CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214273Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION: Approval

NDA 214273
Review # 2

Drug Product Name	ZONISADE (zonisamide)
Dosage Form	Oral suspension
Strength	20 mg/mL
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Azurity Pharmaceuticals
US agent, if applicable	N/A

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	N/A	--
Drug Product	Grace Chiou	Martha Heimann
Manufacturing	Yan Xu	Tianhong Tim Zhou
Microbiology	N/A	--
Biopharmaceutics	N/A	--
Regulatory Business Process Manager	Erica Keafer	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	--	--
Environmental	--	--

SUBMISSIONS REVIEWED

Submission(s)	Document Date	Discipline(s) Affected
SD-16, Quality Amendment	7/29/2021	Drug product, manufacturing
SD-17, Resubmission after CR	1/18/2022	Drug product, manufacturing
SD-20, Labeling/Container	4/18/2022	Drug product

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	II		(b) (4)	Adequate	8/20/2020	J. Medwid
	III			N/A [1]	--	
	III			N/A [1]	--	

[1] DMF was not reviewed. Adequate information in NDA.

B. Other Documents: *IND, RLD, or sister applications*

Document	Application Number	Description
pre-IND	142839	pre-IND final written response (4/11/2019): Agrees-upon pediatric study plan (7/9/2020)
NDA	20789	ZONEGRAN (zonisamide) capsules, referenced under 505(b)(2) to support safety and efficacy of zonisamide

2. CONSULTS

None.

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The Office of Pharmaceutical Quality (OPQ) The Office of Product Quality (OPQ) review team recommends **APPROVAL** of NDA 214273 for ZONISADE (zonisamide oral suspension). From a quality perspective, the application meets all applicable standards to support the identity, strength, quality, and purity that it purports to possess.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Zonisamide was approved in 2000 for adjunctive treatment of partial seizures in adults age 16 years and older. The innovator drug, ZONEGRAN® is available as 25 mg and 100 mg capsules. Multiple generic versions of zonisamide capsules are available in 25 mg, 50 mg, and 100 mg strengths. There are no other approved dosage forms.

This 505(b)(2) NDA was originally submitted on 7/29/2020. The proposed product is a strawberry flavored, aqueous, oral suspension containing zonisamide 20 mg/mL and commonly used excipients. The Agency issued a Complete Response (CR) letter on 5/28/2021 due to facility deficiencies. The 1/18/2022 resubmission addressed the facility deficiencies and provided for minor changes to drug product controls.

Proposed indication(s) including intended patient population	Adjunctive treatment of partial seizures in adults age 16 years and older.
Duration of treatment	Chronic
Maximum daily dose	400 mg
Alternative methods of administration	None

B. Quality Assessment Overview

Drug Substance: **Adequate First Cycle**

No new information was submitted.

Drug Product: **Adequate**

From a drug product perspective, the information provided in the resubmission reflects a change in ownership of the application and information related to the issues in facility inspections as described in the complete response letter to the original submission. The resubmission of this NDA includes new letters of authorizations (LoAs) for the DMFs cross referenced for the container closure components. Additionally, the Applicant provided updated excipient specifications for the compendial excipients that reflects the removal of (b) (4) as the contract testing facility. The information provided in the resubmission is acceptable.

Overall, there is minimal concern to the additional drug product information provided in the resubmission.

Labeling: **Adequate**

Minor revisions will be implemented during final labeling negotiations.

Manufacturing: **Adequate**

The manufacturing process for zonisamide oral suspension was deemed adequate during the first cycle. However, there were two outstanding facility issues that precluded approval of the application. The proposed drug product manufacturing site, L M Manufacturing Ltd (LMML), is a new site that had no FDA inspection history. LMML had been inspected by a Mutual Recognition Agreement (MRA) authority and two 704(a)(4) (document request review in lieu of in person inspection) reviews were conducted for other applications with similar dosage forms/unit operations. The LMML response was not adequate from a quality perspective; therefore, an on-site inspection was necessary to verify that adequate mitigation measures have been taken. Due to the facility location (UK) and Covid-19 travel restrictions it was not possible to perform a facility inspection prior to the PDUFA Goal Date. If inspection of the LMML facility had been the only outstanding issue, action on the NDA would have been delayed until an inspection could be performed. In this case, however, a second facility, (b) (4), which was proposed as a testing site, was under OAI[1] status and a CR letter was issued.

