Office of Clinical Pharmacology Review

NDA Number	NDA 214679
Link to EDR	\\CDSESUB1\evsprod\nda214679
Submission Date	10/06/20
Submission Type	Standard review
Brand Name	NA
Generic Name	Topiramate
Dosage Form and Strength	Solution, 25 mg/mL
Route of Administration	Oral
Proposed Indication	• Monotherapy epilepsy • Adjunctive therapy epilepsy • Migraine
Applicant	Azurity Pharmaceuticals
Associated IND	IND 139533
OCP Review Team	Xiaohan Cai, Ph.D.; Angela Men, M.D., Ph.D.

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1. EXECUTIVE SUMMARY

Azurity Pharmaceuticals is seeking approval for topiramate oral solution, 25 mg/mL for the treatment of epilepsy and the preventative treatment of migraine via 505(b)(2) new drug application. Topiramate oral solution is an alternative dosage form of topiramate for ease of dosing. This application relies on safety and effectiveness of the listed drug (LD), Topamax® (topiramate sprinkle capsules [NDA 020844]) based on pharmacokinetics (PK) bridging. The proposed dosing regimen and indications of topiramate oral solution are the same as those of the LD.

The applicant submitted a relative bioavailability (BA) and food effect study (Study 0786-19) to compare the PK of topiramate oral solution (Test) and Topamax sprinkle capsules (LD) under fasted conditions and evaluate food effect on the test product.

This review primarily evaluates the PK bridging between topiramate oral solution and LD under fasted conditions in healthy subjects and food effect on topiramate oral solution. Inspections at the clinical and analytical site conducting the pivotal BA study are not warranted at this time because OSIS inspected both sites in 2019 with No Action Indicated.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP/DNP) finds the PK bridging acceptable and recommends the approval of topiramate oral solution, 25 mg/mL for the treatment of monotherapy epilepsy and adjunctive therapy for pediatric patients 2 years of age and older, as well as migraine in pediatric patients 12 years age and older.

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

- Topiramate oral solution, 25 mg/mL is bioequivalent to Topamax sprinkle capsule (25 mg) (LD) under fasted conditions.
- Following oral administration of topiramate oral solution 25 mg/mL after the overnight fast and a high-fat and high calorie meal, food did not affect the AUC_{0-t} and $AUC_{0-\infty}$ of topiramate. However, food reduced C_{max} of topiramate by 28.4% and delayed the median T_{max} by 5 hours compared to fasted conditions. Base on the findings from other approved topiramate products, Topamax (topiramate tablets) and Trokendi XR® (topiramate extended release capsules), such reduced C_{max} and delayed T_{max} by food effect is expected to have minimal clinical impact (Refer to section 3.3.2). Therefore, same as the LD, topiramate oral solution can be administered without regard to food.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

Because topiramate oral solution is bioequivalent to Topamax sprinkle capsules (LD), the proposed dosing regimen for topiramate oral solution is the same as that of LD.

Dosing in Monotherapy Epilepsy

For Adults and Pediatric Patients 10 Years of Age and Older:
Starting dose at 25 mg twice daily. Below titration is recommended until the recommended dose of 400 mg in two divided doses.

Table 1: Monotherapy Titration Schedule for Adults and Pediatric Patients 10 years and older

	Morning Dose	Evening Dose
Week 1	25 mg	25 mg
Week 2	50 mg	50 mg
Week 3	75 mg	75 mg
Week 4	100 mg	100 mg
Week 5	150 mg	150 mg
Week 6	200 mg	200 mg

For Pediatric Patients 2 to 9 Years of Age:
Dosing is based on weight. The initial dose is 25 mg/day nightly for the first week. Based upon tolerability, the dosage can be increased to 50 mg/day (25 mg twice daily) for the second week. Dosage can be increased by 25–50 mg/day each subsequent week as tolerated. Titration to the minimum maintenance dose should be attempted over 5–7 weeks of the total titration period. The total daily dose should not exceed the maximum maintenance dose for each range of body weight.

