Coagulation Factor XII Deficient Plasma

FACTOR XII DEFICIENT

Revision bar indicates update to previous version.

CE 0197

Intended Use

FACTOR XII DEFICIENT is an in vitro diagnostic reagent for use in assays for the quantitative determination of coagulation factor XII (FXII) activity as aid to diagnosis of congenital or acquired FXII deficiencies in patients with coagulation disorders in human sodium citrated plasma by means of automated, semiautomated and/or manual coagulometric methods.

The Sysmex FXII assays are calibrated versus a fresh normal pool plasma.

Summary and Explanation

Coagulation factor XII (FXII) is activated via binding to negatively charged surfaces. Activated FXII is crucial for fibrin formation in vitro, but FXII deficiency is not associated with excessive bleeding in vivo. The FXII-driven contact system starts coagulation and inflammatory mechanisms via the intrinsic pathway of coagulation and the bradykinin-producing kallikrein-kinin system, respectively[1–4].

Detection of an activation of the contact phase of blood coagulation can be achieved by measuring the activity of FXI and FXII. FXII is involved in the intrinsic coagulation pathway; hence a prolongation of activated partial thromboplastin time APTT is seen in case of a FXII deficiency. The APTT-based one-stage clotting assay using FXII Deficient Plasma is applied for determination of FXII activity.

The determination of FXII in plasma is indicated in the following cases:

- clarifying the cause of a prolonged APTT,
- diagnosing congenital or acquired factor deficiency states.

Principles of the Procedure

A plasma deficient in any of the factors comprising the intrinsic pathway will result in a prolonged partial thromboplastin time (APTT). Coagulation factor deficient plasma can be used to confirm a factor deficiency, in general, and to identify and quantify coagulation factor deficiency in patient plasma. A mixture of the respective factor deficient plasma and the patient plasma is tested in the APTT assay, and the result is interpreted using a reference curve obtained with dilutions of STANDARD PLASMA or a normal plasma pool mixed with the deficient plasma. A patient plasma deficient in a specific factor will not be able to compensate for the absence of the factor in the corresponding coagulation factor deficient plasma and therefore result in a prolonged APTT.

Reagents

Note: FACTOR XII DEFICIENT 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
Coagulation Factor XII Deficient Plasma FACTOR XII DEFICIENT	Lyophilized reagent containing: • human plasma[a], FXII activity ≤1 % • Stabilizer: • D-Mannitol (reconstituted: 20 g/L)	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	15–25 °C: reconstituted, 8 hours[b]; –20 °C: reconstituted, 4 weeks[b]

[a] from pooled plasma collected from selected healthy blood donor

[b] closed original vial

FACTOR XII DEFICIENT is manufactured by immunoadsorption from normal plasma and is free from the antigen of the respective factor. Fibrinogen is present in a quantity greater than 1.5 g/L, and the remaining coagulation factors are present in an activity greater than 50 % of Norm.

FACTOR XII DEFICIENT can be frozen and thawed once after reconstitution without a loss of coagulation activity. The plasma must be well sealed and frozen as quickly as possible. Thawing should be accomplished at 37 °C within 10 minutes. Thawed plasma should be used within 2 hours when held at 15 to 25 °C.

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.

CAUTION! POTENTIAL BIOHAZARD
Each donor or donor unit was tested and found to be negative for human immunodeficiency virus (HIV) 1 and 2, hepatitis B virus (HBV) and hepatitis C virus (HCV) using either tests that are CE marked or FDA approved for this purpose. Because no known test can offer complete assurance of the absence of infectious agents, all human derived products should be handled with appropriate caution.

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.

Preparing Reagents

FACTOR XII DEFICIENT: Dissolve the contents of a vial with 1 mL of distilled or deionized water. Before use, let stand at least 15 minutes at 15 to 25 °C, then swivel carefully to mix (without foam formation). Mix carefully once more before using.

