CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214273Orig1s000

OTHER REVIEW(S)

Deputy Director for Safety Memorandum

NDA: 214273
Product name: Zonisade (zonisamide) oral suspension
Indication: adjunctive therapy in the treatment of partial seizures in adults with epilepsy
Subject: Pregnancy and lactation labeling
Review date: July 14, 2022
Reviewer: Alice Hughes, M.D.
Deputy Director for Safety, Division of Neurology 2

This memorandum is written to address the consult review from the Division of Pediatrics and Maternal Health (DPMH) dated May 20, 2022, by Wenjie Sun. DN2 consulted DPMH to review the pregnancy and lactation data and labeling submitted by the sponsor in their New Drug Application (NDA) for Zonisade (zonisamide) oral suspension. This application was submitted in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The listed drug (LD) is NDA 020789, Zonegran (zonisamide), which was approved on March 27, 2000. Zonegran itself is in neither Physician Labeling Rule (PLR) nor Pregnancy and Lactation Labeling Rule (PLLR) format.

In their review, DPMH reviewed literature pertaining to the effects of epilepsy on pregnancy outcomes and on fertility as well as the literature pertaining to zonisamide and pregnancy outcomes, lactation, and fertility. They conducted their own literature reviews as well as assessed the literature reviews submitted by the sponsor pertaining to these topics. In addition, they summarized the relevant nonclinical data and noted that there are no relevant clinical trial data.

Based on their review, DPMH recommended removing the Warnings and Precautions section (b) (4) describing the risk of teratogenicity based on animal data (which is consistent with the current Warnings subsection in approved Zonegran labeling), and they also recommended removing the recommendation to advise women of childbearing potential treated with zonisamide to use effective contraception. The basis for this recommendation is their conclusion that available clinical data since Zonegran's approval over 20 years ago do not provide evidence that Zonegran is a major human teratogen. They cite data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry that do not indicate an increased risk of major congenital malformations (MCM) in infants exposed to zonisamide during pregnancy. The frequency of overall MCM was 1.4% in 217 pregnancies exposed to zonisamide monotherapy during the first trimester (95% CI 0.4 to 4.3%).

In making this recommendation, they acknowledged the animal findings that are well described in the labeling; zonisamide has been demonstrated to be teratogenic in multiple animal species (mice, rats, and dogs) and was found to be embryolethal in monkeys when administered during the period of organogenesis. Fetal abnormalities or embryofetal deaths occurred in these species at zonisamide dose or maternal plasma levels similar to or lower than therapeutic levels in humans. They also acknowledged that an increase in

infants who are small for gestational age (SGA) was observed in patients exposed to zonisamide in utero in both the NAAED Pregnancy Registry and the United Kingdom and Ireland Epilepsy Pregnancy Registry (UKIEPR). They also stated that zonisamide can cause metabolic acidosis, which is known to have the potential to result in adverse pregnancy outcomes, such as decreased fetal growth, decreased fetal oxygenation, and fetal death. They also noted that a small prospective study, the UKIEPR mentioned above, reported an increased rate of major congenital malformations of 13% in pregnancies with first trimester zonisamide monotherapy use (n=26). They stated that this study has methodological limitations, including small sample size, selection bias, and inability to account for potential confounders.

I concur with DPMH that data from the NAAED Pregnancy Registry since Zonegran's approval have not demonstrated an increased risk of major congenital malformations. I do not believe, however, that the data from the NAAED Pregnancy Registry provide enough assurance of a lack of a fetal risk in humans to justify removal of the Warnings and Precautions subsection pertaining to fetal risk (b) (4) (which is consistent with the Warnings subsection in the approved Zonegran labeling). The data from the NAAED Pregnancy Registry are based on only 217 pregnancies with first trimester zonisamide monotherapy exposure. This suggests that use of Zonegran during pregnancy has been low, which is expected given both the Warnings subsection and the recommendation for women of childbearing potential to use contraception during zonisamide treatment.

Although the accrual of more data could provide additional support for a lack of a congenital malformation risk in humans, it is also possible that more data could demonstrate evidence of a risk for major congenital malformations. There is certainly precedent for risks related to use during pregnancy to emerge after many years of a product's availability. For example, Depakote (divalproex sodium) was approved in 1983. While the risk for neural tube defects was known much earlier, the risk for developmental delay following in utero exposure was not included in labeling until 2011, and the risk for autism spectrum disorders was not included in labeling until 2014. Topamax (topiramate) was approved in 1996, but the risk for oral clefts following in utero exposure was not added to the labeling until 2014 (in the form of a new Warning), based largely on data from the NAAED Pregnancy Registry in addition to data from the UK Epilepsy and Pregnancy Register. The labeling did describe findings of teratogenicity in multiple animal species prior to that addition. In her March 3, 2011, review of the topiramate supplement that provided for the addition of language pertaining to a risk for oral clefts, safety reviewer Dr. M. Lisa Jones indicated that there were 333 first trimester topiramate monotherapy exposures in the NAAED Pregnancy Registry, which is a substantially greater number of exposures than we currently have for zonisamide.

The current data from the NAAED Pregnancy Registry conflicts with multiple other data sources, including data from a small prospective registry in humans (the UKIEPR) that does indicate the potential for fetal risk. Although I acknowledge the methodological concerns that DPMH has raised about this small study, I do not think these findings in

humans can be dismissed, particularly in light of the animal data, which indicate that zonisamide is a teratogen in multiple species. Moreover, although data from the NAAED Pregnancy Registry may be somewhat reassuring with respect to a major congenital malformation risk, they do indicate the potential for other adverse pregnancy outcomes following in utero exposure. Analyses of data from the NAAED Pregnancy Registry demonstrated a decrease in mean birth weight and birth length among neonates exposed to topiramate or zonisamide in utero compared with neonates exposed to lamotrigine and an unexposed group. An increase in infants who are small for gestational age was also observed in patients exposed to zonisamide in utero in the UKIEPR. This may be the result of metabolic acidosis, which is known to be a risk related to zonisamide and also known to be related to adverse pregnancy outcomes such as decreased fetal growth, decreased fetal oxygenation, and fetal death (although we lack data tying these outcomes to metabolic acidosis related to zonisamide specifically).

Based on the multiple data sources indicating the potential for fetal risk with zonisamide—animal data indicating that zonisamide is a teratogen in multiple species, the known risks to the fetus of metabolic acidosis during pregnancy, the evidence that infants exposed to zonisamide in utero have an increased risk of being SGA, and data from a small registry in humans indicating a higher than expected risk of major congenital malformations—I recommend that, despite the current lack of evidence of major congenital malformations in the NAAED Pregnancy Registry up to this point, Zonisade be approved with a fetal risk Warnings and Precautions subsection and a contraception recommendation. I also recommend that the fetal risk Warnings subsection and the contraception recommendation be retained for Zonegran. The number of first trimester monotherapy exposures in the NAAED Pregnancy Registry is currently not large enough to be sufficiently reassuring in light of the available evidence that indicates that zonisamide does confer a risk to the fetus.

I agree with many of DPMH's suggested labeling changes in Section 8 pertaining to a description of the available data related to use during pregnancy, but I recommend making the discussion of the animal data more prominent. I also agree with their labeling changes pertaining to the lactation section and pertaining to zonisamide's effect on fertility in humans.

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/s/

ALICE HUGHES
07/14/2022 11:50:52 AM

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:	July 1, 2022
To:	Stephanie Parncutt Regulatory Project Manager **Division of Neurology II (DN2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Nyedra W. Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Mary Carroll, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Samuel Fasanmi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ZONISADE (zonisamide oral suspension)
Dosage Form and Route:	oral suspension
Application Type/Number:	NDA 214273
Applicant:	Azurity Pharmaceuticals, Inc.

1 INTRODUCTION

On January 18, 2022, Azurity Pharmaceuticals, Inc. submitted for the Agency's review a Class 2 Resubmission to their original New Drug Application (NDA) 214273 for ZONISADE (zonisamide oral suspension). This 505(b)(2) Application was submitted in response to the Agency's Complete Response Letter issued on May 28, 2021, due to safety, and chemical, manufacturing, and control (CMC) issues. With this submission, the Applicant is proposing an indication as an adjunctive therapy for the treatment of partial seizures in adults with epilepsy.

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 (DN2) on February 1, 2022 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ZONISADE (zonisamide oral suspension).

2 MATERIAL REVIEWED

- Draft ZONISADE (zonisamide oral suspension) MG received on January 18, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 22, 2022.
- Draft ZONISADE (zonisamide oral suspension) Prescribing Information (PI) received on January 18, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 22, 2022.
- Approved ZONEGRAN (zonisamide) labeling dated April 13, 2020.

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. We reformatted the MG document using the Arial font, size 10.

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)
- removed unnecessary or redundant information
- 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 meets 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/

MARY E CARROLL
07/05/2022 10:19:32 AM

DOMENIC G DALESSANDRO
07/05/2022 10:21:52 AM
Signed for Samuel Fasanmi

SHARON W WILLIAMS
07/05/2022 10:32:29 AM

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

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

Memorandum

Date: 07/01/2022

To: Steven Dinsmore, M.D., Clinical Reviewer
Division of Neurology Products (DN II)

Josephine Little, Regulatory Project Manager, (DN II)

Tracy Peters, Associate Director for Labeling, (DN I / II)

From: Samuel Fasanmi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for ZONISADE (zonisamide) oral suspension

NDA: 214273

In response to DN II consult request dated February 01, 2022, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA for ZONISADE (zonisamide) oral suspension.

PI: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DN II on June 22, 2022, and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 17, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Samuel Fasanmi at (301) 796-5188 or samuel.fasanmi@fda.hhs.gov.

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/s/

SAMUEL A FASANMI
07/01/2022 11:28:59 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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 28, 2022
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 214273
Product Name and Strength:	Zonisade (zonisamide) oral suspension, 100 mg/5 mL
Applicant/Sponsor Name:	Azurity Pharmaceuticals, Inc.
OSE RCM #:	2022-140-1
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on June 17, 2022 for Zonisade. The Division of Neurology 2 (DN 2) requested that we review the revised container label and carton labeling for Zonisade (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Morris, C. Label and Labeling Review for Zonisade (NDA 214273). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2022 MAY 11. RCM No.: 2022-140.