Table 2: Monotherapy Target Total Maintenance Dosing for Patients 2 to 9 Years of Age

Weight (kg)	Total Daily Dose (mg/day)* Minimum Maintenance Dose	Total Daily Dose (mg/day)* Maximum Maintenance Dose
Up to 11	150	250
12-22	200	300
23-31	200	350
32-38	250	350
Greater than 38	250	400
* Administered in two equally divided doses		

Dosing in Adjunctive Therapy Epilepsy

For Adults 17 Years of Age and Older:
Starting dose at 25 to 50 mg/day, followed by titration to an effective dose in increments of 25 to 50 mg/day every week. The recommended total daily dose of topiramate oral solution as adjunctive therapy in adults with partial onset seizures or Lennox-Gastaut Syndrome is 200 to 400 mg/day in two divided doses, and 400 mg/day in two divided doses as adjunctive treatment in adults with primary generalized tonic-clonic seizures.

For Pediatric Patients 2 to 16 Years of Age:
Starting dose at 25 mg/day (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week, followed by titration to an effective dose in increments of 1 to 3 mg/kg/day (administered in two divided doses) at 1- or 2-week intervals. The recommended total daily dose of Topiramate Oral Solution as adjunctive therapy for pediatric patients 2 to 16 years of age with partial-onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome is approximately 5 to 9 mg/kg/day in two divided doses. The total daily dose should not exceed 400 mg/day.

Dosing for the Preventive Treatment of Migraine
The recommended total daily dose of Topiramate Oral Solution as treatment for patients 12 years of age and older for the preventive treatment of migraine is 100 mg/day administered in two divided doses. The recommended titration rate for Topiramate Oral Solution for the preventive treatment of migraine is as follows:

Table 3: Preventative Treatment of Migraine Titration Schedule for Patients 12 years and older

	Morning Dose	Evening Dose
Week 1	None	25 mg
Week 2	25 mg	25 mg
Week 3	25 mg	50 mg
Week 4	50 mg	50 mg

2.2.2 Therapeutic individualization
Because topiramate oral solution is bioequivalent to Topamax sprinkle capsules, the dose recommendation due to drug interaction and dose adjustment for specific population are the same as those of the LD.

2.3 Outstanding Issues
None.

2.4 Summary of Labeling Recommendations
None.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background
In 2018, a pre-NDA meeting was held between Eton Pharmaceuticals (Eton) and the FDA to obtain concurrence with the FDA that the contents of the application will meet FDA requirements for the NDA filing. The FDA agreed with the submission of new drug application via 505(b)(2) pathway that relies on FDA's previous findings of safety and efficacy from Topamax® (topiramate capsules) Sprinkle Capsules (NDA 020844).

In 2019, Eton submitted the Initial Pediatric Study Plan and proposes to conduct the clinical pediatric studies post approval of NDA 214679 for topiramate oral solution.

