CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214679Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 27, 2021
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 214679
Product Name and Strength:	Eprontia[a] (topiramate) Oral Solution), 25 mg/mL
Applicant/Sponsor Name:	Azurity Pharmaceuticals Inc. (Azurity)
OSE RCM #:	2020-2160-2
DMEPA 2 Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA 2 Team Leader (Acting):	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted the revised container label on October 4, 2021 for Eprontia (topiramate) Oral Solution. The Division of Neurology 2 (DN 2) requested that we review the revised container label for Eprontia (topiramate) Oral Solution (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 ASSESSMENT AND CONCLUSION

The Applicant implemented all of our previous recommendations. However, based on discussions with the review team, we've determined that the strength presentation on the container label can be improved from a medication error perspective. As such, we have reconsidered our previous recommendation for the expression of strength presentation on the

[a] The proposed proprietary name, Eprontia was found conditionally acceptable on July 23, 2021.

[b] Weitzman, B. Label and Labeling Review for Topiramate (NDA 214679). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUN 9. RCM No.: 2020-2160-1.

container label. We provide a recommendation for the Applicant below. We ask that the Division convey our recommendation to Azurity to be implemented prior to approval of this NDA.

3 RECOMMENDATIONS FOR AZURITY

A. Container Label

1. Based on discussions with the review team, we have reconsidered our previous recommendation to present the strength as both the "amount per mL" and "amount per [redacted] mL" on the container label (i.e., 25 mg/mL [redacted]). At this time, we recommend you consider reverting back to the strength presentation on the container label submitted on May 21, 2021 and only express the strength as "25 mg/mL". Additionally, please ensure the strength presentation (i.e., 25 mg/mL) is in alignment across all labels and labeling. Specifically, ensure the expression of strength is the same throughout the Prescribing Information (i.e., "Dosage Forms and Strengths" in Highlights, "Dosage Forms and Strengths" in Section 3 of the full PI, and "How Supplied" in Section 16 of the full PI).

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/s/

BEVERLY WEITZMAN
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STEPHANIE L DEGRAW
10/27/2021 02:24:54 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 20, 2021

To: Alina Salvatore, Senior Regulatory Project Manager
Division of Neurology II (DN II)

From: Emily Dvorsky, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for EPRONTIA oral solution

NDA: 214679

In response to DN II's consult request dated October 30, 2020, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for EPRONTIA oral solution.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DN II (Tracy Peters) on October 8, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on October 18, 2021.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on October 4, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Emily Dvorsky at (240)402-4256 or Emily.Dvorsky@fda.hhs.gov.

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EMILY M DVORSKY
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 18, 2021
To:	Alina Salvatore Senior Regulatory Project Manager **Division of Neurology II (DN II)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Emily Dvorsky, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	EPRONTIA (topiramate)
Dosage Form and Route:	oral solution
Application Type/Number:	NDA 214679
Applicant:	Eton Pharmaceuticals, Inc.

1 INTRODUCTION

On October 6, 2020, Eton Pharmaceuticals Inc. submitted for the Agency's review an Original New Drug Application (NDA) for topiramate oral solution. The purpose of the submission is to seek approval to market topiramate oral solution, as:

- an initial monotherapy epilepsy for the treatment of partial-onset or primary generalized tonic-clonic seizures in patients 2 years of age and older
- an adjunctive therapy epilepsy 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
- a preventative treatment of migraine in patients 12 years of age and older

On July 23, 2021, the proprietary name EPRONTIA was granted by the agency.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology II (DN II) on November 12, 2020 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for topiramate oral solution.