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/s/

JOHN C MORRIS
06/28/2022 04:44:13 PM

STEPHANIE L DEGRAW
06/28/2022 07:18:36 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Review

Date: 5/19/2022 **Date consulted:** 3/24/2022

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Neurology (DN2)

Drug: Zonisade (zonisamide) oral suspension, 20 mg/mL

NDA: 214273

Applicant: Azurity

Subject: Pregnancy and Lactation Labeling

Proposed Indication: As adjunctive therapy in the treatment of partial seizures in adults with epilepsy

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 214273 dated July 28, 2020, and resubmission on January 18, 2022
- Complete Response Letter dated May 28, 2021
- General Advice Letter dated January 13, 2022
- DN2 consult form for DPMH, DARRTS Reference ID 4957849

Consult Question:

The review team requests DPMH's input on the labeling to be consistent with the Pregnancy and Lactation Labeling Rule. (b) (4)

[redacted] (b) (4)

INTRODUCTION AND BACKGROUND

On January 18, 2022, the applicant (Azurity) submitted an NDA for Zonisade (zonisamide) oral suspension, NDA 214273, as an adjunctive therapy in the treatment of partial seizures in adults with epilepsy. The Division of Neurology (DN2) consulted the Division of Pediatric and Maternal Health (DPMH) on March 24, 2022, to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- Zonisamide has been approved in the U.S. under NDA 020789, tradename Zonegran, as an oral capsule for adjunctive therapy in the treatment of partial seizures in adults with epilepsy since March 27, 2000.
- On July 28, 2020, Azurity submitted NDA 214273 for zonisamide oral suspension in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and indicated as an adjunctive therapy in the treatment of partial seizures in adults with epilepsy. The reference listed drug (RLD) was NDA 020789, Zonegran.
- On May 28, 2021, the Agency sent a Complete Response Letter (CRL) to the applicant due to deficiencies regarding the manufacturing facility. Further advice was given to the applicant in an Advice Letter on January 13, 2022.
- On January 18, 2022, the applicant resubmitted NDA 214273 for review.
- On March 24, 2022, DN2 consulted DPMH to assist with the development of subsections 8.1 and 8.2 of the product's labeling.
- On March 31, 2022, the Agency sent an Information Request (IR) to the applicant to obtain additional information to support labeling under subsections 8.1, 8.2, and 8.3 regarding the use of zonisamide during pregnancy, lactation, and in females and males of reproductive potential.
- On April 7, 2022, the applicant replied to the IR.

Drug Characteristics

Zonisamide Characteristics[1]

Drug Class	Antiepileptic
Mechanism of action	The precise mechanism(s) by which zonisamide exerts its [redacted] (b) (4) effect is unknown. [redacted] (b) (4) Zonisamide may produce these effects through action at sodium and calcium channels. In vitro pharmacological studies suggest that zonisamide blocks sodium channels and reduces voltage-dependent, transient inward currents (T-type Ca2+ currents), consequently stabilizing neuronal membranes [redacted] (b) (4) Other in vitro studies have demonstrated that zonisamide (10–30 µg/mL) suppresses synaptically-driven electrical activity without affecting postsynaptic GABA or glutamate responses (cultured mouse

[1] Based on applicant proposed labeling and discussion with DN2 review team.

	spinal cord neurons) or neuronal or glial uptake of [3H]-GABA (rat hippocampal slices). Thus, zonisamide does not appear to potentiate the synaptic activity of GABA. (b) (4) [redacted] Zonisamide is a carbonic anhydrase inhibitor. The contribution of this pharmacological action to the therapeutic effects of zonisamide is unknown. (b) (4) [redacted]
Molecular weight	212 Daltons
Half-life	63 hours in plasma; 105 hours in red blood cells
Protein Binding	40%

Zonisamide is an oral solution that is given with or without food. Due to its long half-life, it may take up to two weeks to achieve steady state. The initial dose of zonisamide is 100 mg daily. After two weeks, the dose may be increased (b) (4) [redacted] Evidence from controlled trials (b) (4) [redacted] no suggestion of increasing response above 400 mg/day.

Serious adverse reactions[2]

- Potentially Fatal Reactions to Sulfonamides: Fatalities have occurred, although rarely, as a result of severe reactions to sulfonamides (zonisamide is a sulfonamide) including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias.
- Serious Skin Reactions: (b) (4) [redacted]
- Suicidal Behavior and Ideation: (b) (4) [redacted].

Current State of the Labeling for the RLD, Zonegran oral capsule, NDA 020789[3]

- Approved labeling is not in Physician Labeling Rule (PLR) or PLLR format.
- There is no boxed warning.
- There is contraindication for use in patients with known hypersensitivity to sulfonamides or zonisamide.
- Serious Adverse Reactions:

[2] Based on applicant proposed labeling and discussion with the DN2 Clinical Review Team.
[3] According to the currently approved labeling of Zonegran, NDA 020789, at Drugs@FDA. Accessed 3/29/22. Last updated 4/3/2020.

- Potentially fatal reactions to sulfonamides
- Serious skin reactions
- Serious hematologic events: 2 cases of aplastic anemia and one confirmed case of agranulocytosis were reported in the first 11 years of marketing in Japan.
- Drug reaction with eosinophilia and systemic symptoms (DRESS)/multiorgan hypersensitivity
- Oligohidrosis and hyperthermia in pediatric patients
- Acute myopia and secondary angle closure glaucoma
- Suicidal behavior and ideation
- Metabolic acidosis
- Seizures on withdrawal
- Teratogenicity
- Cognitive/neuropsychiatric adverse events
- Hyperammonemia and encephalopathy

Pregnancy

Zonisamide may cause serious adverse fetal effects, based on clinical and nonclinical data. Zonisamide was teratogenic in multiple animal species.

Zonisamide treatment causes metabolic acidosis in humans. The effect of zonisamide-induced metabolic acidosis has not been studied in pregnancy; however, metabolic acidosis in pregnancy (due to other causes) may be associated with decreased fetal growth, decreased fetal oxygenation, and fetal death, and may affect the fetus's ability to tolerate labor. Pregnant patients should be monitored for metabolic acidosis and treated as in the non-pregnant state.

Newborns of mothers treated with zonisamide should be monitored for metabolic acidosis because of transfer of zonisamide to the fetus and possible occurrence of transient metabolic acidosis following birth. Transient metabolic acidosis has been reported in neonates born to mothers treated during pregnancy with a different carbonic anhydrase inhibitor.

Zonisamide was teratogenic in mice, rats, and dogs and embryolethal in monkeys when administered during the period of organogenesis. Fetal abnormalities or embryo-fetal deaths occurred in these species at zonisamide dosage and maternal plasma levels similar to or lower than therapeutic levels in humans, indicating that use of this drug in pregnancy entails a significant risk to the fetus. A variety of external, visceral, and skeletal malformations was produced in animals by prenatal exposure to zonisamide. Cardiovascular defects were prominent in both rats and dogs.

Following administration of zonisamide (10, 30, or 60 mg/kg/day) to pregnant dogs during organogenesis, increased incidences of fetal cardiovascular malformations (ventricular septal defects, cardiomegaly, various valvular and arterial anomalies) were found at doses of 30 mg/kg/day or greater. The low effect dose for malformations produced peak maternal plasma zonisamide levels (25 µg/mL) about 0.5 times the highest plasma levels measured in patients receiving the maximum recommended human dose (MRHD) of 400 mg/day. In dogs, cardiovascular malformations were found in approximately 50% of all fetuses exposed to the high dose, which was associated with

maternal plasma levels (44 µg/mL) approximately equal to the highest levels measured in humans receiving the MRHD. Incidences of skeletal malformations were also increased at the high dose, and fetal growth retardation and increased frequencies of skeletal variations were seen at all doses in this study. The low dose produced maternal plasma levels (12 µg/mL) about 0.25 times the highest human levels.

In cynomolgus monkeys, administration of zonisamide (10 or 20 mg/kg/day) to pregnant animals during organogenesis resulted in embryo-fetal deaths at both doses. The possibility that these deaths were due to malformations cannot be ruled out. The lowest embryolethal dose in monkeys was associated with peak maternal plasma zonisamide levels (5 µg/mL) approximately 0.1 times the highest levels measured in patients at the MRHD.

In a mouse embryo-fetal development study, treatment of pregnant animals with zonisamide (125, 250, or 500 mg/kg/day) during the period of organogenesis resulted in increased incidences of fetal malformations (skeletal and/or craniofacial defects) at all doses tested. The low dose in this study is approximately 1.5 times the MRHD on a mg/m2 basis. In rats, increased frequencies of malformations (cardiovascular defects) and variations (persistent cords of thymic tissue, decreased skeletal ossification) were observed among the offspring of dams treated with zonisamide (20, 60, or 200 mg/kg/day) throughout organogenesis at all doses. The low effect dose is approximately 0.5 times the MRHD on a mg/m^2 basis.

Perinatal death was increased among the offspring of rats treated with zonisamide (10, 30, or 60 mg/kg/day) from the latter part of gestation up to weaning at the high dose, or approximately 1.4 times the MRHD on a mg/m^2 basis. The no effect level of 30 mg/kg/day is approximately 0.7 times the MRHD on a mg/m2 basis.
There are no adequate and well-controlled studies in pregnant women. ZONEGRAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

To provide information regarding the effects of in utero exposure to ZONEGRAN, physicians are advised to recommend that pregnant patients taking ZONEGRAN enroll in the NAAED Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

Labor and Delivery

The effect of ZONEGRAN on labor and delivery in humans is not known.

Use in Nursing Mothers

Zonisamide is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ZONEGRAN, a decision should be made whether to discontinue nursing or to discontinue drug, taking into account the importance of the drug to the mother.

Teratogenicity

Women of childbearing potential who are given zonisamide should be advised to use effective contraception. Zonisamide was teratogenic in mice, rats, and dogs and embryolethal in monkeys when administered during the period of organogenesis. A

variety of fetal abnormalities, including cardiovascular defects, and embryo-fetal deaths occurred at maternal plasma levels similar to or lower than therapeutic levels in humans. These findings suggest that the use of ZONEGRAN during pregnancy in humans may present a significant risk to the fetus (see PRECAUTIONS, Pregnancy subsection). Zonisamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

- There are contraception recommendations.
- There are known drug-drug interactions with hormonal contraceptives

PREGNANCY

Pregnancy and Seizure Disorders[4]

In the U.S., 1.5 million women of childbearing age have epilepsy, and 24,000 women with epilepsy give birth annually.[5] Epilepsy can be categorized as the following:

- Simple partial (now termed focal with preserved awareness)
- Complex partial (focal with altered awareness)
- Generalized (generalized)
- Secondary generalized (focal to bilateral tonic-clonic)

The Effect of Epilepsy on Pregnancy

Several studies have found that mortality rates during pregnancy are approximately 10-fold higher in pregnant women with epilepsy compared with the general population, while the absolute risk remains low at less than 0.1 percent.[6] There is no specific information on the effect of complex partial seizures on pregnancy. There are inconsistent reports of increased risk of stillbirth among women with epilepsy.[7,8] Antiepileptic drug (AED) exposure is associated with an increased risk of preterm births.[9] Other adverse outcomes are also increased. In a large U.S. study that evaluated hospitalizations that occurred at the time of delivery (2007-2011), the following risks were increased in women with epilepsy verses those without epilepsy: cesarean delivery rate (41 versus 33 percent), pregnancy-related hypertension (10.5 versus 7.9 percent), preeclampsia (6.7 versus 4.2 percent), antepartum hemorrhage (2.1 versus 1.5 percent), postpartum hemorrhage (0.7 versus 0.4 percent), preterm labor (11 versus 7 percent) and poor fetal growth (3.7 versus 2.1 percent), respectively.

Additionally, there are concerns regarding the effects of maternal seizure on the fetus. Particularly, generalized tonic-clonic seizures can lead to hypoxia or lactic acidosis in the mother, and therefore, results in decreased placental blood flow and fetal hypoxia. Placental abruption can also result from injury secondary to seizure.

