CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214273Orig1s000

SUMMARY REVIEW

Summary Memorandum for Class 2 NDA Resubmission

Date	July 12, 2022
From	Philip H. Sheridan, MD Nick Kozauer, MD
Subject	Summary Memorandum for Class 2 NDA Resubmission
NDA#	NDA 214273
Applicant	Azurity Pharmaceuticals, Inc.
Date of Submission	January 18, 2022
PDUFA Goal Date	July 18, 2022
Proprietary/ Established (USAN) Name	Zonisade
Dosage forms / Strength	Oral Suspension, 20 mg/ml
Proposed Indication(s)	Adjunctive therapy in the treatment of partial seizures in adults age 16 years and older
Proposed Dosage	Initial dose 100 mg daily. [redacted] (b) (4) dose may be increased [redacted] (b) (4)
Recommended:	Approval

1. Introduction and Regulatory History

This is a Class 2 resubmission for Zonisade (Zonisamide Oral Suspension) following issuance of a Complete Response (CR) letter, on May 28, 2021, because of facility deficiencies regarding manufacturing and product testing.

In this 505(b)(2) resubmission, the applicant again relies on the Agency's prior finding of safety and effectiveness for Zonegran 100 mg oral capsules (NDA 0207893) as the listed drug (LD) and seeks the same indication approved for Zonegran: adjunctive therapy in the treatment of partial seizures in adults age 16 years and older. Zonisamide was originally approved in 2000 as Zonegran capsules. Zonegran is currently available as 25 mg and 100 mg capsules. Multiple generic versions of zonisamide capsules are available in 25 mg, 50 mg, and 100 mg strengths. There are no other approved dosage forms for zonisamide.

The first submission of this NDA was on July 22, 2020, by Eton Pharmaceuticals. During the first review cycle, the Agency was notified, in a letter dated February 9, 2021, that ownership of NDA 214273 was transferred from Eton Pharmaceuticals to Azurity Pharmaceuticals.

No new nonclinical data were required for this 505(b)(2) NDA submission.

The applicant submitted two pivotal bioavailability/bioequivalence studies as the bridging studies for this 505(b)(2) NDA. Study 19-009 was performed with subjects in the fasting state, and Study 19-010 was performed with subjects in the fed state. The Division of Neuropharmacology reviewers concluded that the results of Study 19-009 and Study 19-010 established that Zonisade had comparative bioavailability to the LD, Zonegran, and recommended approval.

The clinical review team concluded that there were no new safety findings in the safety data for Zonisade from Studies 19-009 and 19-010 and also recommended approval.

However, the Office of Product Quality (OPQ) recommended a Complete Response (CR) due to facility deficiencies. Therefore, a CR Letter was issued on May 28, 2021.

The current submission is the Class 2 NDA Resubmission.

2. Review of Class 2 NDA Resubmission

Product Quality Issues:

In its review of the Class 2 NDA resubmission, the OPQ review team now recommends approval.

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

In this Class 2 resubmission, the OPQ review team notes that the updated excipient specifications reflect the removal of (b) (4) as a testing site and transfer of the test methods to LMML. A pre-approval inspection at the LMML facility with specific coverage of the proposed drug product was conducted from January 27, 2022 to February 2, 2022. Based on its review of the inspection files, the OPQ review team now considers the LMML facility acceptable as a drug product manufacturer and concludes that all other facilities remain acceptable.

Therefore, the OPQ review teams concludes that the applicant has adequately addressed the deficiencies identified in the CR letter and recommends approval.

3. Labeling

Current approved labeling for the LD, Zonegran oral capsule, NDA 0207893, is not in Physician Labeling Rule (PLR) or PLLR format. The labeling for Zonisade is in PLR and PLLR format. Please refer to the final negotiated product label. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

4. Postmarketing Requirements

There are two PREA PMRs to allow pediatric extrapolation of efficacy and establishment of appropriate dosing and safety in the pediatric population.

