

Help her have *more* migraine-free days with the right topiramate dose.

Not actual patient. Used for illustrative purposes.

INDICATION

Trokendi XR (topiramate) extended-release capsules are indicated for prophylaxis of migraine headaches in patients 12 years of age and older.

CONTRAINDICATIONS

Trokendi XR is contraindicated in patients with recent alcohol use (within 6 hours prior to and 6 hours after Trokendi XR use).

Please refer to the full Prescribing Information and Important Safety Information (pages 2 and 3) for complete information on Trokendi XR, or visit www.TrokendiXR.com.

ONCE-DAILY FOR MIGRAINE PREVENTION

Trokendi XR[®]
(topiramate) extended-release capsules
25 mg 50 mg 100 mg 200 mg





The right topiramate dose may help you do *more* for migraine patients.

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Trokendi XR[®] (topiramate) extended-release capsules for oral use

INDICATION

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IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Trokendi XR is contraindicated in patients with recent alcohol use (within 6 hours prior to and 6 hours after Trokendi XR use).

WARNINGS & PRECAUTIONS

- A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving topiramate. Symptoms can include acute onset of decreased visual acuity and/or ocular pain, myopia, anterior chamber shallowing, ocular hyperemia, and increased intraocular pressure. Symptoms typically occur within 1 month of initiating topiramate therapy. The primary treatment to reverse symptoms is discontinuation of Trokendi XR as rapidly as possible. Elevated intraocular pressure of any etiology, if left untreated, can lead to serious sequelae including permanent vision loss.
- Visual field defects (independent of elevated intraocular pressure) have been reported in patients receiving topiramate. In clinical trials, most events were reversible after topiramate discontinuation. If problems occur at any time during topiramate treatment, consider discontinuation of the drug.
- Oligohydrosis resulting in hospitalization has been reported in some cases in association with topiramate use. The majority of reports have been in pediatric patients. Patients, especially pediatric patients, should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather. Caution should be used when Trokendi XR is prescribed with other drugs that predispose patients to heat-related disorders.
- Hyperchloremic, non-anion gap, metabolic acidosis has been reported in adults and pediatric patients treated with topiramate. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of topiramate on carbonic anhydrase. Conditions that predispose patients to acidosis may be additive to the bicarbonate-lowering effects of topiramate. Although Trokendi XR is not approved for children under 6 years of age, a study of topiramate as adjunctive treatment in patients under 2 produced metabolic acidosis of a notably greater magnitude than in older children and adults. Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate. The incidence of persistent decreases in serum bicarbonate in placebo-controlled trials with immediate-release topiramate for adults for prophylaxis of migraine was higher than in the epilepsy controlled trials, and higher in adolescents than adults.
- In vitro data show that, in the presence of alcohol, the pattern of topiramate release from Trokendi XR capsules is significantly altered. Alcohol use should be completely avoided within 6 hours prior to and 6 hours after Trokendi XR administration.
- Antiepileptic drugs (AEDs) increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED, including Trokendi XR for any indication, should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Anyone prescribing Trokendi XR must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Many illnesses for which antiepileptic drugs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during Trokendi XR treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.
- Immediate-release topiramate can cause, and therefore Trokendi XR is expected to cause, cognitive/neuropsychiatric adverse reactions. In adults, the most frequent of these can be classified into three general categories: cognitive-related dysfunction, psychiatric/behavioral disturbances, and somnolence or fatigue.



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WARNINGS & PRECAUTIONS (continued)

- Topiramate can cause fetal harm when administered to a pregnant woman. Use during pregnancy and data from pregnancy registries indicate that infants exposed to topiramate in utero can have increased risk of cleft lip and/or cleft palate, and for being small for gestational age. Trokendi XR should only be used during pregnancy if the potential benefit outweighs the potential risk. Patients should be informed of the potential hazard to the fetus. Diarrhea and somnolence have been reported in breastfed infants whose mothers receive topiramate.
- Antiepileptic drugs, including Trokendi XR, should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency.
- Hyperammonemia with and without encephalopathy has been observed in post-marketing reports in patients who were taking topiramate with or without concomitant valproic acid (VPA); hyperammonemia appears more common when used concomitantly with VPA. Although Trokendi XR is not indicated for use in infants or toddlers, topiramate with concomitant VPA produced a dose-related increase in hyperammonemia in this population.
- The concomitant use of Trokendi XR with any other drug producing metabolic acidosis, or potentially in patients on a ketogenic diet, may increase the risk of kidney stone formation and should therefore be avoided.
- Hypothermia has been reported in association with topiramate use with concomitant valproic acid (VPA) both in the presence and in the absence of hyperammonemia. Consideration should be given to stopping topiramate or valproate in patients who develop hypothermia; clinical management should include examination of blood ammonia levels.
- Topiramate is a CNS depressant. Concomitant administration of topiramate with other CNS depressant drugs can result in significant CNS depression. Patients should be watched carefully when Trokendi XR is coadministered with other CNS depressant drugs.