Effect of Pregnancy on Seizures

In early published literature, most studies reported that 20 to 50 percent of women had worsening of

[4] Hessler A, et al. Clinical Updates in Women's Health Care: Seizures. Vol XX, Number I, January 2021. (ACOG)
[5] Sazgar M. Treatment of women with epilepsy. Continuum (Minneap Minn) 2019;25:408-30
[6] Pennell PB, et al. Risks associated with spilepsy during pregnancy and postpartum period. UpToDate. Accessed 4/19/22.
[7] Viale L, Allotey J, Cheong-See F, et al. Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. Lancet 2015; 386:1845.
[8] Pennell PB, French JA, Harden CL, et al. Fertility and Birth Outcomes in Women With Epilepsy Seeking Pregnancy. JAMA Neurol 2018; 75:962.
[9] Hernández-Díaz S, McElrath TF, Pennell PB, et al. Fetal growth and premature delivery in pregnant women on antiepileptic drugs. Ann Neurol 2017; 82:457.

seizures during pregnancy compared with their baseline.[6] A 2019 systematic review of the literature from the International League Against Epilepsy (ILAE) Task Force on Women and Pregnancy concluded that approximately two-thirds of women with epilepsy maintain baseline seizure control during pregnancy.[10]

Some women who experience increased seizure frequency are sleep-deprived or nonadherent with their medications because of concerns about the effects of the medication on the developing fetus.[11,12,13] Altered AED pharmacokinetics also contribute to increased seizure frequency during pregnancy because pregnancy is associated with physiologic changes, including changes in volume of distribution and increased renal clearance and hepatic metabolism, resulting in a need for dose adjustment.

Effect on Fertility

Reproductive dysfunction is common (1/3 have menstrual disorders verses 12-14% of the general population) in women with epilepsy and manifests as menstrual disorders and hirsutism. Reproductive dysfunction may be a direct effect of seizures on the hypothalamic-pituitary-adrenal axis or from the medications used to control the seizures.[14] Overall, the fertility data in women with epilepsy are conflicting. Although an older population study found the fertility rate to be reduced in women with epilepsy,[15] a recent observational cohort study, which compared fertility of 89 women with epilepsy with 109 age-matched controls, without known infertility, noted that both cohorts had a comparable likelihood of achieving pregnancy.[16]

Management

Many antiepileptic drugs are inducers of hepatic enzymes (e.g., carbamazepine, oxcarbazepine, perampanel, phenobarbital, phenytoin, primidone), and therefore, result in drug-drug interactions (DDI) with hormonal contraceptives making hormonal contraceptives less effective. Use of long-acting reversible contraceptives (LARC) (i.e., an intrauterine device or intramuscular depot medroxyprogesterone acetate) is recommended.

The American Academy of Neurology (AAN), American Epileptic Society (AES), and American College of Obstetrics and Gynecology (ACOG) recommend supplementation with 0.4 mg of folic acid per day before and during pregnancy in women with epilepsy and those without epilepsy. According to ACOG, a pre pregnancy antiepileptic drug level is recommended to serve as baseline in pregnancy.

With a few exceptions, alteration of AEDs during an established pregnancy solely for the purpose of

[10] Tomson T, et al. Management of epilepsy in pregnancy: a report from the International League Against Epilepsy Task Force on Women and Pregnancy. Epileptic Disord. 2019;21(6):497.
[11] Tomson T, Battino D, Bromley R, et al. Management of epilepsy in pregnancy: a report from the International League Against Epilepsy Task Force on Women and Pregnancy. Epileptic Disord 2019; 21:497.
[12] Schmidt D, Canger R, Avanzini G, et al. Change of seizure frequency in pregnant epileptic women. J Neurol Neurosurg Psychiatry 1983; 46:751.
[13] Otani K. Risk factors for the increased seizure frequency during pregnancy and puerperium. Folia Psychiatr Neurol Jpn 1985; 39:33.
[14] Bauer J, et al. Reproductive dysfunction in women with epilepsy: menstrual cycle abnormalities, fertility, and polycystic ovary syndrome. Int Rev Neurobiol 2008; 83:135-55.
[15] Webber MP, et al. Fertility in persons with epilepsy: 1935-1974. Epilepsia 1986; 27:746-52.
[16] Pennell PB, et al. Fertility in patients with epilepsy: a population-based study. Neurology 1998;51:71-3.

reducing the risk of AED-related fetal malformations is not recommended. [17] One possible exception is in a situation where a woman is on valproate and whose seizures are not refractory to other AEDs; for this patient, transition off of valproate at any point during pregnancy may lower the risk for neurodevelopmental delay. Another possible situation is in a woman who has an unplanned pregnancy and is on multiple AEDs and seizure control would not be significant effected; in this patient, it may be reasonable to remove one or more of the AEDs she is taking if the drug has an unfavorable or unknown risk profile. Antiepileptic drug levels (ideally trough levels) should be checked at least monthly during pregnancy; dose adjustment may be needed.[17] After delivery, antiepileptic levels can retune to baseline within 2 to 4 weeks and a level should be checked 2 weeks postdelivery. A number of antiepileptic drugs are transferred into the breast milk.

REVIEW

Nonclinical Experience

In a mouse embryofetal development study, treatment of pregnant animals with zonisamide (125, 250, or 500 mg/kg/day) during the period of organogenesis resulted in increased incidences of fetal malformations (skeletal and/or craniofacial defects) at all doses tested. The low effect dose for adverse effects on embryofetal development in the mouse was approximately 1.5 times that in humans at the maximum recommended human dose (MRHD) of 400 mg/day on a mg/m2 basis.

In rats, increased frequencies of malformations (cardiovascular defects) and variations (persistent cords of thymic tissue, decreased skeletal ossification) were observed among the offspring of dams treated with zonisamide (20, 60, or 200 mg/kg/day) throughout organogenesis at all doses. The low effect dose for adverse effects on development in rats was approximately 0.5 times the MRHD on a mg/m2 basis.

Following administration of zonisamide (10, 30, or 60 mg/kg/day) to pregnant dogs during organogenesis, increased incidences of fetal cardiovascular malformations (ventricular septal defects, cardiomegaly, various valvular and arterial anomalies) were found at doses of 30 mg/kg/day or greater. The low effect dose for malformations produced peak maternal plasma zonisamide levels (25 µg/mL) about 0.5 times the highest plasma levels measured in patients receiving the MRHD. In dogs, cardiovascular malformations were found in approximately 50% of all fetuses exposed to the high dose, which was associated with maternal plasma levels (44 µg/mL) approximately equal to the highest levels measured in humans receiving the MRHD. Incidences of skeletal malformations were also increased at the high dose, and fetal growth retardation and increased frequencies of skeletal variations were seen at all doses in this study. The low dose produced maternal plasma levels (12 µg/mL) about 0.25 times the highest human levels.

In cynomolgus monkeys, administration of zonisamide (10 or 20 mg/kg/day) to pregnant animals during organogenesis resulted in embryofetal deaths at both doses. The possibility that these deaths were due to malformations cannot be ruled out. The lowest embryolethal dose in monkeys was associated with peak maternal plasma zonisamide levels (5 µg/mL) approximately 0.1 times the highest levels measured in patients at the MRHD.

Perinatal death was increased among the offspring of rats treated with zonisamide (10, 30, or 60mg/kg/day) from the latter part of gestation up to weaning at the high dose, or approximately1.4 times the MRHD on a mg/m2 basis. The no effect level of 30 mg/kg/day is approximately 0.7 times the

[17] Penelle PB, et al. Management of epilepsy during preconception, pregnancy, and the postpartum period. UpToDate. Accessed 4/19/22.

MRHD on a mg/m2 basis.

For more information, the reader is referred to the full Pharmacology/Toxicology report by Edward Fisher, Ph.D. and Lois Freed, Ph.D. as well as the nonclinical information included above under "Current State of the Labeling for the RLD, Zonegran oral capsule, NDA 020789".

Review of Clinical Trials

Pregnant women were excluded from the clinical trials, and there were no reported pregnancies that occurred in the clinical trials.

Review of Literature

Applicant Review of Literature

The applicant performed a literature search through April 1, 2022 regarding the use of zonisamide in pregnancy. For the search strategy used by the applicant and the narratives of the literature reviewed, the reader is referred to the applicant's response to the FDA IR on April 7, 2022, titled "1114-Info-amend-multimodule" (DocuBridge Sequence 0019, module 1.11.4).

The applicant noted that they contacted (b) (4) about an interim report regarding zonisamide use in pregnant patients from the North American Antiepileptic Drug (NAAED) Pregnancy Registry, and they were unable to obtain a report for another company's zonisamide product.

The applicant noted that zonisamide is teratogenic in animals and included information in their review that currently appears in the nonclinical section of the RLD. The applicant summarized zonisamide pregnancy-related human information from six publications.

In a publication by McCluskey et al, which reviewed data on zonisamide use in pregnancy from the United Kingdom and Ireland Epilepsy Pregnancy Registry (UKIEPR),[18] the authors reported on 112 cases of first trimester exposure to zonisamide in 26 monotherapy users and 86 polytherapy users. There were three cases of major congenital malformations (MCM), including inguinal hernia, anencephaly, and one infant with omphalocele, exstrophy, anus-spinal defects, reported, in monotherapy users (13.0%, 95% CI 4.5-32.1). There were five cases of MCM, including spina bifida, jejunal volvulus, fixed talipes, ventricular septal defect, absent right thumb, hypospadias, in polytherapy users (6.9%, 95% CI 3.0-15.2); of the five infants, four infants were also exposed to valproate and topiramate, which are known teratogens. The authors also noted a high rate of small for gestational (SGA) infants (21% for both groups). The authors noted study limitations, including small numbers of patients, wide confidence intervals, and lack of information regarding maternal smoking status and maternal weight. Although these study findings raise concerns for an increased rate of congenital birth defects with use of zonisamide during pregnancy, the authors noted that given the low numbers of patients, more data are needed.

A published study from the NAAED Pregnancy Registry[24] reported an increase in SGA infants in pregnant women exposed to zonisamide during pregnancy. For a more detailed description of the study, the reader is referred to the DPMH Review of Literature below.

Additional concerns in pregnancy arise from the fact that zonisamide causes metabolic acidosis.[3]

[18] McCluskey G, et al. Zonisamide safety in pregnancy: Data from the UK and Ireland epilepsy and pregnancy register. Seizure. 2021 Oct;91:311-315. doi: 10.1016/j.seizure.2021.07.002. Epub 2021 Jul 9.

Currently approved zonisamide labeling notes that "metabolic acidosis during pregnancy (due to other causes) may result in decreased fetal growth, decreased fetal oxygenation, and fetal death."[3]

The applicant notes that zonisamide serum concentration is altered by pregnancy and dose adjustment may be needed during pregnancy.[29] For a description of the study, the reader is referred to DPMH review of Literature.

The applicant did not find any new information regarding zonisamide use in pregnancy and did not recommend any change to the existing labeling language regarding use of zonisamide during pregnancy. The applicant recommended conversion of the approved labeling (from the RLD) to meet PLLR requirements.

DPMH Review of Literature
DPMH performed a search of published literature using PubMed, Embase, and reference sites (Micromedex,[19] ReproTox,[20] Shepard's[21], TERIS[22]) regarding zonisamide use in pregnancy.

The reader is referred to Appendix A for a list of studies that have investigated zonisamide use in pregnancy.

