Test Thrombin Reagent

TEST THROMBIN

Revision bar indicates update to previous version.

CE 0197

Intended Use

TEST THROMBIN REAGENT is an in vitro diagnostic reagent for the quantitative determination of thrombin time as aid to diagnosis of fibrinogen related hemostasis disorders in patients with signs or at risk of bleeding disorders in human sodium citrated plasma by means of automated, semi-automated and/or manual coagulometric methods.

For thrombin time testing no international reference preparation or method is available.

Summary and Explanation

Thrombin time is a coagulation screening assay commonly performed to investigate bleeding disorders. Thrombin time reflects the kinetic of fibrin generation and polymerization and is correlated to Fibrinogen concentration and function; congenital and acquired defects in Fibrinogen and fibrin polymerization (including elevated levels of fibrin(ogen) degradation products) result in prolongation of thrombin time[1–3].

Furthermore, a dose dependent prolongation of thrombin time is seen in response to unfractionated heparin and direct thrombin inhibitors. Thrombin time can be used to detect the presence of heparin, of parenteral direct thrombin inhibitors, such as argatroban or bivalirudin, and of the direct oral thrombin inhibitor dabigatran[4–6].

Determination of thrombin time can aid in

- screening for disorders of fibrin formation (e.g. dysfibrinogenemia or presence of fibrin(ogen) split products in response to fibrinolytic therapy) or in suspected cases of severe fibrinogen deficiency states[1–3]
- Evaluation of parenteral direct thrombin inhibitors such as argatroban[5]
- Exclusion of even low levels of dabigatran being present[6]

In combination with the heparin insensitive batroxobin time, thrombin time can be used to identify the presence of heparin in the sample, either due to heparin therapy, or due to heparin contamination during sampling.

Principles of the Procedure

Thrombin converts Fibrinogen which is contained in the plasma sample into fibrin, where upon a clot forms. The time to clot formation is measured.

Reagents

Note: TEST THROMBIN can be used manually or on automated coagulation analyzers. Sysmex provides Reference Guides (Application Sheets) for several coagulation analyzers. The Reference Guides (Application Sheets) contain analyzer/assay specific handling and performance information which may differ from that provided in these Instructions for Use. In this case, the information contained in the Reference Guides (Application Sheets) supersedes the information in these Instructions for Use. Please also consult the instruction manual of the instrument manufacturer!

Reagent	Description	Storage	Stability
Test Thrombin Reagent TEST THROMBIN			
REAGENT	Lyophilized reagent containing: • Thrombin, bovine (reconstituted: 1.5 IU/mL) • BSA	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	37 °C: reconstituted, 8 hours; 15–25 °C: reconstituted, 10 hours; 2–8 °C: reconstituted, 7 days; ≤ –20 °C: reconstituted, 4 weeks
REAGENT DILUENT	Ready to use liquid containing: • HEPES (25 mmol/L) • reaction mass of 5-chloro-2-methyl-2H-isothiazol-3-one / 2-methyl-2H-isothiazol-3-one (3:1) pH 7.4	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	2–25 °C: once opened, 12 weeks

Reconstituted TEST THROMBIN REAGENT can be frozen once in the original vial.

On-board stability
Information regarding on-board stability is specified in the Reference Guides (Application Sheets) for the different coagulation analyzers.

Warnings and Precautions

For *in-vitro* diagnostic use only.

For laboratory professional use.

According to EU regulation 2017/746, any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the EU Member State through your local distribution representative in which the user and/or patient is established.

Safety data sheets (MSDS/SDS) available upon request.

TEST THROMBIN REAGENT DILUENT
Hazardous ingredient: reaction mass of 5-chloro-2-methyl-2H-isothiazol-3-one / 2-methyl-2H-isothiazol-3-one (3:1).
May produce an allergic reaction.

Caution
TEST THROMBIN REAGENT
This device contains material of animal origin and should be handled as a potential carrier and transmitter of disease.

Dispose of hazardous or biologically contaminated materials according to the practices of your institution. Discard all materials in a safe and acceptable manner and in compliance with all government requirements.