DOSING GUIDELINES & CONSIDERATIONS

- Refer to the Trokendi XR DOSAGE AND ADMINISTRATION section of the full prescribing information for recommended dosing guidelines for Trokendi XR.
- In patients with renal impairment (creatinine clearance less than 70 mL/min/1.73 m²), one-half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.
- In patients undergoing hemodialysis, to avoid rapid drops in topiramate plasma concentration, a supplemental dose of topiramate may be required. The actual adjustment should take into account the duration of dialysis period, clearance rate of the dialysis system being used, and the effective renal clearance of topiramate in the patient being dialyzed.
- Trokendi XR can be taken without regard to meals. Swallow capsule whole and intact. Do not sprinkle on food, chew, or crush.

ADVERSE REACTIONS

- Trokendi XR has not been studied in a randomized, placebo-controlled phase 3 clinical study; however, it is expected that Trokendi XR would produce a similar adverse reaction profile as that of immediate-release topiramate. See the ADVERSE REACTIONS section of the Trokendi XR full prescribing information for further adverse reaction rates from the clinical trials conducted under widely varying conditions.
- In migraine prophylaxis trials of 100 mg immediate-release topiramate, the most common adverse reactions in adults that were higher than placebo were paresthesia (51% v 6%, 100 mg/day v placebo), anorexia (15% v 6%), upper respiratory tract infection (14% v 12%), weight decrease (9% v 1%), taste perversion (8% v 1%), diarrhea (11% v 4%), difficulty with memory (7% v 2%), hypoaesthesia (7% v 2%), nausea (13% v 8%), and abdominal pain (6% v 5%).

With the right dose, effective prevention may be possible.

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25 mg 50 mg 100 mg 200 mg

Topiramate can be a highly effective molecule for migraine prevention, depending on how it is dosed¹⁻³

Significant reductions in migraine frequency beginning at 100 mg total daily dose¹⁻³

Study overview^{1,2}

Two multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trials evaluating the efficacy of immediate-release topiramate (TPM-IR) in the prophylactic treatment of migraine.

Study 1 was conducted in the US; Study 2 was conducted in the US and Canada. Trial design was identical, enrolling patients 12 to 65 years of age with a history of migraine, with or without aura, for at least 6 months, according to IHS diagnostic criteria.

Patients experiencing cluster, basilar, ophthalmoplegic, hemiplegic, or transformed migraine were excluded.

Treatment^{1,2}

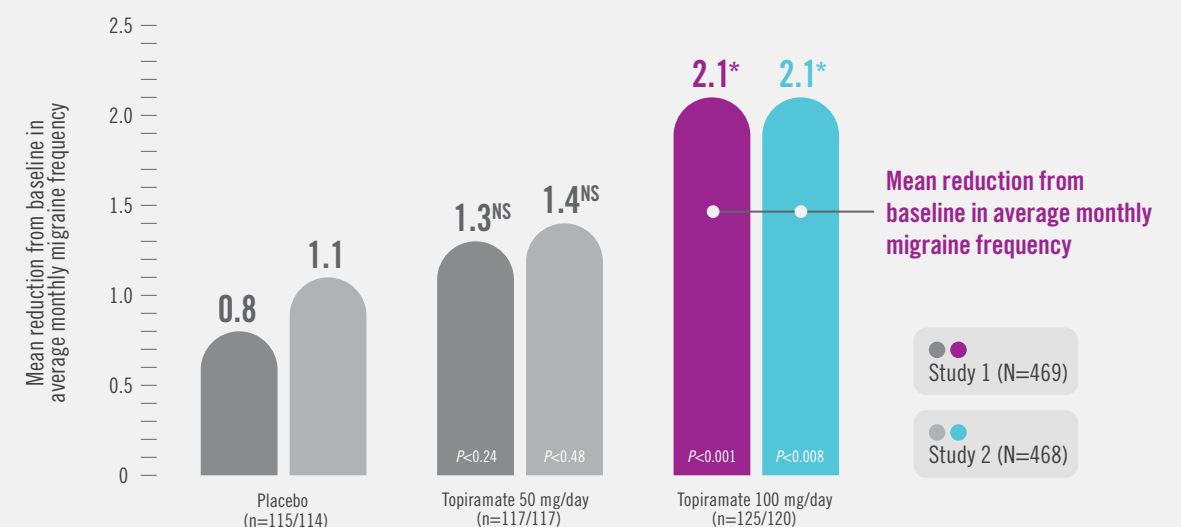
Patients experiencing 3 to 12 migraines over a 28-day prospective baseline phase were randomized to TPM-IR 50 mg/day, 100 mg/day, 200 mg/day, or placebo, and treated for 26 weeks (8-week titration period; 18-week maintenance period).

