antagonism at AMPA/kainate glutamate receptors, and inhibition of carbonic anhydrase isoforms II and IV [shank2000].

Phase III evidence supports adjunctive epilepsy use [faught1996], monotherapy [sachdeo1997], Lennox-Gastaut [sachdeo1999], migraine prophylaxis at 100 mg/day (MIGR-001 [silberstein2004] and MIGR-002 [brandes2004]), pediatric migraine where the CHAMP trial demonstrated no separation from placebo for amitriptyline or topiramate [powers2017], and obesity at lower doses combined with phentermine in CONQUER [gadde2011], EQUIP [allison2012], and the two-year SEQUEL extension [garvey2012]. Well-studied off-label evidence supports topiramate for alcohol use disorder [johnson2003], binge eating disorder associated with obesity [mcelroy2007], idiopathic intracranial hypertension [celebisoy2007], civilian PTSD [yeh2011], and essential tremor [ondo2006, connor2008] [johnson2007]. Cochrane reviews integrate the migraine prophylaxis [linde2013] and bipolar acute affective episode [vasudev2016] literatures.

Safety is dominated by neurocognitive effects (word-finding difficulty, psychomotor slowing, paresthesias) [loring2012, salinsky2007], metabolic acidosis from carbonic anhydrase inhibition, nephrolithiasis [daudon2018, kossoff2002], oligohidrosis in pediatric patients [franco2021], and a documented teratogenic signal for oral clefts in first-trimester exposure [margulis2012, hernandezdiaz2012, hernandezdiaz2018]. Topiramate at doses ≥200 mg/day reduces ethinyl estradiol AUC by approximately 20-30%, with implications for combined oral contraceptive efficacy [doose1997, doose2003]. Generic topiramate is widely available; the compounded 503A role is narrow [fda_label_topamax].

Why Personalized Topiramate

Topamax was approved on doses that worked acceptably across the average of seizure and migraine trials. The commercial tablet strengths are 25, 50, 100, and 200 mg, with the migraine target landing at 100 mg/day. Those numbers were not picked for your tolerance of the word-finding difficulty that gives topiramate its nickname, your history of kidney stones, your bicarbonate baseline, your weight, or the dose at which paresthesias become disruptive. Topiramate is one of the clearest cases where the side effects, cognitive slowing, tingling, stone risk, are dose-dependent, and the dose that finally controls migraines for one patient is the dose that another patient cannot work through.

That is the work a compounding pharmacy does. A prescriber can start at 12.5 mg instead of 25, hold at 18.75 mg for a week before stepping to 25, or settle a patient at 37.5 or 75 mg if that is where benefit and tolerability meet. None of those strengths exist on a manufactured tablet. The molecule is the same one the FDA reviewed in 1996. A pediatric patient who needs a precise weight-based dose, or an adult who reacts to a tablet excipient, can be prepared an allergen-free oral suspension or a custom-strength capsule for that single prescription.

This is what pharmacy looked like before mass manufacturing arrived. A doctor wrote the prescription. A pharmacist prepared it for that patient. Compounded topiramate is that older arrangement, kept honest by modern oversight.

Quick Facts About Topiramate

Category: Sulfamate-substituted monosaccharide anticonvulsant

Active ingredient: Topiramate, a structurally distinct anticonvulsant derived from D-fructose with multiple molecular targets (sodium channels, GABA-A potentiation, AMPA/kainate antagonism, carbonic anhydrase inhibition)

FDA-approved branded forms: Topamax (immediate-release; epilepsy 1996, migraine prophylaxis 2004); Trokendi XR and Qudexy XR (extended-release); Qsymia (phentermine/topiramate ER combination for chronic weight management, 2012)

Routes: Oral (tablets, sprinkle capsules, extended-release capsules); compounded preparations may include suspensions and other patient-specific oral forms

Evidence posture: Multiple pivotal phase III trials support epilepsy adjunctive and monotherapy use, migraine prophylaxis, and the phentermine/topiramate combination for obesity; well-studied off-label evidence exists for alcohol use disorder and binge eating disorder

FDA-approval status: Manufactured Topamax (and generics), Trokendi XR, Qudexy XR, and Qsymia are FDA-approved. Compounded topiramate preparations are not FDA-approved.

Compounded under: 503A, patient-specific prescription only, where the manufactured FDA-approved product is not clinically appropriate (e.g., excipient sensitivity, pediatric custom strength, allergen-free oral suspension)

Pregnancy / contraception cautions: Former FDA pregnancy Category D. Topiramate exposure in the first trimester is associated with an increased risk of oral clefts. Topiramate also reduces ethinyl estradiol exposure, particularly at higher doses, which can lower combined oral contraceptive efficacy.

> **SPECIALS: PATIENT-SPECIFIC PRESCRIPTION ONLY**
>
> Topiramate described in this monograph is a 503A compounded preparation. Every dose is made on a prescription, for a named patient, by a licensed pharmacist. It is not a stocked, mass-manufactured product.
>
> - **Made to order, not off a shelf.** No batch sits in a warehouse waiting for buyers. Your prescription triggers the prep.
> - **Named-patient label.** The bottle carries one patient's name. The batch records carry one prescription.
> - **Dose, strength, and route chosen for the patient.** A prescriber decides what gets compounded, not a manufacturer who set the strength for a trial population.
> - **Licensed pharmacist on the hook.** A real person, with a license that can be pulled, signs off on every prep. State inspectors check the facility.
> - **Compounded drugs are not FDA-approved.** They should not be evaluated using branded-drug trial data alone. Availability varies by state and prescribed medication.

How This Differs from a Research-Use-Only Website

A research-use-only website ships a vial from a warehouse. There is no prescription, no pharmacist, no facility inspection, and no way to recall the product if something is wrong with it. If the vial is mislabeled, contaminated, or under-potent, there is nobody whose license is at stake.

A 503A compounding pharmacy is the other thing. The doctor writes the prescription. A licensed pharmacist, whose name is on the label, prepares the medicine in a facility the state inspects. If something goes wrong, there is a person and a license on the hook, and a documented chain of custody on every lot. That accountability is what makes it safe.

What is Topiramate?

Topiramate is a structurally distinct anticonvulsant, a sulfamate-substituted monosaccharide derived from D-fructose [fda_label_topamax]. It was discovered at the R.W. Johnson Pharmaceutical Research Institute in the late 1980s as part of a program originally aimed at developing fructose-1,6-diphosphatase inhibitors,

and was repositioned as an antiepileptic following positive results in animal seizure models. The compound's chemistry is unrelated to that of the major established anticonvulsant classes, and its multi-target pharmacology contributes to its broad clinical spectrum [shank2000].

Topiramate received its first FDA approval in 1996 as adjunctive therapy for partial-onset seizures in adults under the brand Topamax. The migraine prophylaxis indication followed in 2004 [brandes2004, silberstein2004]. Extended-release oral formulations (Trokendi XR, Qudexy XR) became available in the 2010s, and a fixed-dose combination of phentermine and topiramate extended-release (Qsymia) was approved in 2012 for chronic weight management in adults with obesity [gadde2011, allison2012] [fda_label_qsymia].

Generic immediate-release topiramate is widely available as oral tablets (25, 50, 100, 200 mg) and sprinkle capsules (15, 25 mg) [fda_label_topamax]. Extended-release capsules are available at 25, 50, 100, 150, and 200 mg strengths. Qsymia is supplied as fixed-dose phentermine/topiramate ER capsules at 3.75/23, 7.5/46, 11.25/69, and 15/92 mg [fda_label_qsymia].

How Topiramate Works

Topiramate has multiple molecular targets that together account for its broad-spectrum anticonvulsant activity and its effects in migraine, weight regulation, and other indications. The principal actions characterized in preclinical work include state-dependent blockade of voltage-gated sodium channels, positive allosteric modulation of GABA-A receptors at a non-benzodiazepine binding site, antagonism at AMPA and kainate ionotropic glutamate receptors, blockade of L-type voltage-gated calcium channels, and inhibition of carbonic anhydrase isoforms II and IV [shank2000].

Different molecular targets are thought to dominate in different clinical contexts. The anticonvulsant effect is attributed primarily to sodium-channel modulation, GABA-A potentiation, and AMPA/kainate antagonism. The migraine prophylactic effect is hypothesized to involve cortical excitability dampening through similar channel-level mechanisms plus inhibition of trigeminovascular activation. The weight-loss effect, leveraged in the Qsymia combination, is attributed to appetite suppression and changes in food preference that may involve GABA-A and AMPA modulation in hypothalamic and reward circuits. Carbonic anhydrase inhibition contributes to metabolic acidosis, paresthesias, nephrolithiasis, and oligohidrosis observed as adverse effects [shank2000, daudon2018, kossoff2002].

Biological Role of Topiramate

Topiramate has no native biological role, it is a synthetic small molecule with no endogenous counterpart. Its targets are well-characterized components of normal neuronal excitability (voltage-gated sodium and calcium channels, GABA-A receptors, AMPA/kainate glutamate receptors) and of acid-base/ion physiology

(carbonic anhydrase isoforms). The therapeutic effect comes from chronic, partial modulation of these systems rather than complete inhibition.