In the resubmission, the (b) (4) facility was withdrawn as a testing site and the test methods were transferred to LMML. A pre-approval inspection with specific

[1] OAI: Official Action Indicated

coverage of the proposed drug product was conducted from 01/27/2022 – 02/02/2022 at the LMML facility. Based on the review of the inspection files, the LMML facility is considered acceptable as a drug product manufacturer. All other facilities remain acceptable. Facility status should be verified prior to final action.

Biopharmaceutics: **Adequate First Cycle**

No new information was submitted.

Microbiology: **Adequate First Cycle**

No new information was submitted.

Environmental: **Adequate First Cycle**

No new information was submitted.

C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
Assay/stability	Formulation, container closure, raw materials, process parameters, scale/equipment/site	**Low**	(b) (4)	**Adequate**	
Physical stability (phase separation)	Formulation, raw materials, process parameters, scale/equipment/site	**Low**		**Adequate**	
Physical stability (solid state)	Formulation, raw materials, process parameters, scale/equipment/site	**Low**		**Adequate**	
Dose accuracy	Dosing device, formulation, process parameters, Scale/equipment/site	**Low**		**Adequate**	
Dissolution	Formulation, raw materials, particle size, process parameters, scale/equipment/site	**Low**		**Adequate**	
Palatability	Formulation, excipient changes, raw materials, process parameters	**Moderate**		**Adequate**	
Microbial limits	Formulation, raw materials, process parameters, scale/equipment/site	**Low**		**Adequate**	
Leachables	Formulation, container closure, process parameters, scale/equipment/site	**Moderate**		**Adequate**	

D. List of Deficiencies for Complete Response

Not applicable.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
Senior Pharmaceutical Quality Assessor for Neurology Products
Office of New Drug Products

6/1/2022

Martha Heimann

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: The draft carton label and prescribing information was retrieved from eCTD 0016 submitted on July 29, 2021. The draft container label was accessed from eCTD 0020 submitted on April 18, 2022.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name Route(s) of administration	ZONISADE (Zonisamide oral suspension)	Inadequate Revise to "ZONISADE (zonisamide oral suspension)"
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4)	Inadequate Remove (b) (4) to avoid confusion
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2 FULL PRESCRIBING INFORMATION

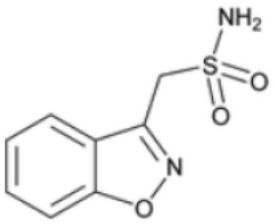
1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	(b) (4) shaken well before every administration. To administer ZONISADE directly into the mouth, it is important that ZONISADE be measured with an accurate measuring device [see Overdosage (10)]. A household teaspoon is not an accurate measuring device. A pharmacist will provide an appropriate device and instructions for measuring the correct dose. (b) (4) orally (b) (4) with or without food. Discard unused portion of ZONISADE 30 days after first opening the bottle.	Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	[redacted] (b) (4)	Adequate
Strength(s) in metric system	[redacted]	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	[redacted] white to off-white [redacted] (b) (4) strawberry flavor [redacted] (b) (4)	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	[redacted]	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s) Dosage form(s) and route(s) of administration If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	ZONISADE (Zonisamide Oral Suspension) (b) (4) [redacted] chemically classified as a sulfonamide (b) (4) [redacted]. The active ingredient is Zonisamide, 1,2-benzisoxazole-3-methanesulfonamide. The empirical formula is C8H8N2O3S with a molecular weight of 212.23. Zonisamide is a white powder, pKa = 10.2, and is moderately soluble in water (0.80 mg/mL) and 0.1 N HCl (0.50 mg/mL). The chemical structure is: 	Inadequate Revise to "(zonisamide oral suspension")

List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	ZONISADE is an aqueous white to off-white liquid suspension. Each mL contains 20 mg of zonisamide. Inactive ingredients include carboxymethylcellulose sodium, citric acid monohydrate, microcrystalline cellulose, purified water, sodium benzoate, strawberry flavor, sucralose, trisodium citrate dihydrate, and xanthan gum.	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	NA	NA
Pharmacological/ therapeutic class	See above	Adequate
Chemical name, structural formula, molecular weight		
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	See above	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	NA	NA

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) Strength(s) in metric system Available units (e.g., bottles of 100 tablets) Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	ZONISADE, (b) (4) is a white to off-white (b) (4). It is supplied in 150 mL amber colored PET bottle with a child resistant cap. NDC Number: 52652-8001-1 Store at 20°C to 25°C (68°F to 77°F), excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature], (b) (4) protected from light. Discard unused portion of ZONISADE 30 days after first opening of the bottle.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	See above	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	NA	NA
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	See above	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	NA	NA
Include information about child-resistant packaging	See above	Adequate

