CLINICAL UPDATE

Brand Name	Eprontia™
Generic Name	topiramate
Drug Manufacturer	Azurity Pharmaceuticals, Inc

Clinical Update

TYPE OF CLINICAL UPDATE

New Brand and Dosage Form

FDA APPROVAL DATE

November 5, 2021

LAUNCH DATE

4th quarter 2021

REVIEW DESIGNATION

Standard

TYPE OF REVIEW

Type 3 - New Dosage Form; New Drug Application (NDA): 214679

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Eprontia™ is indicated for:

- Epilepsy: 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 LennoxGastaut syndrome in patients 2 years of age and older.
- Preventive treatment of migraine in patients 12 years of age and older.

MECHANISMS 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, at pharmacologically relevant concentrations, 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.

This document is designed to be an informational resource to facilitate discussion and should be used neither as a basis for clinical decision-making or treatment nor as a substitute for reading original literature. RxAdvance makes every effort to ensure that the information provided is up-to-date, accurate, and complete, but no guarantee is made to that effect. If this information is provided to clients or vendors, it is subject to any contractual confidentiality provisions. Third-party disclosures are in violation of confidentiality provisions.

CLINICAL UPDATE

DOSAGE FORM(S) AND STRENGTH(S)

Oral solution: 25 mg/mL

DOSE & ADMINISTRATION

Initially, 50 mg/day PO administered in 2 divided doses. Increase the daily dose by 50 mg once per week during weeks 2, 3, and 4. Increase the daily dose by 100 mg once per week during weeks 5 and 6; administer total daily dose in 2 divided doses.

The recommended final dose, 400 mg per day orally in 2 divided doses, is achieved during week 6.

EFFICACY

The safety and efficacy of Eprontia™ are based on the relative bioavailability of Eprontia™ compared to topiramate sprinkle capsules in healthy subjects.

Monotherapy Epilepsy

Patients with Partial-Onset or Primary Generalized Tonic-Clonic Seizures

Adults and Pediatric Patients 10 Years of Age and Older

Study 1 was conducted in 487 patients diagnosed with epilepsy (6 to 83 years of age) who had 1 or 2 well-documented seizures during the 3-month retrospective baseline phase who then entered the study and received topiramate 25 mg/day for 7 days in an open-label fashion. Forty-nine percent of patients Reference ID: 4884258 had no prior AED treatment and 17% had a diagnosis of epilepsy for greater than 24 months. Any AED therapy used for temporary, or emergency purposes was discontinued prior to randomization. In the double-blind phase, 470 patients were randomized to titrate up to 50 mg/day or 400 mg/day. Fifty eight percent of patients achieved the maximal dose of 400 mg/day for >2 weeks, and patients who did not tolerate 150 mg/day were discontinued.

The primary efficacy assessment was a between-group comparison of time to first seizure during the double-blind phase. Comparison of the Kaplan-Meier survival curves of time to first seizure favored the topiramate 400 mg/day group over the topiramate 50 mg/day group. The treatment effects with respect to time to first seizure were consistent across various patient subgroups defined by age, sex, geographic region, baseline body weight, baseline seizure type, time since diagnosis, and baseline AED use.

Pediatric Patients 2 to 9 Years of Age The conclusion that topiramate is effective as initial monotherapy in pediatric patients 2 to 9 years of age with partial-onset or primary generalized tonic-clonic seizures was based on a pharmacometrics bridging approach using data from the controlled epilepsy trials described in labeling. This approach consisted of first showing a similar exposure response relationship between pediatric patients down to 2 years of age and adults when topiramate was given as adjunctive therapy. Similarity of exposure response was also demonstrated in pediatric patients 6 to less than 16 years of age and adults when topiramate was given as initial monotherapy. Specific dosing in pediatric patients 2 to 9 years of age was derived from simulations utilizing plasma exposure ranges observed in pediatric and adult patients treated with topiramate initial monotherapy.

Adjunctive Therapy Epilepsy

Adult Patients with Partial-Onset Seizures

Patients in these studies were permitted a maximum of two antiepileptic drugs (AEDs) in addition to topiramate tablets or placebo. In each study, patients were stabilized on optimum dosages of their concomitant AEDs during baseline phase lasting between 4 and 12 weeks. Patients who experienced a pre-specified minimum number of partial-onset seizures, with or without secondary generalization, during the baseline phase (12 seizures for 12-week baseline, 8 for 8-week baseline or 3 for 4-week baseline) were randomly assigned to placebo or a specified dose of topiramate tablets in addition to their other AEDs. Following randomization, patients began the double-

This document is designed to be an informational resource to facilitate discussion and should be used neither as a basis for clinical decision-making or treatment nor as a substitute for reading original literature. RxAdvance makes every effort to ensure that the information provided is up-to-date, accurate, and complete, but no guarantee is made to that effect. If this information is provided to clients or vendors, it is subject to any contractual confidentiality provisions. Third-party disclosures are in violation of confidentiality provisions.

blind phase of treatment. In five of the six studies, patients received active drug beginning at 100 mg per day; the dose was then increased by 100 mg or 200 mg/day increments weekly or every other week until the assigned dose was reached, unless intolerance prevented increases. In the sixth study (Study 7), the 25 or 50 mg/day initial doses of topiramate were followed by respective weekly increments of 25 or 50 mg/day until the target dose of 200 mg/day was reached. After titration, patients entered a 4, 8 or 12-week stabilization period.

