This package insert follows the Pharmaceuticals, Medical devices and Other Therapeutic Products Act of Japan.

In Vitro Diagnostics
Certification No. 227ADAMX00073000

**Revised: December 2019 (4th edition)
*Prepared: April 2017 (3rd edition)

This package insert must be read carefully prior to use.

Zonisamide assay kit
(Classification No.: 42928000)

Nanopia TDM Zonisamide

General Precautions

1. This product is for in vitro diagnostic use, and must not be used for any other purposes.
2. Clinicians should make a comprehensive clinical decision based on assay results in conjunction with clinical symptoms and other examination results.
3. Please read carefully the "PRECAUTIONS" section, particularly under "Effects on Laboratory Tests" of the package insert of each drug, for information on the influence to the assay result that medications administered to the patient have. Please also read carefully the "2) Cross-reactivity," under "2. Interfering Substances," in the "Procedural Precautions" section, as well as "2. Precautions for Assessment" in the "Assessment of Assay Results" section, of this package insert.
4. This product should be used only as directed in this package insert. Reliability of results cannot be guaranteed if there are any deviations from the instructions in this package insert.
5. If the reagent accidentally comes in contact with eyes and/or mouth, rinse immediately with ample water as first aid, and consult the doctor if required.
6. Carefully read the operating instructions for each type of automated analyzers prior to using this product. Parameters for each type of analyzers are available, and can be requested from SEKISUI MEDICAL CO., LTD. if required.
7. Perform a quality control test prior to assay to ensure accuracy.
8. ZNS Antibody Solution 1 contains human-derived components that have been confirmed to be negative for HBs antigens, HIV antibodies, and HCV antibodies. However, handle this reagent with great care in the same manner as the samples, because it is potentially infectious.

Description (Kit Components)

Component: Ingredients
ZNS Antibody Solution 1:
Anti-zonisamide rabbit polyclonal antibody
ZNS Latex Reagent 2:
Zonisamide-coated latex

Intended Use

Measurement of zonisamide in serum or plasma

Zonisamide is an antiepileptic drug that is used for the treatment of partial, generalized, and mixed seizures in patients with partial or generalized epilepsy. Adverse reactions to this drug include sleepiness, anorexia, and ataxia. Serious adverse reactions that have been reported include toxic epidermal necrolysis (TEN), hypersensitivity syndrome, etc. The package insert for this drug states that measurement of the blood concentration is recommended for adjusting the dosage more appropriately.[1)]

Assay Principle

1. Assay Principle

When a certain amount of anti-zonisamide antibody is added and reacted with a sample, consumption of the antibody depends on its content in the sample. When zonisamide-coated latex is added, residual anti-zonisamide antibody reacts with the beads and forms aggregates. Since the extent of aggregation depends on the zonisamide concentration in the sample, the zonisamide concentration can be determined by measuring aggregation as the absorbance.

Sample (zonisamide) + Anti-zonisamide antibody
⟶ Antigen-antibody reaction

Unreacted anti-zonisamide antibody + Zonisamide-coated latex beads
⟶ Aggregation by antigen-antibody reaction

2. Features

1) Liquid reagents, ready-to-use.
2) Applicable to various automated analyzers.

Procedural Precautions **

1. Properties of Samples and Sampling Methods

1) Samples
Serum and plasma (heparin plasma and EDTA plasma) may be used.
2) Storage of samples
(1) After separation of serum (plasma), samples may be stored for up to 14 days in a refrigerator. If samples cannot be measured within 14 days of serum (plasma) separation, store them at −20°C or lower and measure them within 1 month. Stored samples should be brought to room temperature (15–30°C) before use.
(2) Samples may be frozen and thawed up to twice.

2. Interfering substances

1) Assay results are not affected by free bilirubin (up to 18.9 mg/dL), conjugated bilirubin (up to 20.8 mg/dL), hemoglobin (up to 500 mg/dL), formazine turbidity (up to 1410 FTU), or rheumatoid factors (up to 500 IU/mL).
2) Cross-reactivity
The following table summarizes the cross-reactivity with the zonisamide metabolites and other drugs.
(1) Zonisamide metabolites
If each metabolite is at the concentration mentioned in the table below when zonisamide-free samples and samples containing zonisamide at low and high concentrations are measured, cross-reactivity is as follows.