Treatment was initiated at 25 mg/day for 1 week, then daily dose was increased by 25-mg increments weekly until reaching the assigned target dose or maximum tolerated dose (administered twice daily).

Analysis^{1,2}

Treatment efficacy was assessed by the reduction in migraine frequency, as measured by the change in 4-week migraine rate (migraine classified by IHS criteria) from the baseline phase to double-blind treatment period in each TPM-IR treatment group, compared to placebo, in the ITT population.

Primary endpoint: mean reduction from baseline (5.5 migraines per 28 days) in migraine frequency¹⁻⁴



The 200 mg/day dose group was also statistically different than placebo.
Mean reduction from baseline: Study 1 (n=112): 2.2; Study 2 (n=117): 2.4 ($P<0.001$ for both).^{1,2}

Abbreviations: TPM-IR, immediate-release topiramate; IHS, International Headache Society; ITT, intent-to-treat; NS, not statistically significant.



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Have you asked your patients how they are doing on TPM-IR?

100 mg is the recommended total daily dose of topiramate^{1,2,5}

Adverse reactions in pooled, placebo-controlled migraine trials of Topamax[®] (topiramate)^{4,5}

Incidence ≥5% in any TPM-IR group and greater than the placebo rate

Adverse reactions	Topamax dosage (mg/day)		
	Placebo (n=445) %	50 mg (n=235) %	100 mg (n=386) %
Paresthesia	6	35	51
Fatigue	11	14	15
Anorexia	6	9	15
Upper respiratory tract infection	12	13	14
Nausea	8	9	13
Diarrhea	4	9	11
Weight loss	1	6	9
Taste perversion	1	15	8
Hypoesthesia	2	6	7
Somnolence	5	8	7
Difficulty with memory	2	7	7

Adverse reactions	Topamax dosage (mg/day)		
	Placebo (n=445) %	50 mg (n=235) %	100 mg (n=386) %
Insomnia	5	6	7
Difficulty with concentration/attention	2	3	6
Mood problems	2	3	6
Injury	7	9	6
Language problems	2	7	6
Abdominal pain	5	6	6
Sinusitis	6	10	6
Pharyngitis	4	5	6
Dyspepsia	3	4	5
Anxiety	3	4	5
Arthralgia	2	7	3

It is expected that Trokendi XR would produce a similar adverse event profile to TPM-IR.

Abbreviation: TPM-IR, immediate-release topiramate.

Once-daily dosing may help patients reach the right dose.

