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Calcium Chloride Solution
$CaCl_2$ SOLUTION

Intended Use

Calcium Chloride Solution is used as Supplementary Reagent for various coagulation assays.

Reagent

Materials provided

Calcium Chloride Solution, REF *ORHO37*
10 x 15 mL $CaCl_2$ SOLUTION, Calcium Chloride Solution

Composition

$CaCl_2$ solution 0.025 mol/L

Warnings and Precautions

For *in-vitro* diagnostic use only.

Storage and Stability

Storage at 2 to 25 °C:
The expiry date is indicated on the label.
Stability once opened:
8 weeks at 2 to 25 °C
Information about on-board stability is specified in the Reference Guides (Application Sheets) for the different coagulation analyzers.

Materials required, but not provided

Coagulation Analyzer
Reagents and associated materials according to the respective Instructions for Use of the coagulation assays to be used with Calcium Chloride Solution REF ORHO37.

Procedure

- Calcium Chloride Solution is added automatically by the respective coagulation analyzer when performing the respective assay.
- Please refer to the respective Instructions for Use and Application Sheets for the assays to be used with Calcium Chloride Solution.

Definition of Symbols

	Do not reuse		Use By
LOT	Batch Code	REF	Catalogue Number
	Caution, consult accompanying documents		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 mark
CONTENTS	Contents	→	Reconstitution volume
LEVEL	Level		Keep away from sunlight and heat

2015-10

Siemens Healthcare Diagnostics Products GmbH
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U.S.A. Distributor
Siemens Healthcare Diagnostics Inc.
Newark, DE 19714 U.S.A.

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Control Plasma N

CONTROL N

Intended Use

CONTROL N is an assayed control used for the assessment of precision and analytical deviation of the following analytes in the normal range:

1. Prothrombin time (PT)
2. Activated partial thromboplastin time (APTT)
3. Thrombin time (TT)
4. Batroxobin time
5. Fibrinogen
6. Coagulation factors II, V, VII, VIII, IX, X, XI, XII, XIII and vWF
7. Inhibitors: Antithrombin III, protein C, protein S, α_2-antiplasmin, C1-Inhibitor
8. Complement total activity
9. Plasminogen
10. ProC® line analytes
11. Lupus anticoagulants

The assigned values were determined at Siemens Healthcare Diagnostics using Siemens reagents on mechanical and photo-optical coagulation systems.

Reagents

Materials provided

Control Plasma N, REF *ORKE 41,* REF *10484201*

10 x → 1.0 mL CONTROL N, Control Plasma N

Each pack of CONTROL N contains a table of lot- and method-specific assigned values and ranges.

Composition

CONTROL N is obtained from pooled plasma collected from selected healthy blood donors. CONTROL N is stabilized with HEPES buffer solution (12 g/L) and lyophilized. To avoid contact activation of the coagulation system the preparation is supplied in siliconized vials.

CONTROL N contains no preservatives.

Warnings and Precautions

For *in-vitro* diagnostic use.

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 found to be in conformance with the In Vitro Diagnostic Directive in the EU or FDA approved tests. Because no known test can offer complete assurance of the absence of infectious agents, all human derived products should be handled with appropriate caution.

Plasma preparation

1. Reconstitute CONTROL N by adding 1.0 mL distilled or deionized water.
2. Shake carefully to dissolve (without foam formation).
3. Let stand at 15 to 25 °C at least 15 minutes.
4. Before use, again shake carefully.

Storage and Stability

Store CONTROL N unopened at 2 to 8 °C and use by the expiry date given on the label.

Stability after reconstitution:

at 15 to 25 °C	4 hours
at ≤–20 °C	4 weeks

Reconstituted CONTROL N can be frozen and thawed once. The reconstituted control plasma must be frozen as rapidly as possible in a tightly closed container. Thawing should be accomplished at 37 °C within 10 minutes. The reconstituted control plasma should not be exposed to 15 to 25 °C for longer than 2 hours after thawing.

Equipment

CONTROL N can be used manually or on automated coagulation analyzers. Siemens 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!

Procedure

Use with the corresponding reagents in accordance with the direction in the reagents' Instructions for Use.

CONTROL N should be run at least once every 8 hours for any assays run for patient testing during that interval. Controls should be run after each new calibration curve and after each change of reagent vial. Recalibration may be necessary if control values are outside the target range. Do not report test results if controls are out of range.

Expected Values

Expected values are provided in the enclosed lot- and method-specific table of assigned values. These values are provided as a guideline only; it is recommended that each laboratory establish its own target range.

Limitations of the Procedure

If other measurement principles are employed, the coagulation times obtained may differ from the given assigned values, depending on which instrument is used. The assigned values (mean coagulation times) given for the PT, APTT, thrombin time in seconds and the lupus anticoagulant assay are highly dependent on method, instrument and technique and therefore serve only as a guide.

Definition of Symbols

	Do not reuse		Use By
LOT	Batch Code	REF	Catalogue Number
	Caution, consult accompanying documents		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 mark
CONTENTS	Contents	→	Reconstitution volume
LEVEL	Level		Keep away from sunlight and heat

2015-07

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Control Plasma P

CONTROL P

Intended Use

CONTROL P is an assayed control used for the assessment of precision and analytical deviation of the following analytes in the pathological range:

1. Prothrombin time (PT)
2. Activated partial thromboplastin time (APTT)
3. Fibrinogen (Clauss method)
4. Coagulation factors II, V, VII, VIII, IX, X, XI, XII, XIII and vWF
5. Inhibitors: Antithrombin III, protein C, protein S, α_2-antiplasmin, C1 Inhibitor
6. Complement total activity
7. Plasminogen

The values were determined using Siemens Healthcare Diagnostics reagents on mechanical and photo-optical coagulation analyzers.

Reagents

Material provided

Control Plasma P, REF *OUPZ 17*

10 x → 1.0 mL CONTROL P, Control Plasma P

Each pack of CONTROL P contains a table of lot- and method-specific assigned values and ranges.

Composition

CONTROL P is obtained from pooled plasma collected from selected healthy blood donors. The plasma is adjusted to defined factor concentrations. CONTROL P is stabilized with HEPES buffer solution (12 g/L) and lyophilized. To avoid contact activation of the coagulation system, the preparation is supplied in siliconized vials.

CONTROL P contains no preservatives.

Warnings and Precautions

For *in-vitro* diagnostic use.

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 found to be in conformance with the In Vitro Diagnostic Directive in the EU or FDA approved tests. Because no known test can offer complete assurance of the absence of infectious agents, all human derived products should be handled with appropriate caution.

Plasma Preparation

1. Reconstitute CONTROL P by adding 1.0 mL distilled or deionized water.
2. Shake carefully to dissolve (without foam formation).

3. Let stand at 15 to 25 °C at least 15 minutes.
4. Before use, again shake carefully.

Storage and Stability

Store CONTROL P unopened at 2 to 8 °C and use by the expiry date given on the label.

Stability after reconstitution:

at 15 to 25 °C	4 hours
at ≤–20 °C	4 weeks

Reconstituted CONTROL P can be frozen and thawed once. The reconstituted control plasma must be frozen as rapidly as possible in a tightly-closed container. Thawing should be accomplished at 37 °C within 10 minutes. The reconstituted control should not be exposed for longer than two hours at 15 to 25 °C after thawing.

Equipment

CONTROL P can be used manually or on automated coagulation analyzers. Siemens 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!

Procedure

Use with the corresponding reagents in accordance with the directions in the reagents' Instructions for Use. CONTROL P should be run at least once every 8 hours for any assays run for patient testing during that interval. Controls should be run after each new calibration curve and after each change of reagent vial. Recalibration may be necessary if control values are outside the target range. Do not report test results if controls are out of range.

Expected Values

Expected values are provided in the enclosed lot- and method-specific table of assigned values. These values are provided as a guideline only; it is recommended that each laboratory establish its own target range.

Limitations of the Procedure

If coagulation analyzers with other measurement principles are used, the coagulation times obtained may differ from the values provided.

