TOPAMAX® (topiramate)
Switching From or to Generic Formulations of TOPAMAX

SUMMARY

- Utilize clinical oversight when switching patients to or from generic formulations of TOPAMAX. This document is a summary of the clinical literature and is not intended as an endorsement of any practices, uses, or clinical management not contained in the approved product labeling.
- The United States Food and Drug Administration (US FDA) defines bioequivalence as no significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of action when administered at the same molar dose under similar conditions in an appropriately designed study. Please refer to: Orange Book Preface, US Food and Drug Administration Center for Drug Evaluation and Research Approved Drug Products with Therapeutic Equivalence Evaluations for complete information.[1]
- **Formulation Switch (extended-release/immediate-release)**
  - **Bialer et al (2013)**[2] conducted a randomized, phase 1, open-label, two-way crossover study in 38 healthy adults (18-65 years of age) comparing the steady-state pharmacokinetics (PK) of topiramate extended-release (TPM-ER 200 mg once daily [QD]) with topiramate immediate-release (TPM-IR 100 mg twice daily [BID]). Systemic exposures were equivalent between TPM-ER (200 mg QD) and TPM-IR (100 mg BID) at steady state, demonstrating slower absorption, a longer plateau time (POT), and a reduced fluctuation index (FI)%.
- **Generic Substitution**
  - **Duh et al (2009)**[3] investigated the clinical and economic consequences of single versus multiple generic substitutions of topiramate in 948 patients with epilepsy. Multiple-generic use was associated with higher hospitalization rates and a longer mean hospital stay and increased risk of head injury or fracture compared with branded use.
- **Recommendations from Professional Organizations**
  - **Asadi-Pooya et al (2022)**[4] indicated that switching from brand-to-generic antiseizure medications (ASMs), including topiramate, is generally safe and effective when products are approved by stringent regulatory authorities (FDA, European Medicines Agency [EMA]) and manufactured under Good Manufacturing Practice (GMP) standards.
  - **Elmer et al (2022)**[5] outlined the distinctions between brand-name and generic ASMs, emphasizing key pharmacotherapeutic concerns associated with generics and summarized position statements from major US epilepsy organizations (American Academy of Neurology [AAN], 2007; Epilepsy Foundation [EF], 2006; and American Epilepsy Society [AES], 2016) regarding brand-to-generic and generic-to-generic substitution.
- Additional citations identified during the literature search are included in the REFERENCES section for your review.[6-8]

CLINICAL DATA

Formulation Switch (extended-release/immediate-release)

Bialer et al (2013)[2] conducted a randomized, phase 1, open-label, two-way crossover study in 38 healthy adults (18-65 years of age) to compare the steady-state PK of TPM-ER (200 mg QD) with TPM-IR (100 mg BID).

Patients underwent a 12-day up-titration, two 14-day maintenance periods with immediate crossover, and an 8-day down-titration. Overall, 36 participants completed both treatment sequences and were included in the steady-state PK equivalence analysis. PK parameters

assessed included AUC_{0-24}, C_{max}, C_{min}, average topiramate plasma concentration during dosing interval at steady state (C_{avg}), time to C_{max} (t_{max}), FI, POT, and percent coefficient of variation (%CV) of plasma concentrations. Partial AUC ($AUC_{\_p}$) analyses were also performed to evaluate systemic exposure across clinically relevant intervals.

Results showed that systemic exposure (AUC_{0-24}, C_{min}, C_{max}) was equivalent between TPM-ER and TPM-IR at steady state, with geometric least-squares mean (GLSM) ratios and 90% CI contained within the 80-125% equivalence limits. TPM-ER demonstrated slower absorption (median t_{max} 6 h vs 1 h), a longer POT (13 h vs 4 h), and a lower FI 38% vs 53%. Plasma variability was significantly lower with TPM-ER (%CV 11.9% vs 15.7%; $P<0.05$), and steady-state concentrations were achieved earlier (day 5 vs day 7). Importantly, switching between formulations did not alter steady-state plasma concentrations, with PK equivalence maintained immediately after crossover. See Table: Pharmacokinetic Parameters of TPM-ER and TPM-IR and Table: Pharmacokinetic Parameters Before and After Formulation Switch.

Safety

Treatment-emergent adverse events (TEAEs) occurred in 34 (89.5%) patients, and all TEAEs were mild in intensity and were similar between groups. Common TEAEs (≥10% patients) included diarrhea, headache, and paresthesia. Cognitive disorders and memory impairment were more frequent with TPM-IR, while postural dizziness and contusion were reported with TPM-ER. No serious adverse events or deaths occurred.