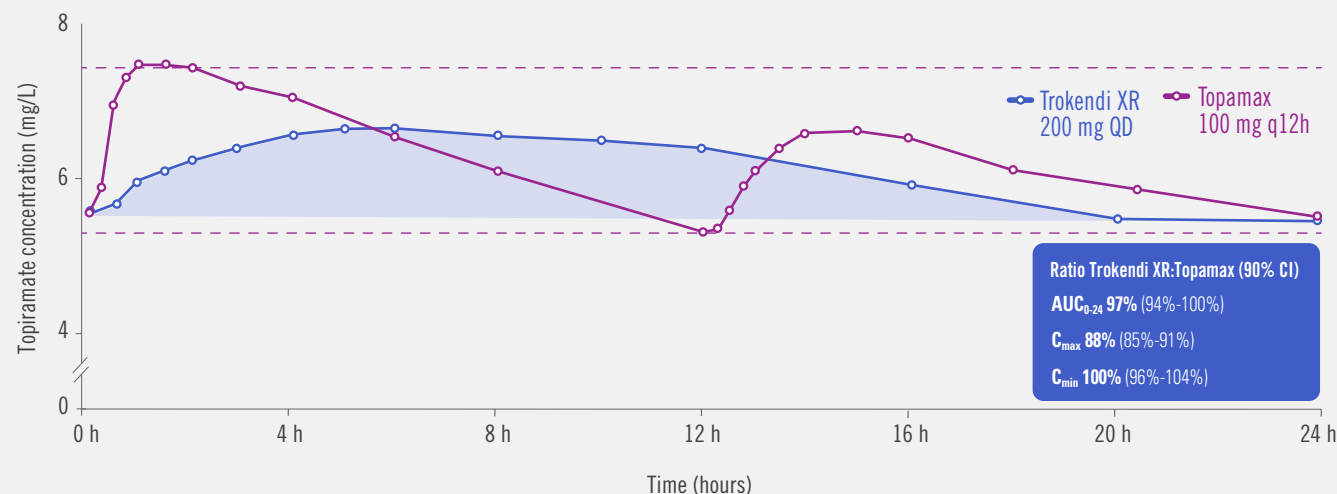
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Trokendi XR delivers all-day migraine prevention coverage^{3,5}

Trokendi XR has a slow rate of rise and low peak-to-trough fluctuation^{3,5}

Once-daily Trokendi XR is bioequivalent to twice-daily Topamax[®] (topiramate)—24-hour mean SS plasma concentration-time profiles^{3,5}

Primary endpoint³—Relative bioavailability of Trokendi XR and Topamax at SS



Fluctuation in plasma concentration of QD Trokendi XR was ~26% for healthy subjects compared to ~40% for subjects taking TPM-IR.^{3,5}

Abbreviations: CI, confidence interval; PK, pharmacokinetic; SS, steady state; TPM-IR, immediate-release topiramate.

Study design³

- A phase 1, single-center, multiple-dose, single-blind, randomized, crossover, PK study of Trokendi XR (200 mg once daily) and Topamax (100 mg twice daily) in 39 healthy adults
- Subjects were titrated to a 200 mg/day dose of either Trokendi XR or Topamax over a period of 3 weeks
- Following titration, subjects were maintained on 200 mg/day for 10 days
- Following a 32-day washout period, subjects crossed over to alternate treatment

Once-daily Trokendi XR uses Microtrol[®] technology—

3 types of specially coated microbeads that help achieve all-day migraine prevention coverage.



- Rapid-release beads
- Intermediate-release beads
- Extended-release beads

For illustration purposes only; does not represent Trokendi XR or the actual time medicine is released.





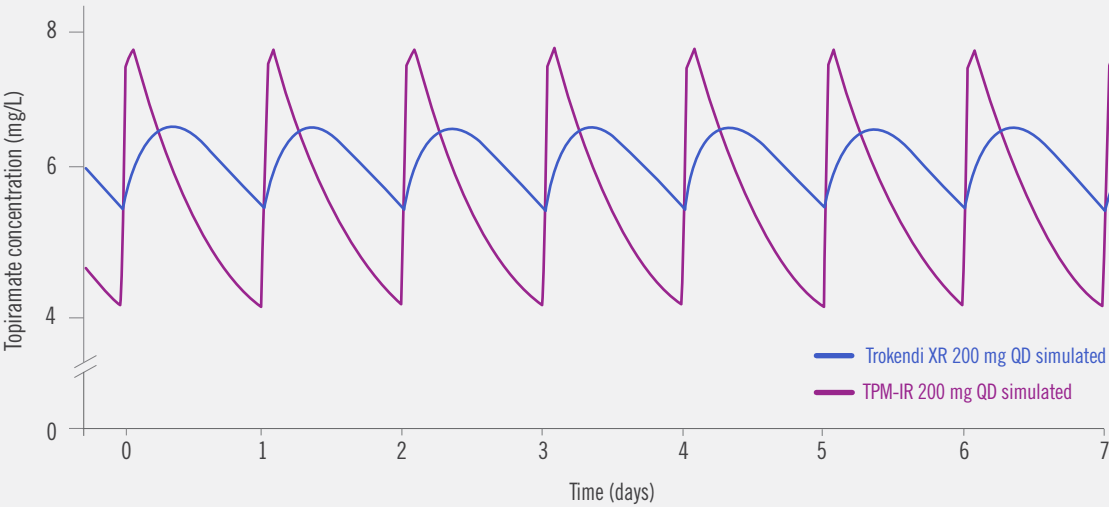
Once-daily dosing may help patients reach the right dose.