In 2021, Azurity Pharmaceuticals (Azurity) notified the FDA that the ownership of NDA 214679 is transferred from Eton to Azurity effective from February 3, 2021.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	The precise mechanisms by which topiramate exerts its anticonvulsant and preventive migraine effects are unknown; however, preclinical studies have revealed four properties that may contribute to topiramate's efficacy for epilepsy and the preventive treatment of migraine. Electrophysiological and biochemical evidence suggests that topiramate blocks voltage-dependent sodium channels, augments the activity of the neurotransmitter gamma-aminobutyrate at some subtypes of the GABA-A receptor, antagonizes the AMPA/kainate subtype of the glutamate receptor, and inhibits the carbonic anhydrase enzyme, particularly isozymes II and IV.
General Information	
Bioanalysis	Concentrations of topiramate in human plasma were measured with a validated LC-MS/MS method. The calibration curve ranged from 2.050 ng/mL to 998.929 ng/mL.
Healthy Volunteers vs Patients	N/A. PK of to-be-marketed formulation was not evaluated in patients.
ADME	
Absorption	Following oral administration of topiramate oral solution in healthy male subjects, C_{max} of topiramate was reached at approximately 2 hours. Following a high calories high fat meal, food does not affect topiramate AUC_{0-t} and $AUC_{0-\infty}$ after oral administration of topiramate oral solution. However, in the presence of food, C_{max} of topiramate is reduced by ~28.4% with the median T_{max} delayed by ~5 hours as compared to fasting condition after oral administration of topiramate oral solution.
Distribution	Topiramate is poorly bound to plasma proteins (9-17%). The mean apparent volume of distribution of Topiramate ranged from 0.6 to 0.8 L/kg for 100-1,200 mg Topiramate, consistent with distribution into total body water.
Metabolism	Topiramate is not extensively metabolized. Six metabolites have been identified in humans, none of which constitutes more than 5% of an administered dose. The metabolites are formed via hydroxylation, hydrolysis, and glucuronidation. CYP2C19 was the only isozyme inhibited by topiramate in vitro.
Elimination	Topiramate is primarily eliminated unchanged in the urine (approximately 70% of an administered dose). The mean plasma elimination half-life is 21 hours.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

A single dose relative bioavailability study (Study 0786-19) was conducted to compare the PK of topiramate of 25 mg topiramate oral solution (25 mg/mL, 1 mL) and 25 mg Topamax sprinkle capsule (LD) under fasted conditions in healthy subjects. Topiramate C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were bioequivalent between topiramate oral solution and LD. These pivotal results established PK bridging between topiramate oral solution and LD.

3.3.2 What is the effect of food on the exposures of topiramate oral solution? Does this product require specific dosing instruction with regard to food?

The food effect on the PK of topiramate after a single dose of 25 mg topiramate oral solution was evaluated in Study 0786-19 in healthy male subjects. When compared to fasting conditions, a high-fat and high calorie meal did not affect topiramate AUC_{0-t} and $AUC_{0-\infty}$ exposures but lowered the C_{max} by approximately 28.4% and delayed the median T_{max} by approximately 5 hours (Figure 1; Appendices, Section 4.2.1, Table 4). As topiramate AUCs were not affected by food, such reduced C_{max} and delayed T_{max} are not considered to have a significant impact on the clinical efficacy. Considering the long half-life of topiramate and the recommended dosing regimen of twice daily dosing, the food impact on C_{max} is not expected to be significant at steady state. The half-life of topiramate is approximate 72 hours based on the results from Study 0786-19. Regarding the T_{max}, the currently approved topiramate drug products, including Topamax, Trokendi XR, Qudexy XR, have varied T_{max} ranging from 2 to 24 hours. Therefore, such delayed T_{max} of 5 hours with food after a single dose of topiramate oral solution does not have a significant impact on clinical efficacy. The clinical review team does not have concerns about the delayed T_{max} and lower C_{max} in the single dose food effect study.

3.3.3 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Dosing recommendation will be the same as the LD, supported by the bioequivalence established between topiramate oral solution and LD.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

N/A.

3.3.4 Are there clinically relevant drug-drug interactions and what is the appropriate management strategy?

No DDI studies have been conducted with topiramate oral solution. The applicant proposed the same DDI section of LD for topiramate oral solution, which is acceptable.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

4.1.1 How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?

Plasma concentrations of topiramate were measured by a validated LC-MS/MS method in human plasma in study 0786-19. Plasma samples from study 0786-19 were analyzed by (b) (4) . Because approval of the topiramate oral solution relies on the pivotal relative BA study 0786-19, a routine inspection of the clinical and bioanalytical sites was requested via Office of Study Integrity and Surveillance (OSIS). Inspections at the clinical and analytical sites are not warranted at this time because OSIS inspected both sites in (b) (4) with No Action Indicated (refer to NDA 214679, Bioequivalence Establishment Inspection Report Review, DARRTS, 1/21/2021).