Metabolite	Concent - ration tested (μg/mL)	Cross-reactivity (%)		
		Zonisami de-free sample (0 μg/mL)	Sample containing a low zonisamide concentration (12 μg/mL)	Sample containing a high zonisamide concentration (31 μg/mL)
N-Acetyl zonisamide (NAZ)	500	0.20	0.20	0.20
	100	ND	ND	ND
	50	ND	ND	ND
	25	ND	ND	ND
	5	ND	ND	ND
Metabolite	Concent - ration tested (μg/mL)	Cross-reactivity (%)		
		Zonisami de-free sample (0 μg/mL)	Sample containing a low zonisamide concentration (12 μg/mL)	Sample containing a high zonisamide concentration (36 μg/mL)
2-Sulfamoyla cetylphenol (SMAP)	500	2.60	2.30	ND
	100	11.30	1.30	ND
	50	2.90	ND	4.40
	25	3.70	ND	5.70
	5	9.30	ND	4.20

ND: Not detectable

(2) Other drugs

If each drug is at the concentration shown in the table below when the zonisamide concentration is approximately 12 or 36 μg/mL, cross-reactivity is ≤ 2%.

Drug name	Concentra-tion tested (μg/mL)	Drug name	Concentra-tion tested (μg/mL)
Clonazepam	0.5	Salicylic acid	500
Diazepam	100	Sulfamethoxazole	400
Ethosuximide	1000	Sulfisoxazole	1000
Phenobarbital	400	Caffeine	100
Topiramate	250	Lamotrigine	300
Valproic acid	1000	Phenytoin	200
Acetaminophen	200	Primidone	100
Carbamazepine	120	Trimethoprim	20
Cyclosporin	50	Theophylline	250
Erythromycin	200	Heparin	8500 U/L
Ibuprofen	400	Levetiracetam	100

※ Based on the Clinical and Laboratory Standards Institute (CLSI) EP7-A2, cross-reactivity was calculated by the following equation.

Cross-reactivity (%) = ({[Concentration of zonisamide in the sample after adding the metabolite or drug] – [Concentration of zonisamide in the sample without the metabolite or concomitant drug]} / [Concentration of the metabolite or drug in the sample]) × 100

3. Others

1) Always use Zonisamide Calibrator for calibration.
2) Precautions for assay range

If the concentration in the sample exceeds the measurement range, dilute the sample with the Zonisamide Calibrator A and perform re-measurement.

Dosage/Administration (Assay Procedure)

1. Preparation of reagents

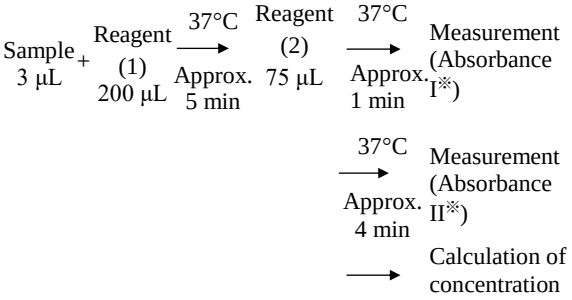
Reagent (1): ZNS Antibody Solution 1 is ready to use.

Reagent (2): ZNS Latex Reagent 2 is ready to use.

Before using this product, gently invert the ZNS Latex Reagent 2 bottle to mix it thoroughly, and check that there are no bubbles.

2. Assay Procedure

This product is compatible with various types of automated analyzer. An example of the assay procedure is indicated below.



※Absorbance I and II: Absorbance at 700 nm

Calibration material: Zonisamide Calibrator (Manufacture's assigned value)

Assessment of Assay Results

1. Reference standard range

The therapeutic range of the blood concentration of zonisamide depends on the severity of epilepsy and varies between individual patients. It has been reported that the therapeutic range is 10–30 μg/mL and the standard value may be approximately 20 μg/mL. However, it has also been reported that the range is 10–40 μg/mL.[2)]

It is recommended that the blood concentration of zonisamide should be measured in a sufficient number of samples for statistical analysis and that its therapeutic range should be determined by each medical institution.