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: Azurity Pharmaceuticals, Inc. Wilmington, MA 01887 Made in United Kingdom	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): With the exclusion of minor edits highlighted in red, the language used is acceptable from a product quality perspective.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

3.2 Carton Labeling

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Zonisade (Zonisamide Oral Suspension)	Inadequate Revise to lower case (i.e., "zonisamide oral suspension")
Dosage strength	(b) (4)	Adequate
Route of administration	For oral use only	
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	NA	
Net contents (e.g. tablet count)	150 mL	
"Rx only" displayed on the principal display	℞ Only	
NDC number	NDC 52652-8001-1	
Lot number and expiration date	LOT: Unvarnished area EXP: 36 x 18 mm	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Date of first opening ___/___/___ Discard unused portion 30 days after first opening.	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	NA
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol		
Bar code	3 52652 80011 9 (b) (4)	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for: azurity pharmaceuticals Wilmington, MA 01887 USA Made in United Kingdom Rev. 00	Adequate
Medication Guide (if applicable)	ATTENTION PHARMACIST: Dispense Medication Guide to each patient. Medication Guide available at: zonisade.com/medication-guide.pdf	
No text on Ferrule and Cap overseal	None present	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	
And others, if space is available	NA	

Assessment of Carton and Container Labeling: ***Adequate***

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Not applicable

Overall Assessment and Recommendation:

Adequate, pending the Applicant's acceptance of the revisions noted above in red.

Martha Heimann

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Grace Chiou

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U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION: Complete Response

NDA 214273
Review # 1

Drug Product Name	ZONISADE (zonisamide)
Dosage Form	Oral suspension
Strength	20 mg/mL
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Azurity Pharmaceuticals (formerly Eton Pharmaceuticals)
US agent, if applicable	N/A

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Jeffrey Medwid	Donna Christner
Drug Product	Grace Chiou	Julia Pinto
Manufacturing	Yan Xu	Joanne Wang
Microbiology	Dionne Coker-Robinson	Denise Miller
Biopharmaceutics	Leah Falade	Ta-Chen Wu
Regulatory Business Process Manager	Kelly Ballard	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	--	--
Environmental	--	--

SUBMISSIONS REVIEWED

Submission(s)	Document Date	Discipline(s) Affected
SD-1, Original NDA	7/29/2020	All
SD-2, Labeling, package insert (PI) draft	9/24/2020	Drug product
SD-4, Response to information request (IR)	10/22/2020	Biopharmaceutics

SD-5, Labeling, PI draft	10/23/2020	Drug product
SD-7, Response to IR	11/6/2020	Drug product
SD-9, Response to IR	12/23/2020	Drug product
SD-10, Labeling, PI draft	2/2/2021	Drug product
SD-11, Labeling, PI draft	2/3/2021	Drug product
SD-14, Response to IR	3/10/2021	Manufacturing
SD-15, Response to IR	3/22/2021	Biopharmaceutics

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	II	(b) (4)		Adequate	8/20/2020	J. Medwid
	III			N/A [1]	--	
	III			N/A [1]	--	

[1] DMF was not reviewed. Adequate information in NDA.

B. Other Documents: *IND, RLD, or sister applications*

Document	Application Number	Description
pre-IND	142839	pre-IND final written response (4/11/2019): Agrees-upon pediatric study plan (7/9/2020)
NDA	20789	ZONEGRAN (zonisamide) capsules, referenced under 505(b)(2) to support safety and efficacy of zonisamide

2. CONSULTS

None

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The Office of Product Quality (OPQ) review team recommends that the Agency issue a **Complete Response Letter (CRL)** for NDA 214273, ZONISADE (zonisamide oral suspension) suspension. From a quality perspective, there insufficient information to ensure that the Applicant can consistently manufacture a product that is suitable for use to treat the intended patients. As discussed in Section II.B. under *Manufacturing*, there are two outstanding facility issues that must be resolved prior to approval of the NDA.

The deficiencies listed in Section II.D. should be communicated in the action letter.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Zonisamide is an antiepileptic drug that was approved in 2000 for adjunctive treatment of partial seizures in adults age 16 years and older. The innovator drug, ZONEGRAN® is available as 25 mg and 100 mg capsule; however, ZONEGRAN 50 mg capsules are discontinued. There are multiple generic versions of zonisamide capsules that are available in 25 mg, 50 mg and 100 mg strengths. There are no other approved dosage forms.

