SIEMENS Healthineers

Enzygnost® F 1+2 (monoclonal)

F 1+2 MONO

CE 0197

Revision bar indicates update to previous version.

Intended Use

F 1+2 MONO is an in vitro diagnostic reagent for the quantitative determination of prothrombin fragment F 1+2 as an aid to diagnosis and monitoring of hyper- and hypocoagulable states in patients with suspicion or signs of blood coagulation disorders in human sodium citrated plasma by means of semi-automated ELISA technology.

For prothrombin fragment F 1+2 testing no international reference preparation or method is available.

Summary and Explanation

The conversion of prothrombin into active thrombin accompanied by formation of fragment 1+2 (F 1+2) is a key event in the coagulation cascade. The immunochemical determination of F 1+2 allows the precise quantification of the in-vivo thrombin generation, within the last 90 to 120 min[1].

F 1+2 is a sensitive marker of in vivo thrombin generation, with elevated F 1+2 levels indicating increased coagulation activation such as pro-thrombotic states, consumption coagulopathy, or cancer.

Decreased or low-normal F 1+2 levels are seen under anticoagulant therapy.

Determination of F 1+2 may aid in the assessment of the hemostatic balance in the following clinical situations:

- Anticoagulation monitoring (traditional and new anticoagulants)[2–5]
- Marker for non-overt DIC[6]
- Monitoring of pregnant women with thrombophilia, preeclampsia or HELLP syndrome[7,8]
- Risk stratification for stroke in atrial fibrillation patients[9]
- Risk stratification for thrombosis and hypercoagulability in cancer patients[10,11]
- Prognostic marker in patients with acute cardiac events in combination with cardiac markers[12,13]

Principle of the Method

F 1+2 MONO is an enzyme immunoassay based on the sandwich principle in microtiter format. It is based on monoclonal mouse antibodies and is used for *in vitro* determination of the human prothrombin fragment F 1+2.

During the first incubation, the F 1+2 antigen in the sample binds to F 1+2 antibodies attached to the surface of the microtitration plate. After washing, peroxidase-conjugated antibodies to human prothrombin are bound to a free F 1+2 determinant in a second reaction. The excess enzyme-conjugated antibodies are removed by washing; the bound enzyme activity is then determined. The enzymatic reaction between hydrogen peroxide and chromogen is terminated by the addition of dilute sulfuric acid. The color intensity, which is proportional to the concentration of F 1+2, is determined photometrically and quantified by means of a calibration curve based on the standards included in the kit.

Reagents

Reagent	Description	Storage	Stability
Enzygnost® F 1+2 (monoclonal) F 1+2 MONO			
MTP	Mictrotiter plate, coated: • monoclonal antibodies to human F 1+2, mouse (10–100 µg)	2–8 °C	2–8 °C[a]: once opened, 4 weeks
CONJUGATE	Ready to use liquid containing: • anti-human prothrombin • monoclonal antibodies, mouse (peroxidase-conjugated) (2–20 mg/L) • Preservative: • Phenol (< 1 g/L)	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	2–8 °C: once opened, n/a[b]; 2–8 °C: diluted 1:57, 4 weeks

REAGENT DILUENT	Ready to use liquid containing:
	• TRIS/HCl
	• Tween 20
	• Preservative:
	  • Sodium azide (< 1 g/L)
	  • Phenol (< 0.3 g/L)
		2–8 °C
		May be used up to the expiry date indicated on the label if stored unopened.
			2–8 °C:
			once opened, 4 weeks

STANDARD 1	Lyophilized reagent containing:
	• F 1+2 preparation, human
	• Preservative:
	  • Gentamicin sulfate (reconstituted: ~100 mg/L)
	  • Amphotericin B (reconstituted: ~5 mg/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;
			≤ –18 °C:
			reconstituted, 4 weeks