The therapeutic landscape topiramate occupies, broad-spectrum anticonvulsant with secondary indications in migraine, obesity, and substance use disorders, reflects its multi-target pharmacology rather than action on a single disease-specific pathway [shank2000]. This profile contrasts with newer single-target agents (e.g., GLP-1 receptor agonists for obesity, CGRP-pathway antibodies for migraine) and explains both topiramate's clinical versatility and its broad adverse-effect profile.

Detailed Mechanism of Topiramate

Sodium-channel modulation by topiramate is state-dependent and frequency-dependent, similar in profile to phenytoin and carbamazepine but with distinct binding kinetics. GABA-A potentiation occurs at a site distinct from the benzodiazepine and barbiturate sites, supporting an inhibitory neurotransmission boost that is additive with established GABAergic anticonvulsants. AMPA/kainate antagonism is selective relative to NMDA receptors and contributes to dampening of excitatory neurotransmission, which is mechanistically attractive in both seizure and migraine contexts. L-type voltage-gated calcium-channel blockade adds a further layer of excitability modulation. Carbonic anhydrase inhibition affects the type II and type IV isoforms preferentially over type I [shank2000].

Pharmacological coverage of multiple targets is why topiramate is described as a 'broad-spectrum' anticonvulsant: it is effective in partial-onset seizures, primary generalized tonic-clonic seizures, and Lennox-Gastaut syndrome [faught1996, sachdeo1997, sachdeo1999]. In migraine, the same pharmacology supports a prophylactic effect demonstrated in MIGR-001 [silberstein2004] and MIGR-002 [brandes2004]. In obesity, the appetite-suppressant and weight-reducing effects are leveraged in the Qsymia combination with phentermine [gadde2011, allison2012, garvey2012]. In alcohol use disorder, dampened glutamatergic neurotransmission and enhanced GABAergic tone are thought to attenuate craving and reduce heavy drinking [johnson2003, johnson2007].

Carbonic anhydrase inhibition has direct safety consequences. Reduced renal bicarbonate reabsorption produces a mild non-anion-gap metabolic acidosis in a substantial fraction of patients on chronic therapy [kossoff2002]. The same enzyme inhibition in renal tubules favors calcium phosphate stone formation, contributing to a documented increase in nephrolithiasis [daudon2018]. Reduced sweating (oligohidrosis), particularly described in pediatric patients, also reflects carbonic anhydrase activity in eccrine sweat glands [franco2021].

Topiramate Research History

Topiramate was synthesized at the R.W. Johnson Pharmaceutical Research Institute in the 1980s. The pivotal adjunctive epilepsy program in adults with refractory partial-onset seizures was reported by Faught

and colleagues (the YD Study Group) in Neurology in 1996, demonstrating dose-dependent seizure reduction at 200, 400, and 600 mg/day [faught1996]. Monotherapy and additional adjunctive evidence in epilepsy followed from Sachdeo and colleagues for partial-onset seizures [sachdeo1997] and for Lennox-Gastaut syndrome (YL Study Group) [sachdeo1999]. The Shank et al. 2000 Epilepsia review consolidated the preclinical pharmacology and PK rationale that supported the broad-spectrum clinical profile [shank2000].

Migraine prophylaxis was established through two parallel pivotal trials reported in 2004: MIGR-001 [silberstein2004] in Archives of Neurology and MIGR-002 [brandes2004] in JAMA, with 100 mg/day emerging as the optimum dose for migraine frequency reduction with acceptable tolerability. The 2013 Cochrane review by Linde et al. integrated topiramate and other agents for episodic migraine prophylaxis [linde2013]. The CHAMP trial reported by Powers and colleagues in NEJM in 2017 tested amitriptyline and topiramate against placebo in pediatric migraine, with neither active arm separating from placebo [powers2017], a result that tempered enthusiasm for prophylactic pharmacotherapy in children with migraine.

The obesity program leveraged topiramate's appetite-suppressant effect, first reported by Wilding et al. in a long-term double-blind monotherapy trial in obese adults at doses up to 384 mg/day [wilding2004]. Topiramate monotherapy at high doses was poorly tolerated, motivating the lower-dose combination with phentermine. The phase III program for the fixed-dose phentermine/topiramate ER combination produced EQUIP (severely obese adults, Allison 2012 [allison2012]), CONQUER (overweight and obese adults with comorbidities, Gadde 2011 [gadde2011]), and the SEQUEL two-year extension [garvey2012], leading to FDA approval as Qsymia in July 2012.

Off-label indications developed largely in academic clinical trials. Johnson and colleagues established efficacy for alcohol dependence in a Lancet RCT in 2003 [johnson2003] and a JAMA RCT in 2007 [johnson2007]. McElroy et al. reported a placebo-controlled trial for binge eating disorder associated with obesity in Biological Psychiatry in 2007 [mcelroy2007]. Çelebisoy et al. compared topiramate with acetazolamide in idiopathic intracranial hypertension [celebisoy2007]. Connor et al. and Ondo et al. demonstrated efficacy in essential tremor in placebo-controlled crossover and parallel-group trials [connor2008, ondo2006]. Yeh et al. reported a positive RCT for civilian PTSD in 2011 [yeh2011]. Vasudev et al. summarized the bipolar acute affective episode literature in a 2016 Cochrane review with predominantly null findings [vasudev2016].

The teratogenicity signal emerged from pregnancy registry analyses. Margulis et al. reported an increased risk of oral clefts in 2012 [margulis2012], consistent with the Hernandez-Diaz comparative AED safety analysis in Neurology in 2012 [hernandezdiaz2012] and confirmed in a larger pregnancy cohort study in Neurology in 2018 [hernandezdiaz2018]. The Doose et al. oral contraceptive PK studies in 1997 and 2003 [doose1997, doose2003] established the dose-dependent reduction in ethinyl estradiol AUC that informs contraceptive counseling for women of reproductive age on topiramate. Pediatric ASM safety surveillance [franco2021] catalogues oligohidrosis and other carbonic-anhydrase-related effects that warrant particular vigilance in children.

Topiramate Timeline

1996 • Faught et al [faught1996]. publish dose-ranging placebo-controlled trial of topiramate 200, 400, and 600 mg/day in refractory partial epilepsy (YD Study Group, Neurology)

1996 • FDA approves Topamax as adjunctive therapy for partial-onset seizures in adults [fda_label_topamax]

1997 • Sachdeo et al [sachdeo1997]. publish topiramate monotherapy in partial-onset seizures (Epilepsia)

1997 • Doose et al [doose1997]. characterize the effect of topiramate on the PK of an oral contraceptive containing norethindrone and ethinyl estradiol in adults with epilepsy (Epilepsia)

1999 • Sachdeo et al [sachdeo1999]. publish double-blind randomized trial of topiramate in Lennox-Gastaut syndrome (YL Study Group, Neurology)

2000 • Shank et al [shank2000]. publish overview of preclinical topiramate pharmacology, PK, and mechanism (Epilepsia)

2002 • Kossoff et al [kossoff2002]. describe kidney stones, carbonic anhydrase inhibitors, and the ketogenic diet, establishing nephrolithiasis as a class effect of carbonic-anhydrase-inhibiting anticonvulsants (Epilepsia)

2003 • Johnson et al [johnson2003]. publish oral topiramate for treatment of alcohol dependence (Lancet RCT)

2003 • Doose et al [doose2003]. extend the oral contraceptive PK characterization to obese and nonobese healthy female subjects on topiramate vs carbamazepine (Epilepsia)

2004 • Brandes et al. (MIGR-002, JAMA) and Silberstein et al [brandes2004; silberstein2004; fda_label_topamax]. (MIGR-001, Archives of Neurology) publish pivotal migraine prophylaxis trials, FDA approves Topamax for migraine prophylaxis in adults

2004 • Wilding et al [wilding2004]. publish long-term double-blind placebo-controlled study of topiramate monotherapy in obese adults (Int J Obes Relat Metab Disord)

2006 • Ondo et al [ondo2006]. publish double-blind placebo-controlled trial of topiramate in essential tremor (Neurology)

2007 • McElroy et al [mcelroy2007]. publish placebo-controlled trial of topiramate for binge eating disorder associated with obesity (Biological Psychiatry)

2007 • Salinsky et al [salinsky2007]. characterize topiramate's EEG and alertness effects in healthy volunteers (Epilepsy & Behavior)

2007 • Diener et al [diener2007]. publish RCT of topiramate in chronic migraine (Cephalalgia)

2007 • Çelebisoy et al [celebisoy2007]. compare topiramate with acetazolamide in idiopathic intracranial hypertension (Acta Neurologica Scandinavica)

2007 • Johnson et al [johnson2007]. publish second pivotal RCT of topiramate for alcohol dependence (JAMA)