In this 505(b)(2) NDA, the applicant requests approval for a zonisamide oral suspension, 20 mg/mL. The proposed product is a strawberry flavored aqueous suspension to be marketed in 150 mL amber PETE bottles. Excipients include commonly used (b) (4), sucralose, strawberry flavor, and sodium benzoate (b) (4). The recommended initial dose of zonisamide is 100 mg/day, the dose may be increased by 100 mg/day at not less than two-week intervals. The maximum recommended dose is 400 mg/day.

Proposed indication(s) including intended patient population	Adjunctive treatment of partial seizures in adults age 16 years and older.
Duration of treatment	Chronic
Maximum daily dose	400 mg
Alternative methods of administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

Zonisamide USP is a well-characterized small molecule that is approved under NDA 20789 and several ANDAs. Information regarding manufacture and control of the bulk drug substance is incorporated by cross-reference to DMF (b) (4)). The DMF was reviewed in support of this NDA and is deemed adequate to support approval. The information submitted directly to the NDA includes general properties of zonisamide, manufacturing facilities, the manufacturer's release specification (summary table) and certificates of analysis, and the drug product manufacturer's acceptance specification, analytical procedures and supporting method validation/verification data. The drug substance meets USP monograph requirements and the specification includes appropriate controls for process impurities, residual solvents and particle size.

Drug Product: Adequate

The proposed product contains zonisamide, 20 mg/mL, in an aqueous suspension for oral administration. The suspension contains compendial excipients (microcrystalline cellulose (MCC), carboxymethylcellulose sodium (CMCNa), sucralose, xanthan gum, sodium benzoate, citric acid monohydrate, and trisodium citrate dihydrate) that are commonly used in oral liquids and strawberry flavor. Zonisamide oral suspension is packaged in a 150 mL PET bottle with a child resistant closure that contains 150 mL of product. The drug product specification includes appropriate tests and acceptance criteria for an oral suspension. All noncompendial test procedures have been adequately validated and the acceptance criteria have been justified by the applicant. Based on the stability data provided, **the proposed shelf life of 24 months for product stored at 20°C - 25°C is granted**.

Labeling: Adequate

The proposed labeling for zonisamide oral suspension is acceptable from a Product Quality perspective. The only deficiencies identified during the review, i.e., incorrect storage statements on container labels and in the package insert, were corrected in the 2/2/20221 (SD-10) and 2/3/20211 (SD-11) amendments, respectively.

Manufacturing: Inadequate

The manufacturing process for zonisamide oral suspension involves (b) (4)

(b) (4) The applicant has adequately justified selection of process parameters and in-process controls

Although the manufacturing process for zonisamide oral suspension is deemed adequate, there are two outstanding facility issues that preclude approval of the application at this time. The proposed drug product manufacturing site, L M Manufacturing Ltd (LMML), is a new site, with no FDA inspection history. LMML has been inspected by a Mutual Recognition Agreement (MRA) authority and two 704(a)(4) (document request review in lieu of in person inspection) reviews were conducted for other applications with similar dosage forms/unit operations. The LMML response has not been adequate from a quality perspective; therefore, an on-site inspection will be necessary to verify that adequate mitigation measures have been taken. Due to the facility location (UK) and Covid-19 travel restrictions it is unlikely that a facility inspection could be performed prior to the PDUFA Goal Date, 5/29/2021. Additionally, a second facility, (b) (4) which proposed as a testing site in the application, is under OAI status. Thus, the application cannot be recommended for approval from a manufacturing perspective.

Biopharmaceutics: Adequate

The acceptability of the proposed dissolution method and acceptance criterion, and formulation bridging were evaluated.

The applicant's proposed dissolution method was shown to have discriminating ability toward API particle size compared to the to-be-marketed (TBM) formulation. However, the method was not shown to be discriminating towards (b) (4)

The Applicant's proposed dissolution method was deemed acceptable for batch release and stability testing of zonisamide oral suspension. (b) (4) The applicant has agreed to the Agency's recommended acceptance criterion. The dissolution method and acceptance criterion below are recommended for approval.

USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance Criterion
2 (paddle)	60 rpm	Deaerated Water	900 mL	Q = (b) (4) % in 20 min

Pivotal clinical studies used the TBM formulation, which was manufactured at proposed commercial site. Therefore, formulation bridging is not needed.

Microbiology: Adequate

(b) (4) Antimicrobial effectiveness testing (AET) performed in accordance

with USP <51> demonstrated that the specification limits for (b) (4) are adequate. Microbial assessment is performed at release and on stability. The limits are consistent with USP <1111> recommendations for aqueous nonsterile drug products for oral use and analytical methods are adequately validated. In-use stability studies support an in-use period of 30 days after opening the drug product bottle.