There are a limited number of published studies on zonisamide use during pregnancy, which is reflective of the limited use of this drug during pregnancy. According to the most recent report from the NAAED Pregnancy Registry, the risk of major congenital malformation (MCM) was not increased in those exposed to zonisamide during pregnancy. The frequency of overall MCM was 1.4% in 217 pregnancies exposed to zonisamide monotherapy during the first trimester (95% CI 0.4 to 4.3%).[23]

A study from the NAAED Pregnancy Registry found a decrease in mean birth weight and birth length among neonates exposed to topiramate or zonisamide *in utero* compared with neonates exposed to lamotrigine and an unexposed group. Data of women (mean gestational length of 39 weeks) who were enrolled from the NAAED Pregnancy Registry between 1997 to 2012[24] showed that when zonisamide monotherapy (n=98) was compared with lamotrigine monotherapy (n=1,581) during pregnancy, mean birth weight was 202g less and neonatal length was 1 cm less ($p<0.01$) in the zonisamide group. The number of pregnancies with SGA infants was 12.2% for the zonisamide group versus 6.8% for the lamotrigine group (RR 1.6, 0.9-2.8). Similar results were found when a group of 457 unexposed neonates (from healthy volunteers that were friends or family of the exposed group) were used as a reference. In their report from 2017, SGA was prevalent in zonisamide monotherapy at RRs of 1.9 (95% CI, 1.2-3.0) compared to the lamotrigine cohort.[25] As a comparison, there was an increased rate of SGA infants in UKIEPR; in that pregnancy registry, the rate of SGA was 21% for monotherapy and

[19] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 3/28/2022.
[20] ReproTox Website: www.Reprotox.org. REPROTOX was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 3/28/22.
[21] 2020 Shepard's: A Catalog of Teratogenic Agent. Accessed 3/28/2022.
[22] TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 3/29/22.
[23] Holmes LB, Hernandez-Diaz S; the Scientific Advisory Committee: North American Antiepileptic Drug Pregnancy Registry--updated data through December 31, 201. Boston, Mass.: Harvard Medical School, 1997-2021. Available at: https://www.aedpregnancyregistry.org/annual-update-for-2022/ Accessed 5/10/22.
[24] Hernandez-Diaz S, Mittendorf R, Smith CR, et al: Association between topiramate and zonisamide use during pregnancy and low birth weight. Obstet Gynecol 2014; 123(1):21-28.
[25] Hernández-Díaz S., et al. Fetal growth and premature delivery in pregnant women on antiepileptic drugs. ANN NEUROL 2017;82:457–465

polytherapy cases respectively.[26]

Several studies suggest that zonisamide use during pregnancy may require dose adjustment.[27] One study showed maternal serum concentrations fell by more than 40% in some pregnant women.[28] In another multicenter, prospective, observational cohort study, zonisamide serum concentration changes were evaluated in 22 pregnant women exposed to zonisamide compared with 9 nonpregnant control women exposed to zonisamide. Zonisamide concentrations were evaluated at each trimester through 9 months postpartum. Compared with postpartum values, dose-normalized concentrations during pregnancy were decreased by 29.8% for zonisamide, with no significant difference across trimesters. Compared with dose-normalized concentrations from control participants, pregnancy dose-normalized median (SE) concentrations decreased significantly by week of gestational age: zonisamide -0.53 (0.14) µg/L/mg.[29] These data suggest higher doses of zonisamide may be needed during pregnancy.

Micromedex,[19] ReproTox,[20] Shepard's,[21] and TERIS,[22] note there are no adequate or well-controlled studies of zonisamide in pregnant women. It is not known if zonisamide crosses the placenta.[19] Increased frequencies of abortion and stillbirth were seen when pregnant cynomolgus monkeys were treated with 1 to 2.5 times the maximum human dose of zonisamide.[30] Visceral anomalies were seen with increased frequencies in the offspring of pregnant mice treated with 62 times the maximum human dose of zonisamide, and skeletal anomalies were seen with doses 31 times the human maximum dose of zonisamide.[30] Increased frequencies of cardiac malformations were observed among the offspring of pregnant rats or dogs treated with 25 or 4 to7 times the maximum human dose of zonisamide, respectively.[31]

Serious adverse events, such as metabolic acidosis, have occurred in adult and pediatric patients using zonisamide,[32] and metabolic acidosis during pregnancy (due to other causes) may result in decreased fetal growth, decreased fetal oxygenation, and fetal death.[33,34] Therefore, zonisamide may cause serious adverse fetal effects.[19] Micromedex recommends that pregnant women who are on zonisamide therapy and infants who were exposed to zonisamide be monitored for metabolic acidosis. [19] There are no additional published studies referenced by these reference site other than those listed above.

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[26] McCluskey G, et al. Zonisamide safety in pregnancy: Data from the UK and Ireland epilepsy and pregnancy register. Seizure. 2021 Oct;91:311-315. doi: 10.1016/j.seizure.2021.07.002. Epub 2021 Jul 9.
[27] Arfman, IJ, et al. Therapeutic Drug Monitoring of Antiepileptic Drugs in Women with Epilepsy Before, During, and After Pregnancy. Clin Pharmacokinet 59, 427–445 (2020). https://doi.org/10.1007/s40262-019-00845-2
[28] Reimers A, Helde G, Becser Andersen N, Aurlien D, Surlien Navjord E, Haggag K, Christensen J, et al. 2018. Zonisamide serum concentrations during pregnancy. Epilepsy Res 144: 25-29.
[29] Pennell PB, Karanam A, Meador KJ, et al. Antiseizure Medication Concentrations During Pregnancy: Results From the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) Study. JAMA Neurol. 2022 Feb 14:e215487.
[30] Terada Y, Fukagawa S, Shigematsu K, Mukumoto K, Nishimura K, Ohnishi K: [Reproduction studies of zonisamide. (4) Teratogenicity study in mice, dogs, and monkeys.] Yakuri To Chiryo 15(11):4435-4451, 1987a.
[31] Terada Y, Mukumoto K, Shigematsu K, Nishimura K, Ohnishi K: [Reproduction studies of zonisamide. (5) A comparison of the teratogenic effect of zonisamide and phenobarbital in rats.] Yakuri To Chiryo 15(11):4453-4469, 1987c.
[32] According to the currently approved labeling of Zonegran, NDA 020789, at Drugs@FDA. Accessed 3/29/22. Last updated 4/3/2020.
[33] De Jong K et al. Severe metabolic acidosis and respiratory distress due to acute starvation in pregnancy: a case report. Obstetrics & Gynecology International Journal. 2020. 11(6): 334-336.
[34] Bobrow C and Soothill P. Causes and Consequences of Fetal Acidosis. BMJ. 80(3): 1999.

Reviewer comment:
Based on animal studies, zonisamide may cause fetal harm. There are additional concerns that zonisamide can cause metabolic acidosis, and metabolic acidosis during pregnancy (due to other causes) may result in adverse pregnancy outcomes, such as decreased fetal growth, decreased fetal oxygenation and fetal death. An increase in SGA infants was observed in patients exposed to zonisamide in utero for both the NAAED pregnancy registry and the UKIEPR. [24,26]

The available published data on the use of zonisamide during pregnancy are limited in number and quality. However, the NAAED pregnancy registry has not identified an increased in rate of MCM in over 200 pregnancies exposed to zonisamide monotherapy during the first trimester over two decades of use. Although one small study from UKIEPR raised some concerns regarding a potential increased risk of birth defects with first trimester monotherapy zonisamide use, this study has methodological limitations, including small sample size and inability to account for potential confounders.

There are no published data to assess a drug-related risk of miscarriage at this time.

Zonisamide use during pregnancy may require dose adjustment because zonisamide serum concentrations during pregnancy were decreased in pregnancy, some by more than 40%. This was discussed with DN2 Clinical Pharmacology Team by personal communication. The Clinical Pharmacology Team is in agreement that dose adjustment may be needed in patients exposed to zonisamide during pregnancy. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

LACTATION
Nonclinical Experience
It is not known if zonisamide is present in animal milk.

Review of Literature
Applicant Review of Literature
The applicant performed a literature search regarding the use of zonisamide during lactation. The applicant cites the following article by Birnbaum AK et al.:

> "In the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study of nursing mother-infant pairs, blood samples were collected from 4 mother-infant pairs at the same visit between 5 and 20 weeks postpartum… Two infants had zonisamide concentrations above the lower limit of quantification, with an estimated average concentration of 6.5 mg/L (range 3.9 to 18.7 mg/L). Consistent with previous findings, infant zonisamide concentration as the percentage of maternal plasma concentration was 44.2% (range, 35.2% - 125.3%), indicating substantially lower concentrations in infants than mothers."[35]

Reviewer comment:
Of the seven antiepileptic drugs evaluated by MONEAD study, zonisamide had the highest range of 35.2 to125.3%. This is not a small clinically insignificant concentration. In one infant, the serum concentration was 18.7 µg/mL which exceeded the maternal concentration of 14.9 µg/mL. This reviewer disagrees with the applicant's assessment above. Zonisamide is readily transferred in human milk and is present in infant serum.

[35] Birnbaum AK, Meador KJ, Karanam A, et al. Antiepileptic Drug Exposure in Infants of Breastfeeding Mothers With Epilepsy. JAMA Neurol. 2020 Apr 1;77(4):441-450.

DPMH Review of Literature

DPMH performed a search of published literature using PubMed, Embase, and reference sites (Micromedex,[36] LactMed,[37] Brigg's,[38] or Hale's[39]) regarding zonisamide use in lactation. There are several studies on the use of zonisamide during lactation. The reader is referred to Appendix B for a full list of the studies.

Zonisamide is present in human milk. The milk-to-plasma concentration ratio (M/P) is reported to be around 0.8 to 0.93.[40,41] The relative infant dose (RID) is reported to be 36% to 57%.[42,43] There are only four cases in the published literature that report on the effects of zonisamide on the breastfed infant, no adverse effects were observed (mostly partially breastfed).[44,45,46] Several studies suggest the transfer to the drug from the mother to the infant is the greatest trans placentally during pregnancy, and the infant's drug level drops significantly after delivery while breastfeeding.[47,48,49]

Two publications indicate that maternal doses of zonisamide up to 400 mg daily produce high levels in milk and infant serum, but infant serum levels in neonates (about 23-28% of the maternal weight adjusted dosage)[50,51] decrease during the first month of life while nursing. Although no adverse reactions have been reported in breastfed infants, the number of infants reported have been small.

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[36] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 9/30/2021.

[37] http;//toxnet nlm nih.gov/newtoxnet/lactmed htm. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The lactMed data base provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfeeding infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility. Access 9/30/21.

[38] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015. Online, accessed 9/30/2021.

[39] Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY. Accessed 9/30/2021.

[40] Shimoyama R, Ohkubo T, & Sugawara K: Monitoring of zonisamide in human breast milk and maternal plasma by solid-phase extraction HPLC method. Biomed Chromatogr 1999; 13:370-372.

[41] Öhman I, Tomson T. Pharmacokinetics of zonisamide in neonatal period and during lactation. Basic Clin Pharmacol Toxicol. 2011;109 Suppl 1:73–Abstract P55.

[42] Ando H, Matsubara S, Oi A, et al: Two nursing mothers treated with zonisamide: Should breast-feeding be avoided? J Obstet Gynaecol Res 2014; 40(1):275-278.

[43] Öhman I, Tomson T. Pharmacokinetics of zonisamide in neonatal period and during lactation. Basic Clin Pharmacol Toxicol. 2011;109 Suppl 1:73–Abstract P55.

[44] Shimoyama R, Ohkubo T, & Sugawara K: Monitoring of zonisamide in human breast milk and maternal plasma by solid-phase extraction HPLC method. Biomed Chromatogr 1999; 13:370-372.

