Multifibren® U

Revision bar indicates update to previous version.

CE 0197

Intended Use

Multifibren® U is an in vitro diagnostic reagent for the quantitative determination of fibrinogen as an aid to diagnosis of congenital or acquired fibrinogen deficiency or dysfunction in patients with bleeding disorders or at risk for fibrinogen deficiency in human sodium citrated plasma by means of automated and manual coagulometric methods.

Fibrinogen determination by Multifibren® U is standardized against the reference methods by Ratnoff-Menzie and Kjeldahl.

In addition, Multifibren® U reagent can be used as an aid in diagnosis and monitoring of fibrinogen consumption in patients at risk or with signs of disseminated intravascular coagulopathy (DIC).

Summary and Explanation

Fibrinogen, a 340 kDa glycoprotein synthesized in the liver, is essential for the formation of a fibrin clot. Cleavage of fibrinogen by thrombin generates fibrin monomers, which spontaneously polymerize, forming a first unstable fibrin clot, which is stabilized by cross-links induced by FXIIIa activity. Decreased or dysfunctional fibrinogen often causes an increased risk for bleeding[1–4].

The function and quantity of fibrinogen in plasma can be altered by both inherited and acquired disorders:

- Inherited defects can lead to a decreased fibrinogen concentration (hypofibrinogenemia) or dysfunctional protein (dysfibrinogenemia). Dysfibrinogenemia can be associated with bleeding or thrombosis, or both[1–3,5].
- Acquired fibrinogen deficiency states can occur as a result of increased consumption (e.g. disseminated intravascular coagulopathy[6], fibrinolytic therapy), reduced synthesis in severe liver disease, or hemodilution[4].

Multifibren® U is a reagent for the quantification of functional fibrinogen according to a modified Clauss method. The determination of fibrinogen in plasma is indicated in the following cases:

- diagnosing congenital or acquired fibrinogen deficiency states,
- monitoring fibrinogen substitution therapy

As fibrinogen reacts as "acute-phase" protein, plasma levels increase in response to acute and chronic inflammation, like infections, trauma, surgery, acute cardiac events or cancer. Elevated fibrinogen levels were shown to be associated with an increased risk for major cardiovascular events as well as nonvascular mortality[1,7].

Principles of the Procedure

Modification of the Clauss method.

Citrated plasma is brought to coagulation by a large excess of thrombin. Here the coagulation time depends largely on the fibrinogen content of the specimen.

Reagents

Note: Multifibren® U 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
Multifibren® U	Lyophilized reagent containing: • Thrombin, bovine (reconstituted: 50 IU/mL) • gly-pro-arg-pro-ala-amide[a] (reconstituted: 0.15 g/L) • Calcium chloride (reconstituted: 1.5 g/L) • Hexadimethrine bromide • polyethylene glycol • Sodium chloride • TRIS/HCl • Bovine serum albumin • Preservative: • Sodium azide (reconstituted: < 1 g/L)	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, 1 day; 2–8 °C: reconstituted, 5 days; ≤ –20 °C: reconstituted, 2 months

[a] fibrin-aggregation retarding peptide

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! Multifibren® U
Hazardous ingredient: Sodium azide (3.47 % [w/w]), Thrombin, bovine (1.71 % [w/w]).
H311: Toxic in contact with skin. **H302**: Harmful if swallowed. **H334**: May cause allergy or asthma symptoms or breathing difficulties if inhaled. **H411**: Toxic to aquatic life with long lasting effects. **P261**: Avoid breathing dust. **P264**: Wash hands thoroughly after handling. **P280**: Wear protective gloves/protective clothing/eye protection/face protection. **P273**: Avoid release to the environment. **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. **P312**: Call a POISON CENTER or doctor/physician if you feel unwell. **P361 + P364**: Take off immediately all contaminated clothing and wash it before reuse. **P391**: Collect spillage. **P501**: Dispose of contents and container in accordance with all local, regional, and national regulations.

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

Contains sodium azide as a preservative. Sodium azide can react with copper or lead plumbing to form explosive metal azides. On disposal, flush reagents with a large volume of water to prevent the buildup of azides. Disposal into drain systems must be in compliance with prevailing regulatory requirements.

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 the Multifibren® U with the amount of distilled or deionized water indicated on the label.

Mix carefully once more before using.

Bring the reagents to 37 °C before measuring (not required for automated coagulation analyzers with heated reagent probes).

Specimen Collection and Handling

Collecting the Specimen

Mix 1 part sodium citrate solution 0.11 mol/L (3.2 %) with 9 parts venous blood.

Centrifuge the blood specimen at 1 500 × g for no less than 15 minutes at room temperature.

Remove the supernatant plasma and store at 15 to 25 °C until required for the test.