1. A study to evaluate the pharmacokinetics, safety, and tolerability of zonisamide oral suspension to determine a dosing regimen as therapy for partial-onset seizures in children 1 month to 17 years of age that provides drug exposures that are similar to the exposures that are effective in adult patients with partial-onset seizures. The efficacy of zonisamide in children 1 month to 17 years of age for treatment of partial-onset seizures will be addressed by a pharmacokinetic analysis to determine pediatric dosing that will match exposures in children to those in adults. This analysis will require pharmacokinetic data from studies of both adult and pediatric patients (1 month to 17 years).

   Draft Protocol Submission: 10/2022

   Final Protocol Submission: 01/2023

   Study Completion: 01/2024

   Final Report Submission: 04/2024

2. Long-term open label safety study of zonisamide oral suspension in children 1 month to 17 years (at dosing levels found to be therapeutic) in the treatment of partial-onset seizures. Routine safety measures should be monitored and the study population must include an appropriate representation of age distributions as shown below. Behavioral and cognitive endpoints should be included. At least 15% of the study population should be in each of the following age brackets:

   - 1 month to less than 2 years
   - 2 years to less than 4 years
   - 4 years to less than 8 years
   - 8 years to less than 12 years
   - Patients greater than 12 years

Draft Protocol Submission: 12/2023

Final Protocol Submission: 02/2024

Study Completion: 02/2027

Final Report Submission: 06/2027

5. Recommended Regulatory Action

Approval.

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

/s/

PHILIP H SHERIDAN
07/13/2022 12:47:31 PM

NICHOLAS A KOZAUER
07/15/2022 11:17:01 AM

Summary Review

Date	May 26, 2021
From	Philip H. Sheridan, MD Nick Kozauer, MD
Subject	Summary Review
NDA/BLA # and Supplement#	214273 SD 01
Applicant	Azurity Pharm
Dates of Submission	July 29, 2020
PDUFA Goal Dates	May 29, 2021
Proprietary Name	Zonisade
Established or Proper Name	Zonisamide
Dosage Form(s)	Oral Suspension 20 mg /ml
Applicant Proposed Indication(s)/Population(s)	Adjunctive therapy in the treatment of partial seizures in adults with epilepsy.
Applicant Proposed Dosing Regimen(s)	Initial dose 100 mg daily. (b) (4) dose may be increased (b) (4)
Recommendation on Regulatory Action	Complete Response

1. Background

The current submission is a 505(b)(2) application for Zonisade (zonisamide oral suspension 20 mg/ml) supported by two bioequivalence studies with healthy adult volunteers to bridge the zonisamide oral suspension to the listed drug Zonegran (100 mg zonisamide capsules). Study 19-009 was performed with subjects in the fasting state, and Study 19-010 was performed with subjects in the fed state.

The Applicant proposes to use the labeling of the approved listed drug, Zonegran (zonisamide 100 mg oral capsule), as the basis of supporting nonclinical pharmacology and toxicology as well as clinical sections of the proposed labeling.

Zonisamide was originally approved in 2000 as Zonegran capsules for the treatment of partial onset seizures in adults.

Summary Review
NDA 214273 SD 01
Zonisade Oral Suspension (zonisamide)

The Agency was notified in a letter dated February 9, 2021, that ownership of NDA 214273 was transferred from Eton Pharmaceuticals to Azurity Pharmaceuticals.

2. Product Quality

The Office of Product Quality (OPQ) review team (Dr. Martha Heimann, technical lead) recommends a Complete Response for this application. The OPQ review team finds that there is insufficient information to ensure that the Applicant can consistently manufacture a product that is suitable for use to treat patients with partial onset seizures.

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

We concur with the OPQ review team recommendation.

3. Nonclinical Pharmacology/Toxicology

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

4. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was written by Dr. Muzeeb Syed (clinical pharmacology reviewer) and Dr. Angela Men (clinical pharmacology team lead).