Definition of Symbols

	Do not reuse		Use By
LOT	Batch Code	REF	Catalogue Number
	Caution, consult accompanying documents		Manufacturer
EC REP	Authorized representative in the European Community		Contains sufficient for <n> tests
	Biological Risks	IVD	*In Vitro* Diagnostic Medical Device
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	Non-sterile		CE mark
CONTENTS	Contents		Reconstitution volume
LEVEL	Level		Keep away from sunlight and heat

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Dade® Innovin®

Revision bar indicates update to previous version.

Intended Use

For use in prothrombin time (PT) determinations and prothrombin time-based assays in citrated human plasma.

Summary and Explanation

Dade® Innovin® Reagent is prepared from purified recombinant human tissue factor produced in *E. coli,* combined with synthetic phospholipids (thromboplastin)[1], calcium, buffers and stabilizers. The reagent initiates clotting via the extrinsic and common pathways in a global screening test, the prothrombin time (PT). Dade® Innovin® Reagent has three major applications based upon the PT[2]:

1. as a rapid screening test to detect single or combined deficiencies of the extrinsic coagulation system indicative of hereditary and acquired coagulation disorders, liver disease or vitamin K deficiency;
2. as a sensitive monitoring test for oral anticoagulant therapy with vitamin K antagonists; and
3. as an assay for specific coagulation factors.

Additionally, various photo-optical coagulation analyzers are able to derive the fibrinogen value from the determination of the prothrombin time.

Dade® Innovin® Reagent is manufactured using recombinant human tissue factor and synthetic phospholipids which do not contain any other clotting factors such as prothrombin, F VII and F X. Therefore, it is highly sensitive to factor deficiencies and oral anticoagulant-treated patient plasma samples. The sensitivity of Dade® Innovin® Reagent is very similar to the WHO human brain reference thromboplastin[3]. Dade® Innovin® Reagent is insensitive to therapeutic levels of heparin. The high sensitivity of Dade® Innovin® Reagent to coagulation factors and its insensitivity to therapeutic heparin make it beneficial in monitoring oral anticoagulant therapy with vitamin K antagonists[3]. In addition, its high sensitivity (i.e. the responsiveness of the reagent to moderately depleted factor activity) allows differentiation of abnormal plasmas, even in the mildly pathological range.

Principle of the Method

The coagulation cascade is activated by incubating plasma with the optimal amount of thromboplastin and calcium; the clotting time is then measured.

Reagents

Note

Dade® Innovin® Reagent can be used manually or on automated coagulation analyzers. Siemens Healthcare Diagnostics 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 such a case, the information contained in the Reference Guides

(Application Sheets) supersedes the information in these Instructions for Use. In addition, please also consult the instruction manual of the instrument manufacturer!

Materials provided

10 x → 4 mL, REF B4212-40
10 x → 10 mL, REF B4212-50, REF 10284500
12 x → 20 mL, REF B4212-100

Composition

Dade® Innovin® Reagent: Lyophilized reagent consisting of recombinant human tissue factor and synthetic phospholipids (thromboplastin), calcium ions, a heparin-neutralizing compound, buffers and stabilizers (bovine serum albumin).

Warnings and Precautions

For *in-vitro* diagnostic use.

Reagent Preparation

Reconstitute a vial of lyophilized Dade® Innovin® Reagent with distilled or deionized water using the volume stated on the vial label.

To ensure complete reconstitution, thoroughly mix the contents of the vial immediately after adding the water. If left to stand, Dade® Innovin® Reagent should be re-mixed before use in order to ensure a homogeneous solution. Store at 2 to 8 °C. Continuous mixing is not necessary.

Note: Do not use water that contains preservatives.

Storage and Stability

Store at 2 to 8 °C. At this temperature, the unopened reagent can be used until its expiry date (see vial label).

Stability after reconstitution:	2 to 8 °C	10 days (closed vial)
	15 to 25 °C	5 days (closed vial)
	37 °C	24 hours (closed vial)

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

Do not freeze!

Signs of expiry: Absence of vacuum when opening the vial; reagent is difficult to reconstitute; results are not reproducible.

Materials required but not provided

Control Plasma N or Dade® Ci-Trol® Level 1

Control Plasma P, Dade® Ci-Trol® Level 2 or Dade® Ci-Trol® Level 3

PT-Multi Calibrator* (Refer to the Instructions for Use for details on use.)

Standard Human Plasma or fresh normal plasma[4] for determining the mean normal PT (MNPT)**

Sodium citrate solution (0.11 mol/L or 0.13 mol/L / 3.2 % or 3.8 %) for blood collection

Distilled or deionized water without preservatives

Plastic tubes

Plastic transfer pipettes

Pipettes for precise measurement of 20.0 mL, 10.0 mL, 1.0 mL, 0.50 mL, 0.20 mL and 0.10 mL

Coagulation analyzer

Specimen Collection and Preparation

Mix nine parts of freshly collected patient blood with one part of 0.11 or 0.13 mol/L (3.2 % or 3.8 %) sodium citrate solution. An evacuated tube system or syringe may be used.

Centrifuge the blood specimen at 1500 x g for no less than 15 minutes at room temperature.

Store in an unopened tube at room temperature. Do not store on ice or at 2 to 8 °C as cold activation of F VII may alter results. Plasma should be tested within 24 hours of blood collection. Samples should not stand at 37 °C for more than 5 minutes. If the patient is on both heparin and coumarin-based anticoagulant therapy, the results may vary with time of storage.

Please refer to CLSI document H21-A5[5] for detailed information on sample preparation and storage.

Procedure

Manual Testing:

Prewarm Dade® Innovin® Reagent to 37 °C.

Pipet into coagulation tubes as follows:

	Test Sample	Control
Plasma	0.1 mL	-
Control	-	0.1 mL
Incubate tubes and samples for 1 to 2 minutes (max. 5 minutes) at 37 °C		
Add prewarmed Dade® Innovin® Reagent	0.2 mL	0.2 mL

Start stopwatch simultaneously with addition of Dade® Innovin® Reagent. Observe time of clot formation.

Internal Quality Control

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

Pathological range: Dade® Ci-Trol® Level 2, Dade® Ci-Trol® Level 3 or Control Plasma P

Two levels of quality control material (normal and pathological range) must 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 control material should be prepared and processed in the same manner as the samples.

A range of allowable variation should be established for controls in each laboratory. New control ranges should be established for each lot of reagent or control material. This range is usually based on ± 2.5 standard deviations (SD) from the control mean.

If the control values are outside of the established range, check the coagulation analyzer, controls and reagents. Do not release patient results until the cause of deviation has been identified and corrected.

Results

Currently, various methods are used for reporting PT results. ISI (International Sensitivity Index) values for Dade® Innovin® Reagent are provided for the particular reagent/instrument combination; these enable the results to be reported in INR (International Normalized Ratio)[4]. Computation and use of the INR are described below. Monitoring of oral anticoagulant therapy with vitamin K antagonists should only be reported with PT results expressed as INR as recommended in official guidelines and in the literature[4]. Alternatively, the patient's PT (in seconds) together with the reference range (in seconds) can be used to report results.

Example: patient result of 18 seconds; reference range 9.9 to 11.8 seconds.

Determination of INR (International Normalized Ratio)

Values using Dade® Innovin® Reagent

International PT (Prothrombin Time) Standardization for Oral Anticoagulant Therapy Monitoring

1. According to the joint recommendations of the World Health Organization (WHO)[4] and the International Committee on Thrombosis and Haemostasis, the PT results for patients on vitamin K antagonist oral anticoagulants should be reported as INR values. Reported INR results are independent of the reagents and methods used, and are specifically intended for assessing patients stabilized on longterm oral anticoagulant therapy.

   The INR is determined[4] according to the following equation:

   $$INR = R^{ISI}, \text{ where } R = \frac{\text{Patient PT}}{\text{MNPT**}}$$

   ISI is the International Sensitivity Index of the reagent/instrument combination.

   The ISI values for Siemens thromboplastin reagents are determined in accordance with WHO recommendations.