Environmental: Adequate

C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
Assay/stability	Formulation, container closure, raw materials, process parameters, scale/equipment/site	**Low**	(b) (4)	**Adequate**	
Physical stability (phase separation)	Formulation, raw materials, process parameters, scale/equipment/site	**Low**		**Adequate**	
Physical stability (solid state)	Formulation, raw materials, process parameters, scale/equipment/site	**Low**		**Adequate**	
Dose accuracy	Dosing device, formulation, process parameters, Scale/equipment/site	**Low**		**Adequate**	
Dissolution	Formulation, raw materials, particle size, process parameters, scale/equipment/site	**Low**		**Adequate**	
Palatability	Formulation, excipient changes, raw materials, process parameters	**Moderate**		**Adequate**	
Microbial limits	Formulation, raw materials, process parameters, scale/equipment/site	**Low**		**Adequate**	
Leachables	Formulation, container closure, process parameters, scale/equipment/site	**Moderate**		**Adequate**	

D. List of Deficiencies for Complete Response

Product Quality

1. During a recent inspection of the [redacted] (b) (4) (FEI: [redacted] (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

2. During a review of records requested under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act, the FDA communicated issues with the L M MANUFACTURING LIMITED, FEI 3015337531 manufacturing facility named in your application. These issues will need to be addressed in order to for your application to be approved. An inspection of the L M MANUFACTURING LIMITED, FEI 3015337531 facility is required before the application can be approved. FDA must ensure that the facility is able to conduct the listed manufacturing operations in compliance with CGMP. FDA will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors. For more information, please see the FDA guidances related to COVID 19. These guidances can be found at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidancedocuments-industry-fda-staff-and-other-stakeholders"

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
CMC Lead for Neurology Products
Office of New Drug Products

4/26/2021

Martha Heimann

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Zonisamide oral suspension	Adequate
Established name(s)		
Route(s) of administration		
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Zonisamide (b) (4) (b) (4) 100 mg/5 mL (b) (4) (b) (4) (3).	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

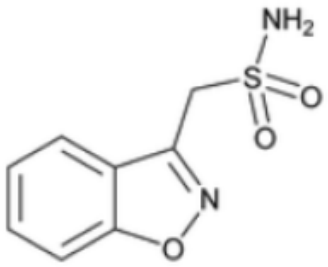
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	(b) (4) shaken well before every administration. To administer zonisamide oral suspension directly into the mouth, it is important that zonisamide oral suspension be measured with an accurate measuring device [see Overdosage (10)]. A household teaspoon is not an accurate measuring device. A pharmacist will provide an appropriate device and instructions for measuring the correct dose. (b) (4) orally (b) (4) with or without food. Discard any unused zonisamide oral suspension remaining 30 days after first opening the bottle.	Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s) Strength(s) in metric system If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	[redacted] oral suspension [redacted] a white to off-white [redacted] strawberry flavor [redacted]	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s) Dosage form(s) and route(s) of administration	Zonisamide oral suspension in an aqueous white to off-white liquid suspension. Each mL contains 20 mg of zonisamide.	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	NA	NA
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Inactive ingredients include carboxymethylcellulose sodium, citric acid monohydrate, microcrystalline cellulose, purified water, sodium benzoate, strawberry flavor, sucralose, trisodium citrate dihydrate, and xanthan gum.	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	NA	NA

Pharmacological/ therapeutic class	Zonisamide is (b) (4) chemically classified as a sulfonamide (b) (4) .	Adequate
Chemical name, structural formula, molecular weight	The active ingredient is Zonisamide, 1,2-benzisoxazole-3-methanesulfonamide. The empirical formula is C8H8N2O3S with a molecular weight of 212.23. Zonisamide is a white powder, pKa = 10.2, and is moderately soluble in water (0.80 mg/mL) and 0.1 N HCl (0.50 mg/mL). The chemical structure is: 	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	Zonisamide is a white powder, pKa = 10.2, and is moderately soluble in water (0.80 mg/mL) and 0.1 N HCl (0.50 mg/mL).	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	NA	NA

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) Strength(s) in metric system Available units (e.g., bottles of 100 tablets) Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Zonisamide oral suspension, (b) (4) is a white to off-white (b) (4). It is supplied in 150 mL amber colored PET bottle with a child resistant cap. NDC Number: (b) (4)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Discard any unused zonisamide oral suspension remaining 30 days after first opening of the bottle.	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	NA	NA
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 25°C (77°F), excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature], (b) (4) protected from light.	*Inadequate* *Replace 25°C with 20°C-25°C per USP controlled room temperature.* *Replace "-" with "to" to avoid confusion with minus sign and replace storage temperature with a range rather than a single temperature.*
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	NA	
Include information about child-resistant packaging	See above.	Adequate