The clinical pharmacology of zonisamide was previously described in the clinical pharmacology review of the original NDA submission.

Summary Review
NDA 214273 SD 01
Zonisade Oral Suspension (zonisamide)

Bioequivalence Studies 19-009 and 19-010

The Applicant conducted two bioequivalence studies to bridge the zonisamide oral suspension (100mg/5ml) to Zonegran, the listed drug (100mg capsules). Study 19-009 was performed with subjects in the fasting state while the second study, Study 19-010 was performed in the fed state.

The objective of both the fasting and fed studies was to compare the rate and extent of absorption of zonisamide from zonisamide oral suspension 100 mg/5ml and zonisamide 100 mg capsules in healthy adult subjects and to monitor the safety and tolerability of a single dose of zonisamide oral suspension in healthy adult subjects.

Study Design for Studies 19-009 and 19-010

Both Studies 19-009 and 19-010 used the same study design. They were randomized, single dose, two treatment, two sequence, two period, crossover studies. In both studies, the order of receiving the test and reference products for each of the 36 subjects during the two periods of the study was determined according to the randomization schedule. Equal allocation of subjects to each sequence was ensured. In these studies, each subject received both the treatments [test drug (T) and reference drug (R)] across the two study periods. Hence, every subject acted as their own control and no separate group of subjects were required to act as the control group.

Study Sequence for both Studies 19-009 and 19-010

	Period 1	Washout	Period 2
Sequence 1 (n=18)	Test (T)*	28d	Reference (R)†
Sequence 2 (n=18)	Reference (R)	28d	Test (T)
*100mg/5ml Suspension †100mg Tablet			

The total duration of each study was 33 days from the day of check-in of the first period till the end of the second period. A washout period of 28 days (i.e., at least five elimination half-lives) was kept between each dose administration.

Results:

Study 19-009 (Fasting State)

Although 36 patients were planned, only 34 patients completed the study because two patients did not report in for the second sequence.

The following graphics, reproduced based on the clinical pharmacology review, summarize the key findings from Study 19-009:

Descriptive Statistics of Formulation Means for Zonisamide obtained by a Non-Compartmental Model (N = 34)

Pharmacokinetic Parameters (Units)	Mean ± SD (Un-transformed data)	
	Test Product (T)	Reference Product (R)
C_{max} (ng/mL)	1240.1543 ± 237.45587	1237.8173 ± 264.94861
AUC_{0-72h} (ng.hr/mL)	53664.6337 ± 9914.00978	53964.5238 ± 8587.89246
K_{el} (hr^{-1})	0.0109 ± 0.00261	0.0115 ± 0.00290
$t_{1/2}$ (hr)	69.7312 ± 32.40216	63.8695 ± 15.85511
T_{max} (hr)	2.349 ± 1.3160	3.694 ± 1.7436
	Median	
T_{max} (hr)	2.165	3.500

Geometric Least Squares Means, Ratios and 90% Confidence Intervals for Pharmacokinetic Parameters (Cmax and AUC0-72h) of Zonisamide (N = 34) (Including Outlier) **