Summary of Safety and Performance (SSP) is available in the European database on medical devices (see Eudamed public website: https://ec.europa.eu/tools/eudamed). In case Eudamed is not available, SSP can be delivered by the manufacturer on request.

Preparing Reagents

To reconstitute a vial of TEST THROMBIN REAGENT dissolve in the labelled quantity of TEST THROMBIN REAGENT DILUENT.

Manual test methods: Prior to the assay warm the reagent solution to 37 °C in the original vial or in a plastic tube.

The manufacturer recommended automated coagulation analyzers prewarm the reagent solution automatically.

Mix carefully once more before using.

Specimen Collection and Handling

Collecting the Specimen

To obtain the plasma, carefully mix 1 part sodium citrate solution 0.11 mol/L (3.2 %) with 9 parts venous blood, avoiding the formation of foam. Centrifuge immediately at no less than 1 500 × g for at least 15 minutes, remove the supernatant plasma and keep at 15 to 25 °C until required in the test. Please refer to CLSI document H21-A5 for further details[7].

Storing the Specimen

Stability of the samples at 15 to 25 °C: 4 hours.

Measure heparin-containing samples within 2 hours.

Procedure

Materials Provided

REF	Contents	
OWHM13	Test Thrombin Reagent TEST THROMBIN	
	Test Thrombin Reagent TEST THROMBIN REAGENT	10 × → 5 mL
	Buffer Solution TEST THROMBIN REAGENT DILUENT	1 × 50 mL

Materials Required but not Provided

Item	Description
REF ORKE41	CONTROL N, Control Plasma N, or
REF 291070	Dade® Ci-Trol® 1, or
REF B4244-10	Ci-Trol CONTROL 1, Dade® Ci-Trol® Coagulation Control Level 1, as control for the normal range
Coagulation analyzers[a], such as:	• Automated Blood Coagulation Analyzer CA-600 series (CA-600 series) • AUTOMATED BLOOD COAGULATION ANALYZER CS-2500 (CS-2500 System) • AUTOMATED BLOOD COAGULATION ANALYZER CS-5100 (CS-5100 System)

[a] Availability of analyzers may vary by country.

Please note that the applications on other analyzers can be validated by the instrument manufacturer in accordance with the requirements of the REGULATION (EU) 2017/746 under their responsibility as long as the intended purpose and performance are not modified.

Manual Testing

Pipette into a test tube pre-warmed to 37 °C:	
Citrated plasma	100 µL
	Incubate at 37 °C for 60 seconds.
TEST THROMBIN (pre-warmed to 37 °C)	200 µL
	On adding the reagent start the stopwatch or timer on the coagulometer and determine the coagulation time.

Internal Quality Control

Normal range: Dade® Ci-Trol® 1,
Ci-Trol CONTROL 1
or,
CONTROL N

A quality control has to be measured at start of the test run, upon reagent vial changes and at least every 8 hours during each day of testing. The control should be processed just like the samples. Each laboratory should determine its own quality control range, either by means of the target values and ranges provided by the manufacturer of the controls or by means of its own range established in the laboratory. If the measured control value lies outside the range previously established, then the reagent and the coagulation analyzer should be examined. Do not release patient results until the cause of deviation has been identified and corrected.

Results

The result is given in seconds.

Limitations

The manufacturer has validated use of these reagents on various analyzers to optimize product performance and meet product specifications. Please note that the applications on other analyzers can be validated by the instrument manufacturer in accordance with the requirements of the REGULATION (EU) 2017/746 under their responsibility as long as the intended purpose and performance are not modified. User defined modifications are not supported by the manufacturer as they may affect performance of the system and assay results. It is the responsibility of the user to validate modifications to these instructions or use of the reagents on analyzers other than those included in Application Sheets or these Instructions for Use.

Results of this test should always be interpreted in conjunction with the patient's medical history, clinical presentation and other findings.

Carry-over of traces of thrombin can interfere with subsequent coagulation analyses.

If possible, use only single-use plastic material.