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for (b) (4) [redacted]	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): The only revision is to alphabetize the inactive ingredients listed in the medication guide. Otherwise, the language used in the medication guide is adequate from a quality perspective.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 Structured Product Labeling

4.0 CARTON AND CONTAINER LABELING

3.1 Container Label

3.2 Carton Labeling

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence Dosage strength Route of administration	Zonisamide oral suspension (b) (4))	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	NA	NA
Net contents (e.g. tablet count)	150 mL	Adequate
"Rx only" displayed on the principal display	Rx Only	Adequate
NDC number	NDC 71863-108-06	Adequate
Lot number and expiration date	(b) (4)	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store Zonisamide Oral Suspension at 25°C (77°F), excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature], (b) (4)	*Inadequate Replace 25°C with 20°C-25°C per USP controlled room temperature.*
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	NA
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA

Bar code	(b) (4)	Adequate
Item	**Information Provided in the NDA**	**Assessor's Comments about Carton Labeling**
Name of manufacturer/distributor	(b) (4)	Adequate
Medication Guide (if applicable)	See Medication Guide	Adequate
No text on Ferrule and Cap overseal	None present	Adequate
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	NA
And others, if space is available	NA	NA

Assessment of Carton and Container Labeling:
Adequate, pending the Applicant's acceptance of the revisions noted above in red.
Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation:

This application is recommended for approval per labeling/labels perspective once the following changes have been made to the label.

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Julia Pinto

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

NDA Number	NDA-214273-ORIG-1
Drug Product Name/ Strength	Zonisamide Oral Suspension, 20 mg/mL (150 mL fill)
Route of Administration	Oral
Applicant Name	Eton Pharmaceuticals, Inc.
Therapeutic Classification/ OND Division	Anticonvulsant/DN2
RLD/RS Number	N020789, Zonegran® Capsules, 100 mg
Proposed Indication	As an adjunctive therapy in the treatment of partial seizures in adults with epilepsy
Primary Reviewer	Leah W. Falade, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

Assessment Recommendation: **Adequate**

Background:
The Applicant seeks approval for its Zonisamide Oral Suspension, 20 mg/mL (150 mL fill) using Zonegran® Capsules, 100 mg (NDA 020789) as the Listed Drug (LD) and is seeking approval under the 505(b)(2) pathway relying on previous established safety and efficacy findings for Zonegran®.

The clinical package in support of this NDA includes 2 clinical studies. Fasting and fed pivotal studies were performed to establish bioequivalence to the LD. The to-be-marketed (TBM) formulation was used in the pivotal studies. In support of the Biopharmaceutics program, a suitable dissolution method was developed for the proposed oral suspension product.

Assessment Summary:
The review focuses on the Biopharmaceutics evaluation and acceptability of 1) the proposed dissolution method and acceptance criterion, and 2) formulation bridging. The key findings are summarized below:

1) **Dissolution Method and Acceptance Criterion:**
The Applicant proposed a dissolution method using USP Apparatus 2 (paddle) at 60 rpm in 900 mL of deaerated water. The proposed dissolution method was shown to have discriminating ability toward API particle size and (b) (4) concentrations.

(b) (4)

The Applicant agreed to the recommended acceptance criterion of Q (b) (4) % in 20 min on 03/22/2021.

The Applicant's proposed dissolution method and acceptance criterion are deemed acceptable for batch release and stability testing of the proposed suspension drug product.

2) **Formulation Bridging:** The pivotal studies (19-009 and 19-101) used the TBM formulation that was manufactured at LM Manufacturing Limited, UK. The commercial batches will be manufactured at the same site. Therefore, bridging is not needed.

Recommendation:
From the Biopharmaceutics perspective, NDA-214273-ORIG-1 for Zonisamide Oral Suspension, 20 mg/mL is recommended for **approval**.

The FDA-approved dissolution method and acceptance criterion for the proposed Zonisamide Oral Suspension, 20 mg/mL, for batch release and stability testing are as follows:

USP Apparatus	Speed	Medium	Volume	Acceptance criterion
2 (paddle)	60 rpm	Deaerated Water	900 mL	Q (b) (4) % in 20 min

List Submissions being assessed:

Document(s) Assessed	Date Received
Original (Seq 0001)	07/29/2020
IR Response (Seq 0004)	10/22/2020
IR Response (Seq 0015)	03/22/2021

Highlight Key Issues from Last Cycle and Their Resolution:
This is the first review cycle.