2. Methods of INR calculation:

   a. Calculators with exponential functions:

   These instructions refer specifically to the Texas Instruments TI-55 II calculator. Other calculators, e.g. Hewlett-Packard models, may require different key stroke sequences. Consult the calculator reference manual and check example problems against the Conversion Table to assure mastery of conversion procedures.

   Enter Patient PT in seconds, press "÷", enter MNPT**, press "=". The display will now show R, the Patient Ratio. Now press the "y^x" key, then enter the specific ISI value of the thromboplastin/instrument combination used and press "=". The result displayed is the patient's INR value.

Press	**Notes**
Example: 24	patient PT
÷	divided by
11.0	MNPT**
=	patient ratio (display shows 2.1818)
y^x	exponential function key
1.1	**example** ISI value
=	result: INR (display shows 2.3588)
	Report as INR = 2.4

   b. Conversion Table:

   First, calculate the patient PT/MNPT** ratio, R. The INR value can then be read from the enclosed INR Conversion Table by looking in the column under the appropriate ISI value, in the row that corresponds to the patient's PT ratio (R).

   c. Automatic:

   INR values can be computed automatically by various coagulometers. For details, consult the relevant instruction manual. Siemens provides Reference Guides (Application Sheets) for several coagulation analyzers.

Derived Fibrinogen

Using Dade® Innovin® Reagent and the appropriate assay on Siemens photometric coagulation analyzers or Sysmex® coagulation analyzers, the fibrinogen concentration may be derived by analyzing the change in optical signal during prothrombin time determinations, using a derived fibrinogen calibration curve. This calibration curve (master curve) is provided by Siemens in the lot-dependent Table of Assigned Values.

Limitations of the Procedure

There are no other clotting factors in recombinant human tissue factor. Factor assay curves using Dade® Innovin® Reagent may therefore give longer clotting times at the lowest levels of the deficient factor than with other reagents. This may result in clotting times greater than 100 seconds for low factor levels in factor assay curves.

Derived fibrinogen results within the reference range can be directly reported. Results outside the reference range should be re-measured by a standard fibrinogen determination method, e.g. Fibrinogen method with Dade® Thrombin Reagent or with Multifibren® U Reagent. Derived fibrinogen testing is not suitable in patients with dysfibrinogenemia[6] or patients with prolonged PT, e.g. under oral anticoagulation[7,8].

Siemens has validated use of these reagents on various analyzers to optimize product performance and meet product specifications. User defined modifications are not supported by Siemens 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 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.

Interfering Substances

Many commonly administered drugs may affect the results obtained in prothrombin time testing[4]. This should be kept in mind especially when unusual or unexpected abnormal results are obtained. Unexpected abnormal results should be followed by additional coagulation studies to determine the source of the abnormality.

Turbidity of lipemic samples, e.g. with parenteral feeding, may preclude accuracy in the derived fibrinogen determination.

Dade® Innovin® Reagent is insensitive to concentrations of unfractionated heparin up to approximately 2.0 units per mL. The heparin sensitivity study was conducted using spiked normal pooled plasma and the sensitivity to heparin was defined by the concentration of heparin in the specimen that prolonged the PT results exceeding the upper limit of the reference range.

Inhibitors such as lupus anticoagulant may interfere with the prothrombin time and result for example in INRs that do not reflect the exact degree of anticoagulation[9].

Hirudin or other direct thrombin inhibitors in therapeutic dose result in prolonged prothrombin times[10,11].

Some blood collection tubes may contain Mg^{2+} ions, which have been shown to interfere with recombinant thromboplastins[12].

Blood plasma substitutes that contain hydroxyethyl starch (HES) may interfere with the analysis. Therefore, it is advised that plasma samples that contain such substitutes should not be analyzed with the PT derived fibrinogen method.

Expected Values

Values for healthy individuals vary from laboratory to laboratory depending on the technique used. Therefore, each laboratory should establish its own reference intervals based on the procedure and coagulation analyzers used.

In studies on the Sysmex® CA-7000 System with ostensibly healthy subjects the following reference intervals were determined:

Analyte	Samples n =	2.5^{th} to 97.5^{th} percentile
PT	158	9.9 to 11.8 seconds
Derived fibrinogen	124	1.8 to 3.5 g/L

Therapeutic Ranges

Therapeutic ranges for INR may vary depending on the indication of oral anticoagulant therapy[13].

Specific Performance Characteristics

Precision

Precision of prothrombin time results is generally limited by the method used. Therefore, within a single lot, the reagent should yield results which are reproducible within the quality control of the laboratory.

The precision of Dade® Innovin® Reagent on the Sysmex® CA-6000 system was estimated with quality control material from a total of six (6) separate runs over three (3) testing days (two runs per day) and four (4) replicates per control level, per run with the following results:

				Coefficient of Variation		
Assay	**Control Level**	**n**	**Mean**	**Intra-Assay**	**Inter-Assay**	**Total**
Prothrombin Time	1	24	12.4 s	1.3 %	2.0 %	2.4 %
	2	24	33.0 s	0.7 %	3.4 %	3.5 %
Derived Fibrinogen	1	24	2.37 g/L	4.0 %	2.8 %	4.9 %
	2	24	3.37 g/L	4.1 %	3.0 %	5.1 %

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Definition of Symbols

	Do not reuse		Use By
LOT	Batch Code	REF	Catalogue Number
	Caution, consult accompanying documents		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 mark
CONTENTS	Contents	→	Reconstitution volume
LEVEL	Level		Keep away from sunlight and heat

* not available in the US

** The mean normal PT (MNPT) is defined as the mean value of the normal range. It must be determined specifically for each thromboplastin lot using the method used to analyze the patient samples and, where appropriate, using the coagulation analyzer used for the analysis. Follow appropriate laboratory guidelines for establishing an MNPT, if applicable. For US customers the appropriate CLSI guideline is recommended.

2015-08

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Dade® Owren's Veronal Buffer

OV BUFFER

Intended Use

Dilution buffer for coagulation testing.

Summary

Owren's Veronal Buffer has been specifically prepared for coagulation studies but may be used in any laboratory test utilizing an isotonic barbital buffer, pH 7.35.

Reagents

Materials provided

OV BUFFER, REF B4234-25

10 x 15 mL, OV BUFFER, Dade® Owren's Veronal Buffer

Composition

Owren's Veronal Buffer: 2.84 x 10^{-2} M sodium barbital in 1.25 x 10^{-1} M sodium chloride; pH 7.35 ±0.1

Warnings and Precautions

For *in-vitro* diagnostic use only.

The pipetting steps must be performed with care in order to avoid contamination. Visible turbidity and flocculation are signs of microbial contamination.

Not for internal or external use by humans or animals.

Preparation of the Reagents

OV BUFFER is ready for use.

More details on the use of OV BUFFER are given in the corresponding assay protocols provided by Siemens Healthcare Diagnostics.

Storage and Stability

Store OV BUFFER unopened at 2 to 8 °C and use by the expiry date given on the label. Once opened, OV BUFFER is stable for 8 weeks at 2 to 8 °C.

Definition of Symbols

	Do not reuse		Use By
LOT	Batch Code	REF	Catalogue Number
	Caution, consult accompanying documents		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
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SIEMENS

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Dade® Thrombin Reagent

THROMBIN REAGENT

Revision bar indicates update to previous version.

Intended Use

For use in the quantitative determination of fibrinogen in plasma and to accelerate coagulation of anticoagulated samples for immunohematology studies.

Summary and Explanation

Depressed levels of fibrinogen are found in acquired and congenital hypo- and afibrinogenemias.

Acquired fibrinogen deficient conditions occur especially as a result of intravascular proteolysis of fibrinogen by thrombin (consumption coagulopathy e.g. in obstetrics, following surgical intervention), snake venom or plasmin (primary hyperfibrinolysis following therapy with streptokinase, urokinase or tPA). Furthermore, moderate hypofibrinogenemias may occur in cases of diminished production (in acute or chronic liver diseases), loss into the intravascular space (e.g. in ascites or acute hemorrhage and burns) or increased degradation (in shock or carcinoma).