Description of method validation parameters (Validation Report # MV(C)-136-20) are provided below:

Table 1: Bioanalytical Method Validation

Table 4: Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	MV(C)-136-20 (Main and Addendum-I) Appendix 16.5.3
Analyte	Topiramate
Internal Standard (IS)	Topiramate-d12
Method description	Topiramate and Topiramate-d12 (ISTD) were extracted from human plasma by supported liquid extraction method using Agela Cleanert SLE extraction plate. The samples were eluted with extraction solvent into collection plate. The contents were evaporated under nitrogen gas stream. The dried contents were than reconstituted with the mobile phase and used for analysis.
Limit of quantitation (ng/mL)	2.050 ng/mL
Average recovery of drug (%) (LQC, MQC and HQC)	50.0%, 52.7% and 54.3%
Average recovery of IS (%)	51.6%
Standard curve concentrations (ng/mL)	2.050 ng/mL to 998.929 ng/mL
QC concentrations (ng/mL) (LOQ QC, LQC, LMQC, MQC, HQC and DQC)	2.050, 6.135 ng/mL, 110.391 ng/mL, 401.421 ng/mL, 787.100 ng/mL and 2990.180 ng/mL
QC intraday precision range (%)	0.9% to 5.0%
QC intraday accuracy range (%)	98.5% to 103.2%
QC interday precision range (%)	3.2% to 5.7%
QC interday accuracy range (%)	98.2% to 103.9%
Bench-top stability (hrs)	17.0 hours (at room temperature)
Stock stability (days)	13 days at -25 ±10°C (for drug stock, ISTD stock and spiking solution stability of drug at higher level, intermediate ISTD dilution and ISTD dilution) 14 days at -25 ±10°C for spiking solution stability of drug at lower level)

Information Requested	Data	
Processed stability (hrs)	121.0 hours (at 7 ± 4°C) 2.0 hours (at room temperature)	
Freeze-thaw stability (cycles)	4 cycles (at -70 ± 10°C)	
Long-term storage stability (days)	60 days at -70 ± 10°C & -25 ± 10°C (Addendum-I)	
Dilution Integrity	2990.180 ng/mL diluted up to 5-fold and 10-fold	
Selectivity	No significant interference at the retention times of analyte and internal standard	
	Anticoagulant	K_2EDTA

Source: Clinical Overview, Module 2.5; page number 27-28

4.2 Clinical PK Assessments

4.2.1 Study 0786-19: Relative bioavailability of topiramate oral solution versus TOPMAX sprinkle capsule and food effect study

Objective:

- To evaluate the relative bioavailability between topiramate oral solution (T1) and Topamax sprinkle capsule (R) under fasting conditions
- To evaluate food effect on topiramate oral solution (T2) under fed conditions.
- To monitor the safety and tolerability of a single oral dose of investigational medicinal products.

Study Design and Methodology:

The study was an open-label, randomized, three period, three sequence, three-way crossover, single-dose, fasting and fed (food-effect) trial in healthy male subjects. A total of 24 subjects were randomized to receive the treatment sequence of T1T2R, RT1T2, or T2RT1. T1, T2, and R treatments are administered as:

- T1: A single dose of topiramate oral solution 25 mg/mL (1 mL) was administered with 240 mL of water after overnight fast of at least 10 hours.
- T2: A single dose of topiramate oral solution 25 mg/mL (1 mL) was administered with 240 mL of water at 30 minutes after a high fat meal.
- R: A single dose of Topamax sprinkle capsule 25 mg was administered with 240 mL of water after overnight fast of at least 10 hours.