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One capsule a day for steady 24-hour coverage^{3,5}

Trokendi XR is designed and approved to be prescribed once daily; immediate-release topiramate is not^{4,5}

Population PK modeling and dosing simulation based on bioavailability in patients with epilepsy^{*,3,6}



*Randomized controlled trials have not explored the consequences of dosing irregularities for an extended-release AED and its q12h counterpart. Because they can be powerful predictive tools, population PK modeling and simulation were used to compare the potential PK consequences of dosing irregularities during SS AED treatment with Trokendi XR QD and TPM-IR q12h. In addition, simulations compared QD dosing of Trokendi XR and TPM-IR to address the perception that, due to the long half-life of topiramate, QD dosing produces relatively constant topiramate concentrations, regardless of formulation.⁶

Simulated fluctuation of topiramate concentrations at SS were approximately⁶:

- 18% for subjects with epilepsy taking once-daily Trokendi XR 200 mg q24h
- 64% for subjects with epilepsy taking once-daily TPM-IR 200 mg q24h



“One of the issues is that patients initially perceive extended release as nothing more than a convenience option. But the once-a-day formulations also smooth out the drug peak and troughs.”^{†,3}

Dr. Stephen D. Silberstein
Professor of Neurology, Thomas Jefferson University

[†]Dr. Silberstein is a paid consultant for Supernus Pharmaceuticals, Inc.
Abbreviations: AED, antiepileptic drug; PK, pharmacokinetic; SS, steady state; TPM-IR, immediate-release topiramate.



Fewer migraines may mean fewer missed days.

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In a pragmatic assessment of clinical charts, patients reported fewer migraines with Trokendi XR⁷

Trokendi XR retrospective record review methodology⁷



Study design

- Study approved by central institutional review board; HIPAA-compliant, deidentified patient data abstracted from randomly selected medical charts
- Physicians identified as Trokendi XR prescribers were recruited for participation
- Data from 23 centers nationally purchased from Symphony Health Solutions
- Data was retrieved from patients treated with Trokendi XR (n=485)
- AEs were not recorded in every chart. It is unknown whether side effects occurred but were not recorded in those charts
- Analyzed as a post hoc subset analysis of patients who switched from TPM-IR to Trokendi XR
- Data abstraction included the following (but not limited to): AEs, previous treatment with TPM-IR, and reason for drug discontinuation



Inclusion criteria

- Trokendi XR initiated from August 2013 to June 2014
- Age ≥6 yr
- Record of Trokendi XR-initiating visit
- ≥1 postinitiation visit



Migraine cohort (N=285)⁷

- 60% previously on another migraine prevention medicine
- **Median dosage of Trokendi XR (100 mg/day) was the same as the previous TPM-IR dosage**
- Median postinitiation follow-up: 92 days³

Responder rate: percent change from preindex migraine frequency associated with Trokendi XR treatment (n=159)⁷

1 in 4 patients migraine free⁷



55% of patients experienced ≥50% reduction in migraine frequency⁷



41% of patients experienced ≥75% reduction in migraine frequency⁷



24% of patients were migraine free⁷

Trokendi XR is bioequivalent to TPM-IR. Approximately 6% of patients taking topiramate in the randomized controlled trials used for the approval of TPM-IR achieved 100% reduction in migraine.^{3,8}

Abbreviations: AEs, adverse events; HIPAA, Health Insurance Portability and Accountability Act; TPM-IR, immediate-release topiramate.



Fewer migraines may mean fewer missed days.