[45] Ando H, Matsubara S, Oi A, et al: Two nursing mothers treated with zonisamide: Should breast-feeding be avoided?. J Obstet Gynaecol Res 2014; 40(1):275-278.

[46] Öhman I, Tomson T. Pharmacokinetics of zonisamide in neonatal period and during lactation. Basic Clin Pharmacol Toxicol. 2011;109 Suppl 1:73–Abstract P55.

[47] Kawada K, Itoh S, Kusaka T, et al. Pharmacokinetics of zonisamide in perinatal period. Brain Dev. 2002;24:95–7.

[48] Birnbaum AK, Meador KJ, Karanam A, et al. Antiepileptic drug exposure in infants of breastfeeding mothers with epilepsy. JAMA Neurol. 2020;77:441–50.

[49] Ando H, Matsubara S, Oi A, et al: Two nursing mothers treated with zonisamide: Should breast-feeding be avoided?. J Obstet Gynaecol Res 2014; 40(1):275-278.

[50] Kimura S. No To Hattatsu. 1998;30:350–1. [Zonisamide: its placental transport, biological half-life in the newborn, and transport into mother's milk--a study of a case of an infant born of a mother who had been treated with zonisamide alone during pregnancy]

[51] Sugawara K, Shimoyama R, Ohkubo T. Determinations of psychotropic drugs and antiepileptic drugs by high-performance liquid chromatography and its monitoring in human breast milk. Hirosaki Med J. 1999;51 Suppl:S81–6.

Hales[37] gives the lactation rating "L4- Limited Data-Possibly Hazardous" and notes that zonisamide "has a long half-life and high pKa which… leads to a high maternal milk and plasma concentrations… Significant caution is recommended with this medication as a number of pediatric adverse effects have been noted in older children such as somnolence, anorexia and severe skin rashes." Hales notes that if infants are exposed to zonisamide during lactation they should be monitored for sedation, irritability, agitation, nausea, poor appetite and elevated temperature.

Micromedex[34] gives the lactation rating "Infant risk cannot be ruled out."

LactMed[35] recommends using an alternative drug during lactation, but if zonisamide must be administered, LactMed[35] recommends monitoring the infant for drowsiness, adequate weight gain, and developmental milestones, especially in younger or exclusively breastfed infants and when using combinations of anticonvulsant drugs. LactMed also notes that "some clinicians recommend that mothers taking zonisamide only partially breastfeed in order to reduce the exposure of the infant to the drug and to consider monitoring infants' serum zonisamide concentrations."

Brigg's[36] notes that although no adverse effects were noted in four nursing infants exposed to zonisamide, the milk concentrations were high enough that clinically significant adverse effects can be observed in breastfed infants. Therefore, if a woman under treatment with zonisamide chooses to breastfeed, close clinical monitoring of her infant is recommended as well as the measurement of infant plasma drug levels. Many experts recommend partial breastfeeding.

Reviewer comment:
Zonisamide is transferred in human milk with a *RID reported to be between 36% to 57%. DPMH discussed the published lactation studies with the DN Clinical Pharmacology Team who noted that since the milk-to-plasma ratio ranges from 0.7 to 0.9 and since the RID dose was calculated in one study, labeling should note that zonisamide is transferred to milk with the inclusion of the milk-to-plasma ratio quantitative information. The Clinical Pharmacology Team preferred that the RID was not included in labeling. Limited reports from the published literature did not identify any adverse effect on the breastfed infant when the mother breastfed nonexclusively. However, the published reports are limited to four cases and adverse events, including acute myopia, angle close glaucoma, oligohydrosis, hyperpyrexia and metabolic acidosis, have been reported in pediatric patients who have been administered zonisamide off-label. Hales, LactMed, and Brigg's note that if the decision is made to use zonisamide during breastfeeding that the infant is monitored for adverse reactions. The effect of zonisamide on milk production is not known. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.*

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience
No evidence of carcinogenicity was found in mice or rats following dietary administration of zonisamide for two years at doses of up to 80 mg/kg/day. In mice, this dose is approximately equivalent to the maximum recommended human dose (MRHD) of 400 mg/day on a mg/m2 basis. In rats, this dose is 1–2 times the MRHD on a mg/m2 basis.

Zonisamide was mutagenic in an in vitro chromosomal aberration assay in CHL cells. Zonisamide was not mutagenic or clastogenic in other in vitro assays (Ames, mouse lymphoma tk assay, chromosomal aberration in human lymphocytes) or in the in vivo rat bone marrow cytogenetics assay.

Female rats treated with zonisamide (20, 60, or 200 mg/kg) before mating and during the initial gestation phase showed signs of reproductive toxicity (decreased corpora lutea, implantations, and live fetuses) at all doses. The low dose in this study is approximately 0.5 times the maximum recommended human dose (MRHD) on a mg/m2 basis.

The reader is referred to the full Pharmacology/Toxicology report by Edward Fisher, Ph.D. and Lois Freed, Ph.D.

Review of Literature

Applicant Review of Literature

The applicant performed a review of literature regarding the effect of zonisamide on human fertility. The applicant did not find any relevant articles.

The applicant notes that according to animal reproduction studies, zonisamide may cause harm to the fetus. Therefore, contraception should be recommended in females of reproductive potential (and for one month following discontinuation of the medication. Additionally, the applicant notes that in healthy subjects, steady state dosing with zonisamide did not affect serum concentrations of ethinyl estradiol or norethisterone in a combined oral contraceptive. However, zonisamide adversely effected fertility in female rats in animal reproduction studies. There are no data on the effect of zonisamide on human fertility.

DPMH Review of Literature

DPMH performed a search of published literature using PubMed, Embase, and the reference sites regarding adverse effect of zonisamide on fertility. No information was found.

According to the approved labeling:[3]

> In healthy subjects, steady state dosing with zonisamide did not affect serum concentrations of ethinyl estradiol or norethisterone in a combined oral contraceptive.

Reviewer comment:

Although zonisamide was found to be teratogenic in animals, data from the NAAED, which includes 217 pregnant women with exposure to zonisamide monotherapy during the first trimester over two decades of use, does not appear to be associated with an increased incidence of overall major birth defects when compared to an unexposed control. Although the sample size is not large enough to rule out rare major birth defects and the study is not randomized with selection bias, zonisamide does not appear to be strongly associated with major birth defects. In this case, the recommendation for contraception and a Warnings and Precaution statement (which appears in the approved labeling of LD) may not be necessary.

Additionally, there are no data regarding the effect of zonisamide on human fertility. In animal fertility studies, there was evidence of reproductive toxicity when zonisamide was used in female rats. There are no drug-to-drug interactions (DDIs) between zonisamide and hormonal contraceptives. The reader is

referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

Although animal reproduction studies suggest that zonisamide may be teratogenic at the clinical dose, clinical data from the NAAED Pregnancy Registry have not identified an increased rate of MCM (1.4%) in over 200 pregnancies exposed to zonisamide monotherapy during the first trimester after two decades of use. Although a small prospective study, the UKIEPR, reported an increased rate of MCM of 13% in pregnancies with first trimester zonisamide monotherapy use (n=26), this study had methodological limitations, including small sample size, selection bias, and inability to account for potential confounders. It is possible that as the UKIEPR study collects additional data on first trimester zonisamide monotherapy use, the rate of MCM will decrease. Subsection 8.1 Pregnancy will include information about both studies. Although the labeling for the RLD includes a Warning for Teratogenicity, DPMH does not recommend a Warnings and Precautions statement for Embryofetal Toxicity for the new NDA. Zonisamide has been approved for over two decades, and no clear signal for teratogenicity has been observed in over 200 first trimester exposures in the NAAED Pregnancy Registry.

The available published data on the use of zonisamide during pregnancy reports are insufficient to assess a drug-related increase in the rate of miscarriage.

There are some concerns regarding the drug-related adverse fetal outcomes. The available prospective cohort studies suggest an increased rate of small for gestational age infants in pregnancies exposed to zonisamide compared to the unexposed healthy pregnancies and pregnancies exposed lamotrigine. The increase in the rate of SGA infants is likely due to metabolic acidosis caused by zonisamide use during pregnancy. Currently approved labeling for the RLD notes that "metabolic acidosis during pregnancy (due to other causes) may result in adverse pregnancy outcomes, such as decreased fetal growth, decreased fetal oxygenation, and fetal death." Therefore, DPMH recommends including language in subsection 8.1, Pregnancy about the potential for metabolic acidosis and for SGA infants if zonisamide is used in pregnant women.

Several pharmacokinetic (PK) studies suggest that zonisamide use during pregnancy may require dose adjustment.[52] The applicant proposed inserting a Clinical Considerations section on Dose Adjustments During Pregnancy and the Postpartum Period. The applicant recommends checking zonisamide serum levels regularly during pregnancy so that zonisamide dosage can be adjusted as needed. A similar approach was used for another antiepileptic. DPMH discussed the proposed Clinical Considerations language regarding dose adjustment and the need for issuing a postmarketing commitment/requirement for a pregnancy PK study with the Clinical Pharmacology team. The Clinical Pharmacology Team concluded that the proposed labeling language regarding dose adjustment based on published PK studies was acceptable and that no further pregnancy PK studies were needed at this time.

Zonisamide has been marketed in US for more than twenty years as an oral capsule. Although this reviewer did not identify any new safety concerns, there are concerns about the safety of zonisamide use during pregnancy. DPMH recommends that the applicant collect safety data on use of zonisamide during

[52] Arfman, IJ, et al. Therapeutic Drug Monitoring of Antiepileptic Drugs in Women with Epilepsy Before, During, and After Pregnancy. Clin Pharmacokinet 59, 427–445 (2020). https://doi.org/10.1007/s40262-019-00845-2

pregnancy. NAAED Pregnancy Registry is currently collecting data on the use of zonisamide during pregnancy. The applicant can consider collaborating with the existing registry.

Lactation

Zonisamide is readily transferred to human milk. Published lactation studies have reported a RID ranging between 36% to 57%. There are four reports from the published literature that described the effect of zonisamide on the breastfed infant; no adverse effects on breastfed infants were identified. However, due to high concentration of zonisamide in human milk, if a breastfed infant were to be exposed to zonisamide, close clinical monitoring of the infant is recommended. Breastfed infants exposed to zonisamide should be monitored for drowsiness, adequate weight gain, and developmental milestones because zonisamide is readily transferred in milk. The effect of zonisamide on milk production is not known. DPMH discussed the published lactation studies with the DN Clinical Pharmacology Team who noted that since the milk-to-plasma ratio ranges from 0.7 to 0.9 and since the RID dose was calculated in one study, labeling should note that zonisamide is transferred to milk with the inclusion of the milk-to-plasma ratio quantitative information. The Clinical Pharmacology Team preferred that the RID was not included in labeling.

Based on published literature, zonisamide is transferred to human milk in significant amounts. Based on the drug's adverse event profile for adverse events observed in both children and adults exposed to the zonisamide, close clinical monitoring is recommended by all breastfeeding experts. Since there is already published information regarding the presence of zonisamide in human milk and no new safety data, DPMH does not recommend a postmarketing clinical lactation study at this time.