The washout period was 19 days between the dosing days of any two consecutive periods. Two subjects were dismissed from the study on the grounds of protocol non-compliance in period-1. A total of 22 subjects completed the study. Plasma concentration of topiramate was quantified using a validated LC-MS/MS assay (refer to section 4.1)

Pharmacokinetics Results:

Table 2: Study 0786-19: Summary of Plasma PK Parameters of Topiramate (PK Population)

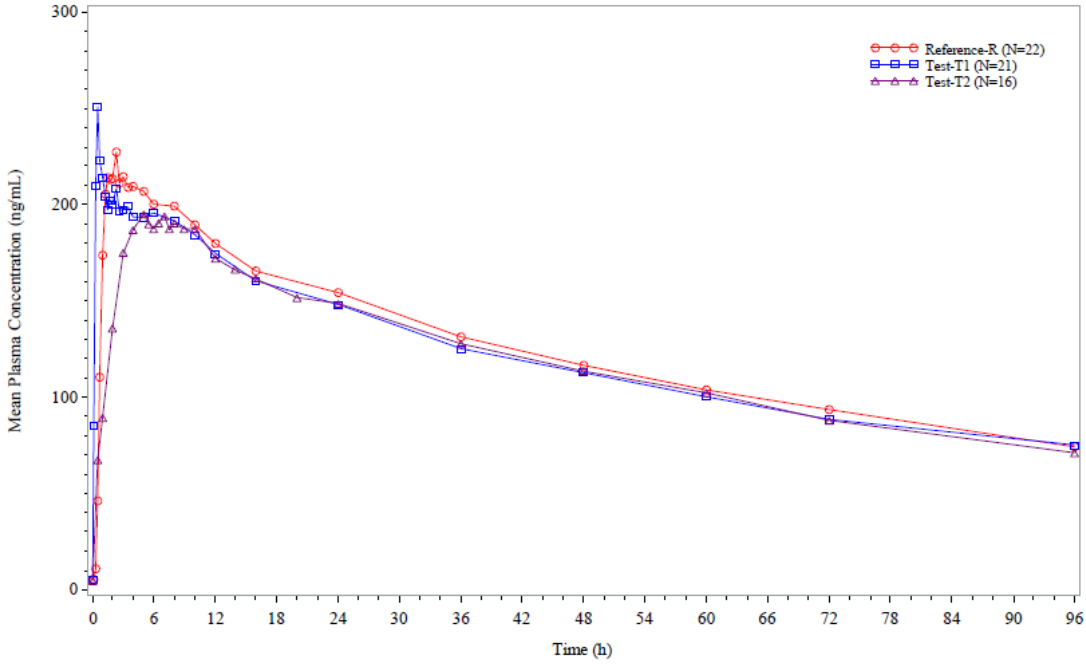
Parameters (Units)	Mean ± SD (untransformed data)		
	Test Product-T1 (N=21)	Test Product-T2 (N=16)	Reference Product-R (N=22)
T_{max} (h)#	0.500 (0.333 - 1.250)	5.509 (3.000 - 8.000)	1.500 (1.000 - 4.000)
C_{max} (ng/mL)	286.040 ± 51.4478	204.905 ± 31.0866	253.274 ± 57.4703
AUC_{0-t} (ng.h/mL)	11707.352 ± 2279.7990	11355.495 ± 1644.4321	11982.263 ± 2383.9193
$AUC_{0-\infty}$ (ng.h/mL)	20016.410 ± 5695.0520	18523.608 ± 2665.5621^	19834.948 ± 5137.4158
λ_z (1/h)	0.010 ± 0.0023	0.010 ± 0.0018^	0.010 ± 0.0021
$t_{½}$ (h)	74.762 ± 24.3050	72.466 ± 15.2805^	71.828 ± 17.8818
AUC_%Extrap_obs (%)	40.011 ± 7.9343	39.105 ± 6.2902^	38.573 ± 6.9515
R^2 adjusted	0.975 ± 0.0210	0.991 ± 0.0115^	0.982 ± 0.0124

#T_{max} is represented as median (min-max) value.

^N = 15 ; Subject no. (b) (6) (Period-I, T2) had AUC_%Extrap_obs > 20% with R^2 adjusted < 0.80. Hence, elimination phase dependent pharmacokinetic parameters were excluded from the pharmacokinetic and statistical analysis.

