CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214679Orig1s000

SUMMARY REVIEW

Summary Review

Date	November 5, 2021
From	Nick Kozauer, MD
Subject	Summary Review
NDA#	214679
Applicant	Azurity Pharma
Dates of Submission	October 6, 2020
PDUFA Goal Dates	November 6, 2021
Proprietary Name	Eprontia
Established or Proper Name	Topiramate
Dosage Form(s)	Oral solution
Applicant Proposed Indication(s)/Population(s)	Initial monotherapy for the treatment of partial-onset or primary generalized tonic-clonic seizures in patients 2 years of age and older Adjunctive therapy for the treatment of partial-onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome in patients 2 years of age and older Preventive treatment of migraine in patients 12 years of age and older
Applicant Proposed Dosing Regimen(s)	Aligned with the Topamax sprinkle capsule labeling
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	As above
Recommended Dosing Regimen(s) (if applicable)	Aligned with the Topamax sprinkle capsule labeling

1. Background

The current new drug application (NDA) contains data intended to establish the efficacy and safety of the Applicant's product, an oral solution formulation of topiramate, by demonstrating an adequate pharmacokinetic (PK) bridge to the listed drug (Topamax) (NDA 020844; topiramate sprinkle capsules for oral use; Janssen Pharmaceuticals) using the 505(b)(2) pathway.

Topamax is approved as initial monotherapy for the treatment of partial onset seizures (POS) and primary generalized tonic-clonic seizures (PGTC) in patients 2 years of age and older and as adjunctive therapy for the treatment of POS, PGTC, and the seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age and older. Topamax is also approved for the preventive treatment of migraine in patients 12 years of age and older.

The Applicant has submitted the results of Study 0786-19, a relative bioavailability (BA) and food effect study, that compared the PK of the Applicant's product to the LD.

2. Product Quality

The Application Team Lead (ATL) for the Office of Product Quality (OPQ) review was Dr. Martha Heimann. Please refer to that review for the complete list of the OPQ team involved in the review of this application.

The OPQ review recommends an approval for this application and concludes that the Applicant has provided adequate assurance of product quality to ensure that the product is suitable for use in the intended patient population.

Of note, a May 28, 2021, response from the Applicant to a March 9, 2021, OPQ information request (IR) was determined to be a Major Amendment to the application and resulted in a review clock extension from August 6, 2021, to November 6, 2021.

3. Nonclinical Pharmacology/Toxicology

No review was written by the nonclinical pharmacology/toxicology review team since no new nonclinical data were submitted.

4. Clinical Pharmacology

Dr. Xiaohan Cai was the Office of Clinical Pharmacology (OCP) reviewer for this application and Dr. Angela Men was the Team Lead.

A single dose relative BA study (Study 0786-19) was conducted by the Applicant to compare the PK of topiramate between the current product (topiramate oral solution; 25 mg/mL,1 mL) to the LD (Topamax sprinkle capsules) under fasted conditions in healthy volunteer subjects (n=24). Based on the results of Study 0786-19, the OCP review concludes that the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, were bioequivalent between topiramate oral solution and the LD.

Study 0786-19 also evaluated the effect of food on the PK of topiramate after a single 25 mg dose of topiramate oral solution. The OCP review indicates that 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 Tmax by approximately 5 hours. However, the OCP review concludes that as topiramate AUCs were not affected by food, the reduced C_{max} and delayed T_{max} are not expected to be clinically significant. The OCP further states that given the prolonged half-life of topiramate (approximately 72 hours) and the recommended twice-daily dosing, any impact of food on C_{max} at steady state is expected to be minimal. Finally, the OCP review observes that the currently approved formulations of topiramate have a T_{max} range between 2 to 24 hours; therefore, a delay of 5 hours in the fed state with the current product would not negatively impact efficacy.

The OCP review team concludes that this Application can be approved with dosing and drug-drug interaction (DDI) recommendations that align with the LD.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical- Efficacy

There is no efficacy data because efficacy is established using the pediatric extrapolation approach.

7. Clinical - Safety

Dr. Steven Dinsmore performed the clinical safety review of this application.

The safety of topiramate oral solution is based on the demonstration of an adequate PK bridge to the LD. Dr. Dinsmore also conducted a review of the safety data from Study 0786-19. Dr. Dinsmore notes that 14 adverse events (AEs) were reported in this trial, with no serious adverse events (SAEs) or withdrawals due to AEs. Fourteen AEs were reported by 6 total subjects in the trial (total enrollment of 24 subjects). With the exception of headache, which was reported in 2 subjects, no other single event occurred in more than 1 subject. All reported AEs were rated as mild. Dr. Dinsmore concludes that no new safety signal is identified with the current product as compared to the LD and recommends that the application be approved.

8. Advisory Committee Meeting

This application was not referred to an Advisory Committee for review because the efficacy and safety of the proposed product were established based on an adequate PK bridge to the LD and there were no issues requiring Advisory Committee input.

9. Other Relevant Regulatory Issues

Dr. Dinsmore concludes in his clinical review that the applicant has adequately disclosed financial interests/arrangements with clinical investigators.

The Division of Medication Error Prevention and Analysis (DMEPA) review has concluded that the Applicant's proposed proprietary name, Eprontia, was acceptable.

10. Pediatrics

The Pediatric Research Equity Act (PREA) postmarketing requirements (PMRs) are discussed below in Section 12, below.

11. Labeling

Please refer to the final negotiated product label. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

12. Postmarketing Requirements

The Applicant has agreed to conduct the following PREA PMRs:

1. A randomized, double blind, placebo controlled efficacy and safety study under PREA to evaluate topiramate oral solution for the preventive treatment of migraine in children 6 through 11 years of age. This efficacy study must be designed to demonstrate superiority of topiramate oral solution over placebo.

   Final Protocol Submission: 03/2022
   Study Completion: 06/2025
   Final Report Submission: 12/2025

2. A pharmacokinetic analysis to determine the dosing regimen that provides similar drug exposure (at levels demonstrated to be effective in adults with partial-onset seizures) in pediatric patients 1 month to 2 years of age and in adult patients. This analysis will require pharmacokinetic data from both the adult and pediatric (1 month t o 2 years of age) populations.

   Final Protocol Submission: 04/2022
   Study Completion: 04/2025
   Final Report Submission: 10/2025

3. Long-term open-label safety study(ies) in pediatric patients 1 month of age and older maintained at topiramate concentrations demonstrated to be therapeutic for partial-onset seizures for a minimum of 6 months of exposure.

   Final Protocol Submission: 04/2022
   Study Completion: 04/2025
   Final Report Submission: 10/2025

13. Recommended Comments to the Applicant

See action letter.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICHOLAS A KOZAUER
11/05/2021 08:00:51 AM