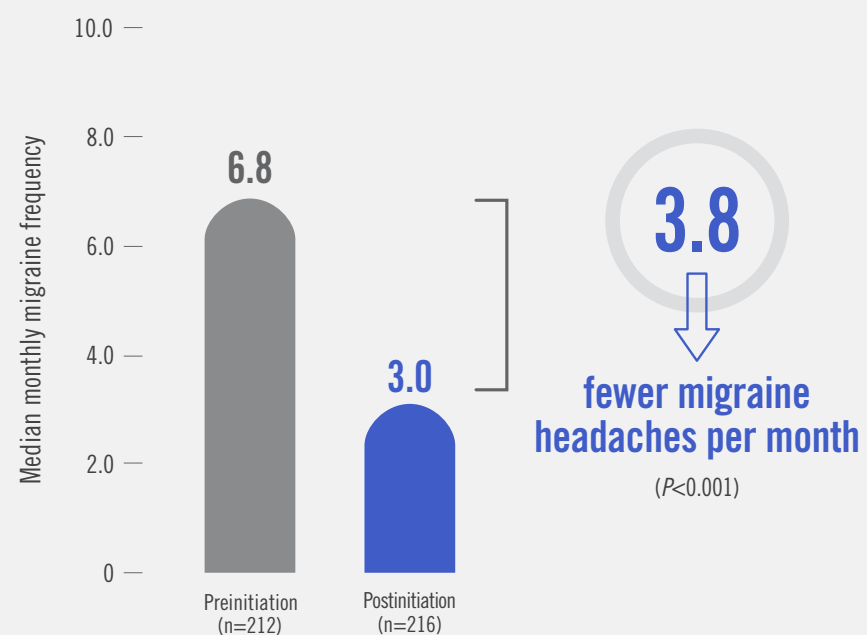
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Relative reduction

Median monthly migraine frequency postinitiation of Trokendi XR was less than preinitiation: 3.0 vs. 6.8 ($P < 0.001$)⁷

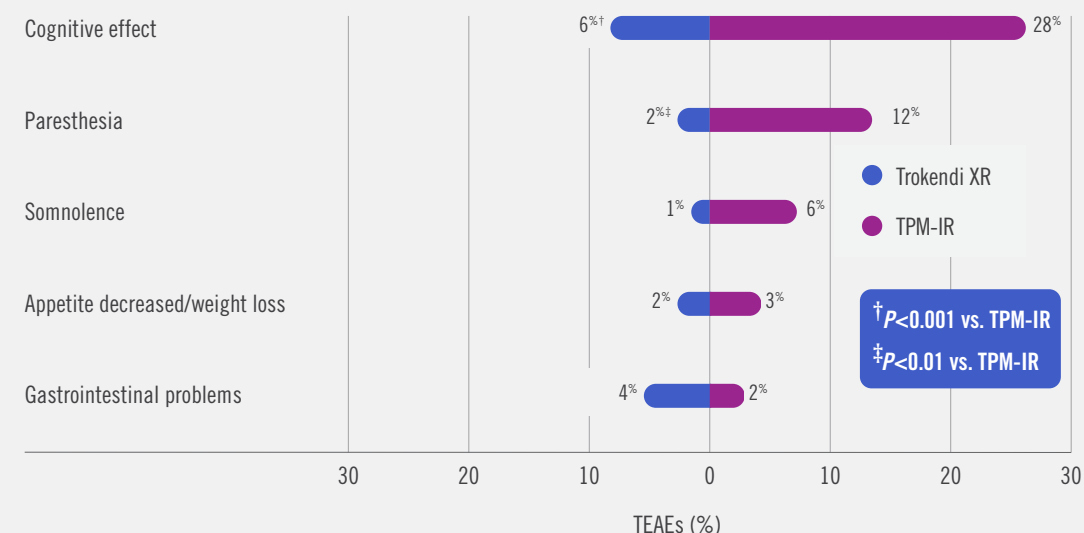
Relative reduction: median monthly migraine frequency pre- vs. postinitiation of Trokendi XR



Larger data sets and prospective studies are needed to confirm observations from this pilot study of Trokendi XR.

Subset analysis

Trokendi XR was associated with a relatively low incidence of any TEAEs (n=124)*,⁷



It is expected that Trokendi XR would produce a similar adverse event profile to TPM-IR.

TPM-IR was dosed BID (as recommended in labeling based on randomized controlled trials) in 54% of patients; Trokendi XR was dosed QD in 98% of patients.⁷

*AEs were not recorded in every chart. It is unknown whether side effects occurred but were not recorded in those charts.

Abbreviations: AEs, adverse events; TEAEs, treatment-emergent AEs; TPM-IR, immediate-release topiramate.



Convert your TPM-IR patients to a therapy they may prefer.



89% of patients preferred Trokendi XR in a 2018 survey³



Participants

All registered patients in the Trokendi XR Customer Relationship Marketing (CRM) database at the time of the survey launch on March 1, 2018, (N=50,663) opted into the program to receive email communications from Supernus Pharmaceuticals.