Concise Description of Outstanding Issues:
None

B.1 BCS DESIGNATION

Assessment:

The Applicant claims that the API is a BCS Class 1 drug substance. However, the Applicant has not requested a BCS waiver.

Solubility:

The Applicant submitted solubility data in media with pH 1.2 to 6.8, and water. (b) (4) The initial dose should be 100 mg/day. After two weeks it may be increased (b) (4) The calculated dose solubility for the highest single dose is 400 mg/250 mL = 1.6 mg/mL. In all conditions, the measured solubility is <1.6 mg/mL and the drug substance is therefore not considered highly soluble, per the FDA's BCS Guidance. The Applicant's solubility data provided in the Dissolution Method Development Report is presented in Table 1.

Table 1. pH Dependent Solubility of Zonisamide in Different Buffer Solutions

Saturation Solubility of Zonisamide	Dissolution Medium	Solubility (mg/mL)
	Purified water	0.83
	1.2 pH (0.1N HCl)	0.81
	4.5 pH acetate buffer	0.83
	6.8 pH phosphate buffer	0.80

Permeability:

The Applicant submitted literature data showing that the drug demonstrates extensive oral bioavailability (approaching 100%).

Dissolution:

See assessment in section B2.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERION

Assessment: A*dequate*

Dissolution Method

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The final proposed dissolution method is acceptable and presented in Table 7.

Table 7. Final Dissolution Method

USP Apparatus	Speed	Medium	Volume
2 (paddle)	60 rpm	Deaerated Water	900 mL

Discriminating Ability of the Dissolution Method

The discriminating ability of the dissolution method was investigated by altering the to-be-marketed (TBM) formulation with respect to (b) (4) concentrations, and API particle size. The formulation variations were in line with those communicated in the IR (Seq 0004) (b) (4) % change). The test product manufactured with the aberrant formulation has slower release in the first 10 minutes (Figure 3). The similarity factor calculated by this reviewer is 31.25.

Figure 3. Comparative dissolution profile for target formulation vs. aberrant formulation with higher (b) (4)

Name	F2-Value
Target Vs Aberrant Formulation	31.25

The test product manufactured with a higher particle size API had slower release up to 30 min than the target formulation (Figure 4). The similarity factor (f2) calculated by this reviewer is 46.38.

Figure 4. Comparative dissolution profile for target formulation vs. aberrant formulation with higher API particle size

Name	F2-Value
Target Vs Higher API Particle Size	46.38

The dissolution method has discriminating ability toward changes in (b) (4) concentrations and API particle size.

Acceptance Criterion

The Applicant proposed "Q= (b) (4) min" for the finished product acceptance criterion. However, based on the data (Table 8) for the pivotal clinical batch (#VAL/18/0076), the proposed acceptance criterion (b) (4). Based on the submitted data, this Reviewer recommended "Q= (b) (4) % in 20 min" for the proposed suspension drug product. The Applicant agreed to the recommended dissolution acceptance criterion on 03/22/2021[2]. Full dissolution profile data was requested for the 2 registration batches in an IR. In response (Seq 0004), the Applicant submitted the 33-month stability data for the 2 registration batches (#VAL/18/0078 and VAL/18/0081). The registration batches meet the approved dissolution acceptance criterion and there is no downward trend in the data for up to 33 months. The profiles for the registration batches are similar to the biobatch.

[2] \\CDSESUB1\evsprod\nda214273\0015\m1\us\ir-quality-response-seq0015.pdf

Table 8. Dissolution Data for Zonisamide Oral Suspension, 20 mg/mL lot #VAL/18/0076

Sr. No.	Vessel number	% Drug Release				
		10 min	20 min	30 min	45min	60min
01	Vessel-1	(b) (4)				
02	Vessel-2					
03	Vessel-3					
04	Vessel-4					
05	Vessel-5					
06	Vessel-6					
07	Vessel-7					
08	Vessel-8					
09	Vessel-9					
10	Vessel-10					
11	Vessel-11					
12	Vessel-12					
Average		86	89	90	91	93
%RSD		1.2	1.2	0.9	0.9	1.1