Pediatric Patients 2 to 16 Years of Age with Partial-Onset Seizures

Patients in this study were permitted a maximum of two antiepileptic drugs (AEDs) in addition to topiramate tablets or placebo. In this study, patients were stabilized on optimum dosages of their concomitant AEDs during an 8-week baseline phase. Patients who experienced at least six partial-onset seizures, with or without secondarily generalized seizures, during the baseline phase were randomly assigned to placebo or topiramate tablets in addition to their other AEDs. Following randomization, patients began the double-blind phase of treatment. Patients received active drug beginning at 25 or 50 mg/day; the dose was then increased by 25 mg to 150 mg/day increments every other week until the assigned dosage of 125, 175, 225, or 400 mg/day based on patients' weight to approximate a dosage of 6 mg/kg/day was reached, unless intolerance prevented increases. After titration, patients entered an 8-week stabilization period.

Patients With Primary Generalized Tonic-Clonic Seizures

Patients in Study 9 were permitted a maximum of two antiepileptic drugs (AEDs) in addition to topiramate or placebo. Patients were stabilized on optimum dosages of their concomitant AEDs during an 8-week baseline phase. Patients who experienced at least three primary generalized tonic-clonic seizures during the baseline phase were randomly assigned to placebo or topiramate in addition to their other AEDs. Following randomization, patients began the double-blind phase of treatment. Patients received active drug beginning at 50 mg/day for four weeks; the dose was then increased by 50 mg to 150 mg/day increments every other week until the assigned dose of 175, 225, or 400 mg/day based on patients' body weight to approximate a dosage of 6 mg/kg/day was reached, unless intolerance prevented increases. After titration, patients entered a 12-week stabilization period.

Patients With Lennox-Gastaut Syndrome

The effectiveness of topiramate as an adjunctive treatment for seizures associated with LennoxGastaut syndrome was established in a multicenter, randomized, double-blind, placebo-controlled trial (Study 10) comparing a single dosage of topiramate with placebo in patients 2 years of age and older. Patients in Study 10 were permitted a maximum of two antiepileptic drugs (AEDs) in addition to topiramate or placebo. Patients who were experiencing at least 60 seizures per month before study entry were stabilized on optimum dosages of their concomitant AEDs during a 4-week baseline phase. Following baseline, patients were randomly assigned to placebo or topiramate in addition to their other AEDs. Active drug was titrated beginning at 1 mg/kg/day for a week; the dose was then increased to 3 mg/kg/day for one week, then to 6 mg/kg/day. After titration, patients entered an 8-week stabilization period. The primary measures of effectiveness were the percent reduction in drop attacks and a parental global rating of seizure severity.

Table: topiramate Dose Summary During the Stabilization Periods of Each of Six Double Blind, Placebo-Controlled, Adjunctive Trials in Adults with Partial-Onset Seizures*

Study	Stabilization Dose	Placebo†	Target topiramate Dosage (mg/day)				
			200	400	600	800	1,000
2	N	42	43	40	41	--	--
	Mean Dose	5.9	200	390	556		
	Median Dose	6.0	200	400	600		

This document is designed to be an informational resource to facilitate discussion and should be used neither as a basis for clinical decision-making or treatment nor as a substitute for reading original literature. RxAdvance makes every effort to ensure that the information provided is up-to-date, accurate, and complete, but no guarantee is made to that effect. If this information is provided to clients or vendors, it is subject to any contractual confidentiality provisions. Third-party disclosures are in violation of confidentiality provisions.

3	N Mean Dose Median Dose	44 9.7 10.0	--	--	40 544 600	45 739 800	40 796 1,000
4	N Mean Dose Median Dose	23 3.8 4.0	--	19 395 400	--	--	--
5	N	30	--	--	28	--	--
	Mean Dose Median Dose	5.7 6.0			522 600		
6	N Mean Dose Median Dose	28 7.9 8.0	--	--	--	25 568 600	--
7	N Mean Dose Median Dose	90 8 8	157 200 200	--	--	--	--

* Dose-response studies were not conducted for other indications or pediatric partial-onset seizures.
† Placebo dosages are given as the number of tablets. Placebo target dosages were as follows: Protocol 3 4 tablets/day; Protocols 1 and 4, 6 tablets/day; Protocols 5 and 6, 8 tablets/day; Protocol 2, 10 tablets/day.