Survey

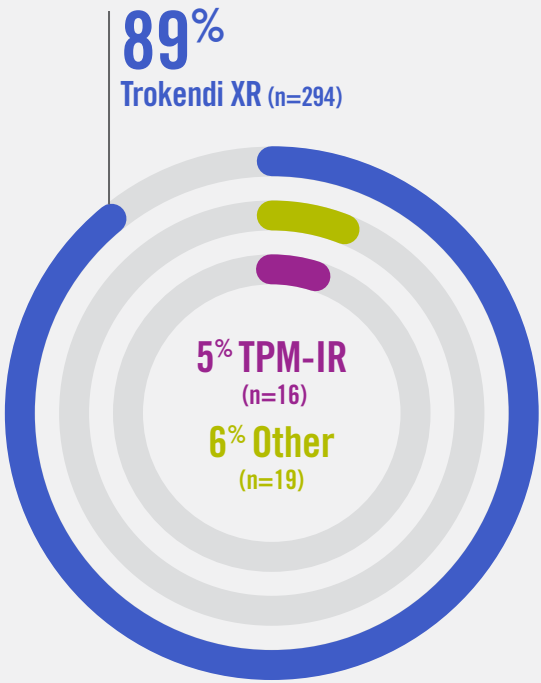
Question 1 determined the flow of the survey:
Are you currently taking Trokendi XR for migraine prevention?
Patients who answered “No” (n=107) were asked only 1 additional multiple choice question regarding why they had not started treatment.
Patients who answered “Yes” (n=340) were asked the remaining 8 survey questions.
Answers were not required for every question, and patients were permitted to skip 1 or more question(s).



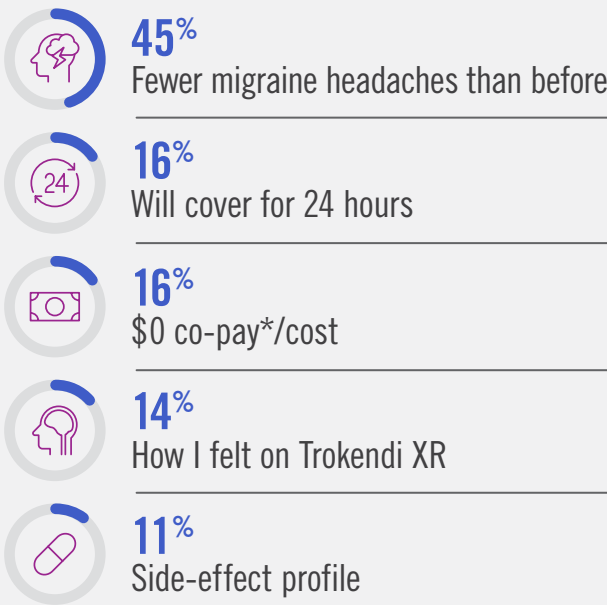
Data

Data was collected upon survey submission through cross referencing of email addresses on survey link and initial CRM registration.

Preference of migraine patients (n=329)³



Top reasons patients prefer Trokendi XR (n=294)³



Additional response: I prefer another therapy (1%)

*Terms and Conditions: Offer applies only to prescriptions (1) that are subject to a private insurance co-pay requirement, or (2) for which the patient has no insurance. Offer not valid for patients who are enrolled in a federal or state program that provides prescription benefits through retail or mail-order pharmacies, including Medicare Part D and Medicaid. Offer void where prohibited. Other restrictions apply. For full terms and conditions, please see the Trokendi XR Co-Pay Card, or visit www.TrokendiXR.com.

Abbreviation: TPM-IR, immediate-release topiramate.

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Seamlessly switch to Trokendi XR for once-daily migraine prevention

Example of next-day conversion for patients taking twice-daily Topamax® (topiramate)*,3

Topamax
50 mg BID



100 mg total daily dose

Trokendi XR
100 mg QD



Daily



100 mg total daily dose

***Recommended dose of Trokendi XR for migraine prophylaxis is 100 mg/day.⁵**

Trokendi XR may be taken without regard to meals. Swallow capsule whole and intact.
Do not sprinkle on food, chew, or crush.

Abbreviation: TPM-IR, immediate-release topiramate.