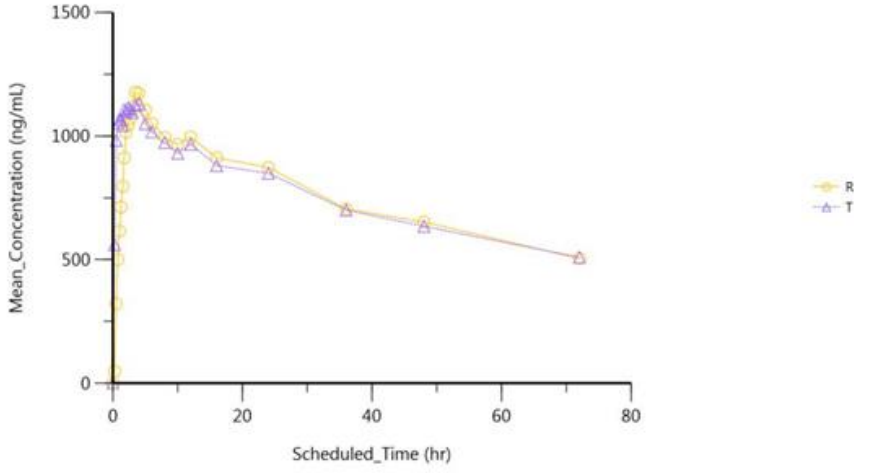
Pharmacokinetic Parameters (Units)	Ln-transformed			90% Confidence Interval (Parametric)	
	Geometric Least Squares Mean				
	Test Product (T)	Reference Product (R)	T/R (%)	Lower	Upper
C_{max} (ng/mL)	1219.0940	1211.0941	100.66	96.15	105.38
AUC_{0-72h} (ng.hr/mL)	52826.6567	53314.1342	99.09	95.95	102.33

Geometric Least Squares Means, Ratios and 90% Confidence Intervals for Pharmacokinetic Parameters (Cmax and AUC0-72h) of Zonisamide (N = 33) (Excluding Outlier) **

Pharmacokinetic Parameters (Units)	Ln-transformed			90% Confidence Interval (Parametric)	
	Geometric Least Squares Mean				
	Test Product (T)	Reference Product (R)	T/R (%)	Lower	Upper
C_{max} (ng/mL)	1208.5503	1216.3830	99.36	95.32	103.56
AUC_{0-72h} (ng.hr/mL)	52482.6984	53430.9931	98.23	95.37	101.17

**Outlier: Subject (b) (6) was identified to be inconsistent in T/R (test/reference) ratios with the rest of the data for the pharmacokinetic parameters Cmax (1.59-fold) and AUC $_{0-72}$ (1.33-fold) for zonisamide. A clinical and bioanalytical investigation was done regarding this subject on various aspects and it was found that there was no root cause observed for inconsistent T/R ratio; however, to avoid introducing bias into the results, statistical analyses were performed on both the data sets (i.e., including as well as excluding the outlier).

Linear Plot of Mean Serum Concentrations of Zonisamide vs. Time for Test Product (T) and Reference Product (R) (N = 34)



Based on these results, the clinical pharmacology review concludes that the 90% confidence intervals of the differences of least squares means for the pharmacokinetic parameters Cmax and AUC0-72h of zonisamide in the fasting state are within the bioequivalence acceptance limits of 80.00 – 125.00%; therefore, zonisamide oral suspension 100 mg/5ml is bioequivalent with the reference product, Zonegran (zonisamide) 100 mg Capsules, in healthy adult human subjects under fasting conditions.

Study 19-0010 (Fed State)

Although 36 patients were planned, only 35 patients completed the study because one patient tested positive for the alcohol breath test when checking in for patients did not report in for the second sequence and was withdrawn from the study.

The following graphics, reproduced based on the clinical pharmacology review, summarize the key findings from Study 19-0010:

Descriptive Statistics of Formulation Means for Zonisamide obtained by a Non- Compartmental Model (N = 35)

Pharmacokinetic Parameters (Units)	Mean ± SD (Un-transformed data)	
	Test Product (T)	Reference Product (R)
C_{max} (ng/mL)	1217.8486 ± 214.60266	1209.0448 ± 218.96807
AUC_{0-72h} (ng.hr/mL)	55214.4323 ± 8477.74679	55339.1469 ± 9386.94075
K_{el} (hr^{-1})	0.0115 ± 0.00340	0.0119 ± 0.00249
$t_{1/2}$ (hr)	65.5987 ± 19.47163	61.0527 ± 13.23597
T_{max} (hr)	4.914 ± 1.0109	5.403 ± 1.6321
	Median	
T_{max} (hr)	5.000	5.000

Geometric Least Squares Means, Ratios and 90% Confidence Intervals for Pharmacokinetic Parameters (Cmax and AUC0-72h) of Zonisamide (N = 35) (Including Outlier)##

