In Vitro Diagnostics
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This package insert must be read carefully prior to use.

Carbamazepine assay kit
(Classification No.: 30395000)

Nanopia TDM Carbamazepine

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. 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.
4. 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.
5. 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.
6. Perform a quality control test prior to assay to ensure accuracy.

Description (Kit Components)

Component: Ingredients
CBZ Antibody Solution 1:
Anti-carbamazepine mouse monoclonal antibody
CBZ Latex Reagent 2:
Carbamazepine-coated latex

Intended Use **

Measurement of carbamazepine in serum or plasma

Carbamazepine (5H-dibenz [b, f] azepine-5-carboxamide) is an antiepileptic drug widely used for the treatment of trigeminal neuralgia,[1] all types of partial seizures (simple partial seizures, complicated partial seizures, and secondary generalized seizures), and generalized tonic-clonic seizures. Approximately 70% of carbamazepine in the bloodstream is bound to plasma protein. Carbamazepine is metabolized to active carbamazepine-10,11-epoxide and then to carbamazepine-10,11-dihydroxide. These metabolites are excreted in the urine. The plasma level of carbamazepine-10,11-epoxide is 15–48% of that of the parent compound,[2)] and its biological half-life (5–8 hours) is shorter than that of carbamazepine (8–60 hours). Both metabolites are excreted in the urine, either unchanged or as glucuronic acid conjugates.
Toxicities of carbamazepine can be dose-dependent or dose-independent.[1)] Nystagmus, blood dyscrasia, and gastrointestinal disorders such as nausea, vomiting, and anorexia are dose-independent. Symptoms related to the central nervous system such as dizziness and diplopia are dose-dependent.
It has been reported that there is considerable individual variation in the absorption, metabolism, and excretion of carbamazepine, and the blood level of its metabolite carbamazepine-10, 11-epoxide increases significantly when carbamazepine is administered with other antiepileptic drugs.
Monitoring the blood level of carbamazepine is useful for avoiding toxicity and for obtaining optimal efficacy by dose adjustment.[1),3)]

Assay Principle

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

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

Unreacted anti-carbamazepine antibody + Carbamazepine-coated latex
⟶ Aggregation by antigen-antibody reaction

2. Features
1) Because a highly specific monoclonal antibody is used, this product shows excellent sensitivity and accuracy.
2) Liquid reagents, ready-to-use.
3) Applicable to various automated analyzers.

Procedural Precautions **

1. Properties of Samples and Sampling Methods
1) Samples
Serum and plasma (heparin plasma, EDTA plasma and citrated plasma) may be used.
2) Storage of samples
If serum or plasma samples cannot be measured on the day of separation, store them as follows.
Avoid repetition of freezing and thawing.
2–8°C: for tests within 7 days
≤ -20°C: for tests within 3 months
Bring samples to room temperature (15–30°C) before use.
3) Caution must be exercised, because a separating agent, etc. in the blood collection tube may affect assay values.[4)]
4) Sampling should be performed after removing insoluble matter from the sample. Highly turbid specimens should be centrifuged before assay.

2. Interfering substances
1) Assay results are not affected by free bilirubin

(up to 20 mg/dL), conjugated bilirubin (up to 20 mg/dL), hemoglobin (up to 500 mg/dL), ascorbic acid (up to 50 mg/dL), formazin turbidity (up to 2500 FTU), or rheumatoid factors (up to 450 IU/mL).

2) Because mouse antibody is used in the assay, artifactual elevation of results may occur if the sample contains human anti-mouse antibody. In this case, perform re-measurement by another method.

3) Cross-reactivity
The following table summarizes drugs related to carbamazepine and cross-reactivity between carbamazepine and other drugs.

Compound	Concentration tested (μg/mL)	Cross-reactivity (%)
Amitriptyline	100	6
Amobarbital	1000	0.05
Carbamazepine-10,11-epoxide	25	31.6
Clorazepate	2000	0.15
Chlordiazepoxide	2000	0.07
Diazepam	250	0.2
Ethosuximide	1000	0
Ethotoin	1000	0.06
Glutethimide	1000	0
p-Hydroxyphenobarbital	2000	0.01
5-(p-Hydroxyphenyl)-henylhydantoin	1000	0.07
Imipramine	200	1.5
Mephenytoin	3000	0.03
Methsucimide	5000	0.02
Nortriptyline	50	24.2
Phenothyazine	200	0.2
2-Phenyl-2-ethylmalonamide	1000	0.02
Phenytoin	400	0
Primidone	1000	0.01
Probenecid	500	0
Promethazine	1500	0.02
Secobarbital	2000	0.02
Valproic acid	7000	0.01

3. Others

1) Always use TDM Calibrator for Nanopia for calibration.