2008 • Connor et al [connor2008]. publish double-blind placebo-controlled crossover trials of topiramate in essential tremor (Clinical Neuropharmacology)

2011 • Gadde et al [gadde2011]. publish CONQUER, phentermine/topiramate combination for weight and associated comorbidities in overweight and obese adults (Lancet)

2011 • Yeh et al [yeh2011]. publish a double-blind RCT of topiramate in civilian PTSD (CNS Neuroscience & Therapeutics)

2012 • Allison et al [allison2012]. publish EQUIP, controlled-release phentermine/topiramate in severely obese adults (Obesity)

2012 • FDA approves Qsymia (phentermine/topiramate ER) for chronic weight management in adults (July 2012) [fda_label_qsymia]

2012 • Garvey et al [garvey2012]. publish SEQUEL, two-year sustained weight loss and metabolic benefits with phentermine/topiramate ER (Am J Clin Nutr)

2012 • Margulis et al. publish topiramate pregnancy oral cleft analysis (Am J Obstet Gynecol) and Hernandez-Diaz et al [margulis2012; hernandezdiaz2012]. report comparative AED safety during pregnancy (Neurology)

2012 • Loring et al [loring2012]. characterize the relationship between topiramate plasma concentration and linguistic behavior, verbal recall, and working memory (Epilepsy & Behavior)

2013 • Linde et al [linde2013]. publish Cochrane review of topiramate for prophylaxis of episodic migraine in adults

2016 • Vasudev et al [vasudev2016]. publish Cochrane review of topiramate for acute affective episodes in bipolar disorder, predominantly null findings

2017 • Powers et al [powers2017]. (CHAMP trial, NEJM) report that neither amitriptyline nor topiramate separated from placebo for pediatric migraine prophylaxis

2018 • Hernandez-Diaz et al [hernandezdiaz2018]. confirm increased oral cleft risk with first-trimester topiramate exposure in a large pregnancy cohort study (Neurology)

2018 • Daudon et al [daudon2018]. review drug-induced kidney stones and crystalline nephropathy with detailed coverage of topiramate-associated calcium phosphate stones (Drugs)

2021 • Franco et al [franco2021]. analyze pediatric adverse reactions to antiseizure medications, including topiramate-associated oligohidrosis and cognitive effects, in the Italian spontaneous reporting system 2001-2019 (Epilepsy & Behavior)

Clinical Contexts for Topiramate

Adjunctive therapy for partial-onset and primary generalized tonic-clonic seizures in adults and pediatric patients ≥2 years FDA APPROVED

FDA-approved indication for Topamax (immediate-release) and Trokendi XR / Qudexy XR (extended-release).

Pivotal dose-ranging trials demonstrated dose-dependent seizure reduction at 200, 400, and 600 mg/day in adults with refractory partial-onset seizures [faught1996]. Adjunctive use in Lennox-Gastaut syndrome was supported by the YL Study Group [sachdeo1999]. Pediatric efficacy data extended labeling to ≥2 years for partial-onset and primary generalized tonic-clonic seizures and ≥2 years adjunctive for Lennox-Gastaut [fda_label_topamax].

Branded product: Topamax (topiramate; Janssen) and generics; Trokendi XR (Supernus); Qudexy XR (Upsher-Smith)

Monotherapy for partial-onset or primary generalized tonic-clonic seizures in patients ≥2 years FDA APPROVED

FDA-approved indication for Topamax monotherapy.

Monotherapy efficacy was supported by Sachdeo et al. in partial-onset seizures [sachdeo1997]. Labeling supports topiramate monotherapy in adults and pediatric patients ≥2 years [fda_label_topamax].

Branded product: Topamax

Migraine prophylaxis in adults FDA APPROVED

FDA-approved indication for Topamax (immediate-release) and Trokendi XR / Qudexy XR (extended-release).

MIGR-001 [silberstein2004] and MIGR-002 [brandes2004] established 100 mg/day as the optimum prophylactic dose for adults with episodic migraine, with significant reductions in mean monthly migraine days vs placebo. The Linde 2013 Cochrane review consolidated topiramate within the migraine prophylaxis evidence base [linde2013] [fda_label_topamax]. Diener et al. extended the evidence into chronic migraine [diener2007].

Branded product: Topamax

Chronic weight management in adults with obesity (phentermine/topiramate ER combination) FDA APPROVED

FDA-approved indication for Qsymia (phentermine/topiramate ER combination, July 2012).

EQUIP [allison2012] demonstrated mean weight reductions of 5.1% and 10.9% with low-dose and full-dose phentermine/topiramate ER vs 1.6% with placebo in adults with severe obesity (BMI ≥35) at 56 weeks [fda_label_qsymia]. CONQUER [gadde2011] demonstrated mean weight reductions of 7.8% and 9.8% with mid-dose and full-dose vs 1.2% placebo in overweight and obese adults with weight-related comorbidities at 56 weeks. The SEQUEL two-year extension [garvey2012] confirmed sustained weight loss and metabolic benefits at 108 weeks. Qsymia is contraindicated in pregnancy (REMS) and requires monthly pregnancy testing in women of reproductive potential.

Branded product: Qsymia (phentermine/topiramate ER; Vivus)

Alcohol use disorder WELL STUDIED

Off-label; well-studied with two pivotal RCTs.

Johnson et al. 2003 [johnson2003] randomized 150 adults with alcohol dependence to topiramate (titrated to 300 mg/day) vs placebo for 12 weeks and reported significant reductions in drinks per day, drinks per drinking day, percent days heavy drinking, and gamma-glutamyltransferase. Johnson et al. 2007 [johnson2007] replicated and extended the finding in a larger 14-week multi-site RCT (N=371). Both studies established topiramate as an evidence-supported option for alcohol use disorder, though it remains off-label in the United States.

Binge eating disorder associated with obesity WELL STUDIED

Off-label; supported by a placebo-controlled RCT.

McElroy et al. 2007 [mcelroy2007] randomized adults with binge eating disorder and obesity to topiramate (mean dose ~212 mg/day) vs placebo for 21 weeks and reported significant reductions in binge episode frequency, BMI, and Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating score. Topiramate has not received FDA approval for this indication.

Idiopathic intracranial hypertension WELL STUDIED

Off-label; supported by a comparator-controlled trial vs acetazolamide.

Çelebisoy et al. 2007 [celebisoy2007] conducted an open-label comparison of topiramate vs acetazolamide in adults with idiopathic intracranial hypertension and reported comparable improvements in visual field and headache outcomes. Topiramate's carbonic anhydrase inhibition is the proposed mechanistic basis for benefit in this condition.

Essential tremor WELL STUDIED

Off-label; supported by placebo-controlled trials.

Ondo et al. 2006 [ondo2006] reported a positive double-blind placebo-controlled trial of topiramate (titrated to 400 mg/day) in adults with essential tremor, with significant reduction in Fahn-Tolosa-Marin tremor rating scale. Connor et al. 2008 [connor2008] reported corroborating evidence in pooled double-blind placebo-controlled crossover trials. Discontinuation rates due to adverse events were high, reflecting the neurocognitive tolerability profile of higher topiramate doses.

Post-traumatic stress disorder WELL STUDIED

Off-label; supported by a positive RCT in civilian PTSD.

Yeh et al. 2011 [yeh2011] conducted a double-blind RCT of topiramate (titrated to 200 mg/day) vs placebo in civilian PTSD over 12 weeks and reported improvements on the Clinician-Administered PTSD Scale. The trial was a single-site study with modest sample size; topiramate has not received FDA approval for PTSD.

Chronic migraine WELL STUDIED

Off-label for chronic migraine (>15 headache days per month); supported by a placebo-controlled RCT.

Diener et al. 2007 [diener2007] randomized adults with chronic migraine to topiramate 100 mg/day vs placebo for 16 weeks and reported significant reductions in monthly headache days. Topiramate is FDA-approved for migraine prophylaxis in adults but the labeled indication is for episodic migraine; chronic migraine use is supported by trial evidence but is off-label.

Off-Label Uses of Topiramate

Pediatric migraine prophylaxis WELL STUDIED

CHAMP trial demonstrated no separation from placebo; evidence does not support routine use in pediatric migraine.

Powers et al. 2017 [powers2017] randomized 361 children and adolescents with migraine to amitriptyline, topiramate, or placebo over 24 weeks (CHAMP trial, NEJM). Neither active arm separated from placebo on the primary endpoint of ≥50% reduction in headache days. The trial tempered enthusiasm for routine prophylactic pharmacotherapy in pediatric migraine.

Acute affective episodes in bipolar disorder WELL STUDIED

Cochrane review reports predominantly null findings; not supported as monotherapy or adjunctive therapy for acute episodes.

Vasudev et al. 2016 Cochrane review [vasudev2016] of topiramate for acute affective episodes in bipolar disorder integrated multiple small RCTs and reported insufficient evidence of benefit for mania, depression, or mixed episodes. The review recommended against routine use of topiramate for acute bipolar episodes.