Pharmacokinetic Parameters of TPM-ER and TPM-IR[2]

Parameter	TPM-ER 200 mg QD (N=36)	TPM-IR 100 mg BID (N=36)	Ratio of TPM-ER/TPM-IR, GLSM% (90% CI)
AUC_{0-24}, mg h/L	158 (32)	153 (33)	104 (102-105)
AUC_{0-T}, mg h/L	158 (32)	78 (17)	NC
C_{min}, mg/L	5.3 (1.2)	5.0 (1.2)	106 (103-109)
C_{max}, mg/L	7.9 (1.5)	8.4 (1.7)	93 (90-97)
C_{avg}, mg/L	6.6 (1.3)	6.5 (1.4)	NC
T_{max}, h[a]	6.0 (2.0, 17)	1.0 (0.5, 14)	NC
POT, h	13 (5)b	4 (2.3)	NA
CV, %	11.9 (2.6)[b]	15.7 (3.1)	NA
FI, %	38 (11)	53 (12)	74 (68-80)[c]

Abbreviations: AUC, area under the concentration-time curve; BID, twice daily; C_{avg}, average plasma concentration; CI, confidence interval; C_{max}, peak plasma concentration; CV, coefficient of variation of TPM steady-state plasma levels; ER, extended-release, FI, fluctuation index; GLSM, geometric least-squares mean; IR, immediate-release; NA, not applicable; NC, not calculated; PE, point estimate; POT, peak occupancy time or plateau time; QD, once daily; T_{max}, time to C_{max}; TPM, topiramate.
Data reported as mean (SD), unless otherwise noted.
[a]Median (min, max).
[b]$P<0.05$ as compared with TPM-IR.
[c]90% CI was not contained within the equivalence limits.

Pharmacokinetic Parameters Before and After Formulation Switch[2]

Parameter	TPM-ER to TPM-IR			TPM-IR to TPM-ER		
	TPM-ER Day 14 (n=19)	TPM-IR Day 15 (n=19)	Ratio of GLSM[a] (90% CI)	TPM-IR Day 14 (n=17)	TPM-ER Day 15 (n=17)	Ratio of GLSM[a] (90% CI)
AUC_{0-24h}, mg h/L	152	150	99 (97-102)	147	148	101 (98-104)
C_{min}, mg/L	5.05	4.95	98 (93-103)	4.89	4.95	101 (99-104)
C_{max}, mg/L	7.62	8.14	107 (102-112)	8.20	7.40	90 (86-95)
C_{avg}, mg/L	6.32	6.39	101 (98-104)	6.25	6.18	99 (96-102)
FI, %	39	49	126 (110-144)	52	38	73 (67-80)

Abbreviations: AUC, area under the concentration-time curve; C_{avg}, average plasma concentration; CI, confidence interval; C_{max}, peak plasma concentration; ER; extended-release; FI, fluctuation index; GLSM, geometric least-squares mean; IR, immediate-release; TPM, topiramate.
[a]GLSM ratio of day 15 to day 14.

Generic Substitution

Duh et al (2009)[3] evaluated the clinical and economic consequences of single- versus multiple-generic substitutions of topiramate in patients with epilepsy. This analysis examined switching patterns of topiramate relative to other antiepileptic drugs (AEDs) and chronic-disease drugs and compared clinical and economic outcomes among patients treated with branded, single-generic, and multiple-generic topiramate.

This retrospective observational study used medical and pharmacy claims data from the RAMQ database from January 2006 to October 2007. The study population included 948 patients with epilepsy treated with topiramate. An open-cohort design was used to classify each patient's observation time into mutually exclusive periods of branded, single-generic, or multiple-generic topiramate use. Switching patterns were assessed using Kaplan-Meier methods, and clinical and economic outcomes were compared across exposure periods using person-time analyses and multivariate regression models adjusted for demographic, clinical, and treatment characteristics.

Switching Patterns

Among antiepileptic drugs (AEDs), including topiramate, 1-year generic substitution rates were 30.5% for AEDs with generic entry after 2000 and 18.2% for those with generic entry before 2000, compared with 35.9% for non-AED chronic-disease drugs. Switchback rates to the brand product were higher for AEDs (14.7% and 19.2%, respectively) than for non-AEDs (7.8%). Patients receiving generic AEDs used 1.4-2.8 generic versions, with 23-49% receiving ≥2 versions during the study period.