2 MATERIAL REVIEWED

- Draft EPRONTIA (topiramate) oral solution MG received on October 6, 2020, and received by DMPP and OPDP on October 8, 2021.
- Draft EPRONTIA (topiramate) Prescribing Information (PI) received on October 6, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 8, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG is met the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
10/18/2021 01:52:55 PM

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LASHAWN M GRIFFITHS
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 9, 2021
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 214679
Product Name and Strength:	Eprontia[a] (Topiramate Oral Solution), 25 mg/mL
Applicant/Sponsor Name:	Azurity Pharmaceuticals Inc. (Azurity)
OSE RCM #:	2020-2160-1
DMEPA Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA Team Leader (Acting):	Celeste Karpow, PharmD, MPH

1 PURPOSE OF MEMORANDUM

The Applicant submitted the revised container label on May 21, 2021 for Topiramate Oral Solution. The Division of Neurology 2 (DN 2) requested that we review the revised container label for Topiramate Oral Solution (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[b]

2 ASSESSMENT AND RECOMMENDATIONS

Table 1 identifies our medication error concerns with the container label, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

[a] The proposed proprietary name, Eprontia, is currently under review.

[b] Weitzman, B. Label and Labeling Review for Topiramate (NDA 214679). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 23. RCM No.: 2020-2160.

Table 1. Identified Issues and Recommendations for Azurity (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			
1.	The placeholder, "TRADENAME" appears in place of the proposed proprietary name.	Once a proprietary name is found acceptable, the placeholder "Tradename" should be replaced with the proprietary name.	If the proposed proprietary name is found acceptable, replace the placeholder "TRADENAME" with the proprietary name and submit to the Agency for review.
2.	We note the total concentration per total volume "(b) (4)" previously included on the container label was removed.	We are concerned patients and providers may have to calculate the concentration per (b) (4) mL.	We recommend including the total concentration per total volume as follows: "25 mg/mL (b) (4)" Additionally, you may consider using different font color or background color to distinguish the strength expression from that of the established name or by other means to increase readability.
3.	It is unclear if the Medication guide will be enclosed or accompanying the product.	We are concerned the pharmacist will not know how the Medication Guide is provided.	We recommend revising the statement to include how the Medication Guide will be provided (i.e., enclosed or accompanying). For example, revise to read as follows: "ATTENTION PHARMACIST: Dispense Accompanying Medication Guide."

3 CONCLUSION

The revised container label is unacceptable from a medication error perspective. Above, we have provided recommendations in Table 1 for Azurity. We ask that the Division convey Table 1 in its entirety to Azurity, so the recommendations are implemented prior to approval of this NDA.

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/s/

BEVERLY WEITZMAN
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CELESTE A KARPOW
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 23, 2021
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 214679
Product Name and Strength:	Topiramate[a] Oral Solution, 25 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Azurity Pharmaceuticals Inc. (Azurity)
FDA Received Date:	March 17, 2021
OSE RCM #:	2020-2160
DMEPA Safety Evaluator:	Beverly Weitzman, PharmD
DMEPA Team Leader (Acting):	Celeste Karpow, PharmD, MPH

[a] Proposed proprietary name was not proposed by Applicant, Azurity Pharmaceuticals Inc.

1 REASON FOR REVIEW

As part of the approval process for Topiramate Oral Solution, 25 mg/mL, the Division of Neurology 2 (DN 2) requested that we review the proposed Topiramate prescribing information (PI), medication guide (MG) and container label for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

NDA 214679 is a 505(b)(2) NDA and the listed drug product is Topamax, NDA 020844.

On February 3, 2021, we received correspondence from Eton Pharmaceuticals, Inc. that ownership of NDA 214679 would change from Eton Pharmaceuticals, Inc. to Azurity Pharmaceuticals, Inc. The Agency received revised labels and labeling for NDA 214679 on March 17, 2021 to reflect the change in ownership of NDA 214679.

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), medication guide (MG) and container label, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

The following table (Table 2) outlines issues and recommendations for the Division:

Table 2. Identified Issues and Recommendations for Division of Neurology Products (DNP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Table 1 does not have gridlines and the headings are not centered.	There is a risk that the poor readability might confuse readers.	Consider adding gridlines to Table 1.
2.	The Dosage and Administration section of the PI (Section 2) lacks a statement regarding the use of a dosing device, such as an oral syringe, to accurately measure and administer the prescribed dose.	The lack of information regarding how to accurately measure the prescribed dose may result in a risk of delayed therapy or wrong dose medication errors.	We recommend adding the following statement to section 2.4 Administration Information: "Measure Topiramate Oral Solution with an appropriate measuring device provided by a pharmacist."
3.	It is unclear if the product expiration date changes after opening.	There is a risk of deteriorated drug errors if the expiration date changes after opening.	Clarify if the product expiration date changes after opening. If the product expiration date changes after opening, consider adding a statement similar to, "Discard the unused portion after XX days [*See How Supplied/Storage and Handling]*".
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	It is unclear if the product expiration date changes after opening.	There is a risk of deteriorated drug errors if the expiration date changes after opening.	Clarify if the product expiration date changes after opening. If the product expiration date changes after opening, include a statement similar to, "Discard the unused portion after XX days after first opening the bottle" in section 16.2 Storage and Handling.
Full Prescribing Information – Section 17 Patient Counseling and Medication Guide			

Table 2. Identified Issues and Recommendations for Division of Neurology Products (DNP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	There is no statement instructing patients or caregivers to use an oral dosing syringe to measure their dose.	We are concerned the lack of information regarding how to accurately measure the prescribed dose may result in a risk of delayed of therapy or wrong dose medication errors.	Add the following statements to Section 17: "Instruct patients or caregivers to use an oral dosing syringe to correctly measure the prescribed amount of medication. Inform patients that oral dosing syringes may be obtained from their pharmacy." Add the following statements to the "How should I take (b) (4)?" section of the Medication Guide: "Use an oral dosing syringe to correctly measure your dose. Ask your pharmacist for an oral dosing syringe if you do not have one."
Medication Guide			
2.	It is unclear if the product expiration date changes after opening.	There is a risk of deteriorated drug errors if the expiration date changes after opening.	Clarify if the product expiration date changes after opening. If the product expiration date changes after opening, include a statement similar to, "Discard the unused portion after XX days after first opening the bottle."

The following table (Table 3) outlines issues and recommendations to convey to the Applicant:

Table 3. Identified Issues and Recommendations for Azurity) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label			

Table 3. Identified Issues and Recommendations for Azurity) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	It is unclear if the product expiration date changes after opening.	There is a risk of deteriorated drug errors if the expiration date changes after opening.	Clarify if the product expiration date changes after opening. If the product expiration date changes after opening, include a statement similar to, "Date of first opening __/__/__. Discard unused portion XX days/weeks/months after first opening." in bold font under storage information on the container label for healthcare providers or patients to write the date that the product is first opened. We recommend "Date of first opening" so patients do not have to calculate the "Discard after" date. Additionally, the "__/__/__" statement will alert the users to write a complete date (month, day, and year) on the container label and carton labeling. Furthermore, we recommend this statement appear sufficiently prominent, through use of bolding, contrasting font color, highlighted text, or other means.
2.	The recommended dosage statement can be improved.	To ensure consistency with the prescribing information.	Revise the statement, "(b) (4) (b) (4) to read "Recommended Dosage: See prescribing information."

Table 3. Identified Issues and Recommendations for Azurity) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	The prominence of the product strength expression can be improved to increase readability.	Product strength is critical information and should be prominent on the principle display panel according to our draft guidance[b].	Ensure the product strength is prominent, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. For example, you may consider using different font color or background color to distinguish the strength expression from that of the established name or by other means to increase readability.
4.	The net quantity statement (i.e., 473 mL) is located in the middle of the principal display panel (PDP).	From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. In addition, the current location of the net quantity statement detracts from other critical information on the PDP of the carton labeling.	Relocate the net quantity statement (473 mL) away from the product strength, such as to the bottom of the PDP.
5.	The statement "FOR ORAL USE ONLY" appears with more prominence than other critical information on	Important information may be easily overlooked and difficult to read (e.g., established name, product strength).	Ensure the statement "FOR ORAL USE ONLY" does not appear more prominent than other critical information (e.g.,

