Thromboclotin®

Revision bar indicates update to previous version.

CE 0197

Intended Use

Thromboclotin® 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 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 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 monitor therapy with parenteral direct thrombin inhibitors such as argatroban or bivalirudin, and sensitively reacts to even low levels 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]
- monitoring parenteral direct thrombin inhibitors[4]
- 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, whereupon a clot forms. The time taken for the fibrin clot to form is measured.

Reagents

Note: Thromboclotin® can be used 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
Thromboclotin®	Lyophilized reagent containing: • Thrombin, bovine (reconstituted: 2.5 IU/mL) • Stabilizer	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	2–8 °C: reconstituted, 7 days; 15–25 °C: reconstituted, 24 hours; ≤ –20 °C[a]: reconstituted, ≤1 month Do not refreeze!

[a] if frozen immediately after reconstitution

Do not freeze again if it was thawed once before.

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.

Danger! Thromboclotin®
Hazardous ingredient: Thrombin, bovine (1.43 % [w/w]).
H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled.
P261: Avoid breathing dust/fume/gas/mist/vapours/spray. **P304 + P340**: IF INHALED: Remove person to fresh air and keep comfortable for breathing. **P342 + P311**: If experiencing respiratory symptoms: Call a POISON CENTER or doctor/physician.

Caution
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

Dissolve and carefully mix 1 vial Thromboclotin® with 10 mL distilled or deionized water. The reconstituted solution is ready to use. It contains approximately 2.5 NIH units of thrombin/mL. Mix carefully once more before using.

Specimen Collection and Handling

To obtain the plasma, carefully mix 1 part sodium citrate solution (0.11 mol/L) with 9 parts venous blood, avoiding the formation of foam. Centrifuge immediately at no less than 1 500 × g for at least 10 minutes, remove the supernatant plasma and keep at 15 to 25 °C until required in the test.

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

Measure heparin-containing samples within 2 hours.

Procedure

Materials Provided

REF	Contents	
281007	Thromboclotin®	10 × → 10 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[b], 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)

[b] 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.

Test Procedure

Pipette into prewarmed coagulation tubes as follows:		
	Plasma	Control Plasma
Plasma	0.2 mL	–
Control Plasma	–	0.2 mL
	Prewarm for 1 - 2 minutes in a waterbath at 37 °C, or 2–4 minutes to be on a thermal block at 37 °C.	
Reconstituted Thromboclotin® solution (do not prewarm)	0.2 mL	0.2 mL
	Start stopwatch simultaneously with the addition of Thromboclotin®.	

Always perform double determinations.

Internal Quality Control

Normal range: Control Plasma N, Dade® Ci-Trol® 1 or Dade® Ci-Trol® Coagulation Control Level 1

A control has to be measured at start of the test run, upon reagent vial changes and at least every eight hours on each day of testing. The control material should be processed as the samples. Each laboratory should establish its own QC ranges based on the assigned values and ranges provided by the control manufacturer or based on values determined by the laboratory. If control values are found outside the defined range, check the instrument, reagent and calibration for problems.

Results

Results are 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.

The release of platelet factor 4 through increased platelet destruction (inappropriate blood collection and sample preparation or storage) has an inhibitory effect on heparin and therefore may cause considerable variance of thrombin times when testing heparinized patient samples.

Expected Values

15 to 22 seconds

Reference intervals vary from laboratory to laboratory depending on the population served and the technique, method, equipment and reagent lot used. Therefore, each laboratory must establish its own reference intervals or verify them whenever one or more of the aforementioned variables are changed.

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

The precision of Thromboclotin® was tested on the CA-1500 System with CONTROL N and a Pathological plasma pool on 5 days in 8-fold determination. The coefficient of variation within series was 1.3 % and 1.9 %, and from day to day it was 2.4 % and 7.6 %, respectively.

The reproducibility was assessed by the manufacturer for Thrombin Time assay with Thromboclotin® based on publicly available proficiency testing information in 2020/2021. The overall reproducibility median CV % was found to be <7 % including lot, instrument, laboratory and operator variability factors.

Technical Assistance

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

Current Version of Application Sheets

Thromboclotin® 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.

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

Siemens Healthcare Diagnostics Products GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany
siemens-healthineers.com