Health Care Utilization and Clinical Outcomes Following Switching

Prescription utilization for both AEDs and non-AEDs was higher during single-generic and multiple-generic use periods compared with branded use, with adjusted analyses showing higher utilization of other AEDs (IRR, 1.16; 95% CI, 1.09-1.23) and non-AED products (IRR, 1.31; 95% CI, 1.28-1.35) during multiple-generic topiramate use. Hospitalization rates were higher during multiple-generic use compared with branded use (IRR, 1.65; 95% CI, 1.28-2.13), and the mean length of hospital stay was longer (adjusted IRR, 1.43; 95% CI, 1.27-1.60). Differences in hospitalization rates between single-generic and branded use were not significant (IRR, 1.08; 95% CI, 0.88-1.34). Outpatient visit rates did not differ significantly across exposure periods.

Generic-to-generic substitution was associated with a higher risk of hospitalization compared with continuous branded use (hazard ratio [HR], 1.62; 95% CI, 1.05-2.50) and a higher risk of fracture or head injury (HR, 2.84; 95% CI, 1.24-6.48). Switching from branded to single-generic topiramate was not associated with significant increases in these risks.

RECOMMENDATIONS FROM PROFESSIONAL ORGANIZATIONS

Asadi-Pooya et al (2022)[4] reported findings from an International League Against Epilepsy (ILAE) Emergency Task Force-led narrative review and consensus report that provided guidance on managing epilepsy during ASM shortages, including recommendations on medication substitution strategies.

Switching from brand to generic ASMs has generally been shown to be safe and effective, particularly when generic products are approved by stringent regulatory authorities (eg, FDA, EMA) and manufactured under GMP standards. The report further highlights practical considerations to support safe transitions, including caution when switching extended-

release formulations, educating patients and caregivers, and conducting appropriate monitoring after formulation changes.

Elmer et al (2022)[5] outlined distinctions between brand-name and generic ASMs, emphasizing key pharmacotherapeutic concerns associated with generics, and summarized position statements from major US epilepsy organizations regarding brand-to-generic and generic-to-generic substitution.

AAN (2007) opposed substituting brand ASMs with generics without prior approval from the treating physician and supported legislation requiring informed consent from both physicians and patients before any generic substitution occurs.

EF (2006) closely aligned with the views suggested by AAN. The EF strongly supported informed consent from both patients and physicians before substituting any ASM, whether switching from brand to generic formulations or between different generic products. It further opposed mandatory substitution without explicit authorization from the treating physician and the patient.

AES (2007) issued an initial position statement in 2007 and updated it in 2016. The revised statement drew on findings from two FDA-funded bioequivalence studies including BioEquivalence in Epilepsy Patients and Equivalence Among Generic Antiepileptic Drugs. Based on the outcomes of these studies, the AES stated that the findings support the current FDA bioequivalence standards for generic ASMs and that there is no difference in bioequivalence between branded and generic ASMs.

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 09 March 2026.

REFERENCES

1. Orange Book Preface, US Food and Drug Administration, Center for Drug Evaluation and Research. Approved Drug Products with Therapeutic Equivalence Evaluations. Accessed 2026-03-09. Available via: https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface.

2. Bialer M, Shekh-Ahmad T, Braun TL, et al. Comparative steady-state pharmacokinetic evaluation of immediate-release topiramate and USL255, a once-daily extended-release topiramate formulation. *Epilepsia*. 2013;54(8):1444-1452.

3. Duh MS, Paradis PE, Latrémouille-Viau D, et al. The risks and costs of multiple-generic substitution of topiramate. *Neurology*. 2009;72(24):2122-2129.

4. Asadi-Pooya AA, Patel AA, Trinka E, et al. Recommendations for treatment strategies in people with epilepsy during times of shortage of antiseizure medications. *Epileptic Disord*. 2022;24(5):751-764.

5. Elmer S, Reddy DS. Therapeutic basis of generic substitution of antiseizure medications. *J Pharmacol Exp Ther*. 2022;381(2):188-196.

6. Johnson JK, Stocks J, Brittain S, et al. Relative bioavailability of an extended-release topiramate (spn-538) compared to immediate-release topiramate. Abstract presented at: 65th Annual Meeting of the American Epilepsy Society (AES); December 2-6, 2011; Baltimore, MD.

7. Doshi D, LeLorier J, Duh M S, et al. Clinical and economic impact of multiple generic substitutions of topiramate. *Epilepsia*. 2008;49(Suppl. 7):111-112. Abstract 1.254.

8. Paradis P, Latremouille-Viau D, Lefebvre P, et al. Impact of generic substitution of topiramate for patients with epilepsy [abstract]. *Epilepsia*. 2009;50(Suppl. 6):1-52. Abstract P208.