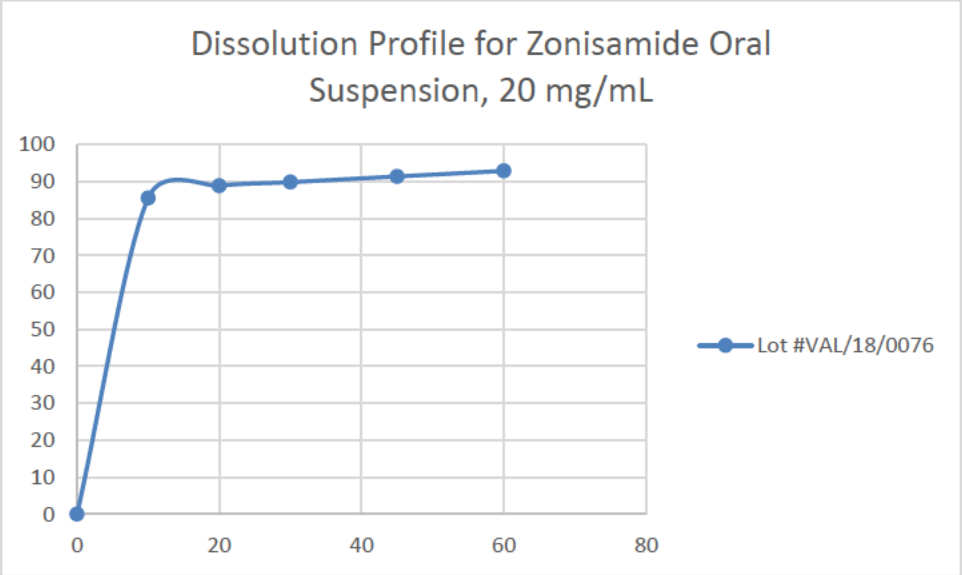

Figure 5. Dissolution profile for Zonisamide Oral Suspension (100 mg), N=12

B.3 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

The pivotal studies (19-009 and 19-101) used the TBM formulation that was manufactured at LM Manufacturing Limited, UK. The commercial batches will be manufactured at the same site. Therefore, bridging is not needed.

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Ta-Chen Wu

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

IQA ANDA Assessment Guide Reference

Product Information	
NDA Number	214273
Assessment Cycle Number	1
Drug Product Name / Strength	Zonisamide Oral Suspension, 20 mg/mL, 150 mL fill
Route of Administration	Oral Solution
Applicant Name	Eton Pharmaceuticals, Inc. 21925 West Field Parkway, Suite 235 Deer Park, Illinois, 60010, USA
Manufacturing Site	LM Manufacturing Limited Sandretto Building, Cavalry Hill Industrial Area, Weedon, Northampton, NN7 4PP, UK
Method of Sterilization	Nonsterile Solution

Assessment Recommendation: **Adequate**

Theme:

☒ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: *view justification statements found at:* **Justification Statements**

N/A
Other (Requires Division Director Approval) – *Assessor writes-in justification here if "other" selected as theme.*

Assessment Summary: The submission is **recommended** for approval on the basis of sterility assurance.

List Submissions Being Assessed (table):

Date Submitted to FDA	Date Received by FDA	Date Assigned to Reviewer
07/28/2020	07/29/2020	08/10/2020

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The submission is in e-CTD format

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): N/A

Supporting Documents: N/A

Select Number of Approved Comparability Protocols: 0

S DRUG SUBSTANCE

S.2. MANUFACTURE

S.2.1 MANUFACTURERS

Assessment:

As the drug product is nonsterile, the drug substance will not be reviewed by microbiology.

Adequate

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –**
  Nonsterile, white off-white solution filled as a 150mL fill into a 150mL amber PET bottle and closed with (b) (4) white (b) (4) child resistant (b) (4) closure. Zonisamide Oral Suspension, 20 mg/mL, 150 mL fill is indicated as an adjunctive therapy in the treatment of partial seizures in adults (b) (4); multiple-dose bottle.

Drug product composition

Ingredient	Function	Quantity/mL	Quantity/Unit

Zonisamide, USP	API	20.00 mg	3000.00mg
Microcrystalline Cellulose and Carboxymethylcellulose Sodium (b) (4) (b) (4)	(b) (4)		
Sucralose			
Xanthan Gum			
Sodium Benzoate			
Citric Acid Monohydrate			
Trisodium Citrate Di-hydrate			
Strawberry Flavor			
Purified Water			

Exhibit Batch: Batch No. VAL/18/0076, VAL/18/0078, VAL/18/0081, (b) (4)

Proposed Commercial Batch: The commercial batch size is (b) (4) times the exhibit batch size

- **Description of container closure system – Drug Product**

Component	Material Code No.	Description	Manufacturer
Bottle	(b) (4)	150mL amber PET Bottle	(b) (4)
Closure	(b) (4)	(b) (4) white (b) (4) child resistant (b) (4) - (b) (4) closure	

Assessment:

Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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Denise Miller

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/s/

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