In all adjunctive trials, the reduction in seizure rate from baseline during the entire double-blind phase was measured. The median percent reductions in seizure rates and the responder rates (fraction of patients with at least a 50% reduction) by treatment group for each study are shown below in Table. As described above, a global improvement in seizure severity was also assessed in the Lennox-Gastaut trial.

		Target topiramate Dosage (mg per day)							
Study#	**#**	**Placebo**	**200**	**400**	**600**	**800**	**1,000**	**≈6mg/kg/day***	
Partial-Onset Seizures Studies in Adults									
2	N	45	45	45	46	--	--	--	
	Median % Reduction	12	27[a]	48[b]	45[c]	--	--	--	
	% Responders	18	24	44[d]	46[d]	--	--	--	
3	N	47	--	--	48	48	47	--	
	Median % Reduction	2	--	--	41[c]	41[c]	36[c]		
	% Responders	9	--	--	40[c]	41[c]	36[d]		
4	N	24	--	23	--	--	--	--	
	Median % Reduction	1	--	41e	--	--	--	--	
	% Responders	8	--	35[d]	--	--	--	--	

This document is designed to be an informational resource to facilitate discussion and should be used neither as a basis for clinical decision-making or treatment nor as a substitute for reading original literature. RxAdvance makes every effort to ensure that the information provided is up-to-date, accurate, and complete, but no guarantee is made to that effect. If this information is provided to clients or vendors, it is subject to any contractual confidentiality provisions. Third-party disclosures are in violation of confidentiality provisions.

© RxAdvance Corporation. Confidential and Proprietary.

5	N	30	--	--	30	--	--	--	
	Median % Reduction	-12	--	--	46[f]	--	--	--	
	% Responders	10	--	--	47[c]	--	--	--	
6	N	28	--	--	--	28	--	--	
	Median % Reduction	-21	--	--	--	24[c]	--	--	
	% Responders	0	--	--	--	43[c]	--	--	
7	N	91	168	--	--	--	--	--	
	Median % Reduction	20	44[c]	--	--	--	--	--	
	% Responders	24	45[c]						
Partial-Onset Seizures Studies in Pediatric Patients									
8	N	45	--	--	--	--	--	41	
	Median % Reduction	11	--	--	--	--	--	33[d]	
	% Responders	20	--	--	--	--	--	39	
Primary Generalized Tonic-Clonic[h,]									
9	N	40	--	--	--	--	--	39	
	Median % Reduction	9	--	--	--	--	--	57[d]	
	% Responders	20	--	--	--	--	--	56[c]	
Lennox-Gastaut Syndrome[i,]									
10	N	49	--	--	--	--	--	46	
	Median % Reduction	-5	--	--	--	--	--	15[d]	
	% Responders	14						28[g]	
	Improvement in Seizure Severity[j]	28						52[d]	
Comparisons with placebo: [a]p=0.080; [b]$p \leq 0.010$; [c]$p \leq 0.001$; [d]$p \leq 0.050$; [e]p=0.065; [f]$p \leq 0.005$; [g]p=0.071; [h]Median % reduction and % responders are reported for PGTC seizures; [i]Median % reduction and % responders for drop attacks, i.e., tonic or atonic seizures; [j]Percentage of subjects who were minimally, much, or very much improved from baseline. * For Studies 8 and 9, specified target dosages (<9.3 mg/kg/day) were assigned based on subject's weight to approximate a dosage of									

This document is designed to be an informational resource to facilitate discussion and should be used neither as a basis for clinical decision-making or treatment nor as a substitute for reading original literature. RxAdvance makes every effort to ensure that the information provided is up-to-date, accurate, and complete, but no guarantee is made to that effect. If this information is provided to clients or vendors, it is subject to any contractual confidentiality provisions. Third-party disclosures are in violation of confidentiality provisions.

6mg/kg per day; these dosages corresponded to mg/day dosages of 125, 175, 225, and 400 mg/day.	

Subset analyses of the antiepileptic efficacy of topiramate tablets in these studies showed no differences as a function of gender, race, age, baseline seizure rate, or concomitant AED.

This document is designed to be an informational resource to facilitate discussion and should be used neither as a basis for clinical decision-making or treatment nor as a substitute for reading original literature. RxAdvance makes every effort to ensure that the information provided is up-to-date, accurate, and complete, but no guarantee is made to that effect. If this information is provided to clients or vendors, it is subject to any contractual confidentiality provisions. Third-party disclosures are in violation of confidentiality provisions.

© RxAdvance Corporation. Confidential and Proprietary.