CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214273Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology

Clinical Pharmacology Review

NDA Number	214273
Serial Number	0001
Link to EDR	\\CDSESUB1\evsprod\NDA214273\0001
Submission Date	28-July-2020
Submission	NDA
Brand Name	Zonisamide oral suspension (ET-104)
Generic Name	Zonisamide
Dosage Form (Strength)	Zonisamide oral suspension (20 mg/mL, 150 mL fill)
Route of administration	Oral
Proposed Indication	Adjunctive therapy in the treatment of partial seizures in adults (>16 years) with epilepsy
Applicant	Eton Pharmaceuticals, Inc
Regulatory pathway	505(b)(2)
Previous submission	PIND142839
Reference Listed drug (RLD)	Zonegran capsules (100 mg); NDA020789; Sunovion Pharmaceuticals Inc
OCP Review Team	Muzeeb Syed, Ph.D., Angela Men, MD. Ph.D.

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1. Executive Summary

The sponsor, Eton Pharmaceuticals, Inc, is seeking the approval of Zonisamide oral suspension, 20 mg/mL as an alternative dosage form for the ease of administration to patients who, due to illness or age, have difficulty in reconstitution of the powder for oral suspension or may prefer a ready to use liquid formulation. Eton submitted a New Drug Application (NDA) via the 505(b)(2) regulatory pathway for zonisamide oral suspension, 20 mg/mL (ET-104) using Zonegran (Zonisamide Capsule; Oral eq. 100 mg base/capsule, NDA 020789 held by Sunovion Pharmaceuticals INC)) as a reference listed drug (RLD).

Eton intends to seek Zonisamide oral suspension prescribed at the same doses, same indication and dosing regimens as Zonegran for the adjunctive therapy in the treatment of partial seizures in adults with epilepsy. The initial dose should be 100 mg daily. (b) (4) .

The sponsor conducted two open-label, randomized, crossover pivotal Pharmacokinetic (PK) bridging studies, in which bioequivalence (BE) was demonstrated between zonisamide oral suspension and zonegran capsules in healthy volunteers under fasting (Study #19-009) and fed (Study #19-010) state. Both the test and reference products were found to be safe and well tolerated by the subjects in both fed and fasted state. There are no efficacy and safety studies conducted. Based on the PK bridging results, the safety and efficacy of zonisamide oral suspension will rely on its RLD Zonegran (Capsule; Oral eq.100 mg base/capsule, NDA 020789 held by Sunovion Pharmaceuticals INC).

In this NDA submission, from a clinical pharmacology perspective, the review focuses on the evaluation of these two BE studies between the oral suspension and the reference zonegran capsules in both fed (Study #19-010) and fasted state (Study #19-009) .

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted under NDA-214273 and recommended approval of Zonisamide 20 mg/mL suspension (ET-104) for the adjunctive therapy in the treatment of partial seizures in adults with epilepsy.

Key review issues with specific recommendations and comments are summarized below in Table 1:

Table 1 Summary of Review Issues and OCP Recommendations

Review Issues	Recommendations and Comments
Evidence of effectiveness and safety:	BE is demonstrated between zonisamide oral suspension and RLD in both fasted and fed state. Effectiveness and safety of zonisamide oral suspension rely on the approved RLD, Zonegran, 100 mg capsule.
General dosing instructions:	The initial dose of Zonegran should be 100 mg daily. (b) (4) .
Labeling	Sponsor plans to rely on the labelling of approved drug zonegran capsules, which is acceptable.
BE between the "oral suspension" and reference listed zonegran capsules	Bio-equivalency is established between the oral suspension and listed drug, zonegran capsules.

2. Summary of Clinical Pharmacology Assessment

2.1 The Pharmacology and Clinical Pharmacokinetics

Zonisamide may produce anticonvulsant 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 Ca^{2+} currents), consequently stabilizing neuronal membranes and suppressing neuronal hyper synchronization.

Eton conducted comparative bioequivalence (BE) studies between Zonisamide Oral Suspension, 20 mg/mL, and Zonegran Capsule, 100mg in healthy volunteers in both fasted (study#19-009) and fed (Study # 19-010) state. In these studies, the rate and extent of absorption, safety and tolerability of zonisamide from zonisamide oral suspension (100 mg/5 mL) and Zonegran (Zonisamide) 100 mg capsules were established. The 90% confidence intervals of the difference of least square means of pharmacokinetic parameters, C_{max} and AUC0-72 h of zonisamide, are within the bioequivalence acceptance limits of 80.0-125.0%. It was concluded that the test product (Zonisamide oral suspension 100 mg/5 mL) was bioequivalent with the reference product Zonegran (100 mg Zonisamide capsule) in healthy, adult human subjects under both fasted and fed state.