Females and Males of Reproductive Potential

There are no data regarding the effects of zonisamide on human fertility. Animal reproductive studies showed signs of reproductive toxicity in female rats. Therefore, DPMH recommends the insertion of language regarding potential adverse effect on female fertility under subsection 8.3. There are no DDIs between zonisamide and oral contraceptives.

In contrast to the RLD, DPMH does not recommend a Warnings and Precaution Statement regarding teratogenicity of zonisamide. New evidence from NAAED has not shown zonisamide to be strongly associated with teratogenicity in humans. DPMH does not recommend a Contraceptive subheading under subsection 8.3 to recommend that females of reproductive potential use effective birth control while treated with zonisamide.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, 8.3, and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

(b) (4)

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

APPENDIX A. Zonisamide Use in Pregnancy in the Published Literature

Studies/Years/Location	Type	N	Timing of Exposure	Set up	Outcome	Strength (S)/Limitations (L)
Arfman IJ, et al.17F[53] 2021	A review paper of PK studies		Anytime during pregnancy	Literature search	In the pregnant state, there may be reduced GI absorption, and hepatic metabolism is assumed to be increased. In pregnancy, renal clearance is increased. There are case reports of zonisamide use in the 1st, 2nd, and 3rd trimester of pregnancy and clearance is increased by 108%, 142%, and 117%, respectively.[54] Serum concentration is decreased >40% in pregnancy with inter-individual variability.[55] There are case reports of decline in zonisamide concentration at 27 weeks gestation[56] and increase in zonisamide concentration by 33-35% within 9 days after delivery.[57] There are reports of increased seizure in 33% of pregnant women using zonisamide. More research is need on dose adjustment.	
Pennell PB, et al.[58] 2022, USA (20-sites)	Multicenter, prospective, observational	22 pregnant women exposed to	Each trimester	MONEAD study; Zonisamide concentrations were	Zonisamide dose-normalized concentrations during pregnancy were decreased by up to 29.8%,	

[53] Arfman, IJ, et al. Therapeutic Drug Monitoring of Antiepileptic Drugs in Women with Epilepsy Before, During, and After Pregnancy. Clin Pharmacokinet 59, 427–445 (2020). https://doi.org/10.1007/s40262-019-00845-2

[54] Reisinger TL, Newman M, Loring DW, et al. Antiepileptic drug clearance and seizure frequency during pregnancy in women with epilepsy. Epilepsy Behav. 2013;29:13–8.

[55] Reimers A, Helde G, Becser Andersen N, et al. Zonisamide serum concentrations during pregnancy. Epilepsy Res. 2018;144:25–9.

[56] Oles KS, Bell WL. Zonisamide concentrations during pregnancy. Ann Pharmacother. 2008;42:1139–41.

[57] Kawada K, Itoh S, Kusaka T, et al. Pharmacokinetics of zonisamide in perinatal period. Brain Dev. 2002;24:95–7.

[58] Pennell PB, Karanam A, Meador KJ, et al. Antiseizure Medication Concentrations During Pregnancy: Results from the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) Study. JAMA Neurol. 2022 Feb 14:e215487.

Studies/Years/Location	Type	N	Timing of Exposure	Set up	Outcome	Strength (S)/Limitations (L)
	cohort study (PK study)	zonisamide compared with 9 nonpregnant control women (7 draws in 18 months) exposed to zonisamide.		evaluated at each trimester (4x) through postpartum (3x) values, months postpartum.	with no significant difference across trimesters. Additionally, compared with dose-normalized concentrations from control participants, pregnancy dose-normalized median (SE) concentrations decreased significantly by week of gestational age: zonisamide -0.53 (0.14) µg/L/mg (P < .001)	
Holmes LB, et al.[59] 2021, USA and Canada (not a publication, publicly disclosed data from the website)	Prospective cohort	205 exposed	First trimester (monotherapy)	North American Antiepileptic Drug Pregnancy Registry (to 12/31/21)	The frequency of overall MCM was 1.5% in 205 exposed pregnancies during the first trimester on monotherapy (95% CI 0.4 to 4.6%) compared to MCM rate about 1% of internal control of 1201 unexposed pregnancies (0.5 to 1.8) and MCM rate of 2% of external comparator (1.7% after subtracting genetic causes) of unexposed infants.	S: prospective, controlled, accounted for confounders (smoking, maternal age, education, race, alcohol use, folic acid supplementation, illicit drug use, chronic disease, calendar year; L: small sample size
McCluskey G, et al.[60] 2021, UK	Prospective cohort	112 exposed	First trimester (26 were monotherapy and 86 were polytherapy)	UK and Ireland Epilepsy and Pregnancy register (UKIEPR) (1996-2020)	MCM: -monotherapy users: 3/26 (13.0%, 95% CI 4.5-32.1) -polytherapy users: 5/86 (6.9%, 95% CI 3.0-15.2). These data raise concerns for MCM, but due to small sample	S: prospective observational study; L: small sample size, not randomized, selection bias; unadjusted for

[59] Holmes LB, Hernandez-Diaz S; the Scientific Advisory Committee: North American Antiepileptic Drug Pregnancy Registry--updated data through December 31, 2021. Boston, Mass.: Harvard Medical School, 1997-2021. Available at: https://www.aedpregnancyregistry.org/annual-update-for-2022/ Accessed 3/29/22.
[60] McCluskey G, et al. Zonisamide safety in pregnancy: Data from the UK and Ireland epilepsy and pregnancy register. Seizure. 2021 Oct;91:311-315. doi: 10.1016/j.seizure.2021.07.002. Epub 2021 Jul 9.

Studies/Years/Location	Type	N	Timing of Exposure	Set up	Outcome	Strength (S)/Limitations (L)
					size, more data will be needed to assess for teratogenicity. SAB: Monotherapy 3 Polytherapy 13 Stillbirth: Monotherapy 0 Polytherapy 3 Induced abortion: Monotherapy 2 Polytherapy 0 SGA: Median birth weight was 71st and 44th centile for monotherapy and polytherapy cases respectively. There was a high rate of SGA, 21% for both.	many important confounders (smoking, maternal weight)
Meador K, et al.[61] 2020, USA	Multicenter, prospective, observational cohort study (PK study)	13	First trimester monotherapy	The Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study	MCM was 1/13 (7.7%), there was zero fetal loss in these 13 cases The case was inguinal hernia and pinna malformation.	
Weston J, et al.[62] 2016 (The specific study from the North American	Cochran meta-analysis: source was North	90 exposed to zonisamide	First trimester (monotherapy)	Meta-analysis of prospective cohort studies and randomized	Only one study was available from North American Register (prospective cohort in USA):	S: prospective; L: small sample size

[61] Meador K, Pennell P, May R, Van Marter L, McElrath T, Brown C, et al. Fetal loss and malformations in the MONEAD study of pregnant women with epilepsy Neurology. MONEAD Investigator Group 2020;94(14):e1502–11.

[62] Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, Hounsome J, McKay AJ, Tudur Smith C, Marson AG. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev. 2016 Nov 7;11(11):CD010224. doi: 10.1002/14651858.CD010224.pub2. PMID: 27819746; PMCID: PMC6465055.

Studies/Years/Location	Type	N	Timing of Exposure	Set up	Outcome	Strength (S)/Limitations (L)
Registry was based from USA)	American Register			controlled trials treated group was compared to controls (women with epilepsy without AED, women without epilepsy). Insufficient data from North American Register (aka North American Antiepileptic Drug Pregnancy Registry)- publication 2012	Overall MCM of zonisamide has the prevalence of 0.28% (95% CI 0.25 to 2.39) Current analysis comparing 90 first trimester exposed to 442 women without epilepsy, the RR of all MCM (0/90 vs 5/442) was non-significant outcome (RR 0.44, 95% CI 0.02 to 7.93)	
Hernandez-Diaz S, et al.[63] 2017, USA and Canada	Prospective cohort	125 exposed to zonisamide	Anytime (monotherapy)	North American Antiepileptic Drug Pregnancy Registry (1997-2016)	SGA was prevalent in zonisamide monotherapy at RRs of 1.9 (95% CI, 1.2-3.0) compared to lamotrigine.	S: prospective, controlled, accounted for confounders (smoking, maternal age, education, race, alcohol use, folic acid supplementation, illicit drug use, chronic disease, calendar year; L: small sample size

[63] Hernández-Díaz S., et al. Fetal growth and premature delivery in pregnant women on antiepileptic drugs. ANN NEUROL 2017;82:457–465

Studies/Years/Location	Type	N	Timing of Exposure	Set up	Outcome	Strength (S)/Limitations (L)
Hernandez-Diaz S, et al.[64] 2014, USA and Canada	Prospective cohort	98 exposed to zonisamide	Anytime (monotherapy)	North American Antiepileptic Drug Pregnancy Registry (1997-2012)	Compared with lamotrigine (monotherapy, n=1,581) (was considered weight neutral) Mean birth weight was 202g less in zonisamide group Neonatal length was 1 cm less ($p<0.01$) SGA was 12.2% for zonisamide and in comparison, 6.8% in lamotrigine group (RR 1.6, 0.9-2.8). Similar results were found when a group of 457 unexposed neonates (from healthy volunteers that were friends or family of the exposed group) were used as reference.	S: prospective, controlled, accounted for confounders (smoking, maternal age, education, race, alcohol use, folic acid supplementation, illicit drug use, chronic disease, calendar year; L: small sample size
Hernandez-Diaz S, et al.[65] 2012, USA and Canada	Prospective cohort	90 exposed	First trimester (monotherapy)	North American Antiepileptic Drug Pregnancy Registry (1997-2011)	Overall MCM of zonisamide has a prevalence of 0.28% (95% CI 0.25 to 2.39); not statistically significant with wide CI, not informative	S: prospective, controlled, accounted for confounders (smoking, maternal age, education, race, alcohol use, folic acid supplementation, illicit drug use, chronic disease, calendar year; L:

[64] Hernández-Díaz, Sonia MD, DrPH; Mittendorf, Robert MD, DrPH; Smith, Caitlin R. MSc; Hauser, W. Allen MD; Yerby, Mark MD; Holmes, Lewis B. MD for the North American Antiepileptic Drug Pregnancy Registry Association Between Topiramate and Zonisamide Use During Pregnancy and Low Birth Weight, Obstetrics & Gynecology: January 2014 - Volume 123 - Issue 1 - p 21-28

[65] Hernandez-Diaz S, Smith CR, Shen A, et al. Comparative safety of antiepileptic drugs during pregnancy. Neurology 2012;78:1692–1699.

Studies/Years/Location	Type	N	Timing of Exposure	Set up	Outcome	Strength (S)/Limitations (L)
						small sample size
Kondo T, et al.[66] 1996, Japan	Case series, prospective cohort, uncontrolled	26 exposed with or without other AED	Anytime	Questionnaire send to 381 hospitals to collect pregnancy outcomes on zonisamide exposed pregnancies from 1989-1994, 250 hospitals responded.	2/26 reported MCM (7.7%) -1 was anencephaly diagnosed at 16 weeks during elective termination -1 case of atrial septal defect in a term c-section deliver.	