STANDARD 2	Lyophilized reagent containing:
	• F 1+2 preparation, human
	• Preservative:
	  • Gentamicin sulfate (reconstituted: ~100 mg/L)
	  • Amphotericin B (reconstituted: ~5 mg/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;
			≤ –18 °C:
			reconstituted, 4 weeks

Reagent	Description	Storage	Stability

STANDARD 3	Lyophilized reagent containing:
	• F 1+2 preparation, human
	• Preservative:
	  • Gentamicin sulfate (reconstituted: ~100 mg/L)
	  • Amphotericin B (reconstituted: ~5 mg/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;
			≤ –18 °C: reconstituted, 4 weeks

STANDARD 4	Lyophilized reagent containing:
	• F 1+2 preparation, human
	• Preservative:
	  • Gentamicin sulfate (reconstituted: ~100 mg/L)
	  • Amphotericin B (reconstituted: ~5 mg/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;
			≤ –18 °C: reconstituted, 4 weeks

CONTROL	Lyophilized reagent containing:
	• human plasma
	• Preservative:
	  • Gentamicin sulfate (reconstituted: ~100 mg/L)
	  • Amphotericin B (reconstituted: ~5 mg/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;
			≤ –18 °C: reconstituted, 4 weeks

DILUENT	Ready to use liquid containing: • TRIS/HCl • Tween 20 • Sodium chloride • Preservative: • Sodium azide (< 1 g/L)	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	2–8 °C: once opened, 4 weeks
WASH POD	Ready to use liquid containing: • Phosphate buffer • Tween 20 • Preservative: • Phenol (< 1 g/L)	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	2–8 °C: once opened, n/a[b]; 2–8 °C: diluted 1:20, 1 week; 18–25 °C: diluted 1:20, 1 day
SUBSTRATE TMB	Ready to use liquid containing: • Urea hydrogen peroxide (0.275 g/L) • Preservative: • n-butanol (< 1 %)	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	2–8 °C: once opened, n/a[b]

Reagent	Description	Storage	Stability
CHROMOGEN TMB	Ready to use liquid containing: • Tetramethyl benzidine dihydrochloride (~0.01 mol/L) • Preservative	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	2–8 °C: once opened, n/a[b]
STOP POD	Ready to use liquid containing: • sulfuric acid (0.25 mol/L)	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	2–8 °C: once opened, n/a[b]
EMPTY VIAL CHROM SOL			
Adhesive foil			
Polyethylene bag			

[a] in the bag with desiccant
[b] expiry date

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 in which the user and/or patient is established.

Safety data sheets (MSDS/SDS) available on siemens-healthineers.com/sds.

Danger! STOP POD
Hazardous ingredient: sulfuric acid (2.47 % [w/w]).
H290: May be corrosive to metals. **H314**: Causes severe skin burns and eye damage.
P234: Keep only in original container. **P264**: Wash hands thoroughly after handling. **P280**: Wear protective gloves/protective clothing/eye protection/face protection. **P390**: Absorb spillage to prevent material damage. **P301 + P330 + P331**: IF SWALLOWED: rinse mouth. Do NOT induce vomiting. **P303 + P361 + P353**: IF ON SKIN (or hair): Remove/Take off immediately all contaminated clothing. Rinse skin with water/shower. **P305 + P351 + P338**: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. **P310**: Immediately call a POISON CENTER or doctor/physician. **P501**: Dispose of contents and container in accordance with all local, regional, and national regulations.

Warning! CHROMOGEN TMB
Hazardous ingredient: Hydrochloric acid (0.205 % [w/w]).
H290: May be corrosive to metals.
P234: Keep only in original container. **P390**: Absorb spillage to prevent material damage.

Warning! STANDARD 1, STANDARD 2, STANDARD 3, STANDARD 4
Hazardous ingredient: Ethylenediaminetetraacetic acid disodium salt dihydrate (20.7 % [w/w]).
H319: Causes serious eye irritation. **H373**: May cause damage to organs through prolonged or repeated exposure.
P280: Wear protective gloves/protective clothing/eye protection/face protection. **P260**: Do not breathe dust. **P337 + P313**: If eye irritation persists: Get medical advice/attention. **P314**: Get medical advice/attention if you feel unwell.