Storing the Specimen

Stability of the samples:

15 to 25 °C	4 hours

Procedure

Materials Provided

REF	Contents		
OWZG19	Multifibren® U Lot- and method-specific evaluation Table	10 × →	2 mL
OWZG23	Multifibren® U Lot- and method-specific evaluation Table	10 × →	5 mL

Materials Required but not Provided

Item	Description
REF OQVK11	FIBRINOGEN CALIBRATOR, Fibrinogen Calibrator Kit
REF ORKE41 REF 291070 REF B4244-10	CONTROL N, Control Plasma N Dade® Ci-Trol® 1, or Ci-Trol CONTROL 1, Dade® Ci-Trol® Coagulation Control Level 1, as control for the normal range
REF OUPZ17	CONTROL P, Control Plasma P
Coagulation analyzers[b], such as:	• Automated Blood Coagulation Analyzer CA-600 series (CA-600 series)

[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

Bring Multifibren® U to 37 °C before using.
Pipette into a test tube pre-warmed to 37 °C:

Sample	100 µL
	Incubate at 60 seconds for 37 °C.
Multifibren® U (37 °C)	200 µL
	Determine coagulation time

Automatic:

See chapter "Reagents", page 1.

Performing Calibration

Calculating the reference curve is done with the FIBRINOGEN CALIBRATOR.

These calibrators are tested as samples in the particular coagulation analyzer. The graphic representation of the values obtained is best plotted in a log-log format.

A new reference curve must be calculated each time there is a change in the device used or a change in the lot of Multifibren® U.

Internal Quality Control

Normal range: CONTROL N

Dade® Ci-Trol® 1, Ci-Trol CONTROL 1, or

Pathological range: CONTROL P

Two levels of quality control material (normal and pathologic range) have to be measured at start of the test run, with each calibration, upon reagent vial changes and at least every eight hours on each day of testing. The controls 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 control values lie outside the range determined beforehand, then the reagent, calibration curve and coagulation analyzer should be checked. Do not release patient results until the cause of deviation has been identified and corrected.

Results

The results can be evaluated either with the enclosed table or with a reference curve calculated in the laboratory.

Fibrinogen concentration is given in g/L. The data provided in the evaluation table are only valid for reagents with matching lot numbers and the indicated coagulation analyzers.

A separate reference curve must be calculated for each coagulation analyzer, automated or not.

The reference curves from the evaluation table can be verified with the help of CONTROL N, Dade® Ci-Trol® 1 or with CONTROL P. If the measured results lie outside of the indicated range, then a reference curve specific to the laboratory should be calculated.

Limitations

Degradation products of fibrin(ogen) lead to prolonged coagulation times and therefore to diminished recovery of fibrinogen. Heparin (up to 2 U/mL) does not affect the test. Therapy with direct thrombin inhibitors, e.g. hirudin, may contribute to diminished recovery[8].

Dabigatran may cause false low Clauss fibrinogen levels with Multifibren® U[9].

Direct thrombin inhibitors may interfere with fibrinogen assays according to Clauss Method. Test results from patients under DTI therapy should be interpreted with caution[10].

Blood plasma substitutes that contain hydroxyethyl starch (HES) may interfere with the analysis.

Some analyzers in the KC 4/10/40 series may yield false results when running the test.

With the artificially prepared (e.g. diluted) control plasmas for the lower range of some manufacturers, recovery may be above the declared range if the sample matrix is not sufficiently plasma-like. In such cases, it is recommended that the Control Plasma P should be used.

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.

Expected Values

1.8 to 3.5 g/L[11]

Systematic deviations from this range may be determined by the particular device. It may be necessary to calculate a reference range specific to the laboratory.

Performance Characteristics

Measuring Range

The generic measuring interval is from 0.6 g/L to 8.0 g/L and can be extended on some coagulation analyzers. 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 Multifibren® U in the BCS® was calculated with CONTROL N and CONTROL P for 5 days in 8-fold determination.

The coefficient of variation within series was 2.9 % and 7.2 % for CONTROL N and CONTROL P, respectively. From day to day, it was 1.6 % and 3.4 %.

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

The reproducibility was assessed by the manufacturer for fibrinogen with Multifibren® U based on publicly available proficiency testing information in 2019. The overall reproducibility median CV% was found to be <8 % 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

Multifibren® U 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

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10. Zhang L, Yang J, Zheng X, Fan Q, Zhang Z: Influences of argatroban on five fibrinogen assays. Int J Lab Hematol. 2017 Dec;39(6):641-644. doi: 10.1111/ijlh.12719.
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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
Σ	Contains sufficient for <n> tests		Biological Risks
IVD	*In Vitro* Diagnostic Medical Device		Temperature Limitation
	Consult instruction for Use	NON STERILE	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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