Help patients save with just a couple of steps



You

Prescribe Trokendi XR for your TPM-IR patients



Your patient

Activates the Trokendi XR savings card and picks up Rx at their local pharmacy



Trokendi XR



Eligible, commercially insured patients
pay as little as \$0 for up to 12 months*

Download the savings card at [TrokendiXRhcp.com/patient-savings](https://www.TrokendiXRhcp.com/patient-savings).

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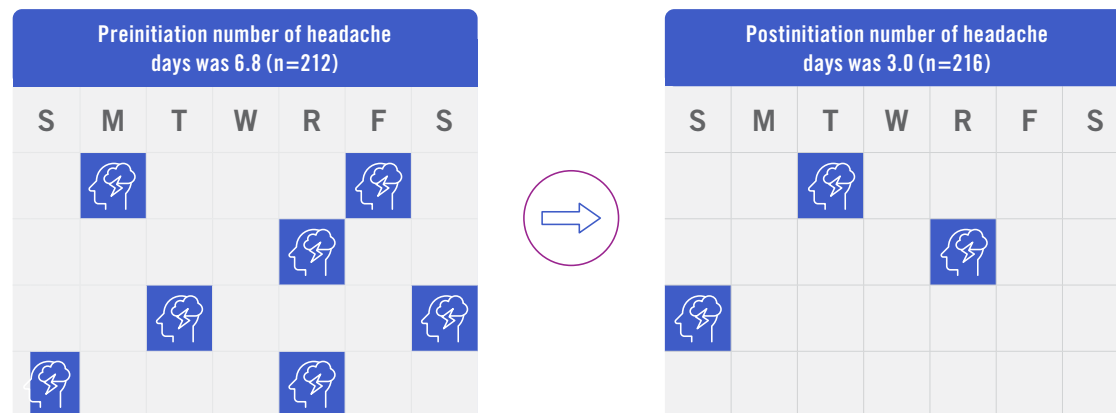
25 mg 50 mg 100 mg 200 mg

Help her have *more* migraine-free days
with the right topiramate dose.

Not actual patient. Used for illustrative purposes.

Once-daily dosing with Trokendi XR may help patients achieve effective migraine prevention

At a median dosage of 100 mg/day, patients experienced 3.8 fewer migraines per month with Trokendi XR
($P < 0.001$) in the Trokendi XR pragmatic assessment.⁷



Larger data sets and prospective studies are needed to confirm observations from this pilot study of Trokendi XR. Please see page 8 for a complete description of the study.

INDICATION

Trokendi XR (topiramate) extended-release capsules are indicated for prophylaxis of migraine headaches in patients 12 years of age and older.

CONTRAINDICATIONS

Trokendi XR is contraindicated in patients with recent alcohol use (within 6 hours prior to and 6 hours after Trokendi XR use).

References:

1. Silberstein SD, Neto W, Schmitt J, Jacobs D; MIGR-001 Study Group. Topiramate in migraine prevention. *Arch Neurol*. 2004;61:490-495. 2. Brandes JL, Saper JR, Diamond M, et al. Topiramate for migraine prevention: a randomized controlled trial. *J Amer Med Assoc*. 2004;291:965-973. 3. Data on file. Supernus Pharmaceuticals, Inc. 4. Topamax [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; May 2019. 5. Trokendi XR [package insert]. Rockville, MD: Supernus Pharmaceuticals, Inc.; February 2019. 6. Brittain ST, Wheless JW. Pharmacokinetic simulations of topiramate plasma concentrations following dosing irregularities with extended-release vs. immediate-release formulations. *Epilepsy Behav*. 2015;52:31-36. 7. O'Neal W, Hur E, Liranso T, Barr P. Pragmatic assessment of Trokendi XR[®] (extended-release topiramate) in migraine prevention. Poster presented at: 59th Annual Scientific Meeting of the American Headache Society[®]; June 8-11, 2017. Boston, MA. 8. Bussone G, Diener HC, Pfeil J, Schwalen S. Topiramate 100 mg/day in migraine prevention: a pooled analysis of double-blind randomized controlled trials. *Int J Clin Pract*. 2005;59:961-968.

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Well-established safety profile with more than 1.7 million prescriptions for migraine prevention³



Simple conversion to once-daily Trokendi XR from Topamax[®] (topiramate) is next day, with no washout and no titration^{3,5}



All commercially approved patients pay as little as \$0 for the next 12 prescriptions*

*For full terms and conditions, please see the Trokendi XR Co-pay Card, or visit [TrokendiXR.com](https://www.trokendixr.com).