2. Precautions for Assessment

There may be reactions or interfering reactions with non-target substances. If assay results appear to be unreliable, repeat the measurement (if necessary, after dilution) or try another analytical methods.

Performance

1. Sensitivity

(1) The change of absorbance per minute with the standard solution (0.0 μg/mL) is ≥ 50 mAbs. /min.

(2) The difference between the change of absorbance per minute with the standard solution (0.0 μg/mL) and that with another standard solution (80.0 μg/mL) is ≥ 35 mAbs. /min.

2. Accuracy: 80–120 % of the expected assay value

3. Within-run Reproducibility:

Coefficient of variation ≤ 15 %

(Test methods used for 1.–3. are in-house methods.)

4. Measurement Range[3)] (On Hitachi 7180 automated analyzer)

3.0–80.0 μg /mL

5. Correlation[3)]

1) Serum N=66 r=0.997 y=1.06x+0.22
Control method: Approved in vitro diagnostic (latex agglutination method)
2) Plasma N=61 r=0.990 y=1.04x+0.66
Control method: Approved in vitro diagnostic (enzyme immunoassay)

6. Standard Material

Zonisamide (in-house standard material)

Precautions for Use or Handling

1. Precautions for Handling (to Ensure Safety)

1) All samples used in the test should be handled as a material possibly infected with HIV, HBV, HCV, or other viruses. To prevent infection, use disposable gloves and avoid mouth pipetting during the test.
2) Sodium azide is added as an antiseptic agent in the ZNS Antibody Solution 1 and ZNS Latex Reagent 2. Therefore, if the reagent comes in accidentally contact with eyes, mouth or skin, rinse immediately with ample water as first aid, and consult the doctor if required.

2. Precautions for use

1) This product should be stored as directed, without freezing. Freezing can deteriorate the reagents, which can produce inaccurate results. Therefore, avoid using the reagents which have been previously frozen.
2) Do not use expired reagents. Use of such reagents cannot guarantee the reliability of measurement values.
3) Do not replenish the reagents.
4) After completion of measurement, this product should be tightly stoppered and stored in a refrigerator.
5) Do not mix materials from different kit lot numbers.
6) Do not perform the assay under direct sunlight

3. Precautions for Disposal

1) Before disposal, used samples and their containers must be immersed in sodium hypochlorite solution at a concentration of greater than 0.1% for longer than 1 hour or autoclaved at 121ºC for 20 minutes.
2) To prevent infections from spilled samples or solutions containing samples, wipe the spilled area thoroughly with disinfectants such as sodium hypochlorite solution at a concentration of greater than 0.1%.
3) The reagents and treated samples should be discarded as medical waste or industrial waste according to the waste disposal regulations.
4) Sodium azide has been added as an antiseptic agent in the ZNS Antibody Solution 1 and ZNS Latex Reagent 2. It can react with lead or copper pipes to produce the highly explosive metal azide. Therefore, the reagent should be flushed with large amounts of water during disposal.

4. Other precautions

Do not use the containers for other purposes.

Storage and Shelf Life ＊

1. Storage temperature: 2–8°C
2. Shelf life: 15 months from the date of manufacture (The expiration date is printed on the outer package.)

Packaging

Name		Package
Nanopia TDM Zonisamide	ZNS Antibody Solution 1	1 × 20 mL
	ZNS Latex Reagent 2	1 × 8 mL

References ＊＊

1) Package Insert of Excegran Tablets 100mg and Excegran Powder 20%.
2) The Japanese Society of Therapeutic Drug Monitoring. [Guideline for therapeutic drug monitoring (TDM) for antiepileptic drug 2018]. Tokyo: Kanehara Shuppan; 2018. pp. 16-17.
3) In house data, SEKISUI MEDICAL CO., LTD.

Contact

SEKISUI MEDICAL CO., LTD.
international@sekisui.com

Manufacturer

SEKISUI MEDICAL CO., LTD.
1-3, Nihonbashi 2-chome, Chuo-ku, Tokyo, Japan