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

In Vitro Diagnostics
Marketing Notification No. 13A2X00197218106

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This package insert must be read carefully prior to use.

Theophylline assay kit
(Classification No.: 30417000)

Nanopia TDM Theophylline

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
THE Antibody Solution 1:
Anti-theophylline mouse monoclonal antibody
THE Latex Reagent 2:
Theophylline-coated latex

Intended Use

Measurement of theophylline in serum or plasma

Theophylline (1,3-dimethylxanthine) is a methyl xanthine derivative that is widely used for the treatment of bronchial asthma, asthmatic bronchitis, and neonatal apnea. The main action of theophylline is relaxation of bronchial smooth muscle. It also activates the central nervous system and the respiratory center in the medulla oblongata, reduces peripheral vascular resistance, stimulates the heart, and causes diuresis.
The clinical effects of theophylline are closely correlated with its blood level. Symptoms of theophylline toxicity usually occur at a concentration > 20 μL/mL in adults.[2] However, mild symptoms of toxicity may develop at a concentration > 15 μg/mL, depending on the person. Mild symptoms of toxicity include anorexia, nausea, vomiting, headache, and nervousness. Severe symptoms of toxicity include an increased heart rate, arrhythmia, cerebral seizure, respiratory arrest, and cardiac arrest. These symptoms occur at concentrations > 40 μg/mL, but also at a lower concentration in some patients.
Clearance of theophylline shows individual variation. Because severe symptoms of toxicity may occur in patients who have not previously shown even mild symptoms of toxicity, monitoring of the blood level of theophylline is important during treatment. The rate of clearance of theophylline from the blood may also vary due to other factors. For example, clearance from the blood is delayed in obese patients, patients with liver disorders, and patients on a high-carbohydrate/low-protein diet. It is known that clearance of theophylline from the blood is very slow in premature infants,[1] but is rapid in smokers.[2]
Therefore, monitoring the blood level of theophylline along with consideration of other clinical data is useful for adjusting the dosage of this drug so that the optimum clinical response can be obtained without symptoms of toxicity.

Assay Principle

1. Assay Principle

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

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

Unreacted anti-theophylline antibody + Theophylline-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 U/L).
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 theophylline and cross-reactivity between theophylline and other drugs.

Substance	Concentration tested (μg/mL)	Cross-reactivity (%)
1,3,7-Trimethyluric acid	1000	0.02
1,3-Dimethyluric acid	200	2.29
1,7-Dimethyluric acid	1000	0.09
1,7-Dimethylxanthine	1000	1.09
1-Methyluric acid	1000	0.06
1-Methylxanthine	1000	0.49
3,7-Dimethyluric acid	1000	0
3-Methyluric acid	1000	0.09
3-Methylxanthine	1430	0.65
7-(β-hydroxyethyl) theophylline	1430	0.79
7-(2-Hydroxypropyl) theophylline	1818	0.58
7-Methylxanthine	1000	0.05
8-Chlorotheophylline	360	1.34
Allopurinol	1000	0.01
Ampicillin	2000	0.04
Caffeine	645	2.60
Clindamycin	2000	0.05
Diprophylline	2000	0.46
Heparin	2000	0
Hypoxanthine	1000	0
Phenobarbital	2000	0.03
Prednisone	2000	0
Pseudoephedrine	2000	0.01
Terbutaline	2000	0
Theobromine	800	1.85
Urea	2000	0
Uric acid	1000	0.03
Xanthine	1000	0.03
Xanthosine	1000	0.03

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): THE Antibody Solution 1 is ready to use.
Reagent (2): THE Latex Reagent 2 is ready to use.

Before using this product, gently invert the THE 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 2 μL + Reagent (1) 180 μL → 37°C 270 sec → Reagent (2) 30 μL → 37°C 70 sec → Measurement (Absorbance I※)
→ 37°C 247 sec → Measurement (Absorbance II※)
→ Calculation of concentration

※Absorbance I and II: Absorbance at 700 nm
Calibration material: TDM Calibrator for Nanopia (manufacture's assigned value)

Assessment of Assay Results * *

1. Reference standard range

The effective concentration of theophylline is 5–15 μg/mL[5] in adults and 5–10 μg/mL[6] in infants. However, the effective concentration range may overlap with the toxic concentration range. Therefore, interpretation of assay results should also be based on the patient's clinical findings and other examination results.
It is recommended that the blood concentration of theophylline 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. 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 0.145–0.300.
2) The ratio between the change of absorbance per minute with the standard solution (0 μg/mL) and that with another standard solution (2.5 μg/mL) is 45–85 %.

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[7]: (On Hitachi 7170S automated analyzer)

0.2–40 μg/mL

5. **Correlation**[7)]
   1) Serum N=60 r=0.993 y=1.05x+0.51
   Control method: Approved in vitro diagnostic (enzyme immunoassay)
   2) Plasma N=77 r=0.999 y=1.06x–0.45
   Control method: Approved in vitro diagnostic (enzyme immunoassay)
6. **Standard Material**
   Theophylline (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 THE Antibody Solution 1 and THE 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 THE Antibody Solution 1 and THE 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: 16 months from the date of manufacture (The expiration date is printed on the outer package.)

Packaging

Name		Package
Nanopia TDM Theophylline	THE Antibody Solution 1	1 × 36 mL
	THE Latex Reagent 2	1 × 6 mL

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

References ＊

1) Ogilvie R. I. : Clinical pharmacokinetics of theophylline. Clinical Pharmacokinetics, 3 : 267−293, 1978.
2) Hendeles L., Weinberger M. M. : Theophylline 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, vol. 1, 31−66, 1981.
3) Aranda J. V., et al. : Pharmacokinetic aspects of theophylline in premature newborns, N. Engl. J. Med., 295 : 413−416, 1976.1)
4) Sawada T. et al.: J Med Pharm Sci, 51(1), 131−141, 2004.
5) Japanese Society of Allergology: Asthma prevention and management guidelines 2015, 116–136, Kyowa Planning, 2015.
6) Ministry of Health, Labour and Welfare, Pharmaceutical and Food Safety Bureau, Safety Division: Guidelines for the appropriate use of drugs for infantile bronchial asthma, 13, 2006.
7) In house data, SEKISUI MEDICAL CO., LTD.

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