STANDARD 1, STANDARD 2, STANDARD 3, STANDARD 4
Hazardous ingredient: Gentamicin sulfate (0.557 % [w/w]).

CONTROL
Hazardous ingredient: Gentamicin sulfate (0.116 % [w/w]).
May produce an allergic reaction.

CAUTION! POTENTIAL BIOHAZARD

STANDARD 1, STANDARD 2, STANDARD 3, STANDARD 4, CONTROL

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

CONJUGATE, REAGENT DILUENT, STANDARD 1, STANDARD 2, STANDARD 3, STANDARD 4, CONTROL, DILUENT

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

It is advisable to wear protective gloves throughout the entire test procedure.

For disposal, it is recommended that solid infectious materials be autoclaved for at least 1 hour at 121 °C. All aspirated liquids should be collected in two receptacles connected in series. The receptacles should both contain a disinfectant suitable for deactivating pathogenic human viruses. The concentrations and reaction times specified by the manufacturer must be observed.

When performing a test, use test plates, standards, control plasma, conjugate, sample buffer and conjugate buffer from test kits with the same lot number only. Do not mix these components from test kits with different lot numbers!

Avoid skin contact with Chromogen, Chromogen Buffer/Substrate Solution and Stopping Solution.

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 Siemens Healthineers on request.

Preparation of the Reagents

Satisfactory performance of the test is guaranteed only if the reagents used have the required lot number; the required combination of lot numbers is listed on the test kit.

Dilute 100 mL **Washing Solution POD** with distilled or deionized water to make 2 000 mL (sufficient for 2 test plates). If less than 2 test plates are required, dilute an appropriate portion of the Washing Solution with distilled or deionized water.

Add 250 µL **Anti-Human Prothrombin/POD-Conjugate** for one filling of Conjugate Buffer (coag.) (14 mL) and mix by shaking gently (sufficient for 1 test plate): conjugate solution.

Reconstitute **Standards 1 to 4 and Control Plasma** by adding 1 mL distilled or deionized water to each vial and incubate for 15 minutes at 15 to 25 °C.

If it is necessary to use a control in the lower measuring range, a portion of the reconstituted Control Plasma can be diluted 1+1 in sample buffer. The expected value is then equal to 1/2 of the assigned value ±20 %.

Chromogen Working Solution: For each test plate, dilute 1.5 mL Chromogen TMB with 15 mL Buffer/Substrate TMB in the plastic bottle supplied (chromogen working solution) and store protected from light. Rinse the bottle carefully with distilled water after using. For technical reasons (overfill), it is not permissible to pool the full contents of the Chromogen TMB vial and the full contents of the Buffer/Substrate TMB vial.

	Storage	Stability
Chromogen Working Solution	2–8 °C 15–25 °C closed container protected from light	5 days 8 hours

Bring all reagents and test samples to 15 to 25 °C before the start of the test. Do not remove the test plates from the container while doing this.

Please Note: Buffer/Substrate, the solution of Chromogen in Buffer/Substrate and Stopping Solution must not be allowed to come into contact with heavy metal ions or oxidizing substances (Do not use pipette tips with metal parts). If laboratory vessels are used to prepare larger quantities of Chromogen Buffer/Substrate Solution, these must be rinsed well and dried at 120 °C beforehand.

Specimens

Collecting the Specimen

To obtain the plasma, carefully mix 1 part citrate buffer solution or sodium citrate solution 0.11 mol/L (0.32 %) with 9 parts venous blood, avoiding the formation of foam. Centrifuge immediately for at least 10 minutes at a minimum of 1 500 × g and remove any supernatant plasma.