Temporarily elevated levels of fibrinogen are found as a result of the behavior of fibrinogen as an "acute-phase protein":

a. Transitory hyperfibrinogenemias may occur after operations, traumas, myocardial infarction and infections[1].
b. Persistent hyperfibrinogenemias may be found in patients with neoplasias and chronic inflammatory diseases.

Levels of fibrinogen are found to increase slightly with age.

Elevated fibrinogen levels are a risk factor for cardiovascular disease[2].

Blood samples collected from patients who have received heparin may not clot and units of plasma may need to be converted to serum prior to laboratory use. Thrombin can be used to accelerate clotting of anticoagulated samples and units of plasma for use in immunohematologic tests[3].

Principle of the Method

The enzyme thrombin converts the soluble plasma protein fibrinogen into its insoluble polymer, fibrin. The clotting time for diluted plasma is inversely proportional to the fibrinogen concentration of the plasma[4-6]. By using this principle, Clauss[4] developed a simple procedure for determining fibrinogen based on measuring the clotting time of diluted plasma after the addition of thrombin. The clotting time obtained in this manner is then compared with that of a standardized fibrinogen preparation.

Reagents

Note: Dade® Thrombin Reagent can be used manually or on automated coagulation analyzers. Siemens Healthcare Diagnostics 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!

Materials provided

THROMBIN REAGENT, REF B4233-25
10 x → 1 mL, THROMBIN REAGENT, Dade® Thrombin Reagent
THROMBIN REAGENT, REF B4233-27
10 x → 5 mL, THROMBIN REAGENT, Dade® Thrombin Reagent

Composition

Dade® Thrombin Reagent: Lyophilized bovine thrombin preparation (approx. 100 IU/mL) with stabilizers and buffers.

Warnings and Precautions

For *in vitro* diagnostic use only.

Preparations of the Reagents

Dissolve the THROMBIN REAGENT with the amount of distilled or deionized water indicated on the vial label. Close the vial and let stand until the contents have dissolved. Carefully swirl the contents to mix. Do not shake. Mix carefully once more before using.

Note: Do not use any water containing preservatives.

Always store THROMBIN REAGENT in the original vial.

Indication that the reagent cannot be used: Lack of reproducible values.

Storage and Stability

THROMBIN REAGENT can be used up to the expiry date indicated on the label if stored unopened at 2 to 8 °C.

Stability after reconstitution: 5 days at 2 to 8 °C (closed vial)
8 hours at 15 to 25 °C (closed vial)

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

Additional materials required, but not provided

Sodium citrate solution for blood collection for coagulation tests
Standard Human Plasma, REF ORKL
Dade® Owren's Veronal Buffer, REF B4234
Control Plasma N, REF ORKE *or*
Dade® Ci-Trol® Coagulation Control Level 1 REF B4244–10
Control Plasma P, REF OUPZ *or*
Dade® Data-Fi® Abnormal Fibrinogen Control Plasma, REF B4233-22
Coagulation analyzer

Specimens

To obtain the plasma, carefully mix one part sodium citrate solution (0.11 mol/L) with nine parts venous blood, avoiding the formation of foam. Centrifuge as soon as possible for no less than 15 minutes at 1 500 to 2 500 x g and remove the supernatant plasma.

If analysis is to take place immediately, the plasma can either remain on the packed cells or be separated. To separate, transfer the plasma with a plastic pipette into a plastic tube and store at 2 to 8 °C. Do not store on ice.

Although investigations[8] have shown that there is no significant change in fibrinogen values when plasma samples are stored at 4 °C for up to 72 hours, it is advisable to test the samples as quickly as possible after collection.

Please refer to CLSI document H21-A5[7] for detailed information on sample preparation and storage.

Test Procedure

Fibrinogen Determination

Manual:

Dilute patient and control plasma 1:10 with Dade® Owren's Veronal Buffer.

Pipette into prewarmed coagulation tubes as follows:		
	Patient Plasma	Control Plasma
Plasma sample (diluted 1:10) Control Plasma (diluted 1:10)	0.2 mL –	– 0.2 mL
	incubate in waterbath at 37 °C 1 to 2 minutes or in a heat block at 37 °C for 2 to 4 minutes (no longer than 5 minutes)	
Dade® Thrombin Reagent (stored at 15–25 °C)	0.1 mL	0.1 mL
	Start stopwatch simultaneously with addition of Dade® Thrombin Reagent	

Always test samples and controls in duplicate.

Calculating the Reference Curve

Prepare five dilutions of Standard Human Plasma with Dade® Owren's Veronal Buffer ranging from 1:4 to 1:32. Carefully mix the contents of each tube with a clean pipette for each tube.

Example:

Test Tube	Dade® Owren's Veronal Buffer	Standard Human Plasma	Transfer from Tube 1	Dilution	Conversion Factor*
1	1.5 mL	0.5 mL	-	1:4	x 2.5
2	0.4 mL	-	0.6 mL	1:6.67	x 1.5
3	0.6 mL	-	0.4 mL	1:10	x 1
4	0.3 mL	-	0.1 mL	1:16	x 0.625
5	0.7 mL	-	0.1 mL	1:32	x 0.312

* The corresponding fibrinogen content of each standard dilution in relation to a 1:10 dilution is determined by multiplying the indicated Standard Human Plasma concentration with the respective conversion factor.

These dilutions are used for establishing the reference curve rather than the 1:10 dilutions used in the assay for patient or control sample. Plot the average clotting time for each of the 5 points on double logarithmic paper. Record the fibrinogen concentration on the x-axis and the time in seconds on the y-axis. The reference line is produced by connecting the points.

A new reference curve must be established each time there is a change in equipment or a new lot of Dade® Thrombin Reagent is used.

Internal Quality Control

Normal range:	Control Plasma N or Dade® Ci-Trol® Coagulation Control Level 1
Pathological range:	Control Plasma P or Dade® Data-Fi® Abnormal Fibrinogen Control Plasma

Two controls (one in the normal range and one in the pathological range) have to be measured at least once every 8 hours for assays run for patient testing during that interval.

Controls should be run after each new calibration curve and after each change of reagent vial. Recalibration may be necessary if control values are outside the target range. Do not release patient results until the cause of deviation has been identified and corrected.

Calculating the Analytical Results (manual method)

Determine the fibrinogen concentration of the patient plasmas in g/L by using the calibration curve and the clotting time obtained with the 1:10 plasma dilutions.

1. If very short times are obtained (high concentration of fibrinogen), dilute the plasma 1:20 (0.1 mL + 1.9 mL buffer) and analyze again. Then multiply the value in g/L read from the curve with the dilution factor (2).
2. If very long times are obtained (low concentration of fibrinogen), dilute the plasma only 1:5 (0.2 mL + 0.8 mL buffer) or 1:2 (0.4 mL + 0.4 mL buffer) and analyze again. Then divide the value in g/L read from the curve with the dilution factor 5 or 2 respectively.
3. No clotting in the 1:2 dilution of a patient plasma indicates a fibrinogen concentration of less than 0.15 g/L.

Clotting of Heparinized Patient Samples

To whole blood or separated plasma, add the amount of dry thrombin that adheres to the tips of several applicator sticks, or add 1 to 2 drops (0.1 mL) of reconstituted Dade® Thrombin Reagent (100 units/mL) per 1 mL of sample. Mix and incubate at 37 °C for 5 to 10 minutes.

Clotting of Units of Plasma

To 250 mL of plasma, add 1 to 2 mL of reconstituted Dade® Thrombin Reagent (100 units/mL). Mix and incubate at 37 °C for 30 minutes to 1 hour.

Note: Clotting can be further accelerated by reconstituting the Dade® Thrombin Reagent in 1 M $CaCl_2$ instead of distilled or deionized water and label accordingly.

Limitations of the Procedure

Levels of the following do not appear to interfere with Dade® Thrombin Reagent on the Sysmex® CA-1500 analyzer:

	Up to
Bilirubin	6 mg/dL
Hemoglobin (free)	100 mg/dL
Triglycerides	284 mg/dL
Heparin (LMW)	0.4 U/mL
Heparin (unfractionated)	0.6 U/mL

The results obtained may be influenced by the presence of heparin or fibrino(geno)lytic degradation products in patient plasma. Significant amounts of each of these substances may lead to a false low value for fibrinogen in the test[9].