An early T_{max} (2 hrs) with suspension formulation was observed compared to the capsule formulation (3.5 hrs) in fasted state. There was no difference in T_{max} (5 hrs) between the suspension formulation and capsule formulation in fed state.

Both test (Oral suspension) and reference products (Capsule) were found to be safe and well tolerated in both fasted and fed state.

The proposed indication for Zonisamide oral suspension is the same as the indication for the RLD Zonegran. Eton proposes to use the same doses and routes of administration for its liquid product as those approved for the RLD.

2.2 Dosing and Therapeutic Individualization

General dosing

The initial dose of zonisamide should be 100 mg daily. (b) (4) [redacted]. Zonisamide is given orally and can be taken with or without food.

Note: The dosing information is similar to the reference listed drug, Zonegran Capsules.

2.3 Outstanding Issues

None.

3. Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

Zonisamide capsule received approval for adjunctive therapy in the treatment of partial seizures in adults with epilepsy.

In this submission, the sponsor developed oral suspension of zonisamide (20 mg/mL , 100 mg/5mL) for the ease of administration to patients who, due to illness or age, have difficulty in reconstitution of the powder for oral suspension or may prefer a ready to use liquid formulation. BE is demonstrated between these two formulations in both fasted and fed state.

3.2 General Pharmacological and Pharmacokinetic Characteristics

The pharmacokinetic properties of zonisamide are summarized in the Table below.

Table 2. Summary of Pharmacological and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Zonisamide may produce these effects through action at sodium and calcium channels

Active Moieties	Zonisamide

General Information	
Bioanalysis	The concentrations of zonisamide human serum were determined using a validated LC-MS/MS method .
Healthy Subjects vs. Patients	No significant difference in pharmacokinetics (PK) between healthy subjects and patients
Dose Proportionality	Zonisamide exhibits dose proportional pharmacokinetics over the dose range of 200 to 400 mg . but the C_{max} and AUC increase disproportionately at 800 mg

Absorption	
Bioavailability	The mean absolute bioavailability of zonisamide is almost 100%
T_{max}	Capsule : ~2-6 hours- fasted; 4-7 hours fed. Suspension: ~1.0-3.6 hours (early Tmax) fasted; 4-6 hours fed.
Food Effect	Food has no significant effect on the PK of zonisamide. T_{max} is slightly delayed, which is not expected to have significant impact on the clinical responses.

Distribution	
Apparent Volume of Distribution	1.45 L
Protein Binding	~10%

Elimination	
Elimination half-life	In plasma : 63 hours In RBC: 105 hours

Metabolism	
Metabolic Pathway	Zonisamide undergoes acetylation to form N-acetyl zonisamide and reduction to form the open ring metabolite, 2–sulfamoylacetyl phenol (SMAP). Of the excreted dose, 35% was recovered as zonisamide, 15% as N-acetyl zonisamide, and 50% as the glucuronide of SMAP. Reduction of zonisamide to SMAP is mediated by cytochrome P450 isozyme 3A4 (CYP3A4).
Inhibitor / Inducer	Zonisamide does not induce its own metabolism. Plasma clearance of zonisamide is approximately 0.30–0.35 mL/min/kg in patients not receiving enzyme-inducing anti-epileptic drugs (AEDs). The clearance of zonisamide is increased to 0.5 mL/min/kg in patients concurrently on enzyme-inducing AEDs
Excretion	
Excretion Pathway	Zonisamide is excreted primarily in urine as parent drug and as the glucuronide of a metabolite. Following multiple dosing, 62% of the ^{14}C dose was recovered in the urine, with 3% in the feces by day 10

3.3 Clinical Pharmacology Questions

To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Sponsor did not conduct any efficacy study with the zonisamide oral suspension formulation. Sponsor submitted this New Drug Application (NDA) via the 505(b)(2) regulatory pathway for approval of Zonisamide Oral suspension, 20mg/mL (ET-104) by conducting the Bioequivalence (BE) studies with the reference listed drug Zonegran (100 mg capsule). The following two pivotal PK studies demonstrated BE between zonisamide oral suspension and RLD and the efficacy of oral suspension is completely relied on the approved Zonegran (Zonisamide capsule).