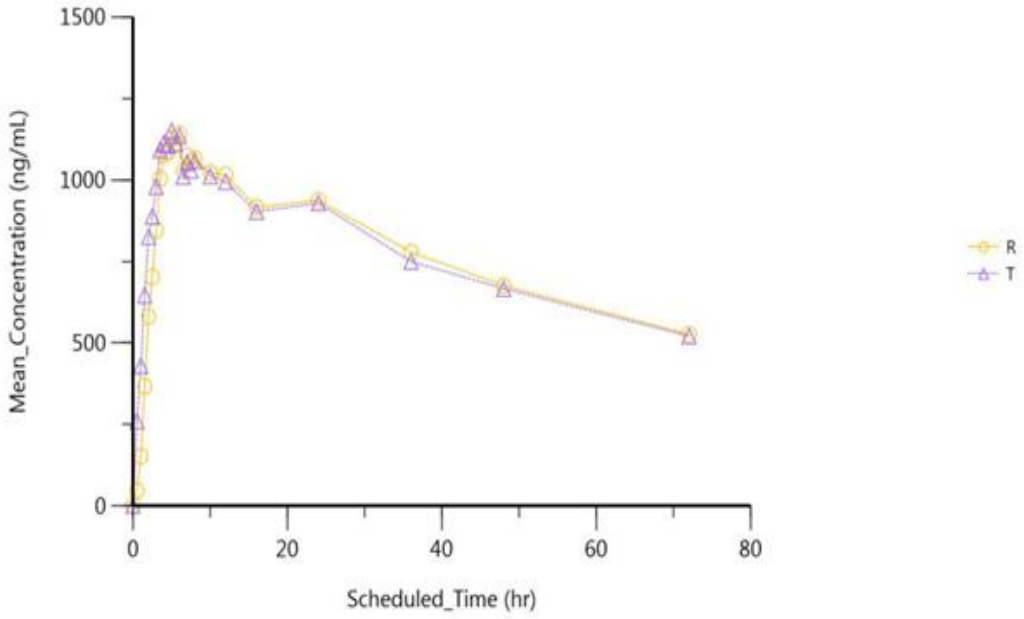
Pharmacokinetic Parameters (Units)	Ln-transformed			90% Confidence Interval (Parametric)	
	Geometric Least Squares Mean				
	Test Product (T)	Reference Product (R)	T/R (%)	Lower	Upper
C_{max} (ng/mL)	1200.4297	1192.2964	100.68	98.00	103.44
AUC_{0-72h} (ng.hr/mL)	54638.8153	54619.4901	100.04	98.45	101.65

Outlier: Subject (b) (6) was identified to be inconsistent in T/R (test/reference) ratios with the rest of the data for the pharmacokinetic parameters Cmax (1.59-fold) and AUC $_{0-72}$ (1.33-fold) for zonisamide. A clinical and bioanalytical investigation was done regarding this subject on various aspects and it was found that there was no root cause observed for inconsistent T/R ratio; however, to avoid introducing bias into the results, statistical analyses were performed on both the data sets (i.e., including as well as excluding the outlier).

Geometric Least Squares Means, Ratios and 90% Confidence Intervals for Pharmacokinetic Parameters (Cmax and AUC0-72h) of Zonisamide (N = 34) (Excluding Outlier)

Pharmacokinetic Parameters (Units)	Ln-transformed			90% Confidence Interval (Parametric)	
	Geometric Least Squares Mean				
	Test Product (T)	Reference Product (R)	T/R (%)	Lower	Upper
C_{max} (ng/mL)	1189.6247	1192.3652	99.77	97.54	102.05
AUC_{0-72h} (ng.hr/mL)	54444.9045	54635.1999	99.65	98.17	101.15

Linear Plot of Mean Serum Concentrations of Zonisamide vs. Time for Test Product (T) and Reference Product (R) (N = 35)



Based on these results, the clinical pharmacology review concludes that the 90% confidence intervals of the differences of least squares means for the pharmacokinetic parameters Cmax and AUC0-72h of zonisamide in the fed state are within the bioequivalence acceptance limits of 80.00 – 125.00%; therefore, zonisamide oral suspension 100 mg/5ml is bioequivalent with the reference product, Zonegran (zonisamide) 100 mg Capsules, in healthy adult human subjects under fed conditions.