Siemens has validated use of these reagents on various analyzers to optimize product performance and meet product specifications. User defined modifications are not supported by Siemens 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 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.

Reference values

1.8 - 3.5 g/L[10]

Reference values vary from laboratory to laboratory depending on technique used and population under study. Therefore, each laboratory should establish its own reference interval. (For more information on establishing reference intervals see CLSI document C28-A3[11]).

Specific Performance Characteristics

The data obtained with the thrombin clotting time method correlated excellently with other methods often used for the quantitative determination of fibrinogen[8,12].

Precision and Reproducibility

The Dade® Thrombin Reagent assay was used to measure fibrinogen concentrations in normal and pathological controls and patient pools. Eight determinations per day over 5 days (n = 40) were performed using a Sysmex® CA-1500 analyzer.

	Mean value (g/L)	Within run CV (%)	Run to run CV (%)	Total CV (%)
Control Plasma N	2.6	5.9	0.0	5.9
Control Plasma P	0.89	4.8	0.0	4.8
Low Plasma Pool	0.95	7.1	2.3	7.4
Normal Plasma Pool	2.8	3.5	0.0	3.5
Dade® Data-Fi® Abnormal Control	1.1	3.8	2.4	4.5

Method Comparison

Dade® Thrombin Reagent was compared to Dade® Fibrinogen Determination Reagents kit, using the Sysmex® CA-1500 analyzer, by evaluating 80 plasma samples with concentrations ranging from 0.50 to 8.6 g/L fibrinogen. Regression analysis of the results yielded the following equations:

Dade® Thrombin Reagent	(n =)	Slope	Intercept	Correlation Coefficient
	80	1.03	-0.063 g/L	0.995

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Definition of Symbols

	Do not reuse		Use By
LOT	Batch Code	REF	Catalogue Number
	Caution, consult accompanying documents		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 mark
CONTENTS	Contents	→	Reconstitution volume
LEVEL	Level		Keep away from sunlight and heat

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INNOVANCE® D-Dimer

Revision bar indicates update to previous version.

Intended Use

INNOVANCE® D-Dimer is a particle-enhanced, immunoturbidimetric assay for the quantitative determination of cross-linked fibrin degradation products (D-dimers) in human plasma for use on coagulation analyzers. The INNOVANCE® D-Dimer assay is indicated for use in conjunction with a clinical pretest probability (PTP) assessment model to exclude deep vein thrombosis (DVT) and pulmonary embolism (PE) disease in outpatients suspected of DVT or PE. INNOVANCE® D-Dimer can be used for the monitoring of the relative change in D-dimer concentration.

Summary and Explanation

Coagulation activation results in the cleavage of fibrinogen to fibrin monomer. The fibrin monomers spontaneously aggregate to fibrin and are cross-linked by factor XIII; this produces a fibrin clot. In response to the coagulation process the fibrinolytic system is activated resulting in the conversion of plasminogen into plasmin, which cleaves fibrin (and fibrinogen) into the fragments D and E. Due to cross-linkage between D-domains in the fibrin clot, the action of plasmin releases fibrin degradation products with cross-linked D-domains. The smallest unit is D-dimer. Detection of D-dimers, which specifies cross-linked fibrin degradation products generated by reactive fibrinolysis, is an indicator of coagulation activity. Fibrin degradation products are not consistently "D-dimer" but are a mixture of fragments and complexes of different molecular mass (e.g. DD 195 kD, DD/E 228 kD DXXD 693 kD, YXD/DXY 850 kD) containing the D and E domain[1]. An association between a certain mixture or molecular mass and the clinical condition has not been demonstrated. The in-vivo half life of D-dimer is approximately 8 hours[2].

Elevated D-dimer levels are observed in all diseases and conditions with increased coagulation activation, e.g. thromboembolic disease, disseminated intravascular coagulopathy (DIC), acute aortic dissection, myocardial infarction, malignant diseases, obstetric complications, third trimester of pregnancy, surgery or polytrauma[3-8].

The major diagnostic application of D-dimer testing is in the exclusion of thromboembolic events, such as deep vein thrombosis or pulmonary embolism. If D-dimer results are below the decision threshold, a thromboembolic event can be excluded with a test-specific negative predictive value (NPV). The use of D-dimer testing in combination with a well-validated clinical pretest probability score represents an efficient and safe screening tool for the exclusion of thromboembolic events[3,4]. However, symptoms being present since a certain period of time, e.g. longer than a week, may produce normal D-dimer values[9].

For the diagnosis of DIC a scoring system has been suggested, in which elevated D-Dimer levels represent the major indicator of DIC[5].

Furthermore, increased D-dimer levels have been shown to be associated with the risk for recurrent thromboembolic events after discontinuation of oral anticoagulant therapy[6,10,11], and a poor prognosis in cardiac diseases, such as ischemic heart disease, chronic atrial fibrillation or heart failure[7]. It has been demonstrated that ETP and D-dimer with INNOVANCE® D-Dimer were independently associated with the risk of recurrence of VTE: Patients with high ETP and/or high INNOVANCE® D-Dimer values may benefit from prolonged anticoagulation[10].

For exclusion of venous thrombosis or pulmonary embolism the analyte D-dimer should not be used as an aid in patients with[9]:

- Therapeutic dose anticoagulant therapy for > 24 hours
- Fibrinolytic therapy within previous 7 days
- Trauma or surgery within previous 4 weeks
- Disseminated malignancies
- Aortic aneurysm
- Sepsis, severe infections, pneumonia, severe skin infections
- Liver cirrhosis
- Pregnancy, or only with specific reference ranges.

Trimester-specific reference ranges during pregnancy have been suggested for INNOVANCE® D-Dimer[12].

Thrombosis superimposed on a ruptured or unstable atherosclerotic plaque is the leading cause of most ischemic cardiovascular events. Elevated INNOVANCE® D-Dimer levels have been demonstrated to be significant prognostic markers in patients with angiographically confirmed coronary artery disease[13].

Patients with acute coronary syndrome mostly show normal levels of D-dimer. In contrast, patients with aortic dissection or aortic aneurysm mostly have highly elevated levels of D-dimer. Therefore, the detection of D-dimer in patients with acute chest pain may help to differentiate between both clinical conditions[9].

Principle of the Procedure

Polystyrene particles covalently coated with a monoclonal antibody (8D3)[14] are aggregated when mixed with samples containing D-dimer. The D-dimer cross-linkage region has a stereosymmetrical structure, i.e. the epitope for the monoclonal antibody occurs twice. Consequently, one antibody suffices in order to trigger an aggregation reaction, which is then detected turbidimetrically via the increase in turbidity.

Reagents

Note:

INNOVANCE® D-Dimer can be used with many automatic coagulation analyzers. Siemens Healthcare Diagnostics provides Reference Guides (Application Sheets) for several coagulation analyzers. The Reference Guides (Application Sheets) contain analyzer/assay specific handling 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.

Composition

INNOVANCE® D-Dimer	Form	Ingredient	Concentration	Source
REAGENT	Lyophilized	Polystyrene particles coated with monoclonal antibodies to D-dimer[a)] Human serum albumin Preservatives: amphotericin B, gentamicin	0.1 g/L 0.5 g/L	Mouse Human

INNOVANCE® D-Dimer	Form	Ingredient	Concentration	Source
BUFFER	Liquid	Saline buffer Dextrane Imidazole Preservative: sodium azide	 13 g/L < 1 g/L	
SUPPLEMENT	Liquid	Saline buffer Heterophilic blocking reagent Preservative: sodium azide	 0.63 g/L < 1 g/L	Mouse
DILUENT	Liquid	Saline buffer Imidazole Preservative: sodium azide	 6.8 g/L < 1 g/L	
CALIBRATOR	Lyophilized	Human plasma, D-dimer preparation[b)] Preservatives: 5-chloro-2-methyl-4-isothiazole-3-one and 2-methyl-4-isothiazole-3-one sodium azide	 5.0 mg/L (FEU) < 1.0 mg/L < 1 g/L	Human

a) antibody concentration may vary from lot to lot
b) nominal value per vial

Precautions

For *in-vitro* diagnostic use.