FDA-Approved Uses of Topiramate

Brand	Indication	Year	Route
Topamax (immediate-release) and generic topiramate	Adjunctive therapy and monotherapy for partial-onset seizures and primary generalized tonic-clonic seizures (≥2 years); adjunctive therapy for Lennox-Gastaut syndrome (≥2 years); prophylaxis of migraine in adults	1996	Oral
Trokendi XR / Qudexy XR (extended-release)	Same epilepsy and migraine indications as Topamax in the labeled age range	2013	Oral, extended-release
Qsymia (phentermine/topiramate ER fixed-dose combination)	Chronic weight management in adults with BMI ≥30 or BMI ≥27 with at least one weight-related comorbidity, as adjunct to reduced-calorie diet and increased physical activity	2012	Oral

Topamax (immediate-release topiramate, originally Janssen / Ortho-McNeil) was first approved by FDA in 1996 for adjunctive therapy of partial-onset seizures in adults [fda_label_topamax]. Subsequent approvals expanded the indication to monotherapy, to pediatric patients ≥2 years, to adjunctive Lennox-Gastaut

syndrome, and (in 2004) to migraine prophylaxis in adults. Generic immediate-release topiramate has been available for many years. Extended-release products (Trokendi XR, Qudexy XR) were approved in the 2010s and offer once-daily dosing for the same indications.

Qsymia (phentermine/topiramate ER) was approved by FDA in July 2012 for chronic weight management in adults with BMI ≥30 or BMI ≥27 with a weight-related comorbidity, on the basis of the EQUIP, CONQUER, and SEQUEL trials [allison2012, gadde2011, garvey2012] [fda_label_qsymia]. The Qsymia label carries a Risk Evaluation and Mitigation Strategy (REMS) program requiring pregnancy testing and contraception counseling in women of reproductive potential due to the oral cleft teratogenic signal.

Compounded Topiramate (503A)

Generic immediate-release topiramate tablets and sprinkle capsules cover the majority of patient needs at low cost, and extended-release products (Trokendi XR, Qudexy XR) provide a once-daily option for adherence [fda_label_topamax]. The compounded 503A role for topiramate is therefore narrow and case-specific.

Documented patient-specific clinical reasons that may justify compounded topiramate under 503A include: (1) pediatric dose individualization at strengths not commercially available, where commercial sprinkles and tablets do not provide the prescribed dose; (2) excipient sensitivity to a component of the commercial tablet, capsule, or sprinkle formulation (dye, lactose, gluten, or other excipient); (3) preparation of an oral liquid suspension for a patient who cannot swallow capsules or tablets when commercial sprinkles are not appropriate; and (4) very rarely, custom-strength preparations for off-label indications where commercial strengths do not allow the prescribed titration [fda_label_topamax]. Cost or preference does not justify compounding under 503A [fda503a, fda_essentially_a_copy].

Transdermal and topical topiramate preparations have been explored for migraine prophylaxis in small clinical and observational settings but remain experimental; there is no FDA-approved transdermal topiramate product, and the systemic absorption profile of topical topiramate has not been adequately characterized to support claims of equivalence to oral therapy. RonanRx does not promote transdermal topiramate as an established alternative to oral therapy [fda_label_topamax].

Most patients prescribed topiramate are well-served by the commercial generic or branded products. RonanRx compounds topiramate only when the prescriber documents that the patient cannot use a commercially available formulation for a specific clinical reason [fda_label_topamax].

Topiramate Formulations and Routes

Form	Concentration	Description
Compounded oral suspension (503A)	Custom, typically 5-30 mg/mL	Sterile or low-bioburden oral liquid prepared under USP <795> standards for nonsterile compounding on a patient-specific prescription, typically for pediatric patients or adults unable to swallow tablets or sprinkle capsules. Container closure, excipient profile, vehicle, and concentration are documented per batch and matched to the patient's clinical profile.
Compounded oral capsules (503A)	Custom strengths outside the commercially available 15, 25, 50, 100, 150, or 200 mg increments	Patient-specific custom strengths prepared under USP <795> when the prescribed dose cannot be achieved with commercial strengths or when a documented excipient sensitivity precludes the commercial product.
Manufactured oral tablets (reference product)	25, 50, 100, 200 mg	Topamax (immediate-release) and generic topiramate are FDA-approved oral tablets for adults and pediatric patients ≥2 years.
Manufactured sprinkle capsules (reference product)	15, 25 mg	Topamax sprinkle capsules for pediatric use and for adults with swallowing difficulty.
Manufactured extended-release capsules (reference product)	25, 50, 100, 150, 200 mg	Trokendi XR (Supernus) and Qudexy XR (Upsher-Smith) once-daily extended-release capsules for the same epilepsy and migraine indications as Topamax in the labeled age range.
Manufactured Qsymia fixed-dose combination (reference product)	Phentermine 3.75/7.5/11.25/15 mg + topiramate ER 23/46/69/92 mg	Qsymia (Vivus) is the FDA-approved phentermine/topiramate ER combination for chronic weight management in adults, supplied as once-daily oral capsules at four fixed-dose strengths with a REMS pregnancy prevention program.

Routes used in published literature: oral.

Topiramate Dosing

Route	Population	Range	Duration	Study type
Oral	Adults with partial-onset or primary	Start 25-50 mg at bedtime; titrate by 25-50 mg/week to a target range of		FDA-approved labeled regimen

Route	Population	Range	Duration	Study type
	generalized tonic-clonic seizures (Topamax adjunctive regimen)	200-400 mg/day in two divided doses. Maximum 1600 mg/day not associated with additional benefit.	Indefinite while clinically beneficial	following Faught 1996 and adjunctive program
Oral	Adults with migraine for prophylaxis	Start 25 mg/day in the evening; titrate by 25 mg/week to 100 mg/day in two divided doses (50 mg AM + 50 mg PM). Doses above 100 mg/day do not increase efficacy and worsen tolerability per MIGR-001 and MIGR-002.	Indefinite while clinically beneficial	FDA-approved labeled regimen following MIGR-001 and MIGR-002
Oral	Pediatric patients ≥2 years with partial-onset or primary generalized tonic-clonic seizures	Initial 1-3 mg/kg/day at bedtime, titrated by 1-3 mg/kg/week to a target of 5-9 mg/kg/day in two divided doses.	Indefinite while clinically beneficial	FDA-approved pediatric regimen
Oral	Adults with obesity (Qsymia labeled regimen)	Initiate at phentermine 3.75 mg / topiramate ER 23 mg once daily for 14 days, then phentermine 7.5 mg / topiramate ER 46 mg once daily. Reassess at 12 weeks: if <3% weight loss, escalate to phentermine 11.25 mg / topiramate ER 69 mg for 14 days then phentermine 15 mg / topiramate ER 92 mg once daily; if still <5% at 12 additional weeks, discontinue.	Indefinite while clinically beneficial; SEQUEL extension confirms sustained benefit at 108 weeks	FDA-approved labeled regimen following EQUIP, CONQUER, SEQUEL
Oral	Adults with alcohol use disorder (off-label)	Titrated from 25 mg/day to a target of 200-300 mg/day in two divided doses over approximately 6-8 weeks, with maintenance for 12+ weeks per the Johnson 2003 and 2007 protocols.	12+ weeks in the pivotal trials; clinical use varies	Off-label; protocol from RCTs

Doctor-prescribed and titrated. Slow titration is the primary tolerability lever for topiramate: most neurocognitive and paresthesia-related adverse events occur during dose escalation, and a 25-50 mg/week increment is the standard. For epilepsy, target maintenance is typically 200-400 mg/day in two divided doses for adults [fda_label_topamax]. For migraine prophylaxis, 100 mg/day is the labeled optimum dose with no additional benefit above this dose [brandes2004, silberstein2004]. For Qsymia, the labeled

regimen uses lower topiramate ER doses (23-92 mg/day) in combination with phentermine and includes a 12-week response checkpoint with discontinuation if <5% weight loss after escalation [fda_label_qsymia].

Compounded preparations should mirror the manufactured-product dosing for the indication unless the prescriber documents a patient-specific reason for variance. Off-label use for alcohol use disorder, binge eating disorder, essential tremor, IIH, and PTSD typically targets 200-300 mg/day in two divided doses with the same slow titration.

Topiramate Safety

Topiramate safety is dominated by neurocognitive effects, paresthesias, metabolic acidosis, nephrolithiasis, oligohidrosis (especially in children), weight loss, and a documented teratogenic signal for oral clefts in first-trimester exposure. Neurocognitive adverse events, word-finding difficulty, psychomotor slowing, attention impairment, and verbal fluency reduction (colloquially 'dopamax'), are dose-related and disproportionately affect verbal/expressive language. Loring et al. demonstrated a relationship between topiramate plasma concentration and decrements in linguistic behavior, verbal recall, and working memory in adults with epilepsy [23] [32]. Salinsky et al. characterized EEG slowing and alertness reduction in healthy volunteers at therapeutic doses [14].