APPENDIX B. Zonisamide milk level in breastfeeding

Author/Year/ Location	Timing	Dose (oral)	Method	Subjects	Milk level (mean)	M/P Ratio (mean)	Infant serum level	RID	Infant
Shimoyama R, et al.[67] 1999, Japan	0 (plasma only), 3-, 14-, and 30-days postpartum (pp)	300 mg/day (also on other antipsychotics)	HPLC*	1	9.41± 0.95 ug/mL (1.5 to 2.5 hours after dosing)	0.93± 0.09			No adverse events (AE) observed
Ando H, et al.[68] 2014,	5 days pp (exclusive	300 mg/day and (during	HPLC	2	18 mcg/mL	0.7 (first 5	14.4 µg/mL; Drop to	44% (5	No adverse effect was

[66] Kondo T, Kaneko S, Amano Y, Egawa I. Preliminary report on teratogenic effects of Zonisamide in the offspring of treated women with epilepsy. Epilepsia 2004;37: 1242–4.
[67] Shimoyama R, Ohkubo T, & Sugawara K: Monitoring of zonisamide in human breast milk and maternal plasma by solid-phase extraction HPLC method. Biomed Chromatogr 1999; 13:370-372.
[68] Ando H, Matsubara S, Oi A, et al: Two nursing mothers treated with zonisamide: Should breast-feeding be avoided?. J Obstet Gynaecol Res 2014; 40(1):275-278.

Japan	breastfed until 9-day pp changed to partial breastfeeding per recommendation 2x/day, supplement 7-8x per day) 2 weeks pp (stopped breastfeeding 2-week pp due to low supply)	pregnancy also) 100 mg/day (during pregnancy also)			5.1 mcg/mL	days) 0.9	below detection at day 34 3.4-5.1 µg/mL	day PP) 36%	observed in both infants
Kawada K, et al[69] 2002, Japan	1 to 10 days pp	400 mg/day (carbamazepine 1 g, and clonazepam 1 mg) during pregnancy also 400 mg/day (and carbamazepine 800 mg/day) during pregnancy also	HPLC	2	Range of 8.9 to 10.9 mg/L		High initially due to placental transfer, 17.5 and 18.9 µg/ml day 0 and 2, 23.4 and 25.2 µg/ml on day 9, and falls to 8.9 and 10.9 µg/ml. It drops further to 3.9 mg/L at 24 days post-		

[69] Kawada K, Itoh S, Kusaka T, et al. Pharmacokinetics of zonisamide in perinatal period. Brain Dev. 2002;24:95–7.

							delivery.		
Ohman I, et al[70] (abstract)	9 days pp	Unknown dose (during pregnancy also)	HPLC	1	3.6 mg/L	0.8	10.1 µmol/L	41-57%	No AE observed
Birnbaum AK, et al.[71] 2020, USA	5- and 20-weeks pp	350 (200-500) mg/day		9 (4 were matched and gave infant blood samples)	NA		6.5 (3.9-18.7) (2 had measurable levels)		

*HPLC= high-performance liquid chromatography

[70] Öhman I, Tomson T. Pharmacokinetics of zonisamide in neonatal period and during lactation. Basic Clin Pharmacol Toxicol. 2011;109 Suppl 1:73–Abstract P55.
[71] Birnbaum AK, Meador KJ, Karanam A, et al. Antiepileptic drug exposure in infants of breastfeeding mothers with epilepsy. JAMA Neurol. 2020;77:441–50.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	May 11, 2022
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 214273
Product Name and Strength:	Zonisade (zonisamide) oral suspension, 20 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Azurity Pharmaceuticals, Inc. (Azurity)
FDA Received Date:	July 29, 2021; January 18, 2022; April 18, 2022
OSE RCM #:	2020-1606-2
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

Azurity submitted additional information and a Class 2 resubmission to address deficiencies cited in a previous complete response letter, on July 29, 2021 and January 18, 2022, respectively for Zonisade (zonisamide) oral suspension. Further, Azurity submitted a revised container label on April 18, 2022. The Division of Neurology 2 (DN 2) requested that we review the proposed Zonisade prescribing information (PI), medication guide (MG), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

NDA 214273 is a 505(b)(2) NDA and the listed drug product is Zonegran, NDA 020789. Azurity submitted the original NDA 214273 on July 29, 2020, and we performed two label and labeling reviews of the submission during that review cycle[ab]. Our recommendations were sent to Azurity during that review cycle. However, the application received a complete response (CR) on May 29, 2021. The CR letter noted that Agency is unable to conduct inspections during the review cycle; however, Azurity may respond to deficiencies in the CR Letter while the travel restrictions remain in effect.

Therefore, on July 29, 2021, Azurity submitted quality information to address the CR letter deficiencies. The submission included revised labels and labeling which are the subject of this review. Azurity submitted the official Class 2 response on January 18, 2022, which did not contain any labeling updates.

2 MATERIALS 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

[a] Morris, C. Label and Labeling Review for zonisamide (NDA 214273). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JAN 15. RCM No.: 2020-1606.
[b] Morris, C. Label and Labeling Review for zonisamide (NDA 214273). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 FEB 22. RCM No.: 2020-1606-1.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)

*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

3 ASSESSMENT

All product characteristics remain the same as those submitted during the previous review cycle.

We note Azurity made minor changes to the container label and carton labeling that were submitted on February 3, 2021, which were previously found to be acceptable from a medication safety perspective. Those changes include updating the sponsor name, adding the conditionally approved proprietary name, Zonisade, removal of "100 mg/5 mL" from the strength expression, and revising the color scheme on the carton labeling and container label. (b) (4) dditionally, we note the updated color scheme (i.e., (b) (4)) lacks sufficient contrast and may decrease readability. (b) (4) We provide our recommendations to Azurity below in Section 6.

As part of our review, we considered whether the proposed revisions to the PI would require revisions to the container label or carton labeling to ensure consistency and decrease the risk of confusion and medication errors. Our evaluation did not identify any additional necessary revisions to the container label or carton labeling, aside from those noted above. However, our review of the PI and MG determined that language for patients/caregivers describing how they will receive an appropriate measuring device should be added to Section 17 of the PI and to the MG. We provide our recommendation for the Division below in Section 5.

4 CONCLUSION AND RECOMMENDATIONS

The proposed PI, MG, container label, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 5 for the Division and in Section 6 for Azurity Pharmaceuticals, Inc.

5 RECOMMEDATIONS FOR DIVISION OF NEUROLOGY 2 (DN 2)

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 17 Patient Counseling and Medication Guide			
1.	The product is not proposed to be co-packaged with a measuring device and the labeling does not describe how patients/caregivers will receive an appropriate measuring device.	Including measure device information may reduce the risk for delay of therapy or wrong dose medication errors.	We recommend adding the following statement to the first paragraph of Section 17 and to the Medication Guide in the Section titled "How should I take Zonisade?": "A pharmacist will provide an appropriate device and instructions for measuring the correct dose."

6 RECOMMENDATIONS FOR AZURITY PHARMACEUTICALS, INC.

Table 3. Identified Issues and Recommendations for Azurity Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	The color contrast of the (b) (4) text on the (b) (4) background appears difficult to read.	Low contrast is a common cause of unreadable text.	We recommend you consider revising the text and/or background color to improve the contrast and readability of the product name and strength.
2.	As currently presented, the strength is not stated as 100 mg/5 mL.	Since the starting dose is 100 mg or 5 mL and is titrated in increments of 100 mg or 5 mL, the strength may be presented as 100 mg/5 mL.	We recommend (b) (4) presenting the strength as 100 mg/5 mL.
3.	The "Dispense with Medication Guide" statement on the principal display panel (PDP) does not explicitly	Per 21 CFR 208.24(d), the label of each container or package, where the container label is too small, of drug product for which a	Revise your MG statement to ensure it appears in accordance with 21 CFR 208.24(d). For example, state "Dispense Medication Guide to

Table 3. Identified Issues and Recommendations for Azurity Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	state how the MG is provided (e.g., accompanied, enclosed, or provided separately).	MG is required shall instruct the authorized dispenser to provide a MG to each patient to whom the drug product is dispensed and shall state how the MG is provided. These statements shall appear on the label in a prominent and conspicuous manner.	each patient. Medication Guide available at: zonisade.com/medication-guide.PDF" on the PDP. If more space is needed, we recommend moving the "manufactured for" information and company logo to the side panel.
Container Label			
1.	We note the proposed orientation of the linear barcode is horizontal, (b) (4) in the container label submitted on February 3, 2021.	Positioning the linear barcode in a horizontal orientation may affect the readability due to the curvature of the bottle.	We recommend you verify the readability of the linear barcode while affixed on the intend to market container and provide the output of that verification to the Agency. Alternatively, consider reorienting the linear barcode to a vertical position to ensure the scannability of the barcode.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Error! Reference source not found. presents relevant product information for Zonisade that Azurity Pharmaceuticals, Inc. submitted on July 29, 2021.

Table 4. Relevant Product Information for Zonisade and the Listed Drug		
Product Name	Zonisade	Zonegran[c] (NDA 020789)
Initial Approval Date	n/a	March 27, 2000
Active Ingredient	zonisamide	
Indication	Adjunctive therapy in the treatment of partial seizures in adults with epilepsy	
Route of Administration	oral	
Dosage Form	Oral suspension	capsule
Strength	20 mg/mL	25 mg, 100 mg
Dose and Frequency	Initial dose: 100 mg once daily Titration: on day 14 may increase by up to 100 mg every two weeks to a maximum dose of 400 mg once daily	
How Supplied	Carton containing one 150 mL bottle	Bottles containing 100 capsules
Storage	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.	Store at 25°C (77°F), excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature], in a dry place and protected from light.
Container Closure	PET amber bottle[d]	HDPE bottle

[c] Zonegran [Prescribing Information]. FDALabel. U.S. Food and Drug Administration, accessed MAR 29, 2022. Available from: http://fdalabel.fda.gov/fdalabel-r/services/spl/set-ids/d12de43e-3ac3-4335-bc85-70d7366a91eb/spl-doc?hl=zonegran

[d] Container closure information available at: \\CDSESUB1\evsprod\nda214273\0001\m3\32-body-data\32p-drug-prod\zonisamide-oral-suspension-lm\32p7-cont-closure-sys\32p7-container-closure-system.pdf

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 28, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, zonisamide and NDA 214273. This search is documented in OSE RCM# 2020-1606.

On March 29, 2022, we conducted a gap search to identify any reviews finalized since our last search. We identified one additional review, which is referenced in Section 1.1.

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 Zonisade labels and labeling submitted by Azurity Pharmaceuticals, Inc. .

- Container label received on April 18, 2022
- Carton labeling received on July 29, 2021
- Prescribing Information and Medication Guide (Image not shown) received on July 29, 2021, available from: \\CDSESUB1\evsprod\nda214273\0016\m1\us\prescribing-info-pdf.pdf

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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JOHN C MORRIS
05/11/2022 08:25:42 AM

STEPHANIE L DEGRAW
05/11/2022 09:01:30 AM

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

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

Memorandum

Date: June 10, 2021

To: Stephanie Parncutt, Regulatory Project Manager
Division of Neurology II (DN II)

Tracy Peters, Associate Director for Labeling, DN II

From: Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for zonisamide oral suspension

NDA: 214273

This memo is in response to the DN II labeling consult request dated September 3, 2020. Reference is made to a Complete Response letter that was issued on May 28, 2021. Therefore, OPDP defers comment on the proposed labeling at this time, and request that DN II submit a new consult request during the subsequent review cycle. If you have any questions, please contact Dhara Shah at (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

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/s/

DHARA SHAH
06/10/2021 01:27:11 PM

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:	June 3, 2021
To:	Stephanie Parncutt Regulatory Project Manager **Division of Neurology 2 (DN 2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Medication Guide
Drug Name (established name):	ZONISADE (zonisamide)
Dosage Form and Route:	oral suspension, for oral administration
Application Type/Number:	NDA 214273
Applicant:	Azurity Pharmaceuticals, Inc.