Contains sodium azide (< 1 g/L) as a preservative. Sodium azide can react with copper or lead pipes in drain lines to form explosive compounds. Dispose of properly in accordance with local regulations.

CAUTION! POTENTIAL BIOHAZARD
INNOVANCE® D-Dimer REAGENT and INNOVANCE® D-Dimer CALIBRATOR contain human source material. 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 found to be in conformance with the In Vitro Diagnostic Directive in the EU or FDA approved tests. Because no known test can offer complete assurance of the absence of infectious agents, all human derived products should be handled with appropriate caution.

Reagent Preparation

All kit components are lot-specific except INNOVANCE® D-Dimer DILUENT. The combination of lots other than those specified for the particular kit lot may lead to incorrect results.

Follow the preparation instructions prior to use according to the table below. Storage instructions are detailed in section "Storage and Stability".

Instructions for the preparation of the kit components

Instructions	INNOVANCE® D-Dimer REAGENT	INNOVANCE® D-Dimer BUFFER / SUPPLEMENT / DILUENT	INNOVANCE® D-Dimer CALIBRATOR
Reconstitution	1. Dissolve with 4.0 mL distilled water 2. Invert 3 times 3. Leave the vial for at least 15 minutes at 15–25 °C	Ready to use	1. Dissolve with 1.0 mL distilled water 2. Mix carefully without foam formation 3. Leave the vial for at least 15 minutes at 15–25 °C
Prior to placing on the system	1. Mix well (again) by inverting 3 times 2. Avoid foam formation 3. Remove bubbles	1. Avoid foam formation 2. BUFFER only: resuspend potential precipitates by gently swirling. Any residual precipitates after resuspension do not impact test results 3. Remove bubbles	1. Mix (again) carefully 2. Do not use if the vial contains a visible clot
Aliquoting	1. Mix well (again) by inverting 3 times 2. Aliquot into an empty vial provided with the same kit 3. Discard empty vials if unused until complete consumption of the kit	1. Aliquot into an empty vial provided with the kit 2. Discard empty vials if unused until complete consumption of the kit	n.a.
Freeze and thaw	1. Use the original container or the empty vial provided with the kit 2. Follow storage instructions in section "Storage and Stability" 3. Thaw at 37 °C within 10 minutes and mix carefully. Thereafter the vial may no longer be stored at 2–8 °C 4. Do not freeze again after thawing		Refer to section "Storage and Stability" Mix carefully after thaw
Placing on the system	Use position indicated in the respective Reference Guides (Application Sheets)		
Note	The reconstitution, opening or freezing date may be documented on the vial label using the framed free space		

Storage and Stability

The kit may be used up to the expiry date indicated on the label if stored unopened at 2 to 8 °C.

Stability after reconstitution or first opening (closed vial)

Temperature	INNOVANCE® D-Dimer REAGENT	INNOVANCE® D-Dimer BUFFER	INNOVANCE® D-Dimer SUPPLEMENT	INNOVANCE® D-Dimer DILUENT	INNOVANCE® D-Dimer CALIBRATOR
2–8 °C	4 weeks	4 weeks	4 weeks	4 weeks	-
≤ –18 °C•	4 weeks	4 weeks	4 weeks	4 weeks	-
15–25 °C	-	-	-	-	4 hours

• Do not refreeze after thawing. Follow the freeze and thaw instructions in section "Preparation of the Reagents".

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

Specimen Collection and Handling

– Use citrated platelet poor plasma for testing.
– Obtain the plasma by carefully mixing 1 part sodium citrate solution (0.11 mol/L or 3.2 %) with 9 parts venous blood. Avoid foam formation.
– An evacuated tube system or syringe may be used.
– Centrifuge the blood tube directly after blood collection for 15 minutes at 1500 x g to 2500 x g. Please refer to CLSI guideline H21-A5[15] for further details. The manufacturer's instructions for the sampling equipment must also be observed.
– Clarify turbid plasma once more by centrifugation at approx. 15,000 x g for 10 minutes.

Stability of the Plasma Samples

15 to 25 °C	4 hours
2 to 8 °C	24 hours
≤ –18 °C	4 weeks••

•• If frozen within 4 hours of blood collection.

Preparation of Frozen Samples

– Freeze plasma within 4 hours of blood collection at ≤ –18 °C.
– Thaw frozen plasma within 10 minutes at 37 °C, homogenize by carefully mixing without foam formation and centrifuge at approx. 15,000 x g for 10 minutes. Then carry out the D-dimer determination within 2 hours. Do not freeze more than two times.
– For specific handling information on the various analyzers, please consult the respective Reference Guides (Application Sheets).

Procedure

Materials Provided

INNOVANCE® *D-Dimer Kit,* REF *OPBP 03 with*

3 x → 4.0 mL	INNOVANCE® D-Dimer REAGENT, reagent
3 x 5.0 mL	INNOVANCE® D-Dimer BUFFER, buffer
3 x 2.6 mL	INNOVANCE® D-Dimer SUPPLEMENT, supplementary reagent
3 x 5.0 mL	INNOVANCE® D-Dimer DILUENT, sample diluent
2 x → 1.0 mL	INNOVANCE® D-Dimer CALIBRATOR, calibrator
12 x	EMPTY VIAL, empty vials 3 x each for INNOVANCE® D-Dimer REAGENT, INNOVANCE® D-Dimer BUFFER, INNOVANCE® D-Dimer SUPPLEMENT, and INNOVANCE® D-Dimer DILUENT

INNOVANCE® *D-Dimer Kit ,* REF *OPBP 07 with*

6 x → 4.0 mL	INNOVANCE® D-Dimer REAGENT, reagent
6 x 5.0 mL	INNOVANCE® D-Dimer BUFFER, buffer
6 x 2.6 mL	INNOVANCE® D-Dimer SUPPLEMENT, supplementary reagent
6 x 5.0 mL	INNOVANCE® D-Dimer DILUENT, sample diluent
2 x → 1.0 mL	INNOVANCE® D-Dimer CALIBRATOR, calibrator

Additional materials required but not provided

INNOVANCE® D-Dimer Controls, REF OPDY
INNOVANCE® D-Dimer Sample Diluent, REF OPBR
Coagulation analyzer
Distilled water
Pipettes

Calibration

Calibration Material	INNOVANCE® D-Dimer CALIBRATOR
Calibration Scheme	6 levels, n = 2 per level
Units	mg/L FEU (Fibrinogen Equivalent Units)
Typical Calibration Levels	INNOVANCE® D-Dimer CALIBRATOR is diluted automatically with INNOVANCE® D-Dimer DILUENT by the instrument. The respective levels are defined by the actual concentration of the INNOVANCE® D-Dimer CALIBRATOR as provided in the Table of Analytical Values, and by the system-specific dilution settings for calibration.
Calibration Frequency	A new calibration is required • For each new reagent lot of INNOVANCE® D-Dimer. Use the INNOVANCE® D-Dimer CALIBRATOR provided with INNOVANCE® D-Dimer Kit only. • After major maintenance or service, if indicated by quality control results • As indicated in laboratory quality control procedures • When required by government regulations

Internal Quality Control

– INNOVANCE® D-Dimer Controls must be tested at least every eight hours on each testing day and for each vial of reagent for the respective measurement range to ensure that the system is functioning correctly. Control of the lower measurement range is performed with INNOVANCE® D-Dimer CONTROL 1, and for the upper range with INNOVANCE® D-Dimer CONTROL 2.
– The measured values obtained must be within the ranges given in the respective Table of Assigned Values.
– If the values obtained are outside of the ranges, the measurement must be repeated. If the deviations are confirmed, a new calibration must be performed.
– Do not report patient results unless the cause of deviating control results has been identified and corrected!

Results

- INNOVANCE® D-Dimer results are provided in mg/L FEU.
- Results in mg/L FEU may be converted to µg/mL FEU, µg/L FEU or ng/mL FEU as shown with an example below.