Samples frozen at ≤ -60 °C must be thawed for 10 minutes at 37 °C and measured within 4 hours.

Samples with an F 1+2 concentration exceeding the measuring range (> 1 200 pmol/L) can be measured again in a sufficient dilution (maximum 1:20) with sample buffer.

Storing the Specimen

Stability of the samples:

2 to 8 °C	8 hours
15 to 25 °C	4 hours
≤ -60 °C	6 months

Procedure

Materials Provided

REF	Contents		Number of Tests
OPBD03	Enzygnost® F 1+2 (monoclonal) F 1+2 MONO		2 × 96
	Enzygnost® Anti-Human F 1+2 test plate MTP	2 pcs.	
	Anti-Human Prothrombin/POD-Conjugate CONJUGATE	1 × 0.5 mL	
	Conjugate Buffer (coag.) REAGENT DILUENT	2 × 14 mL	
	Standard 1 STANDARD 1	2 × → 1 mL	
	Standard 2 STANDARD 2	2 × → 1 mL	
	Standard 3 STANDARD 3	2 × → 1 mL	
	Standard 4 STANDARD 4 Table of Analytical Values	2 × → 1 mL	
	Control Plasma CONTROL Table of Assigned Values	2 × → 1 mL	
	Sample Buffer (F 1+2) DILUENT	2 × 14 mL	
	Washing Solution POD WASH POD	1 × 100 mL	
	Buffer/Substrate TMB SUBSTRATE TMB	1 × 30 mL	
	Chromogen TMB CHROMOGEN TMB	1 × 3 mL	
	Stopping Solution POD STOP POD	1 × 100 mL	
	Empty bottle for Chromogen Working Solution EMPTY VIAL CHROM SOL	1 pc.	
	Adhesive foil	6 pc.	
	Polyethylene bag	1 pc.	

The test plate, the conjugate and the conjugate buffer must be used in the given combination of 6-digit lot numbers printed on the package.

The same applies to the reagents Chromogen TMB and Buffer/Substrate TMB.

Materials Required but not Provided

Item	Description
–	Piston-type pipettes: 50 µL, 100 µL, 200 µL, 1 mL (variable), multiple-channel pipette (e.g., 8 channels) For performing the test manually: Incubation: Water bath (37 °C, circulating) Washing equipment: Microtiter plate washer or a dispenser for about 0.3 mL with aspiration system Photometer: Photometer suitable for microtiter plates, measuring wave length 450 nm, reference wavelength 650 nm

Please note that the applications on automatic 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

Note: All determinations (standards, controls, patient samples) must be performed in duplicate (CV ≤ 15 %). A reference curve has to be established for each series of measurements and each individual test plate using the standards 1 to 4. Filling a test plate by pipetting the individual plasma samples must be completed within 10 minutes. **The incubation time starts when the test plate is placed in the water bath!**

Avoid the formation of air bubbles when pipetting. Do not allow the test plate to dry unfilled between incubation steps. Incubation times must be kept within the indicated time limits and must be the same for all assays in a series.