APTT reagent: Use according to the respective Instructions for Use.

$CaCl_2$ SOLUTION 0.025 mol/L: warm to 37 °C (not required for automated coagulation systems with heated reagent probes).

Specimen Collection and Handling

Collecting the Specimen

To obtain the plasma, carefully mix one part of 0.11 or 0.13 mol/L (3.2 % or 3.8 %) sodium citrate solution with nine parts of freshly collected patient blood, avoiding the formation of foam. Centrifuge the blood specimen at 1 500 × g at least 15 minutes at 15 to 25 °C[5].

Storing the Specimen

Stability of the samples:

15 to 25 °C	3 hours
−20 °C	4 weeks

Plasma stored at −20 °C is to be thawed in a water bath within 10 minutes at 37 °C, mixed gently and then tested immediately. If testing cannot be performed immediately after thawing, the specimen may be held for a maximum of 2 hours at 4 °C until tested(H21–A5)[5].

Procedure

Materials Provided

REF	Contents		
OSDG13	Coagulation Factor XII Deficient Plasma FACTOR XII DEFICIENT	3 × →	1 mL

Materials Required but not Provided

Item	Description
REF OQGS29, OQGS35	Pathromtin® SL, or
REF B4218-1, B4218-2	ACTIN, Dade® Actin® Activated Cephaloplastin Reagent, or
REF B4218-20, B4218-100	ACTIN FS, Dade® Actin® FS Activated PTT Reagent, or
REF B4219-1, B4219-2	ACTIN FSL, Dade® Actin® FSL Activated PTT Reagent
REF ORHO37	$CaCl_2$ SOLUTION, Calcium Chloride Solution
REF OQAA33 REF B4234-25 REF B4265-35, B4265-37 –	IMIDAZOLE BUFFER, Imidazole Buffer Solution, or OV BUFFER, Dade® Owren's Veronal Buffer, or CA SYSTEM BUFFER, Dade® CA System Buffer, or Physiological Saline Solution
REF ORKL17	STANDARD PLASMA, Standard Human Plasma
REF ORKE41	CONTROL N, Control Plasma N
REF OUPZ17	CONTROL P, Control Plasma P
Coagulation analyzers[c], such as:	• AUTOMATED BLOOD COAGULATION ANALYZER CS-2500 (CS-2500 System) • AUTOMATED BLOOD COAGULATION ANALYZER CS-5100 (CS-5100 System) • Automated Blood Coagulation Analyzer CN-3000/CN-6000 (CN-3000/ CN-6000 System)

[c] 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.

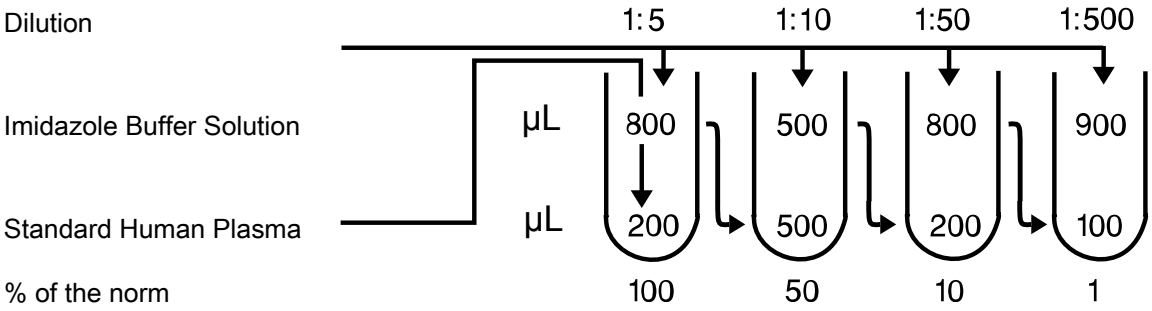
Manual Testing

Pre-warm $CaCl_2$ SOLUTION at 37 °C
Immediately before the measurement: Dilute plasma sample 1:5 in IMIDAZOLE BUFFER (equilibrated at 15–25 °C).