Example for the conversion of units

INNOVANCE® D-Dimer result as reported by the system (example):	1.25 mg/L FEU
The reported example result equals:	1.25 µg/mL FEU
Result in mg/L converts to µg/L or ng/mL (factor of 1000):	1250 µg/L FEU or 1250 ng/mL FEU

Measuring Range

0.17 to 4.40 mg/L FEU with BCS®/BCS® XP Systems. Measuring ranges are instrument dependent and given in the Reference Guides (Application Sheets).

Samples initially outside the measuring range may be diluted with INNOVANCE® D-Dimer DILUENT. The BCS®/BCS® XP Systems automatically perform a sample dilution, resulting in a measuring range of up to 35.2 mg/L FEU.

Limitations of the Procedure

- Turbidity and particles in the samples may interfere with the determination. Therefore, samples containing particles must be centrifuged for 10 minutes at approx. 15,000 x g again prior to testing.
- Lipemic samples or samples that contain particles that cannot be clarified by centrifuging must be excluded from testing.
- Due to matrix effects, inter-laboratory survey samples (External Quality Assessment; EQA) and control samples may yield results that differ from those obtained with other methods. It may therefore be necessary to assess these results in relation to method-specific target values.
- Patient samples may contain heterophilic antibodies (e.g. human anti-mouse antibodies (HAMA) and rheumatoid factors) that could react in immunoassays to give a falsely elevated or depressed result. This assay has been designed to minimize interference from heterophilic antibodies. Nevertheless, complete elimination of this interference from all patient specimens cannot be guaranteed.
- Siemens has validated use of these reagents on various analyzers to optimize product performance and meet product specifications. User defined modifications are not supported by Siemens 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 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.**
- A very low percentage of patients with DVT may yield D-dimer results below the cut-off of 0.50 mg/L FEU. This is known to be more prevalent in patients with distal DVT[7].
- Patients with subsegmental/peripheral PE or distal DVT may have a normal INNOVANCE® D-Dimer result[16,17].

Clinical performance data were determined on an outpatient population. Therefore, clinical performance results should not be extrapolated to an inpatient population.

Expected Values

Plasma specimens obtained from apparently healthy donors (n = 150) were tested using the INNOVANCE® D-Dimer assay on the BCS®/BCS® XP System with the following results:

90^{th} percentile 0.55 mg/L FEU

It is recommended that each laboratory establishes its own reference range, which may be unique to the population it serves, depending on geographical, patient and environmental factors.

Increases in D-dimer concentration observed with thromboembolic events can be variable due to localization, extension and age of the thrombus. Therefore, a thromboembolic event cannot be excluded with certainty solely on the basis of an increased D-dimer concentration being within the reference range of ostensibly healthy persons[18].

Specific Performance Characteristics

Precision

Precision studies were conducted with the BCS®/BCS® XP System, as described in the CLSI guideline EP5-A2[19], using INNOVANCE® D-Dimer CONTROL 1 (control plasma in the normal range) and INNOVANCE® D-Dimer CONTROL 2 (control plasma in the pathological range) as well as 3 concentration levels in human plasma, i.e., normal, low pathological and high pathological.

	Precision (n = 80)		
Sample	**Mean (mg/L FEU)**	**Repeatability CV (%)**	**Within-device/lab CV (%)**
INNOVANCE® D-Dimer CONTROL 1	0.3	4.1	4.3
INNOVANCE® D-Dimer CONTROL 2	2.6	1.4	2.2
Normal plasma pool	0.2	7.8	7.9
Low plasma pool	0.8	3.4	4.5
High plasma pool	3.6	1.5	2.6

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

Specificity and crossreactivity

In a representative study, fibrinogen degradation products (X, Y, D und E) were tested according to CLSI guideline EP7-A2[20] with the following cross-reactivity:

Cross-reactant	**concentration**	**% cross-reactivity**
Fibrinogen degradation products	2.0 – 20.0 mg/L	≤ 2.5

% cross-reactivity = apparent D-dimer concentration minus true concentration divided by concentration of the cross-reactant multiplied by 100[16]. The cross-reactivity observed resulted in an increase of apparent D-dimer concentrations.

Method Comparison

A study was performed to compare the INNOVANCE® D-Dimer assay to Stratus® CS DDMR Test Pak and to another commercially available assay for the measurement of D-dimer. The results from the Passing-Bablok regression analysis are summarized in the following table:

	Stratus® CS DDMR (n = 1067)	**Commercially available assay (n = 1417)**
Concentration range of plasma samples investigated	0.17 mg/L FEU to 35.2 mg/L FEU	0.17 mg/L FEU to 35.2 mg/L FEU
Regression equation	y = 1.036 x + 0.023 mg/L FEU	y = 1.312 x + 0.172 mg/L FEU
Coefficient of Correlation	r = 0.978	r = 0.961

Diagnostic Sensitivity and Specificity

The diagnostic utility of the INNOVANCE® D-Dimer assay to exclude the diagnosis of Venous Thromboembolism (VTE) was validated in a prospective management study.

- Samples were collected prospectively from out-patients suspected of DVT / PE at four different sites. Patients with therapeutic or prophylactic anticoagulation and pregnant women were excluded from the study. The diagnosis of DVT and/or PE was confirmed by applying approved diagnostic algorithms including the assessment of pre-test probability and/or application of imaging methods. Patient follow-up was conducted after 3 months. The age of patients included in the study ranged between 18 and above 90 years, with a majority of patients above 61 years.
- The prevalence of VTE was 21 % in the population studied.
- Samples were stored frozen until further analysis.
- The INNOVANCE® D-Dimer results were analyzed using a clinical cut-off of 0.50 mg/L FEU whereby a result of ≥ 0.50 mg/L FEU was considered positive and a result of < 0.50 mg/L FEU was considered negative.
- For the SYSMEX CS-2000i/CS-2100i System a different study population was used with the same age distribution. The prevalence of VTE was 27.3 % in this population.

Test performance is summarized in the following table. Two samples tested false negative with INNOVANCE® D-Dimer consistently across all systems derived from patients being diagnosed with distal DVT. These samples were tested false negative with two comparison methods, too.

Regarding the SYSMEX CS-2000i/CS-2100i System two samples tested false negative with INNOVANCE® D-Dimer, which were derived from a patient being diagnosed with distal DVT and from a patient being diagnosed with a proximal DVT within the follow-up period. These two samples were tested false negative with INNOVANCE® D-Dimer consistently across all systems and with two comparison methods, too.

System	**Cut-Off (mg/L FEU)**	**Diagnostic Sensitivity / LCL (%)**	**Diagnostic Specificity / LCL (%)**	**Negative Predictive Value (NPV) LCL (%)**	**Sample n =**
BCS®/BCS® XP System	0.50	99.4 / 98.0	38.2 / 35.8	99.5 / 98.6	1425
BCT® System	0.50	99.2 / 97.4	40.4 / 37.7	99.4 / 98.4	1128[#]
SYSMEX CA-1500 System	0.50	99.4 / 98.0	39.3 / 36.9	99.5 / 98.7	1425

System	Cut-Off (mg/L FEU)	Diagnostic Sensitivity / LCL (%)	Diagnostic Specificity / LCL (%)	Negative Predictive Value (NPV) LCL (%)	Sample n =
SYSMEX CA-7000 System	0.50	99.4 / 98.0	38.3 / 35.9	99.5 / 98.7	1425
SYSMEX CA-560/CA-660 System	0.50	99.4 / 98.0	37.8 / 35.4	99.5 / 98.6	1425
SYSMEX CS Systems	0.50	98.8 / 96.2	34.2 / 30.5	98.7 / 96.4	612†

LCL = lower 95 % confidence limit. The study design is described in the respective publications[21,22].

Samples collected at one study site were not measured with the BCT® System.

† A different study population was used for the SYSMEX CS System.