2) Precautions for assay range
If the concentration of a target substance in the sample exceeds the measurement range, dilute the sample with a separately sold diluent (manufactured by SEKISUI MEDICAL CO., LTD.), and perform re-measurement.

Dosage/Administration (Assay Procedure) *

1. Preparation of reagents

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

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

Before using this product, gently invert the CBZ Latex Solution 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 2 μL + Reagent (1) 220 μL → 37°C 270 sec → Reagent (2) 60 μL → 37°C 70 sec → Measurement (Absorbance I※) → 37°C 247 sec → Measurement (Absorbance II※) → Calculation of concentration

※Absorbance I and II: Absorbance at 600 nm

Calibration material: TDM Calibrator for Nanopia (manufacture's assigned value)

Assessment of Assay Results * *

1. Reference standard range

The effective therapeutic concentration of carbamazepine has been reported to be 4−12 μg/mL[2), 3)], but when other antiepileptic drugs such as phenobarbital or phenytoin are used in conjunction, the target blood concentration is set as 4−8 μg/mL. It has been reported that sedation occurs when the single dose exceeds 10 μg/mL, but adverse reactions may also occur within the therapeutic range.[5)] Therefore, interpretation of assay results should also be based on the patient's clinical findings and other examination results.

2. 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 of the standard solution (0 μg/mL) per minute is 0.090–0.230.

2) The ratio between the change of absorbance per minute with the standard solution (0 μg/mL) and that with another standard solution (2 μg/mL) is 50–85%.

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

3. Within-run Reproducibility:

Coefficient of variation ≤ 10 %

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

4. Measurement Range[6)]: (On Hitachi 7170S automated analyzer)

0.4–20 μg/mL

5. Correlation[6)]

1) Serum N=66 r=0.992 y=0.93x+0.25
Control method: Approved in vitro diagnostic (enzyme immunoassay)

2) Plasma N=76 r=0.991 y=0.97x–0.29
Control method: Approved in vitro diagnostic (enzyme immunoassay)

6. Standard Material

Carbamazepine (U.S. Pharmacopoeia)

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 CBZ Antibody Solution 1 and CBZ 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) Do not mix materials from different kit lot numbers.
5) 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) The reagents should be disposed of in accordance with the Water Pollution Control act or related regulations.
5) Sodium azide has been added as an antiseptic agent in the CBZ Antibody Solution 1 and CBZ 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: 14 months from the date of manufacture
(The expiration date is printed on the outer package.)

Packaging

Name		Package
Nanopia TDM Carbamazepine	CBZ Antibody Solution 1	1 × 44 mL
	CBZ Latex Reagent 2	1 × 12 mL

Constituent reagents are available in other configurations. For further details please contact SEKISUI MEDICAL CO., LTD.

References ＊＊

1) Morselli P. C.: Carbamazepine: absorption distribution and excretion, in complex partial seizures and their treatment, Advances in Neurology. Vol. Ⅱ, edited by Penry J.K., Daly D. D. New York, Raven Press, pp 279−393, 1975.
2) Warner A, Privitera M and Bates D.: Standards of laboratory practice: antiepileptic drug monitoring. Clin Chem. 44（ 5）, 1085−1095（1998）
3) Mackichan J. J., Kutt H.: Carbamazepine: Therapeutic use and serum concentration monitoring.: In Taylor, W.J., Finn, A.L.（eds.）: Individualizing Drug Therapy: Practical Applications of Drug Monitoring, Gross, Townsend, Frank Inc., New York, 2: 1−25, 1981.
4) Sawada T. et al.: J Med Pharm Sci, 51(1), 131−141, 2004.
5) The Japanese Society of Therapeutic Drug Monitoring. [Guideline for therapeutic drug monitoring (TDM) for antiepileptic drug 2018]. Tokyo: Kanehara Shuppan; 2018. pp. 12-13, pp. 49-56.
6) In house data, SEKISUI MEDICAL CO., LTD.

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Manufacturer ＊

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