3.3.1 Bioequivalence study of oral suspension and capsule in fasted condition

Study (#19-009) : An open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study of Zonisamide oral suspension 100mg/5ml with Zonegran (Zonisamide) 100 mg Capsules in healthy, adult, human subjects under fasting condition.

Objectives:

- To compare the rate and extent of absorption of Zonisamide from Zonisamide oral suspension 100mg/5ml and Zonegran (Zonisamide) 100 mg Capsules in healthy, adult, human subjects under fasting conditions.

- To monitor the safety and tolerability of a single dose of Zonisamide oral suspension 100mg/5ml in healthy, adult, human subjects under fasting conditions

Number of Subjects: Subjects planned: 36; subjects enrolled: 36+02 (additional subjects as back-up); subjects dosed : Period 01-36 ; period 02: 34; Number of subjects completing the study: 34; Number of subjects dropped out from the study : 02 (2 subjects did not report to the clinical facility for period 02 check in and they are considered as "dropout". Dropout subjects were not replaced.

Pharmacokinetic and Statistical Evaluation for Zonisamide:

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

Reviewer note: As per the draft guidance on zonisamide , since zonisamide has long half-life, sponsor can consider parallel design study, truncating the AUC at 72 hours.

Geometric Least Squares Means, Ratios and 90% Confidence Intervals for Pharmacokinetic Parameters (C_{max} and AUC_{0-72h}) of Zonisamide (N = 34)

(Including Outlier)

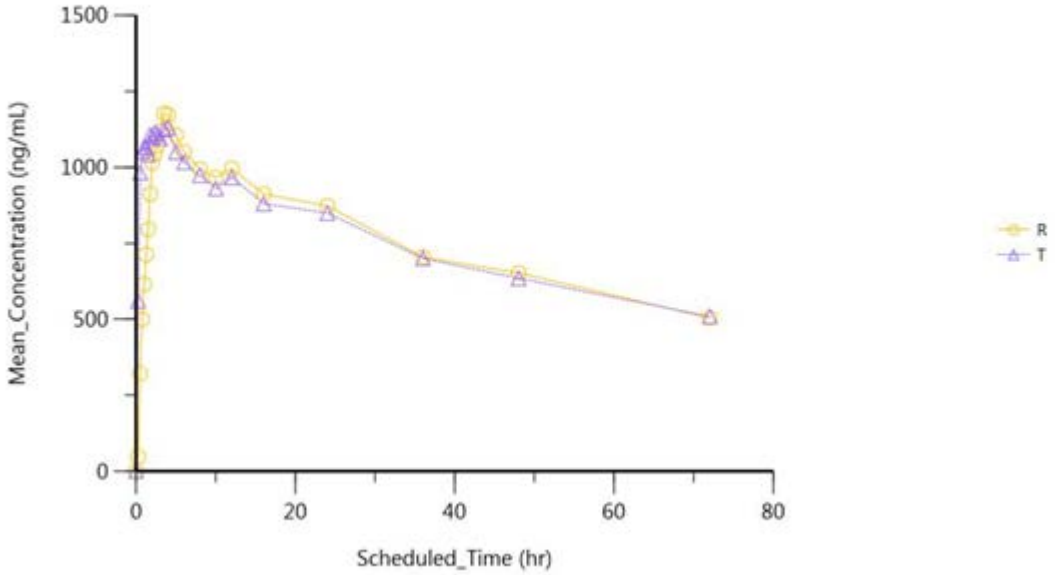
Pharmacokinetic Parameters (Units)	Ln- transformed			90% Confidence Interval (Parametric)	
	Geometric Least Squares Mean				
	Test Product (T)	Reference Product (R)	T/R (%)	Lower	Upper
C_{max} (ng/mL)	1219.0940	1211.0941	100.66	96.15	105.38
AUC_{0-72h} (ng.hr/mL)	52826.6567	53314.1342	99.09	95.95	102.33

Geometric Least Squares Means, Ratios and 90% Confidence Intervals for Pharmacokinetic Parameters (C_{max} and AUC_{0-72h}) 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 no. (b) (6) was identified to be inconsistent in T/R (test/reference) ratios with the rest of the data for Pharmacokinetic parameters Cmax (1.59-fold) and AUC_{0-72} (1.33-fold) for zonisamide. A clinical and bioanalytical investigations was done regarding outlier subject on various aspects and it was found that there was no root cause observed for inconsistent T/R ratio for this outlier subject of zonisamide. However, to avoid the biasedness in the results , the statistical analyses was performed 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)



SAFETY CONCLUSIONS

- Both 100mg test (Zonisamide oral suspension 100mg/5ml) and reference products were found to be safe and well tolerated in healthy, adult, human subjects under fasting conditions.