Carbonic anhydrase inhibition produces a non-anion-gap metabolic acidosis (reduced serum bicarbonate) in a substantial fraction of patients on chronic therapy [6]. Nephrolithiasis, predominantly calcium phosphate stones, is documented across the pediatric and adult populations on chronic topiramate, reflecting carbonic anhydrase activity in renal tubules [296] [32]. Oligohidrosis with risk of heat-related hyperthermia has been reported particularly in pediatric patients and is included in pediatric ASM pharmacovigilance signals [31]. Other common adverse events include fatigue, dizziness, somnolence, paresthesias, anorexia, weight loss, and taste perversion (especially for carbonated beverages).

Reproductive-age women require specific counseling. First-trimester topiramate exposure is associated with an increased risk of oral clefts (cleft lip ± cleft palate) on the order of 2- to 5-fold relative to unexposed pregnancies, established by the Margulis et al. 2012 sentinel analysis [24], the Hernandez-Diaz et al. 2012 comparative AED pregnancy safety analysis [22], and the Hernandez-Diaz et al. 2018 pregnancy cohort [30]. Topiramate at ≥200 mg/day reduces ethinyl estradiol AUC by approximately 18-30% with implications for combined oral contraceptive efficacy [37] [32]. The Qsymia label carries a REMS pregnancy prevention program with monthly pregnancy testing requirements [33].

Less common but clinically important adverse events include acute myopia with secondary angle-closure glaucoma (idiosyncratic, typically within the first month), hyperammonemia and encephalopathy when combined with valproate, and rare cases of severe metabolic acidosis or suicidal ideation (class warning for antiepileptic drugs). Bipolar acute affective episode evidence is predominantly null [27] and topiramate is not recommended as monotherapy or adjunctive therapy for acute bipolar episodes [32].

Contraindications

Topiramate is contraindicated in known hypersensitivity to topiramate or any excipient in the manufactured product [32]. Qsymia is additionally contraindicated in pregnancy, glaucoma, hyperthyroidism, during or within 14 days of monoamine oxidase inhibitor therapy, and in known hypersensitivity to sympathomimetic amines (the phentermine component) [33].

Topiramate is not recommended without contraception counseling and a documented contraception plan in women of reproductive potential due to the oral cleft teratogenic signal in first-trimester exposure [2430]. Combined oral contraceptive efficacy is reduced at topiramate doses ≥200 mg/day [37]; patients should be advised to use a non-oral contraceptive method or add a barrier method, and to discuss alternative anticonvulsant or migraine prophylactic options if pregnancy is planned [32].

Drug interactions

Topiramate induces CYP3A4 at doses ≥200 mg/day, with the principal clinically relevant consequence being a reduction in ethinyl estradiol exposure that can lower combined oral contraceptive efficacy [37]. Topiramate is also a weak inhibitor of CYP2C19 and may modestly increase phenytoin levels when co-administered. Topiramate plasma concentrations are reduced by concomitant enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin) and may be increased by valproate in some patients [32].

Combination with valproate has been associated with hyperammonemia and encephalopathy in adults and children. Combination with other carbonic anhydrase inhibitors (acetazolamide, zonisamide) increases the risk of metabolic acidosis and nephrolithiasis [629]. CNS depressants (alcohol, benzodiazepines, opioids) potentiate the cognitive and sedative adverse effects of topiramate; alcohol is specifically contraindicated with Trokendi XR [32]. Concomitant therapy with other agents that can cause oligohidrosis (anticholinergics, antihistamines, carbonic anhydrase inhibitors) increases the risk of heat-related illness, particularly in pediatric patients [31].

Adverse events

Across the pivotal epilepsy, migraine, and obesity programs, the most common adverse events with topiramate (or phentermine/topiramate ER) included paresthesias, fatigue, dizziness, somnolence, anorexia, weight loss, taste perversion, nausea, constipation, dry mouth, and cognitive/psychiatric effects (word-finding difficulty, difficulty with concentration, memory impairment) [101921]. Adverse-event-driven discontinuation rates were approximately 15-25% on full-dose topiramate monotherapy at 200-400 mg/day in epilepsy and migraine trials and were lower (~5-15%) on the lower-dose Qsymia regimens [149].

Cognitive adverse events deserve specific mention. Loring et al. demonstrated that linguistic behavior, verbal recall, and working memory decrements correlate with topiramate plasma concentration [23]. Salinsky et al. characterized EEG slowing and alertness reduction in healthy volunteers at therapeutic doses [14]. The colloquial label 'dopamax' captures the disproportionate effect on verbal fluency and word-finding that

patients report. Slow titration and lower maintenance doses (e.g., 100 mg/day for migraine) substantially reduce the incidence and severity of these effects.

Less common but clinically important adverse events include nephrolithiasis (calcium phosphate stones from carbonic anhydrase inhibition) [296], oligohidrosis and heat-related illness particularly in pediatric patients [31], acute myopia with secondary angle-closure glaucoma (idiosyncratic, typically within the first month), metabolic acidosis with chronic dosing [6], hyperammonemia and encephalopathy in combination with valproate, and a class warning for suicidal ideation that applies to all antiepileptic drugs. Pregnancy exposure carries a 2- to 5-fold increased risk of oral clefts on the basis of pregnancy cohort and registry data [242230].

Monitoring Topiramate Therapy

Baseline assessment should include weight, blood pressure, heart rate, serum bicarbonate, renal function, a history focused on nephrolithiasis and ophthalmologic disease, a contraception plan in women of reproductive potential, and pregnancy testing prior to initiation (mandatory for Qsymia per REMS) [fda_label_qsymia]. Cognitive baseline (especially of verbal fluency) should be documented in patients in whom cognitive adverse events would be clinically significant.

On therapy: serum bicarbonate at 1, 3, and 12 months and as clinically indicated to detect metabolic acidosis; weight at each visit (especially in pediatric patients where excessive weight loss may be clinically problematic); periodic renal function; pregnancy testing per Qsymia REMS in women of reproductive potential; reassessment of cognitive tolerability at each titration step. Patients should be counseled to maintain hydration to reduce nephrolithiasis risk, to avoid heat exposure (particularly children), to report new visual symptoms immediately (acute myopia/angle-closure glaucoma), and to use contraception consistent with topiramate dose [doose1997, doose2003] [fda_label_topamax; fda_label_qsymia; kossoff2002].

Topiramate in Special Populations

Topiramate Evidence Quality

Evidence supporting the manufactured topiramate products is strong across the FDA-approved indications [johnson2007]. Adjunctive and monotherapy epilepsy use is supported by the Faught dose-ranging trial [faught1996] and the Sachdeo monotherapy and Lennox-Gastaut trials [sachdeo1997, sachdeo1999]. Migraine prophylaxis is supported by two large pivotal trials (MIGR-001 and MIGR-002) that converged on 100 mg/day as the optimum dose [silberstein2004, brandes2004] and a Cochrane review [linde2013]. The

Qsymia obesity program rests on EQUIP [allison2012], CONQUER [gadde2011], and the two-year SEQUEL extension [garvey2012], all phase III placebo-controlled with consistent effect sizes.

Off-label use is supported with varying quality. Alcohol use disorder has two well-conducted RCTs [johnson2003] and is the strongest off-label indication [johnson2007]. Binge eating disorder [mcelroy2007], idiopathic intracranial hypertension [celebisoy2007], essential tremor [ondo2006, connor2008], and civilian PTSD [yeh2011] each have single or small numbers of placebo- or comparator-controlled trials supporting efficacy. Pediatric migraine evidence is null on placebo comparison [powers2017]. Bipolar acute affective episode evidence is null [vasudev2016].

Compounded topiramate has no separate efficacy program. Compounded preparations are an extrapolation from the commercial generic and branded products, justified case by case by patient-specific factors (excipient sensitivity, custom strength for pediatric dosing, or oral liquid for swallowing-impaired patients) [fda_essentially_a_copy]. PK and dosing should mirror the commercial product unless the prescriber documents a patient-specific reason for variance. Most patients are well-served by commercial generic immediate-release or extended-release topiramate [johnson2007].