[b] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

Table 3. Identified Issues and Recommendations for Azurity) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	the principal display panel (PDP).		established name, product strength) on the PDP.
6.	As currently presented, the linear bar code is displayed in a horizontal position.	Barcodes placed in a horizontal position may not scan due to container curvature.[c] The bending of barcodes around a curved surface affects how light reflects off them, and, if it is distorted in such a way, scanners cannot capture the entire barcode.	Consider reorienting the linear barcode to a vertical position to ensure the scannability of the barcode.
7.	As currently presented, there is no reminder to the pharmacist to dispense an oral dosing syringe with the product.	A reminder on the container label may prevent a delay in therapy or wrong dose medication error.	We recommend you consider including a statement to remind the pharmacist to dispense and oral dosing syringe with the product.
8.	As currently presented, the statement, "(b) (4) " on the principal display panel is not appropriate.	We are concerned this statement clutters the principal display panel and takes readers' attention away from important information such as proprietary and proper names and strength. In addition, the intent of this statement is unclear.	We recommend you consider removing this statement from the principal display panel to a side panel, if appropriate. In addition, clarify the intent of this statement.
9.	The name "azurity" appears larger than critical information on the principle display panel.	The name "azurity" competes in prominence with critical information such as the product name, strength, and dosage form,	Revise the container label to ensure the proprietary name, established name and strength are the most prominent information on the PDP. You may consider

[c] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

Table 3. Identified Issues and Recommendations for Azurity) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		on the principle display panel of the container label.	relocating the manufacturer information to the side panel or decrease the prominence of this information on the PDP.

5 CONCLUSION

Our evaluation of the proposed prescribing information (PI), medication guide (MG) and container label identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Azurity Pharmaceuticals Inc. so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for container that Azurity) submitted on March 17, 2021 and the listed drug (LD).

Table 4. Relevant Product Information for Topiramate and the Listed Drug Topamax[d]

Product Name	No proprietary name proposed. Sponsor using established name, Topiramate.	Topamax (NDA 020844)
Initial Approval Date	N/A	10/26/1998
Active Ingredient	Topiramate	
Indication of Use	• 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 Lennox-Gastaut syndrome in patients 2 years of age and older. • Preventive treatment of migraine in patients 12 years of age and older.	
Route of Administration	Oral	
Dosage Form	Oral solution	Sprinkle Capsules
Strength	25 mg/mL	15 mg and 25 mg
Dose and Frequency	Dosing in Monotherapy Epilepsy: Adults and Pediatric Patients 10 Years of Age and Older: The recommended dose for TOPAMAX® (NDA) or TOPIRAMATE (ANDA) monotherapy in adults and pediatric patients 10 years of age and older is 400 mg/day in two divided doses. The dose should be achieved by titration according to the following schedule (Table 1):	

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

[d] Topamax (topiramate) Sprinkle Capsules (NDA 020844) Prescribing Information. Available in Drugs@FDA under NDA 020844/S052: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020505s061,020844s052lbl.pdf

Pediatric Patients 2 to 9 Years of Age: Dosing in patients 2 to 9 years of age is based on weight. During the titration period, the initial dose of TOPAMAX (NDA) or TOPIRAMATE (ANDA) 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) in 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. Based upon tolerability and clinical response, additional titration to a higher dose (up to the maximum maintenance dose) can be attempted at 25-50 mg/day weekly increments. The total daily dose should not exceed the maximum maintenance dose for each range of body weight (Table 2).

Table 2: Monotherapy Target Total Daily 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:
Adults (17 Years of Age and Older):
The recommended total daily dose of TOPAMAX (NDA) or TOPIRAMATE (ANDA) 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. TOPAMAX (NDA) or Topiramate (ANDA) should be initiated at 25 to 50 mg/day, followed by titration to an effective dose in increments of 25 to 50 mg/day every week. Titrating in increments of 25 mg/day every week may delay the time to reach an effective dose. Doses above 400 mg/day have not been shown to improve responses in adults with partial-onset seizures.

Pediatric Patients 2 to 16 Years of Age:
The recommended total daily dose of TOPAMAX® (NDA) or TOPIRAMATE (ANDA) 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

<table>
<tr><td></td><td colspan="2">two divided doses. Titration should begin at 25 mg/day (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week. The dosage should then be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses), to achieve optimal clinical response. Dose titration should be guided by clinical outcome. The total daily dose should not exceed 400 mg/day.