CONCLUSIONS

- The 90 % confidence intervals of the differences of least squares means for the pharmacokinetic parameters C_{max} and $AUC_{0\text{-}72h}$ of zonisamide are within the bioequivalence acceptance limits of 80.00 – 125.00%.

- It is concluded that the test product (T) Zonisamide oral suspension 100mg/5ml was found to be bioequivalent with reference product (R) Zonegran (Zonisamide) 100 mg Capsules in healthy, adult, human subjects under fasting conditions.

3.3.2 Bioequivalence study of oral suspension and capsule in fed condition:

Study (#19-010) An open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study of Zonisamide oral suspension 100mg/5ml with Zonegran (Zonisamide) 100 mg Capsules in healthy, adult, human subjects under fed condition.

Objectives:

- To compare the rate and extent of absorption of Zonisamide from Zonisamide oral suspension 100mg/5ml (test product) and Zonegran (Zonisamide) 100 mg Capsules (reference product), in healthy, adult, human subjects under fed conditions.
- To monitor the safety and tolerability of a single dose of Zonisamide oral suspension 100mg/5ml in healthy, adult, human subjects under fed conditions.

Number of Subjects: Subjects Planned: 36; Subjects enrolled: 36 +02 (additional as back up); Subjects dosed: for period 01: 36, Period 02: 35; Number of subjects completing the study: 35; Number of subjects withdrawn from study: 01[#]

 # Subject number (b) (6) was tested positive for alcohol breath test on the day of period 02 check in and hence was withdrawn from the study

Pharmacokinetic and Statistical Evaluation for Zonisamide:

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

Reviewer note: As per the draft guidance on zonisamide , since zonisamide has long half-life, sponsor can consider parallel design study, truncating the AUC at 72 hours.

Geometric Least Squares Means, Ratios and 90% Confidence Intervals for Pharmacokinetic Parameters (C_{max} and AUC_{0-72h}) of Zonisamide (N = 35) (Including Outlier)##

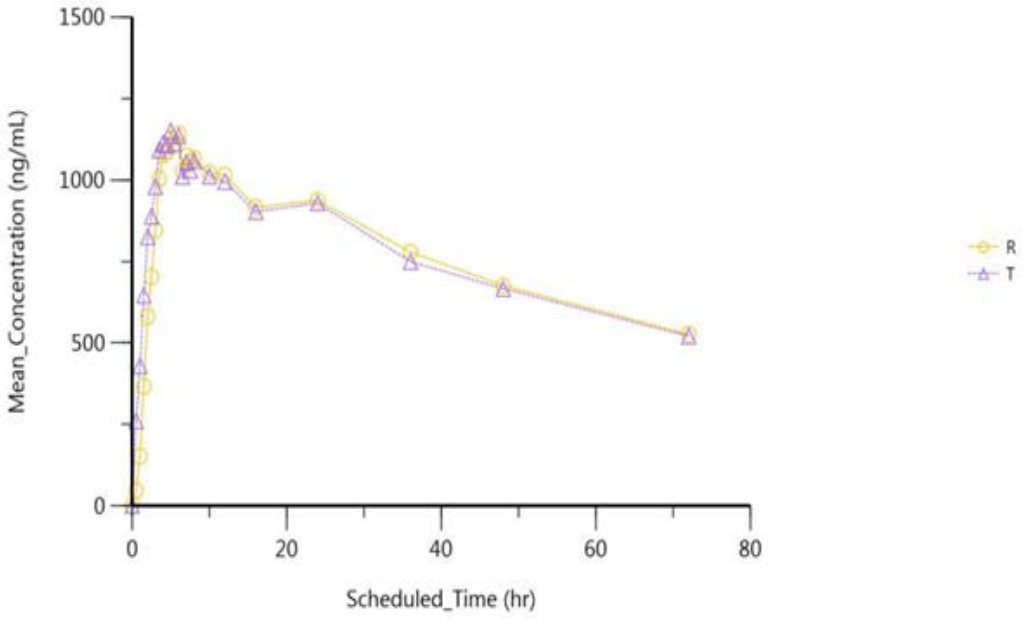
Pharmacokinetic Parameters (Units)	Ln-transformed			90% Confidence Interval (Parametric)	
	Geometric Least Squares Mean				
	Test Product (T)	Reference Product (R)	T/R (%)	Lower	Upper
C_{max} (ng/mL)	1200.4297	1192.2964	100.68	98.00	103.44
AUC_{0-72h} (ng.hr/mL)	54638.8153	54619.4901	100.04	98.45	101.65