Overall Clinical Pharmacology Conclusion from Studies 19-009 and 19-010

The Clinical Pharmacology reviewers concluded that, since bioequivalence was demonstrated in both the fasted and fed states, it is appropriate that the proposed doses are the same as those already approved for the oral capsule for treatment of partial-onset seizures in adults.

We concur with Clinical Pharmacology reviewers' conclusion that, based on their review, there is adequate support for approval of the zonisamide oral suspension.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical- Efficacy

The effectiveness of zonisamide oral suspension is established through bioequivalence with the approved listed drug, zonisamide oral capsule for which efficacy has previously been established in the treatment of partial onset seizures in adults.

7. Safety

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

As described in Section 5 of this summary review, the Applicant conducted two bioequivalence studies to bridge the zonisamide oral suspension (100 mg/5ml) to the listed drug (100 mg capsules). Study 19-009 was performed with 36 subjects in the fasting state, and Study 19-010 was performed with 36 in the fed state.

Two subjects in Study 19-009 did not report for the period 2 dose (Subject (b) (6) in the TR sequence and Subject (b) (6) in the RT sequence). One subject in Study 19-010 was withdrawn from the study by the investigators when his alcohol breath test was positive prior to beginning period 2.

Dr. Dinsmore reviewed the safety data from the 69 healthy adult subjects (34 from Study 19-009 and 35 from Study 19-010).

There were no deaths or adverse events (AEs) requiring discontinuation. No clinical AEs were reported in either study. The AEs observed in both studies consisted of changes in clinical laboratory values of liver enzymes (ALT and AST) and of minor deviations in hematological values, described below, similar to those described in the labeling for the listed drug.

Study 19-009

Clinical Laboratory Values:

There were four AEs from among 3 patients. The most notable laboratory abnormality was an increase in ALT value from within reference range at baseline / screening to 1.8 X upper-limits-of-normal (ULN) in one subject at the end-of-study (EOS) measurement, 3 days after test product administration. The remaining abnormal laboratory investigations included one each of AST, ALT, and potassium values measured at EOS. These were lessor elevations with a maximum of 1.3 X ULN. Laboratory studies were not obtained after each study period but only at screening (baseline), prior to period 1, and EOS, after period 2. Interpretation of the abnormal values obtained at EOS is difficult due to the absence of laboratory values from both study periods that would allow comparison of individual subject responses to both test and reference products. The limited abnormalities that are identified do not indicate a safety signal for the treatment with test product.

Hematology Values:

There were 6 entries from six subjects with hematology values greater than 1 X ULN. These occurred in the measurement of eosinophils in 5 subjects and lymphocytes in one subject. In 4 of the six entries, the excess over reference range was 1.1 X ULN while in the remaining two entries, where both were eosinophil values, the out-of-reference-range (OORR) high values were 1.2 and 1.3 X ULN. These deviations from reference range are not clinically significant in this context of this bioequivalence study.

There were five entries from five subjects with EOS hematology value entries that were out-of-OORR low. These all occurred in hemoglobin measurements. In one subject there was no change from baseline hemoglobin value while in a second there was an increase hemoglobin value from baseline to EOS. In the remaining 3 instances where subjects had an OORR low value, the percent changes from baseline were -6.3%, -1.7%, and -0.8%. These deviations from reference range are not clinically significant in the context of this bioequivalence study.

Vital Signs:

Analysis of vital sign measurements following both test and reference product administration was performed with examination of baseline and after 3 hours post dose. The vital sign screen did not reveal a clinically significant difference between test and reference products.