Major Topiramate Clinical Studies

Study	Design	Participants	Duration	Finding
Faught et al. (1996, Neurology), YD Study Group adjunctive epilepsy dose-ranging	Phase III randomized double-blind placebo-controlled dose-ranging trial of topiramate 200, 400, and 600 mg/day as adjunctive therapy in adults with refractory partial-onset seizures	181	12 weeks (after 8-week baseline)	Dose-dependent reduction in median monthly seizure frequency; 41% of topiramate-treated patients achieved ≥50% seizure reduction vs 8% on placebo. Supported the original 1996 FDA approval of Topamax for adjunctive therapy of partial-onset seizures in adults [faught1996].
Sachdeo et al. (1997, Epilepsia), Topiramate monotherapy for partial-onset seizures	Phase III randomized double-blind comparative dose monotherapy trial in adults with partial-onset seizures	—	Conversion-to-monotherapy design	Established topiramate monotherapy efficacy in adults with partial-onset seizures, supporting subsequent FDA approval of monotherapy use [sachdeo1997].
Sachdeo et al. (1999, Neurology), YL Study	Phase III randomized double-blind placebo-	98	11 weeks	Reduction in drop-attack seizure frequency on

Study	Design	Participants	Duration	Finding
Group Lennox-Gastaut syndrome	controlled trial of topiramate as adjunctive therapy in Lennox-Gastaut syndrome			topiramate vs placebo; supported FDA approval for adjunctive Lennox-Gastaut syndrome in patients ≥2 years [sachdeo1999].
Shank et al. (2000, Epilepsia), Preclinical pharmacology overview	Comprehensive review of preclinical pharmacology, pharmacokinetics, and mechanism of action of topiramate	—	—	Consolidated the multi-target pharmacology, sodium channel blockade, GABA-A potentiation, AMPA/kainate antagonism, L-type calcium channel blockade, carbonic anhydrase inhibition, that underpins topiramate's broad clinical spectrum [shank2000].
Brandes et al. (2004, JAMA), MIGR-002 migraine prophylaxis	Phase III randomized double-blind placebo-controlled trial of topiramate 50, 100, 200 mg/day for migraine prophylaxis in adults	483	26 weeks	Mean reduction in monthly migraine days of 1.4, 2.1, and 2.4 on 50, 100, and 200 mg/day vs 0.8 on placebo. Established 100 mg/day as the optimum dose with no further benefit and worse tolerability at 200 mg/day. Supported 2004 FDA approval for migraine prophylaxis in adults [brandes2004].
Silberstein et al. (2004, Archives of Neurology), MIGR-001 migraine prophylaxis	Phase III randomized double-blind placebo-controlled trial of topiramate 50, 100, 200 mg/day for migraine prophylaxis in adults	487	26 weeks	Parallel MIGR program trial converging on the same 100 mg/day optimum dose with significant reduction in monthly migraine days vs placebo. Together with MIGR-002 supported 2004 FDA migraine prophylaxis approval [silberstein2004].
Wilding et al. (2004, Int J Obes Relat Metab	Randomized double-blind placebo-controlled trial of	—	60 weeks	Dose-dependent weight reduction; high-dose monotherapy poorly

Study	Design	Participants	Duration	Finding
Disord), Long-term obesity monotherapy	topiramate monotherapy at escalating doses up to 384 mg/day in obese adults			tolerated due to neurocognitive and paresthesia-related adverse events, motivating the lower-dose combination with phentermine [wilding2004].
Ondo et al. (2006, Neurology), Essential tremor RCT	Phase III randomized double-blind placebo-controlled trial of topiramate titrated to 400 mg/day in adults with essential tremor	208	24 weeks	Significant reduction in Fahn-Tolosa-Marin tremor rating scale on topiramate vs placebo; discontinuation rate ~32% in the topiramate arm due to adverse events [ondo2006].
McElroy et al. (2007, Biological Psychiatry), Binge eating disorder	Randomized double-blind placebo-controlled trial of topiramate (mean ~212 mg/day) in adults with binge eating disorder and obesity	394	21 weeks	Significant reductions in binge episode frequency, BMI, and Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating vs placebo [mcelroy2007]. Establishes well-studied off-label use; not FDA-approved for this indication.
Salinsky et al. (2007, Epilepsy & Behavior), Topiramate EEG and alertness	Healthy-volunteer study of topiramate effects on EEG and alertness at therapeutic doses	—	—	Documented EEG slowing and alertness reduction at therapeutic plasma concentrations; characterized topiramate's distinct neurotoxicity profile relative to other antiepileptic drugs [salinsky2007].
Diener et al. (2007, Cephalalgia), Chronic migraine RCT	Randomized double-blind placebo-controlled trial of topiramate 100 mg/day in adults with chronic migraine	—	16 weeks	Significant reduction in monthly headache days on topiramate vs placebo; supports off-label use in chronic migraine in addition to the labeled episodic migraine indication [diener2007].
		—	12 months	

Study	Design	Participants	Duration	Finding
Çelebisoy et al. (2007, Acta Neurologica Scandinavica), IIH topiramate vs acetazolamide	Open-label comparison of topiramate vs acetazolamide in adults with idiopathic intracranial hypertension			Comparable improvements in visual fields, headache severity, and papilledema between topiramate and acetazolamide; topiramate's carbonic anhydrase inhibition is the proposed mechanistic basis [celebisoy2007].
Johnson et al. (2003, Lancet), Topiramate for alcohol dependence (initial RCT)	Phase II randomized double-blind placebo-controlled trial of topiramate titrated to 300 mg/day in adults with alcohol dependence	150	12 weeks	Significant reductions in drinks per day, drinks per drinking day, percent days heavy drinking, and gamma-glutamyltransferase on topiramate vs placebo. Established topiramate as a candidate pharmacotherapy for alcohol use disorder [johnson2003].
Johnson et al. (2007, JAMA), Topiramate for alcohol dependence (multi-site RCT)	Phase III randomized double-blind placebo-controlled multi-site trial of topiramate titrated to 300 mg/day in adults with alcohol dependence	371	14 weeks	Replication of the 2003 result with a 3.4-percentage-point reduction in percent heavy drinking days vs placebo; established topiramate as an evidence-supported (though off-label) option for alcohol use disorder [johnson2007].
Connor et al. (2008, Clinical Neuropharmacology), Essential tremor crossover trials	Pooled double-blind placebo-controlled crossover trials of topiramate in adults with essential tremor	—	—	Significant reduction in tremor severity on topiramate vs placebo; corroborates the Ondo 2006 finding with crossover-design evidence [connor2008].
Gadde et al. (2011, Lancet), CONQUER phentermine/topiramate ER	Phase III randomized double-blind placebo-controlled trial of low- and full-dose phentermine/	2487	56 weeks	Mean weight reductions of 7.8% and 9.8% with mid-dose (7.5/46) and full-dose (15/92) phentermine/topiramate ER vs 1.2% on

Study	Design	Participants	Duration	Finding
	topiramate ER in overweight and obese adults with weight-related comorbidities			placebo; ≥5% weight loss in 62% and 70% vs 21% on placebo [gadde2011]. Supported the 2012 FDA approval of Qsymia.
Yeh et al. (2011, CNS Neuroscience & Therapeutics), Civilian PTSD RCT	Double-blind randomized placebo-controlled trial of topiramate titrated to 200 mg/day in adults with civilian PTSD	—	12 weeks	Significant improvement on the Clinician-Administered PTSD Scale (CAPS) with topiramate vs placebo; supports off-label use in civilian PTSD; topiramate is not FDA-approved for PTSD [yeh2011].
Allison et al. (2012, Obesity), EQUIP phentermine/ topiramate ER in severe obesity	Phase III randomized double-blind placebo-controlled trial of low-dose and full-dose phentermine/ topiramate ER in adults with severe obesity (BMI ≥35)	1267	56 weeks	Mean weight reductions of 5.1% and 10.9% with low-dose and full-dose phentermine/topiramate ER vs 1.6% on placebo; ≥10% weight loss in 7%, 47%, and 7% respectively [allison2012]. Co-pivotal with CONQUER for Qsymia approval.
Garvey et al. (2012, Am J Clin Nutr), SEQUEL two-year phentermine/ topiramate ER extension	Phase III randomized placebo-controlled 52-week extension of CONQUER (total 108 weeks of treatment) with mid- and full-dose phentermine/ topiramate ER	676	108 weeks total	Sustained weight loss of 9.3% and 10.5% on mid- and full-dose vs 1.8% on placebo at 108 weeks; sustained improvement in metabolic parameters (HbA1c, lipids, blood pressure); supported long-term use of Qsymia [garvey2012].
Loring et al. (2012, Epilepsy & Behavior), Topiramate plasma concentration and language	Observational analysis of the relationship between topiramate plasma concentration and linguistic behavior, verbal recall, and working	—	—	Concentration-dependent decrements in linguistic behavior, verbal recall, and working memory; provides the mechanistic substrate for the colloquial 'dopamax' description of topiramate's

Study	Design	Participants	Duration	Finding
	memory in adults with epilepsy			effect on word-finding and verbal fluency [loring2012].
Margulis et al. (2012, AJOG), Topiramate pregnancy and oral clefts	Population-based pregnancy cohort study using insurance claims data to assess topiramate exposure and oral cleft risk	—	—	Increased risk of oral clefts among infants of women with first-trimester topiramate exposure relative to unexposed comparators; sentinel analysis prompting label change and Qsymia REMS [margulis2012].
Hernandez-Diaz et al. (2012, Neurology), Comparative AED pregnancy safety	Comparative safety analysis of antiepileptic drugs during pregnancy using a multi-source pregnancy registry	—	—	Confirmed elevated oral cleft risk with first-trimester topiramate exposure in the context of broader AED comparative safety; informed contemporaneous regulatory action [hernandezdiaz2012].
Linde et al. (2013, Cochrane Database of Systematic Reviews), Topiramate migraine prophylaxis review	Systematic review and meta-analysis of randomized placebo-controlled trials of topiramate for episodic migraine prophylaxis in adults	—	—	Topiramate 100 mg/day reduces mean monthly migraine days by ~1 day relative to placebo with consistent effect sizes across trials; 200 mg/day does not increase efficacy and worsens tolerability [linde2013].
Vasudev et al. (2016, Cochrane), Topiramate for acute affective episodes in bipolar disorder	Cochrane systematic review and meta-analysis of topiramate for acute mania, depression, and mixed episodes in bipolar disorder	—	—	Predominantly null findings; insufficient evidence to support topiramate as monotherapy or adjunctive therapy for acute bipolar affective episodes [vasudev2016].
Powers et al. (2017, NEJM), CHAMP pediatric migraine	Phase III randomized double-blind placebo-controlled trial of amitriptyline 1 mg/kg/day, topiramate 2	361	24 weeks	Neither active arm separated from placebo on the primary endpoint of ≥50% reduction in headache days; the trial was stopped early for futility.

