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

In Vitro Diagnostics
Marketing Approval No. 22500AMX01789000

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This package insert must be read carefully prior to use.

Topiramate assay kit
(Classification No.: 83023000)

Nanopia TDM Topiramate

General Precautions

1. Whether measurement with this product is necessary should be determined in consideration of the patient's symptoms and response to treatment.
2. This product is for in vitro diagnostic use, and must not be used for any other purposes.
3. Clinicians should make a comprehensive clinical decision based on assay results in conjunction with clinical symptoms and other examination results.
4. 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. 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.
5. 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.
6. 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.
7. 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.
8. Perform a quality control test prior to assay to ensure accuracy.

Description (Kit Components)

Component: Ingredients
TPM Antibody Solution 1:
Anti-topiramate sheep polyclonal antibody
TPM Latex Regent 2:
Topiramate-coated latex

Intended Use

Measurement of topiramate in serum or plasma

Assay Principle

1. Assay Principle

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

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

Unreacted anti-topiramate antibody + Topiramate-coated latex
⟶ 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 (EDTA plasma) may be used.
2) Storage of samples
(1) After separation of serum (plasma), samples may be stored for up to 7 days in a refrigerator. If samples cannot be measured within 7 days of serum (plasma) separation, store them at −20°C and measure them within 21 days. Stored samples should be brought to room temperature (15–30°C) before use.
(2) Samples may be frozen and thawed up to twice.
3) Sampling should be performed after removing insoluble matter from the sample. Very cloudy specimens should be centrifuged before assay.

2. Interfering substances

1) Assay results are not affected by free bilirubin (up to 20.8 mg/dL), conjugated bilirubin (up to 20.0 mg/dL), hemoglobin (up to 484 mg/dL), formazin turbidity (up to 1430 FTU), or rheumatoid factors (up to 500 IU/mL).
2) 9-Hydroxytopiramate is a metabolite of topiramate that can affect assay values. However, the metabolite has no influence on assay values obtained with this product, because it is usually detected in the urine and its serum or plasma concentration is low.[1),2)]

Metabolite	Concentration tested (μg/mL)	Cross-reactivity ※ (%)
9-Hydroxytopiramate	4.00	19.75
	8.00	22.63
	32.00	15.56

3) If each concomitant drug is at the concentration shown in the table below when the topiramate concentration is approximately 5 μg/mL, cross-reactivity is as follows.

Drug name	Concentra-tion tested (μg/mL)	Cross-reactivity ※ (%)
Acetaminophen	31	0.74
Acetazolamide	40	0.33
Alprazolam	2.00	0.50
Amitriptyline	1	–2.00
Acetylsalicylic acid	598	0.02
Atenolol	10.33	1.84
Caffeine	60	–0.05
Carbamazepine	30	0.93
Clonazepam	0.18	–11.11
Clorazepate	2.00	4.50
Diazepam	5.1	0.00
Dichlorphenamide	32.00	0.38
Ethosuximide	252	0.15
Famotidine	0.97	9.28
Flurazepam	17.50	0.63
Furosemide	3.70	2.97
Gabapentin	93	0.22
Hydrochlorothiazide	6.00	2.17
Ibuprofen	500	0.09
Lamotrigine	45	0.22
Levetiracetam	124	0.11
Metoprolol	5.25	0.76
Nadolol	121	0.23
Naproxen	509	0.02
Nortriptyline	1	2.00
Phenobarbital	40	0.23
Phenytoin	20	5.50
Primidone	40	0.58
Salicylic acid	598	0.03
Tolbutamide	642	0.02
Valproic acid	100.67	–0.06
Verapamil	2	4.50
Zonisamide	122	0.09

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

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

3. Others

1) Always use Topiramate Calibrator for Nanopia for calibration.
2) Precautions for assay range
   If the concentration in the sample exceeds the measurement range, dilute the sample with the Topiramate Calibrator A for Nanopia (0.0 μg /mL) and perform re-measurement.

Dosage/Administration (Assay Procedure) *

1. Preparation of reagents

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

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

Before using this product, gently invert the TPM 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.

Sample 3 μL + Reagent (1) 180 μL → (37°C, Approx. 5 min) → Reagent (2) 120 μL → (37°C, Approx. 1 min) → Measurement (Absorbance I※)

→ (37°C, Approx. 2 min) → Measurement (Absorbance II※)

→ Calculation of concentration

※Absorbance I and II: Absorbance at 700 nm

Calibration material: Topiramate Calibrator for Nanopia (Manufacture's assigned value)

Assessment of Assay Results **

1. Reference standard range

The standard of effective blood concentration of topiramate is considered as 5–20 μg/mL, but it has been reported that it is also effective lower than 5 μg/mL[4]. Assay results should be assessed while taking into consideration the patient's clinical findings and other laboratory data.