Subject no. (b) (6) was identified to be inconsistent in T/R (Test/Reference) ratios with the rest of the data for pharmacokinetic parameters C_{max} for zonisamide. A clinical and bioanalytical investigation was done regarding outlier subject on various aspects and it was found that there was no root cause observed for inconsistent T/R ratio for this outlier subject of zonisamide. However, to avoid the biasedness in the results, the statistical analysis was 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 (C_{max} and AUC_{0-72h}) 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)



Safety conclusions:

- Both 100mg test (Zonisamide oral suspension 100mg/5ml) and reference products were found to be safe and well tolerated in healthy, adult, human subjects under fasting conditions.

Conclusion:

- The 90 % confidence intervals of the differences of least squares means for the pharmacokinetic parameters C_{max} and AUC_{0-72h} of zonisamide are within the bioequivalence acceptance limits of 80.00 – 125.00%.

  Hence, it is concluded that the test product (T) Zonisamide oral suspension 100 mg/5ml was found to be bioequivalent with reference product (R) Zonegran (Zonisamide) 100 mg Capsules, in healthy, adult, human subjects under fed conditions.

Is the proposed dosing regimen appropriate for the general population for which the indication is being sought?

Yes, there is no change in dosing regimen between the zonisamide oral suspension and the reference listed drug zonegran.

4. OSIS Inspection

An inspection request of the pivotal BE study was send to the the division of New Drug Study integrity (DNDSI) within the Office of the Study Integrity and Surveillance (OSIS). It is determined that an inspection is not warranted at this time for the site. The office of regulatory affairs (ORA) inspected the site in February 2020, which falls within the surveillance interval. The final classification for the inspection was No Action indicated (NAI).

5. APPENDICE

Bioanalytical method of Zonisamide used in Bioequivalence study of oral suspension and capsule in fasted condition

Analytical Validation Report Location(s)	Appendix 16.5.3 of clinical study report			
The analytical method used in the following studies	19-010			
Short description of the method	An LC-MS/MS method for the estimation of Zonisamide in human serum by extracting samples using Solid phase extraction method (MV-191-01).			
Biological matrix	Human serum			
Analyte **Location of product certificate**	Zonisamide Appendix 16.5.3.2 of clinical study report			
Internal standard (IS) **Location of product certificate**	Zonisamide D4 Appendix 16.5.3.2 of clinical study report			
Calibration concentrations (Units)	10.051–3500.446 ng/mL			
Lower limit of quantification (Units)	LLOQ		Precision %	4.83%
			Accuracy %	90.90%
QC concentrations (units/mL)	LLOQ QC	:	10.069 ng/mL	
	LQC	:	27.601 ng/mL	
	LMQC	:	175.581 ng/mL	
	MQC	:	1463.177 ng/mL	
	HQC	:	2787.004 ng/mL	
Between-run accuracy	Average of P & A 01 to 04		For LQC, LMQC, MQC & HQC: 98.23% to 103.68%	
			For LLOQQC: 102.86%	
Between-run precision	Average of P & A 01 to 04		For LQC, LMQC, MQC & HQC: 1.94% to 3.48%	
			For LLOQQC: 6.45%	
Within-run accuracy	P & A 01		For LQC, LMQC, MQC & HQC: 99.22% to 104.38%	
			For LLOQQC: 106.70%	
Within-run precision	P & A 01		For LQC, LMQC, MQC & HQC: 0.56% to 3.15%	
			For LLOQQC: 5.03%	

Conclusions:

- % Accuracy , Precision (% CV) are within acceptable range.
- No bioanalytical issues were observed during sample analysis of zonisamide.
- Zonisamide and its internal standard were stable in human serum for 29 days when stored at -20^{0}C and -80^{0}C

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