Study	Design	Participants	Duration	Finding
	mg/kg/day, or placebo in children and adolescents 8-17 years with migraine			Tempered enthusiasm for routine prophylactic pharmacotherapy in pediatric migraine [powers2017].
Hernandez-Diaz et al. (2018, Neurology), Topiramate pregnancy oral clefts cohort	Large pregnancy cohort study using nationwide insurance claims to assess oral cleft risk with first-trimester topiramate exposure	—	—	Confirmed approximately 2- to 3-fold increased risk of oral clefts with first-trimester topiramate exposure vs unexposed comparators across the migraine and epilepsy indications [hernandezdiaz2018].
Daudon et al. (2018, Drugs), Drug-induced kidney stones review	Comprehensive review of drug-induced kidney stones and crystalline nephropathy, including detailed coverage of topiramate-associated calcium phosphate stones	—	—	Topiramate-associated nephrolithiasis is predominantly calcium phosphate driven by carbonic anhydrase inhibition with reduced citrate excretion and alkaline urine; management includes hydration, dietary modification, and consideration of dose reduction or alternative therapy in recurrent stone formers [daudon2018].
Kossoff et al. (2002, Epilepsia), Kidney stones, CA inhibitors, ketogenic diet	Clinical analysis of nephrolithiasis risk in pediatric patients on carbonic anhydrase inhibitors (including topiramate) and the ketogenic diet	—	—	Documented increased nephrolithiasis incidence in pediatric patients on topiramate, particularly in combination with the ketogenic diet; established nephrolithiasis as a class effect of CA inhibitors [kossoff2002].
Doose et al. (1997, Epilepsia), Topiramate	Pharmacokinetic study of topiramate's effect on the PK of an	—	—	Topiramate at higher doses reduces ethinyl estradiol AUC by approximately

Study	Design	Participants	Duration	Finding
and oral contraceptive PK in epilepsy	oral contraceptive containing norethindrone and ethinyl estradiol in patients with epilepsy			18-30%, with implications for combined oral contraceptive efficacy [doose1997]. Established the basis for contraception counseling on topiramate.
Doose et al. (2003, Epilepsia), Topiramate or carbamazepine OC PK in healthy obese and non-obese	Pharmacokinetic study comparing topiramate and carbamazepine on PK of an oral contraceptive containing norethindrone and ethinyl estradiol in healthy obese and nonobese female subjects	—	—	Extended the 1997 result into a healthy-volunteer population; confirmed dose-dependent reduction in ethinyl estradiol exposure on topiramate [doose2003].
Franco et al. (2021, Epilepsy & Behavior), Pediatric ASM AE Italian reporting analysis	Analysis of pediatric adverse reactions to antiseizure medications in the Italian spontaneous reporting system 2001-2019	—	—	Catalogued pediatric-specific adverse events to topiramate including oligohidrosis, metabolic acidosis, nephrolithiasis, and cognitive effects; informs pediatric monitoring practice [franco2021].

Topiramate Pharmacokinetics & Pharmacodynamics

Pharmacokinetics

Topiramate is rapidly absorbed after oral administration with bioavailability of approximately 80% and a time to maximum plasma concentration of 1-4 hours for immediate-release tablets and 5-15 hours for extended-release capsules. It is approximately 15-41% protein-bound. Steady-state is reached after approximately 4-8 days of dosing in patients with normal renal function. The elimination half-life is approximately 21 hours, supporting twice-daily immediate-release or once-daily extended-release dosing [shank2000].

Approximately 70% of topiramate is eliminated unchanged in the urine; the remainder is metabolized by hydrolysis, hydroxylation, and glucuronidation. Renal clearance is the principal elimination pathway and dose reduction is required in moderate to severe renal impairment. Topiramate is removed by hemodialysis with supplemental dosing required on dialysis days [fda_label_topamax].

Topiramate is a weak inducer of CYP3A4 at doses ≥200 mg/day, reducing ethinyl estradiol exposure by approximately 18-30% [doose1997, doose2003]. It is a weak inhibitor of CYP2C19. Concomitant enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin) reduce topiramate plasma concentrations by approximately 40-50% via induction of topiramate's minor metabolic pathways.

Pharmacodynamics

Pharmacodynamic effects reflect topiramate's multi-target pharmacology and are reliably observed across the clinical indications. Anticonvulsant effects (reduction in seizure frequency for partial-onset, primary generalized tonic-clonic, and Lennox-Gastaut drop-attack seizures) dominate the labeled epilepsy indications [faught1996, sachdeo1999]. Migraine prophylactic effects (reduction in monthly migraine days) are observed at 100 mg/day with no additional benefit at higher doses [brandes2004, silberstein2004]. Weight reduction is dose-related and is the basis for the Qsymia obesity combination [gadde2011, allison2012, garvey2012].

Secondary pharmacodynamic effects include reduction in serum bicarbonate (mild non-anion-gap metabolic acidosis) from carbonic anhydrase inhibition [kossoff2002], reduction in urinary citrate excretion contributing to calcium phosphate nephrolithiasis [daudon2018], reduction in sweat output (oligohidrosis, particularly in pediatric patients) [franco2021], and dose-related decrements in verbal fluency, word-finding, and working memory [loring2012, salinsky2007].

↓↑ Comparing Topiramate Formulations

Manufactured topiramate is available as immediate-release tablets (25, 50, 100, 200 mg; Topamax and generics), sprinkle capsules (15, 25 mg; Topamax), and extended-release capsules (25, 50, 100, 150, 200 mg; Trokendi XR and Qudexy XR) [fda_label_topamax]. Qsymia is supplied as fixed-dose phentermine/topiramate ER capsules at 3.75/23, 7.5/46, 11.25/69, and 15/92 mg with a REMS pregnancy prevention program [fda_label_qsymia].

Compounded topiramate preparations are oral capsules, oral suspensions, or other patient-specific oral forms prepared under USP <795> [usp_795]. They are not bioequivalent to the commercial products; clinicians should anticipate that local PK and tolerability may differ from manufactured-product published data and re-evaluate titration when switching from a commercial product to a compounded preparation.

Topiramate Storage and Handling

Manufactured topiramate tablets, sprinkle capsules, and extended-release capsules are stored at room temperature (20-25°C) in the original container; protection from moisture is recommended [fda_label_topamax]. Qsymia is stored at room temperature with the same conditions [fda_label_qsymia]. Compounded oral suspensions and capsules are stored per the pharmacy's stability data and beyond-use date assignment under USP <795>; refrigerated storage is typical for oral liquids to extend stability [usp_795].

Topiramate Compounding & Operations

503A compounding

Compounded topiramate is prepared under 503A on patient-specific prescriptions in state-licensed compounding pharmacies. RonanRx prepares oral capsules, oral suspensions, and other oral dosage forms per USP General Chapter <795>, the official compendial standard for nonsterile pharmaceutical compounding, with documented active ingredient sourcing, gravimetric verification, and beyond-use date assignment per the pharmacy's quality-management system [fda503a; usp_795].

Ingredient identity verification, beyond-use dating, and stability assessment follow USP <795> requirements [fda503a]. Each compounded batch is documented per state board of pharmacy retention rules with full traceability from API lot through dispensing. Generic topiramate is widely available, so the compounded role is narrow; RonanRx does not fill prescriptions that read as routine substitution of compounded for commercial topiramate without documented clinical rationale [fda_essentially_a_copy].

Pharmacist review

Each prescription for compounded topiramate undergoes pharmacist review prior to dispensing. The review confirms: a documented patient-specific clinical reason that the commercial Topamax, generic immediate-release, extended-release, sprinkle, or Qsymia product is not appropriate (excipient sensitivity, custom strength for pediatric dosing, oral liquid for swallowing-impaired patients); absence of contraindications (hypersensitivity to topiramate, pregnancy without REMS-equivalent counseling for weight-management use, untreated narrow-angle glaucoma); appropriate concomitant medication review including oral contraception counseling at topiramate doses ≥200 mg/day [doose1997, doose2003] and consideration of CNS depressant and carbonic anhydrase inhibitor interactions; and a prescribed regimen consistent with the labeled or evidence-based titration unless the prescriber documents a patient-specific reason [fda_label_topamax; fda_label_qsymia].