Pipette into a test tube pre-warmed to 37 °C:	
FACTOR XII DEFICIENT	100 µL
Plasma (diluted)	100 µL
APTT reagent	100 µL
	Mix well. Incubate at 37 °C for 2 minutes.
$CaCl_2$ SOLUTION (pre-warmed)	100 µL
	On addition of $CaCl_2$ SOLUTION start stop-watch or timer on the coagulation analyzer and determine the coagulation time.

Establishment of the Reference Curve

Use either STANDARD PLASMA or fresh citrated pooled plasma of at least 10 healthy donors. Using IMIDAZOLE BUFFER, prepare dilutions as shown in the following scheme and determine the coagulation times as described under "Manual Testing", page 3. A new reference curve must be generated if there is a change in the instrument or in the lot of reagent used, or if there is any change in the experimental conditions.



Additional dilutions can be prepared if necessary. Plot the measured coagulation times (ordinate) on log graph paper against the corresponding percentage factor activities (abscissa). The coagulation times are dependent on the measurement principle and thus also on the coagulation analyzer used. Therefore, each laboratory must establish its own reference curve.

Internal Quality Control

Normal range: CONTROL N
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 like the samples. Each laboratory should establish 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 confidence ranges established in the laboratory. If the control values lie outside the range the reagent, calibration curve and coagulation analyzer should be checked. Patient results must not be released until the cause of the deviation is identified and corrected.

Results

Read the coagulation factor content from the reference curve in % of Norm. If the given nominal value of the STANDARD PLASMA is not 100 % of Norm, but e.g. only 95 % of Norm, multiply the result read from the curve by 0.95. In the case of coagulation times which correspond to a coagulation factor content of more than 100 % of Norm, further determination will be required using higher dilutions of specimen (e.g. 1:10). The percentage of norm value read from the reference curve for such a higher dilution must be multiplied by a correction factor corresponding to the dilution; e.g. for a dilution of 1:10 by a correction factor of 2.

Limitations

Therapeutic doses of hirudin or other direct thrombin inhibitors lead to an erroneously lower factor activity[6,7].

Specific inhibitors against plasmatic coagulation factors may also modify the real factor activity[8]. Partial activation of the coagulation factors due to incorrect sample handling can lead to falsely elevated single factor results. In single factor determination, lupus anticoagulant can affect the apparent factor activity. Non-parallelism upon dilution may occur when a lupus anticoagulant is present in the test sample[9].

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[10]

Factor XII 70 to 150 % of Norm

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 Guide of the instrument.

Precision

The results of all precision studies with applications of the assay Factor XII showed a precision for controls (repeatability and within-device/lab precision) of lower or equal than 9 %.

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

The reproducibility was assessed by the manufacturer for coagulation Factor XII based on publicly available proficiency testing information in 2019/2020. The overall reproducibility median CV% was found to be <9 % including APTT reagent used, lot, instrument, laboratory and operator variability factors.

Method Comparison

In a study, the determination of FXII on the Atellica® COAG 360 System was compared to the CS-2000i System.

The correlation resulted in the following:

	n	Slope	Intercept [% of Norm]	Correlation Coefficient
Factor XII	115	1.04	−0.02	0.990

Technical Assistance

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

Current Version of Application Sheets

FACTOR XII DEFICIENT 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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3. de Maat S, Maas C. Factor XII: form determines function. J Thromb Haemost. 2016;14:498-506.
4. Renné T, Schmaier AH, Nickel KF, et al. In vivo roles of factor XII. Blood. 2012;120:4296-303.
5. 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.
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8. Feinstein, DI. Immune coagulation disorders. In: Colman, RW, et al., editors. Hemostasis and Thrombosis. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 1003-20
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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
	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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