1. Determine the number of strips (8 connected wells) required (2 wells each for standards, control and samples). Remove strips which are not required from the holder and store them sealed in the polyethylene bag with desiccant at 2 to 8 °C.
2. Dispense 50 µL Sample Buffer F 1+2 into each well. Subsequently, add 50 µL of standards, control or samples into the wells. Agitate the filled test plate thoroughly (e.g. by aspirating with a multiple-channel pipette at least twice) to ensure sufficient mixing of each sample. The use of an 8-channel pipette is recommended.
3. Cover the test plate with adhesive foil and incubate for 30 ±2 minutes at 37 °C (water bath).
4. Remove the adhesive foil, aspirate all wells, fill with 0.3 ±0.01 mL diluted washing solution and aspirate again. Repeat the washing process once, and remove any remaining washing solution by tapping the inverted test plate on absorbant paper (time required: 3 minutes maximum).
5. Dispense 100 µL conjugate solution into each well (start with well 1). Avoid spilling onto the edge of the well.
6. Cover with fresh adhesive foil and incubate for 15 ±1 minutes at 37 °C.
7. Remove the foil, aspirate all wells completely, and wash three times as described above. Tap the inverted test plate on absorbant paper again to remove remainders of the conjugate solution (time required: 3 minutes maximum).
8. Dispense 100 µL of the Chromogen Buffer/Substrate working solution into the wells.
9. Cover with fresh adhesive foil, incubate for 15 ±1 minutes at 15 to 25 °C **protected from light** (e.g. place in a dark drawer).
10. Remove the self-adhesive foil and add 100 µL of Stopping Solution POD to each well, keeping to the same timing as for the dispension of the Chromogen Buffer/Substrate Solution (Step 8).
11. Measure with a spectrophotometer within one hour; measuring wavelength 450 nm, reference wavelength 650 nm.

Internal Quality Control

The Control Plasma for F 1+2 MONO must be processed with each series of patient samples. Before reporting patient results, verify that Control Plasma results reported in concentration units are within the range listed lot dependent in the respective table of values.

Results

Manual Evaluation

Calculate the mean absorbance value of all standards, control plasmas and samples. Construct a reference curve by plotting the mean absorbance value for each standard on double-logarithmic graph paper (abscissa: concentration 20 to 1 200 pmol/L, ordinate: $Absorbance_{450\ nm}$ 0.01 to 3).

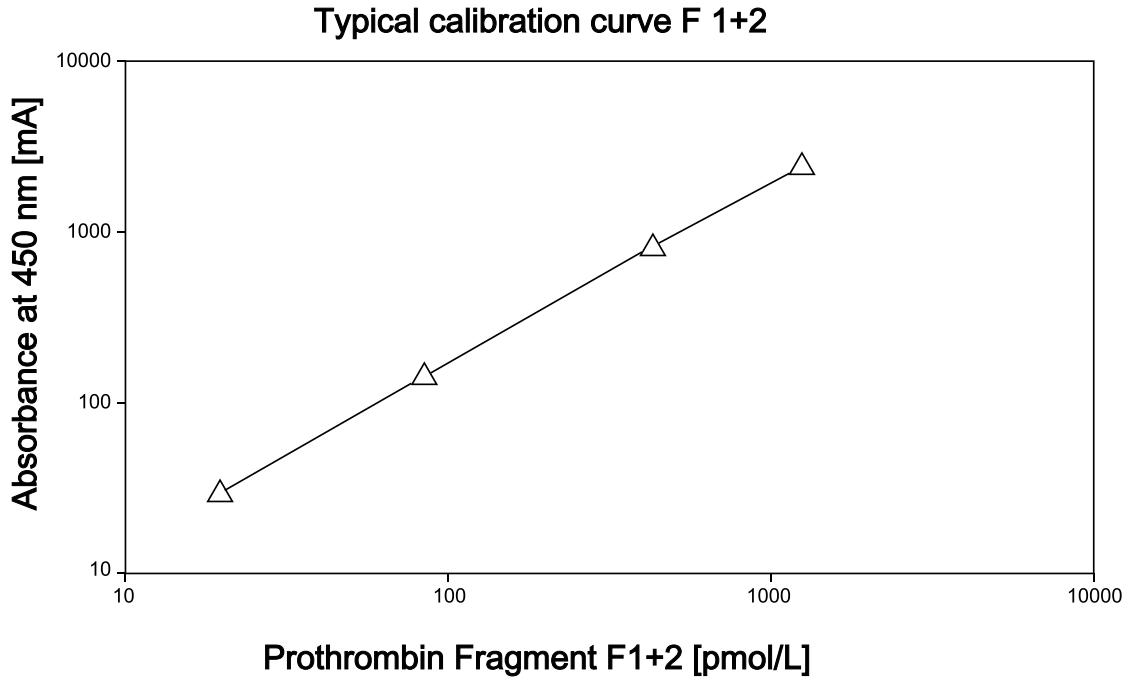
The F 1+2 concentrations for control plasmas and samples can be read directly from the reference curve using the calculated mean absorbance values.