Expected Values

14 to 21 seconds.

Systematic deviations from this range may be due to the instrument used. If necessary, the laboratory will have to establish its own reference interval.

Performance Characteristics

Measuring Range

The measuring range depends on the individual application of the assay due to instrument related conditions. Application specific performance data is listed in the respective Reference Guides of the instruments.

Precision

In an individual study for normal plasmas using the manual method the coefficient of variation within series is 2.0 % (n = 20) and from day to day 3.0 % (n = 10).

Other system specific results are given in the respective Reference Guides (Application Sheets).

The reproducibility was assessed by the manufacturer for Thrombin Time with TEST THROMBIN REAGENT based on publicly available proficiency testing information in 2020. The overall reproducibility median CV% was found to be <7 % including lot, instrument, laboratory and operator variability factors.

Method Comparison

A comparison test of TEST THROMBIN REAGENT with another commercial thrombin time reagent using normal and heparin containing plasmas yielded a correlation coefficient of 0.803.

Technical Assistance

For customer support, contact your local technical support provider or distributor.

Current Version of Application Sheets

TEST THROMBIN can be used in combination with various automated coagulation analyzers. Sysmex provides Reference Guides/Application Sheets for the coagulation analyzers listed in section "Materials Required but not Provided", page 3 under the dedicated link below:

sysmex-ifu.com/ag

As the manufacturer continuously monitors the product performance and safety, the users are required to ensure that they work with the correct revision of the instructions for the product lots in use. Please periodically review the availability of new electronic labeling revisions to ensure safe use of the product.

The IFU version number is visible on each product box label. Sysmex ensures that all products lots bearing the same IFU version number are compatible with the electronic labeling provided via sysmex-ifu.com.

References

1. Hayward CP, Moffat KA. Laboratory testing for bleeding disorders: strategic uses of high and low-yield tests. Int J Lab Hematol 2013; 35:322-33.
2. Verhovsek M, Moffat KA, Hayward CP. Laboratory testing for fibrinogen abnormalities. Am J Hematol. 2008; 83:928-31.
3. Hill M, Dolan G. Diagnosis, clinical features and molecular assessment of the dysfibrinogenaemias. Haemophilia. 2008; 14:889-97.
4. Peters GL, Erwin PB, Pitlick MK, et al. Utilization of coagulation assays in clinical therapeutics. Pharmacotherapy 2013; 33:1214-22.
5. Beiderlinden M, Werner P, Bahlmann A, et al. Monitoring of argatroban and lepirudin anticoagulation in critically ill patients by conventional laboratory parameters and rotational thromboelastometry - a prospectively controlled randomized double-blind clinical trial. BMC Anesthesiol. 2018; 18:18.
6. Conway SE, Hwang AY, Ponte CD, et al. Laboratory and Clinical Monitoring of Direct Acting Oral Anticoagulants: What Clinicians Need to Know. Pharmacotherapy. 2017; 37:236-248 doi: 10.1002/phar.1884.
7. CLSI. Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays and Molecular Hemostasis Assays. Approved Guideline – Fifth Edition. CLSI document **H21-A5** [ISBN 1-56238-657-3]. CLSI, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898 USA, 2008.

Definition of Symbols

The following symbols may appear on the product labeling:

	Do not reuse		Use By
LOT	Batch Code	REF	Catalogue Number
	Caution		Manufacturer
EC REP	Authorized representative in the European Community	CH REP	Authorized representative in Switzerland
	Contains sufficient for <n> tests		Biological Risks
IVD	*In Vitro* Diagnostic Medical Device		Temperature Limitation
	Consult instruction for Use		Non-sterile
CE	CE marking of conformity	CE 0197	CE marking of conformity with notified body ID number. Notified body ID number can vary.
CONTENTS	Contents		Reconstitution volume
LEVEL	Level		Keep away from sunlight and heat
WARNING	Warning	DANGER	Danger
RxOnly	Prescription device (US only)	UDI	Device Identification (UDI) barcode
REACH xx/xx/xx	REACH Authorization Number		

Legal Information

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