1 INTRODUCTION

On July 28, 2020, Azurity Pharmaceuticals, Inc. submitted for the Agency's review a New Drug Application (NDA) for zonisamide oral suspension, for oral administration. The purpose of the submission was to seek approval for the use of oral suspension as adjunctive therapy in the treatment of partial seizures in adults with epilepsy.

On July 31, 2020, the Division of Neurology II (DN 2) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed MG for zonisamide oral suspension.

This memorandum documents the DMPP review deferral of the Applicant's proposed MG for zonisamide oral suspension.

2 CONCLUSIONS

On May 28, 2021 DN 2 issued a Complete Response (CR) letter, due to safety and chemical, manufacturing, and control (CMC) issues. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed if the Applicant resubmits the application. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

SHARON W WILLIAMS
06/03/2021 10:36:44 AM

LASHAWN M GRIFFITHS
06/03/2021 11:48:35 AM

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: May 27, 2021

TO: Norman Stockbridge, M.D.
Director
Division of Cardiology and Nephrology
Office of New Drugs

Nick Kozauer, M.D.
Director (Acting)
Division of Neurology II
Office of New Drugs

Partha Roy, Ph.D.
Director
Office of Bioequivalence (OB)
Office of Generic Drugs (OGD)

FROM: Melkamu Getie-Kebtie, Ph.D., R.Ph.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

Kara Scheibner, Ph.D.
DGDSI
OSIS

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
DGDSI
OSIS

SUBJECT: Remote Record Review (RRR) of [redacted] (b) (4)

1. RRR Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a Remote Record Review (RRR) of the analytical portion of studies 19-009 and 19-010 (NDA 214273, zonisamide), [redacted] (b) (4)

conducted at [redacted] (b) (4).

We observed objectionable findings that impact the reliability of some study data.

1.1. Recommendation

Based on our review of the RRR observations and the firm's response, we conclude the RRR observations impact the reliability of data from the audited study (b) (4) (see Sections 4.1.3 and 4.1.4). The following data from study (b) (4) (NDA (b) (4)) are not reliable.

(b) (4)

However, the objectionable conditions were isolated in nature and did not impact the reliability of all studies. Therefore, the data from studies 19-009 and 19-010 (NDA 214273), (b) (4) (b) (4) are reliable.

2. Reviewed Studies

Study 19-009 (NDA 214273)
"An open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study of Zonisamide oral suspension 100mg/5ml of LM Manufacturing Limited, UK with Zonegran (Zonisamide) 100 mg Capsules, Marketing Authorization holder: (b) (4) (b) (4) in healthy, adult, human subjects under fasting condition"
Sample Analysis Period: 7/2/2019 – 7/13/2019

Study 19-010 (NDA 214273)
"An open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study of Zonisamide oral suspension 100mg/5ml of LM Manufacturing Limited, UK with Zonegran (Zonisamide) 100 mg Capsules, Marketing Authorization holder: (b) (4) (b) (4) in healthy, adult, human subjects under fed condition"
Sample Analysis Period: 7/15/2019 – 7/27/2019

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(b) (4)

5. Conclusion

We conclude that some of the data in study (b) (4) are not reliable. (b) (4)

(b) (4)

However, the data from studies 19-009 and, 19-010 (NDA 214273), (b) (4) are reliable.

cc: OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Lewin/Skelly/Au/Scheibner/Getie-Kebtie

Draft: MG 5/13/2021, 5/19/2021, 5/25/2021, 5/26/2021, 5/27/2021;
KAS 5/7/2021, 5/24/2021, 5/25/2021, 5/26/2021

Edit: SA 05/14/2021, 5/24/2021, 5/25/2021, 5/26/21, 5/27/21; JC 05/25/2021, 5/26/21, 5/27/21

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL/ (b) (4)
(b) (4)

OSIS File #: (b) (4)
(b) (4)

Attachments

(b) (4)

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/s/

MELKAMU GETIE KEBTIE
05/27/2021 01:51:52 PM

KARA A SCHEIBNER
05/27/2021 01:52:57 PM

STANLEY AU
05/27/2021 02:06:56 PM
Team Lead

SEONGEUN CHO
05/27/2021 02:10:35 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: 3/31/2021

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 214273

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 site in February 2020, which falls within the surveillance interval. The inspection was conducted under the following submission: ANDA 213853.

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

(b) (4)

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Synapse Labs	Majestic Plaza, S. No. 21/5, Kharadi-Mundhwa Bypass, Kharadi, Pune, Maharashtra, India

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/s/

NICOLA M FENTY-STEWART
03/31/2021 05:20:19 PM

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:	February 22, 2021
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 214273
Product Name and Strength:	zonisamide[a] oral suspension, 20 mg/mL
Applicant/Sponsor Name:	Eton Pharmaceuticals, Inc. (Eton)
OSE RCM #:	2020-1606-1
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Acting Team Leader:	Celeste Karpow, PharmD, MPH

1 PURPOSE OF MEMORANDUM

Eton submitted revised container label and carton labeling on February 3, 2021 for zonisamide oral suspension. The Division of Neurology 2 (DN 2) requested that we review the revised container label and carton labeling (Appendix A) to determine if they are 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 CONCLUSION

Eton implemented all of our recommendations and we have no additional recommendations at this time.

[a] Proposed proprietary name is currently under review by the agency.
[b] Morris, C. Label and Labeling Review for zonisamide (NDA 214273). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JAN 15. RCM No.: 2020-1606.

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/s/

JOHN C MORRIS
02/22/2021 12:06:28 PM

CELESTE A KARPOW
02/22/2021 12:08:23 PM

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:	January 15, 2021
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 214273
Product Name, Dosage Form, and Strength:	zonisamide[a] oral suspension, 20 mg/mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eton Pharmaceuticals, Inc. (Eton)
FDA Received Date:	July 29, 2020
OSE RCM #:	2020-1606
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader (Acting):	Celeste Karpow, PharmD, MPH

[a] Proposed proprietary name is currently under review by the agency.

1 REASON FOR REVIEW

As part of the review process for zonisamide oral suspension, the Division of Neurology 2 (DN2) requested we review the prescribing information (PI), medication guide (MG), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 REGULATORY BACKGROUND

NDA 214273 is a 505(b)(2) NDA and the listed drug product is Zonegran, NDA 020789.

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

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 PI, MG, container label, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 1. Identified Issues and Recommendations for Select one			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	There is no space between the volume, 5 mL, and the unit of measure.	To improve readability.	Place adequate space between the volume and unit of measure (e.g. 5 mL instead of 5mL).
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			

Table 1. Identified Issues and Recommendations for Select one			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The temperature unit of measure, °C or °F, is not presented after each numeric digit in the storage statement.	To reduce the risk for misinterpretation and degraded product medication errors.	We recommend the temperature unit of measure (°C or °F) be presented after each numeric digit in the storage statement.
Full Prescribing Information – Section 17 Patient Counseling and Medication Guide			
1.	The product is not proposed to be copackaged with a measuring device.	To reduce the risk for delay of therapy or wrong dose medication errors.	We recommend adding the following statement to the first paragraph of Section 17 and the Medication Guide Section "How should I take zonisamide"? "A pharmacist will provide an appropriate device and instructions for measuring the correct dose."

Table 2. Identified Issues and Recommendations for Eton Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General - Container Label and Carton Labeling			
1.	The recommended dosage statement can be improved.	To ensure consistent language with the prescribing information.	We recommend you revise the statement, "(b) (4) [redacted]" to read "Recommended Dosage: See prescribing information."
2.	The temperature unit of measure, °C or °F, is not presented after each numeric digit in the storage statement.	To reduce the risk for misinterpretation and degraded product medication errors.	We recommend the temperature unit of measure (°C or °F) be presented after each numeric digit in the storage statement.
3.	The format for the expiration date is not defined.	We are unable to evaluate the expiration date format from a medication error perspective.	To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the expiration date format you intend to use and define whether the month will be represented as numeric or alphabetical characters.

Table 2. Identified Issues and Recommendations for Eton Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			We recommend the human-readable expiration date include a year, month, and non-zero day. We recommend the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend a slash or a hyphen be used to separate the portions of the expiration date.
4.	The name "eTon" appears larger than critical information on the principle display panel of the Container Label and Carton Labeling.	The name "eTon" competes in prominence with critical information such as the product name, strength, dosage form, and route of administration on the principle display panel of the Container Label and Carton Labeling.	We recommend you decrease the prominence of the name "eTon".
Container Label			
1.	As currently presented, there is no space to write the post-opening expiration date on the container label.	To reduce the risk for degraded drug medication errors.	We recommend including a space for healthcare providers or patients to write the date that the product is first opened. For example: "Date of first opening __/__/__. Discard unused portion 30 days after first opening."

Table 2. Identified Issues and Recommendations for Eton Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			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 increased prominence of this statement, through use of bolding, contrasting font color, highlighted text, or other means to draw attention to this important information.

5 CONCLUSION

Our evaluation of the proposed PI, MG, container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we 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 Eton so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for zonisamide received on July 29, 2020 from Eton Pharmaceuticals, Inc., and the listed drug (LD).

Table 4. Relevant Product Information for zonisamide and the Listed Drug		
Product Name	Pending	Zonegran[bcd] (NDA 020789)
Initial Approval Date	n/a	March 27, 2000
Active Ingredient	zonisamide	
Indication	Adjunctive therapy in the treatment of partial seizures in adults with epilepsy	
Route of Administration	oral	
Dosage Form	oral suspension	capsule
Strength	20 mg/mL	25 mg, 100 mg
Dose and Frequency	Initial dose: 100 mg once daily Titration: on day 14 may increase by up to 100 mg every two weeks to a maximum dose of 400 mg once daily	
How Supplied	Carton containing one 150 mL bottle	Bottles containing 100 capsules
Storage	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. Discard any unused zonisamide oral suspension remaining 30 days after first opening of the bottle.	Store at 25°C (77°F), excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature], in a dry place and protected from light.
Container Closure	PET amber bottle	HDPE bottle

[b] Zonegran [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2020 DEC 14. Available from: http://fdalabel.fda.gov/fdalabel-r/services/spl/set-ids/d12de43e-3ac3-4335-bc85-70d7366a91eb/spl-doc?hl=zonegran

[c] Approval date accessed 2020 DEC 14. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=020789

[d] Container closure information accessed 2020 DEC 14. Available from: \\CDSESUB1\evsprod\nda020789\0078\m3\32-body-data\32p-drug-prod\zonegran-capsules\32p7-cont-closure-sys\container-closure-system.pdf

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 28, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, zonisamide and NDA 214273. Our search did not identify any previous reviews.

APPENDIX G. LABELS AND LABELING

G.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 n/a labels and labeling submitted by Eton Pharmaceuticals, Inc. on July 29, 2020.

- Container label
- Carton labeling
- Prescribing Information and Medication Guide (Images not shown), available from \\CDSESUB1\evsprod\nda214273\0001\m1\us\draft-labeling-text-package-insert-word-eton.docx

G.2 Label and Labeling Images

Container label

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

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