F 1+2 concentrations of healthy donors are expected to be within the reference interval (see below). F 1+2 concentrations above the reference range can indicate a hypercoagulable state (e.g., thrombosis), whereas concentrations below the reference range can indicate hypocoagulable states (e.g., oral anticoagulation).

If any absorbance values exceed those of the highest standard, retest those samples with a sufficient dilution (maximum 1:20); the results obtained are then to be corrected for the dilution factor. Samples should be diluted with Sample Buffer at a dilution ratio that allows the concentration of F 1+2 to be read within the measuring range (between 20 and 1 200 pmol/L).

Computer generated analysis

Results may also be obtained by using computer generated linear regression analyses.



Limitations of the Procedure

Please Note: Improper collection of blood samples, e. g. insufficient mixing of sample and citrate solution, can lead to falsely elevated F 1+2 values.

Repeated freezing and thawing of samples and reconstituted control plasma for F 1+2 MONO is not permitted.

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

Assay kits containing mouse monoclonal antibodies may yield falsely elevated results when testing plasma samples from patients containing heterophilic antibodies or human anti-mouse antibodies (HAMA; e.g., from patients who have received preparations of mouse monoclonal antibodies)[14,15].

Siemens Healthineers 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 Siemens Healthineers 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 Siemens Healthineers Application Sheets or these Instructions for Use.

Reference Intervals

	n	Median	95 % Reference Interval 2.5^{th}–97.5^{th} Percentile
Citrated plasma of healthy adults	137	115 pmol/L	69–229 pmol/L

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.

For more information on establishing reference intervals see CLSI document C28-A3c, "Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory, Approved Guidline".

Specific Performance Characteristics

Measuring Range

The measuring range of F 1+2 MONO is 20 to 1 200 pmol/L.

Specificity

The test is specific for the human prothrombin fragments F 2 and F 1+2.

Precision

In the range between 49 and 754 pmol/L, the coefficients of variation were between 3.6 and 5.5 % within run and 4.4 and 11.2 % between run. Total precision was 6.8 to 11.8 % CV.

The reproducibility was assessed by Siemens Healthineers for Enzygnost F 1+2 (monoclonal) based on variance of the sensitivity of ten production lots. The lot-to-lot variability was found to be < 12 % (samples < 80 pmol/L); < 10 % (samples between 80 and 400 pmol/L); < 15 % (samples > 400 pmol/L).

Method Comparison

The F 1+2 MONO assay was compared to a commercially available F 1+2 (polyclonal) assay by evaluating 190 plasma samples ranging from 21 to 1 170 pmol/L. A correlation coefficient of 0.96 was obtained, with a regression equation of y = 0.28 x - 23.22 pmol/L.

Interference

Levels of the following do not appear to interfere with the F 1+2 MONO:

Substance	No Interference up to...
Bilirubin	60 mg/dL
Hemoglobin (free)	600 mg/dL
Lipids	3 000 mg/dL
Rheumatoid Factors	197 IU/mL

Technical Assistance

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

siemens-healthineers.com

Current Version of Applicable Version of electronic Instructions for Use

As Siemens Healthineers 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. Siemens Healthineers ensures that all products lots bearing the same IFU version number are compatible with the electronic labeling provided via siemens-healthineers.com/eIFU.

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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		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

Enzygnost is a trademark of Siemens Healthineers.
All other trademarks are the property of their respective owners.

Siemens Healthineers Headquarters
Siemens Healthcare GmbH
Henkestraße 127
91052 Erlangen
Germany
Phone: +49 9131 84-0
siemens-healthineers.com

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