Study 19-010

Clinical laboratory values:

There were 12 adverse events that occurred from among 8 healthy adult subjects. Seven of these adverse events were mild elevations of ALT while 5 were mild elevations in AST.

The elevations of ALT and AST exceeded twice the ULN in only one instance (Subject (b) (4). The timing of test product administration 31 days before the identified abnormality does not support a causal relationship to the test product. There was no elevation greater than twice the ULN in any other occurrence. In only 3 of eight subjects was the increase in ALT or AST temporally related to administration of test product. There was no associated elevation to OORR high of alkaline phosphatase or total bilirubin on examination in these subjects. Therefore, no safety signal was identified.

Hematology

There were 4 entries from 4 patients with EOS hematology parameters that were OORR low. These four entries were all hemoglobin values. Three of these subjects had no change or an increase in hemoglobin from baseline value. In the remaining case there was a decline from 12.8g/dl at baseline to 11.9 g/dl at EOS in the RT study sequence. These changes were not clinically significant.

There were five entries from five patients that had OORR high values for eosinophil percent value. Two subjects had OORR high baseline values. From among the remaining 3 subjects, two were in the TR sequence with absence of temporal relationship to the test product. The remaining subject had a 29% increase in eosinophils from baseline to EOS (5.6% to 7.2%). This value is 1.2 X ULN and is not clinically significant.

Vital Signs

Examination of systolic blood pressure and pulse change from baseline to 3 hours after test product administration revealed no clinically significant change.

Overall Clinical Conclusion from Studies 19-009 and 19-010

Dr. Dinsmore examined the safety data included in this application and found that the AEs reported were similar to those identified in current Zonegran labeling. Changes in laboratory values from screening visit to end of study were examined. He concluded that the AE profile, laboratory data, and vital sign screening revealed that zonisamide oral suspension had no safety signal that was different from the reference product.

We concur with Dr. Dinsmore's conclusion that, based on the clinical review, there is adequate support for approval of the zonisamide oral suspension.

8. Advisory Committee Meeting

This application was not referred to an Advisory Committee for review because the two bioequivalence study designs were acceptable and the safety profile of zonisamide oral suspension was similar to that of the approved oral capsule formulation.

9. Other Relevant Regulatory Issues

No Good Clinical Practice issues were identified in Dr. Dinsmore's clinical review.

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

The Division of Medication Error Prevention and Analysis (DMEPA) (Safety Evaluator John C. Morris, PharmD, MPH and Team Leader Celeste Karpow, PharmD, MPH) reviewed the Applicant's revisions of container label and carton labeling made in response to DMEPA recommendations to reduce potential medication errors and found them to be acceptable.

10. Pediatrics

The Pediatric Research Equity Act (PREA) is triggered. See Section 14 below.

11. Office of Scientific Integrity (OSI) Review

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection related to the clinical bioequivalence trials is not warranted at this time for the Clinical Synapse Labs in Maharashtra, India, because The Office of Regulatory Affairs (ORA) inspected the site in February 2020, which falls within the surveillance interval.

12. Labeling

No labeling negotiations with the applicant were conducted in this review cycle because the product quality issues described above prevent approval.

13. Postmarketing Requirements (PMRs) and Postmarketing Commitments (PMCs)

The agreed iPSP was reviewed at the Pediatric Review Committee (PeRC) meeting of April 6, 2021. PeRC concurred with the Applicant's postmarketing plan to use pediatric extrapolation (with supportive PK and long-term safety studies) to establish efficacy and safety for Zonisade for children age 1 month and older for partial onset seizures. Since this NDA cannot be approved in this review cycle, the corresponding PREA PMRs will not be included in the Complete Response letter.

14. Recommended Comments to the Applicant

See Complete Response letter.

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

/s/

PHILIP H SHERIDAN
05/27/2021 03:18:20 PM

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05/28/2021 11:49:02 AM