Source: Study Report 0786-19; Module 5.3.1.2; page number 49

Figure 1: Study 0786-19: Mean Plasma Concentration vs. Time Curve for Topiramate



Source: Study Report 0786-19; Module 5.3.1.2; page number 104; figure 14.2.3.1

Table 3: Study 0786-19: Geometric Mean Ratios (90% CI) of Topiramate following a Single Dose of Test Product (T1) and Reference Product (R) under a Fasting Condition

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T1 (N = 21)	Reference Product-R (N = 22)	Ratio (T1/R)%			
lnC_{max}	281.635	249.501	112.9	105.93 - 120.28	11.9	100.0
$lnAUC_{0-t}$	11582.446	11881.573	97.5	95.06 - 99.96	4.7	100.0
$lnAUC_{0-\infty}$	19689.317	19410.206	101.4	95.79 - 107.42	10.7	100.0

Source: Study Report 0786-19; Module 5.3.1.2; page number 50

Table 4: Study 0786-19: Geometric Mean Ratios (90% CI) of Topiramate following a Single Dose of Test Product under Fed (T2) and Fasting Conditions (T1)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T2 (N = 16)	Test Product-T1 (N = 21)	Ratio (T2/T1) %			
lnC_{max}	202.669	282.879	71.6	66.92 - 76.70	11.1	99.9
$lnAUC_{0-t}$	11160.586	11579.467	96.4	93.88 - 98.95	4.1	100.0
$lnAUC_{0-\infty}$	19113.162^	19602.192	97.5	91.43 - 103.99	9.9	100.0

^N = 15

Source: Study Report 0786-19; Module 5.3.1.2; page number 52

Reviewer's comments:

- *The $T_{1/2}$ (72-75 hours) estimated from study 0786-19 is longer than that from Topamax labeling (21 hours). The longer $T_{1/2}$ may be related to a more sensitive bioanalytical assay used for study 0786-19, which had an LLOQ of 2.5 ng/mL comparing to the LLOQ of 100 ng/mL of the bioanalytical assay supporting the BA study of topiramate tablets. In addition, the $T_{1/2}$ is comparable among T1, T2, and R treatments in the current BA study.*
- *Due to the long half-life of topiramate of approximate 72-75 hours estimated from study 0786-19, the Extrapolation% for $AUC_{0-\infty}$ was approximately 39% for all treatments of T1, T2, and R. Because the last time point for sample collection was 96 hours and the intra-subject variability for λ_z was 15.2% (based on the reviewer's analysis), the extrapolation% at 39% should have minimal impact on the estimation of $AUC_{0-\infty}$.*
- *The following subjects were excluded from the PK analysis because the subject had pre-dose topiramate concentration above 5% of C_{max} from the same period*
  - *T1 treatment: 1 subject (# (b) (6))*
  - *T2 treatment: 6 subjects (# (b) (6))*

- *One subject (# (b) (6)) receiving T2 treatment was excluded from the statistical analysis on $AUC_{0-\infty}$, but not on C_{max} and AUC_{0-t}, based on the pre-specified protocol criteria. The AUC_%Extrap_obs was found to be > 20% with R^2 adjusted < 0.80 for λz estimation for subject (b) (6) T2.*
- *The reviewer was able to verify the applicant's analyses and results.*

Discussion and Conclusion

The test product of topiramate oral solution 25 mg/mL (T1) was bioequivalent to Topamax Sprinkle Capsule 25mg (R) under fasting condition because the 90% Confidence Interval of test to reference ratio for log-transformed topiramate C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ was within 80-125%.

When evaluating the food effect of topiramate oral solution 25 mg/mL, the study results showed that High fat high calorie meal did not affect topiramate AUC_{0-t} and $AUC_{0-\infty}$ but reduced topiramate C_{max} by 28.4% with the median T_{max} delayed by 5 hours when compared to the fasting condition. Such changes on C_{max} are not expected to result in significant clinical responses.

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