Dosing for the Preventive Treatment of Migraine:
The recommended total daily dose of TOPAMAX® or TOPIRAMATE (ANDA) 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
(Table 3). The recommended titration rate for TOPAMAX® for the preventive treatment of migraine is as follows:

Table 3: Preventive Treatment of Migraine Titration Schedule for Patients 12 Years of Age and Older
<table><tr><th></th><th>Morning Dose</th><th>Evening Dose</th></tr><tr><td>Week 1</td><td>None</td><td>25 mg</td></tr><tr><td>Week 2</td><td>25 mg</td><td>25 mg</td></tr><tr><td>Week 3</td><td>25 mg</td><td>50 mg</td></tr><tr><td>Week 4</td><td>50 mg</td><td>50 mg</td></tr></table>Dose and titration rate should be guided by clinical outcome. If required, longer intervals between dose adjustments can be used.
Dosing in Patients with Renal Impairment:
In patients with renal impairment (creatinine clearance less than 70 mL/min/1.73 m2), one-half of the usual adult dose of TOPAMAX® (NDA) or TOPIRAMATE (ANDA) is recommended.

Dosing in Patients Undergoing Hemodialysis:
To avoid rapid drops in topiramate plasma concentration during hemodialysis, a supplemental dose of TOPAMAX® (NDA) or TOPIRAMATE (ANDA) may be required. The actual adjustment should take into account 1) the duration of dialysis period, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed.</td></tr>
<tr><td>How Supplied</td><td>Topiramate Oral Solution 25 mg/mL is a colorless to slightly yellow colored clear viscous liquid. It is supplied as 16 fl. oz. (473 mL) in white HDPE bottles</td><td>TOPAMAX (topiramate capsules) Sprinkle Capsules contain small, white to off-white spheres. The gelatin capsules are white and clear and are marked as follows:
• 15 mg capsule with “TOP” and “15 mg” on the side</td></tr>
</table>

		and are available in bottles of 60 • 25 mg capsule with “TOP” and “25 mg” on the side and are available in bottles of 60
Storage	Topiramate Oral Solution is stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59° to 86°F) [see USP Controlled Room Temperature].	TOPAMAX Sprinkle Capsules should be stored in tightly-closed containers at or below 25°C (77°F). Protect from moisture.
Container Closure	The primary packaging system consists of 16 oz (473 mL) white HDPE (b) (4) bottles (b) (4) fitted with 28mm white (b) (4) (b) (4) caps with an aluminum seal as the closure.	HDPE Bottles with (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 24, 2021 we searched for previous DMEPA reviews relevant to this current review using the terms, topiramate and NDA 214679. Our search identified zero previous reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following topiramate labels and labeling submitted on March 17, 2021 by Azurity Pharmaceuticals Inc.

- Container label
- Medication Guide (Image not shown)
- Prescribing Information (Image not shown)
  Refer to link in docuBridge for Prescribing information and Medication Guide:
  Annotated: \\CDSESUB1\evsprod\nda214679\0008\m1\us\11412-annotated-draft-labeling.pdf
  Clean: \\CDSESUB1\evsprod\nda214679\0008\m1\us\package-insert-word.docx

F.2 Label and Labeling Images

Container label

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

BEVERLY WEITZMAN
04/23/2021 05:50:08 PM

CELESTE A KARPOW
04/23/2021 07:17:05 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 1/21/2021

TO: Division of Neurology II (DN II)
Office of Neuroscience (ON)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 214679

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) inspected the clinical site in July 2019, which falls within the surveillance interval. The inspection was conducted under the following submissions: (b) (4) (b) (4)

OSIS inspected the analytical site in (b) (4) which falls within the surveillance interval. The inspection was conducted under the following submissions: (b) (4) (b) (4)

The final classification for the inspections was No Action Indicated (NAI).

Therefore, based on the rationale described above, inspections are not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Lambda Therapeutic Research, Inc.	460 Comstock Road, Toronto, Ontario, Canada
Analytical	(b) (4)	

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/s/

JAMES J LUMALCURI
01/21/2021 04:35:38 PM