RonanRx does not fill prescriptions that read as routine substitution of compounded for commercial topiramate, consistent with FDA guidance on compounded copies of commercially available drugs [fda_essentially_a_copy] [fda_label_topamax]. Pregnancy testing and a documented contraception plan are reviewed for every patient of reproductive potential [margulis2012, hernandezdiaz2018].

Quality and traceability

Active pharmaceutical ingredients are sourced from FDA-registered facilities with documented certificates of analysis. Each batch is recorded with lot numbers traceable to API source, compounding date, beyond-use date, identity verification test result, and dispensing pharmacist of record. Finished product lot records are retained per state board of pharmacy retention requirements.

Cold chain

Compounded topiramate capsules are stored and shipped at room temperature [fda_label_topamax]. Compounded oral suspensions are typically refrigerated to extend stability and are shipped with appropriate cold-chain controls when assigned a refrigerated beyond-use date. Manufactured topiramate is stored at room temperature with protection from moisture per labeling.

Frequently Asked Questions About Topiramate

Is compounded topiramate the same as Topamax or generic topiramate?

No. Topamax and the immediate-release generics, Trokendi XR, Qudexy XR, and Qsymia are FDA-approved manufactured topiramate products [fda_label_topamax; fda_label_qsymia]. Compounded topiramate is pharmacy-prepared on a patient-specific prescription and is not bioequivalent to the manufactured products. Compounded drugs are not FDA-approved [fda503a].

When is a compounded version appropriate?

Per FDA guidance, a compounded version of an FDA-approved drug is generally restricted unless the prescriber documents a patient-specific clinical need that the manufactured product cannot meet, for example, excipient sensitivity, a custom strength for pediatric dosing outside the commercial increments, or an oral liquid suspension for a patient unable to swallow capsules or tablets [fda_essentially_a_copy]. Cost or preference does not qualify under section 503A.

What is topiramate FDA-approved for?

Topiramate (Topamax and generics) is FDA-approved for adjunctive therapy and monotherapy of partial-onset and primary generalized tonic-clonic seizures (ages ≥2 years), adjunctive therapy of Lennox-Gastaut syndrome (≥2 years), and migraine prophylaxis in adults [fda_label_topamax]. Qsymia (phentermine/

topiramate ER) is FDA-approved for chronic weight management in adults with BMI ≥30 or BMI ≥27 plus a weight-related comorbidity [fda_label_qsymia].

What are the most common side effects?

Paresthesias (tingling in hands and feet), fatigue, dizziness, somnolence, decreased appetite, weight loss, taste perversion (especially for carbonated beverages), and cognitive/word-finding difficulty colloquially called 'dopamax'. Most are dose-related and improve with slow titration or dose reduction [kossoff2002; franco2021]. Less common but important: kidney stones, mild metabolic acidosis, reduced sweating in children with risk of heat-related illness, and acute myopia with angle-closure glaucoma in the first month [loring2012; salinsky2007; daudon2018].

Why is topiramate a concern in pregnancy?

First-trimester topiramate exposure increases the risk of oral clefts (cleft lip with or without cleft palate) approximately 2- to 5-fold relative to unexposed pregnancies [margulis2012; hernandezdiaz2018]. Qsymia is contraindicated in pregnancy and requires monthly pregnancy testing under a REMS program [fda_label_qsymia]. For epilepsy or migraine prophylaxis in women of reproductive potential, contraception counseling is essential and alternative agents should be considered preconceptionally where reasonable.

Does topiramate make birth control pills less effective?

Yes, at doses ≥200 mg/day topiramate reduces ethinyl estradiol exposure by approximately 18-30%, which can lower combined oral contraceptive efficacy [doose1997; doose2003]. Patients on these doses should use a non-oral contraceptive method or add a barrier method. At lower doses (e.g., 100 mg/day for migraine prophylaxis), the effect is smaller but contraception counseling is still appropriate.

Does RonanRx sell compounded topiramate directly to patients?

No. Compounded topiramate requires a patient-specific prescription written by a licensed doctor for an identified patient with a documented clinical reason that a commercial product is not appropriate, plus pharmacist review before dispensing [fda_essentially_a_copy]. RonanRx is not a direct-to-consumer storefront [fda503a].

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How to Access Topiramate

Compounded Topiramate is dispensed under 503A on a patient-specific prescription. Depending on your role, the next step looks different.

FOR PRESCRIBING CLINICIANS

Offer this medication

A pharmacist will follow up within two business days. We'll cover state availability, supported formulations, and what integration looks like for your clinic.

ronanrx.com/request-partnership-call

PATIENT WITH A DOCTOR

Receive your prescription

If your doctor has prescribed Topiramate, sign up so we can prepare and ship your medication. The signup wizard collects intake and connects you to the prescribing workflow.

ronanrx.com/patients

PATIENT WITHOUT A DOCTOR

Find a partner clinic

RonanRx prescribes through partner clinics — we don't initiate prescriptions on this site. Read how the referral process works and how to find a partner clinic in your state.

ronanrx.com/find-clinic

Other compounds RonanRx makes

This monograph is one of many in the RonanRx formulary. Every compound below is prepared under 503A on a patient-specific prescription. Browse the full catalog at ronanrx.com/medications and ronanrx.com/peptides, or scan the codes at right for each index.

Medications

Peptides

MEDICATIONS (40)

Alpha-Lipoic Acid (ALA) — Antioxidant & mitochondrial
Coenzyme Q10 (CoQ10) — Antioxidant & mitochondrial
Glutathione — Antioxidant & mitochondrial
NAD+ / NMN — Antioxidant & mitochondrial
Compounded Topical Anesthetics (BLT, LET) — Dermatology
Topical Minoxidil — Dermatology
Topical Tretinoin — Dermatology
Compounded Magnesium — Energy & nutritional
Cyanocobalamin — Energy & nutritional
High-Dose Vitamin D — Energy & nutritional
Hydroxocobalamin — Energy & nutritional
Iron (Compounded) — Energy & nutritional
L-Carnitine — Energy & nutritional
Methylcobalamin (B12) — Energy & nutritional
Methylfolate — Energy & nutritional
Anastrozole — Hormone optimization
Clomiphene & Enclomiphene — Hormone optimization
DHEA — Hormone optimization
Estradiol — Hormone optimization
Estriol — Hormone optimization
Human Chorionic Gonadotropin (HCG) — Hormone optimization
Pregnenolone — Hormone optimization
Progesterone — Hormone optimization
Testosterone — Hormone optimization
Compounded Metformin — Metabolic & weight
Compounded Semaglutide — Metabolic & weight
Compounded Tirzepatide — Metabolic & weight
Lipotropic Injection (MIC, MICC) — Metabolic & weight
Low-Dose Naltrexone (LDN) — Metabolic & weight
Naltrexone-Bupropion Combination — Metabolic & weight
Topiramate — Metabolic & weight
Bremelanotide / PT-141 — Sexual health
Compounded Sildenafil — Sexual health
Compounded Tadalafil — Sexual health
Trimix Injection — Sexual health
Compounded Gabapentin — Sleep & recovery
Compounded Melatonin — Sleep & recovery
Compounded T3 (Liothyronine) — Thyroid
Compounded T3/T4 Combinations — Thyroid
Compounded T4 (Levothyroxine) — Thyroid

PEPTIDES (21)

Sermorelin — Available now

Tesamorelin — Available now

AOD-9604 — Growth-hormone axis (under FDA review)

CJC-1295 — Growth-hormone axis (under FDA review)

GHRP-2 / GHRP-6 — Growth-hormone axis (under FDA review)

Hexarelin — Growth-hormone axis (under FDA review)

Ipamorelin — Growth-hormone axis (under FDA review)

MK-677 / Ibutamoren — Growth-hormone axis (under FDA review)

5-Amino 1MQ — Metabolic & longevity (under FDA review)

Epitalon / Epithalon — Metabolic & longevity (under FDA review)

MOTS-C — Metabolic & longevity (under FDA review)

Thymosin Alpha-1 / Thymalin — Metabolic & longevity (under FDA review)

DSIP, Delta Sleep-Inducing Peptide — Neuro & cognitive (under FDA review)

Selank — Neuro & cognitive (under FDA review)

Semax — Neuro & cognitive (under FDA review)

Vasoactive Intestinal Peptide (VIP) — Neuro & cognitive (under FDA review)

BPC-157 — Tissue repair (under FDA review)

KPV — Tissue repair (under FDA review)

LL-37 — Tissue repair (under FDA review)

Pentadeca Arginate (PDA) — Tissue repair (under FDA review)

TB-500 / Thymosin Beta-4 — Tissue repair (under FDA review)