It is recommended that the blood concentration of topiramate should be measured in a sufficient number of samples for statistical analysis and that its clinical effective concentration 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.

Clinical Significance **

Topiramate is an antiepileptic drug with a sulfamate structure in a fructopyranose skeleton. It is used in combination with other antiepileptic drugs for the treatment of partial seizures (including secondary generalized seizures) in patients for whom the other antiepileptic drugs are not sufficiently effective.

The main adverse reactions to topiramate are reported to be somnolence, weight loss, dizziness, anorexia, and bulimia syndrome. Serious adverse reactions include secondary angle closure glaucoma, acute myopia due to secondary angle closure glaucoma, renal and urinary calculus, metabolic acidosis, hypohidrosis, and hyperthermia secondary to hypohidrosis.

It was reported overseas that the incidence of adverse events in the early period after starting topiramate therapy could be reduced by decreasing the initial dosage and by slower dose escalation (e.g., the initial dosage was set at 50 mg/day and then was increased by 50 mg each every week). Therefore, before starting treatment with topiramate it is necessary to consider whether the initial dose should be 50 mg/day depending on the condition of the patient and whether dose escalation should be modified from 100 mg/day

to 50 mg/day.[3] It is recommended to measure the blood concentration of topiramate and adjust the dosage carefully in patients with renal dysfunction (Creatinine clearance < 70 mL/min), in whom the blood concentration of topiramate is considered to fluctuate, and the patients used in conjunction with CYP3A4 revulsive or hydrochlorothiazide.[4] Monitoring the blood concentration is considered to be especially important when adverse reactions occur, seizures cannot be controlled, compliance needs to be confirmed, pregnancy is expected, and during pregnancy.[5]

Performance

1. Sensitivity

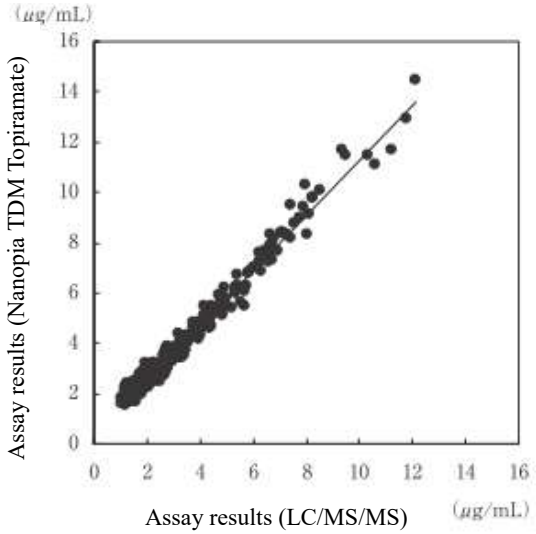
1) Absorbance of standard solution (0.0 μg/mL) is ≥ 1900 (Abs. × 10000).
2) The difference of absorbance between standard solution (0.0 μg/mL) and another standard solution (2.0 μg/mL) is ≥ 500 (Abs. × 10000).

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[6]: (On Hitachi 7180 automated analyzer)
1.5–32.0 μg /mL

5. Correlation[6]
Serum
N = 199, r = 0.989, y (obtained with Nanopia TDM Topiramate) = 1.09x (obtained by the control method) + 0.38
Control method: LC/MS/MS



6. Standard Material
Topiramate (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 TPM Antibody Solution 1 and TPM 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 this product. 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: 18 months from the date of manufacture
(The expiration date is printed on the outer package.)

Packaging

Name		Package
Nanopia TDM Topiramate	TPM Antibody Solution 1	1 × 18 mL
	TPM Latex Reagent 2	1 × 12 mL

References **

1) Britzi M., Soback S., et al. : Ther Drug Monit. 25(3),314-22(2003)
2) Britzi M., Perucca E., et al. : Epilepsia. 46(3), 378-84(2005)
3) Topina tablets 25mg, 50mg, 100mg package insert
4) Japanese Society of Therapeutic Drug Monitoring. [Guideline for therapeutic drug monitoring (TDM) for antiepileptic drug 2018]. Tokyo: Kanehara

Shuppan; 2018. pp. 28-29, pp. 102-107.
5) Tsuji S. and Ukawa Y. (eds.): Epilepsy Textbook New Version (1st edition), Tokyo, Nakayama Shoten, 2012, pp. 204-205.
6) In house data, SEKISUI MEDICAL CO., LTD.

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