Interference

- The D-dimer method was evaluated for interference according to CLSI guideline EP7-A2[20].
- Bias is the difference in the results between the control sample (without the interferent) and the test sample (contains the interferent) expressed in percent. Bias exceeding 10 % is considered interference.
- The potential interference by bilirubin, hemoglobin and lipids is described in the analyzer specific Reference Guides (Application Sheets).
- In isolated cases, unspecific reactions may occur independent of the D-dimer concentration. Therefore, in particular cases sample dilution may lead to aberrant results[23].

Substance tested (BCS®/BCS® XP System)	Substance concentration	S.I. units	D-dimer concentration	Bias* (%)	D-dimer concentration	Bias* (%)
Hemoglobin (hemolysate)	200 mg/dL	124 µmol/L	0.29 mg/L	3.4	2.43 mg/L	1.2
Bilirubin (unconjugated)	60 mg/dL	1026 µmol/L	0.29 mg/L	-3.3	2.56 mg/L	0.8
Triglycerides (commercial emulsion)	600 mg/dL	6840 µmol/L	0.28 mg/L	-3.6	2.32 mg/L	0.4

* Analyte results should not be corrected based on this bias.

Non-Interfering Substances

The following substances do not interfere with the INNOVANCE® D-Dimer method when present in plasma at the concentrations indicated. Inaccuracies (biases) due to these substances are less than 10 % at D-dimer concentrations of 0.45 mg/L to 0.55 mg/L.

Substance	Test concentration	S.I. units
Acetaminophen	20 mg/dL	1324 µmol/L
Acetylsalicylic acid	60 mg/dL	3.33 mmol/L
Amikacin	15 mg/dL	256 µmol/L
Ampicillin	5.3 mg/dL	152 µmol/L
Ascorbic acid	5.0 mg/dL	284 µmol/L

Substance	Test concentration	S.I. units
Caffeine	6.0 mg/dL	308 µmol/L
Captopril	20 mg/dL	922 µmol/L
Carbamazepine	3.0 mg/dL	127 µmol/L
Chloramphenicol	5.0 mg/dL	155 µmol/L
Chlordiazepoxide	1.0 mg/dL	33.3 µmol/L
Chlorpromazine	0.2 mg/dL	6.3 µmol/L
Cimetidine	2.0 mg/dL	79.2 µmol/L
Cyclosporin A	35 mg/dL	291 µmol/L
Dalteparin sodium (anti-factor Xa)[24]	5 IU/mL	n.a.
Dextrane 40	1800 mg/dL	n.a.
Diazepam	0.5 mg/dL	18 µmol/L
Digoxin	5 ng/mL	6.4 nmol/L
Erythromycin	6.0 mg/dL	81.6 µmol/L
Ethanol	400 mg/dL	86.8 mmol/L
Ethosuximide	25 mg/dL	1770 µmol/L
Furosemide	6.0 mg/dL	181 µmol/L
Gentamicin	12 mg/dL	251 µmol/L
Heparin, ammonium-[25]	3 U/mL	n.a.
Heparin, lithium-[25]	3 U/mL	n.a.
Heparin, sodium-[25]	3 U/mL	n.a.
Ibuprofen	50 mg/dL	2425 µmol/L
Lidocaine	1.2 mg/dL	51.2 µmol/L
Lithium chloride	2.3 mg/dL	3.2 mmol/L
Nicotine	0.1 mg/dL	6.2 µmol/L
Penicillin G[26]	25 U/mL	n.a.
Pentobarbital	8.0 mg/dL	354 µmol/L
Phenobarbital	10 mg/dL	431 µmol/L
Phenytoin	5.0 mg/dL	198 µmol/L
Primidone	4.0 mg/dL	183 µmol/L
Propoxyphene	0.2 mg/dL	6.1 µmol/L
Propranolol	0.5 mg/dL	19 µmol/L
Theophylline	4.0 mg/dL	222 µmol/L
Valproic acid	50 mg/dL	3472 µmol/L
Warfarin	11 mg/dL	357 µmol/L

Endogenous Interferences

The following substances do not interfere with the INNOVANCE® D-Dimer method when present in plasma at the concentrations indicated. Studies have been performed either by adding the interferent or by performing mixing studies with samples containing the interferents in a low and high concentration. The recovery was in the range of 100 ± 10 %.

Substance	Test Concentration	S.I. units
Creatinin	30 mg/dL	2655 µmol/L
Albumin	6 g/dL	60 g/L
Cholesterol	315 mg/dL	8.1 mmol/L
Rheumatoid Factors[27]	1330 IU/mL	n.a.
Fibrinogen	10 g/L	29.4 µmol/L
Urea	500 mg/dL	83.3 mmol/L
Uric Acid	20 mg/dL	1.2 mmol/L
Immunoglobulin G (IgG)	5 g/dL	50 g/L

Recovery

Recovery of a mixture of low and high samples ranged from 94 % to 105 % with a mean recovery of 98 %.

Antigen Excess

The INNOVANCE® D-Dimer method shows no high-dose hook effect up to 500 mg/L D-dimer.

Limit of detection

The Limit of Detection (LoD - the lowest concentration that can be detected reliably) for D-dimer is 0.05 mg/L FEU. It was determined consistent with CLSI guideline EP17-A[28] and with proportions of false positives (α) less than 5 % and false negatives (β) less than 5 %; based on 16 determinations, with 4 blank and 4 low level samples. The Limit of Blank (LoB) is the highest concentration that is likely to be observed for a blank sample; it is 0.02 mg/L FEU.

Other system specific results are provided with the respective Reference Guides (Application Sheets).

Note

The values cited for specific performance characteristics represent typical results and are not to be regarded as specifications for the INNOVANCE® D-Dimer.

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Definition of Symbols

	Do not reuse		Use By
LOT	Batch Code	REF	Catalogue Number
	Caution, consult accompanying documents		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 mark
CONTENTS	Contents		Reconstitution volume
LEVEL	Level		

2013-01

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SIEMENS

INNOVANCE® D-Dimer Controls
INNOVANCE® D-Dimer CONTROLS

See shaded sections - updated information versus edition from June 2008

Intended Use
INNOVANCE® D-Dimer Control 1 and INNOVANCE® D-Dimer Control 2 are assayed controls for the assessment of precision and analytical bias in the normal and pathological range for the determination of D-dimer on Siemens and Sysmex® Systems.

Reagents
Materials provided
INNOVANCE® D-Dimer CONTROLS REF OPDY 03 with
5 x ⟶ 1 mL INNOVANCE® D-Dimer CONTROL 1, Control 1
5 x ⟶ 1 mL INNOVANCE® D-Dimer CONTROL 2, Control 2
1 x table of lot- and method-specific assigned values and ranges.

Contents
INNOVANCE® D-Dimer Control 1 and INNOVANCE® D-Dimer Control 2 are lyophilized human plasma based products containing D-Dimer.

Preservatives: 5-chloro-2-methyl-4-isothiazol-3-one *and*
2-methyl-4-isothiazol-3-one (< 1 mg/L)
sodium azide (< 1 g/L)

Warnings and Precautions
1. For *in-vitro* diagnostic use.
2. Contains sodium azide (< 1 g/L) as a preservative. Sodium azide can react with copper or lead pipes in drain lines to form explosive compounds. Dispose of properly in accordance with local regulations.
3. INNOVANCE® D-Dimer Control 1 and INNOVANCE® D-Dimer Control 2 contain components of human origin.
   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 found to be in conformance with the In Vitro Diagnostic Directive in the EU or FDA approved tests. Because no known test can offer complete assurance of the absence of infectious agents, all human derived products should be handled with appropriate caution.

Additional materials required, but not provided
INNOVANCE® D-Dimer
INNOVANCE® D-Dimer kit, REF OPBP
Distilled water
Pipettes
Coagulation analyzer
Stratus® CS Acute Care* Diagnostic System:
DDMR TestPak, REF CDDMR
DDMR CalPak, REF CDDMR-C
DDMR DilPak, REF CDDMR-D
Stratus® CS STAT Flourometric Analyzer

Preparation of the Control Plasmas
Dissolve INNOVANCE® D-Dimer CONTROL 1 and INNOVANCE® D-Dimer CONTROL 2 with 1 mL of distilled water each and mix carefully (without foam formation). Allow to stand for at least 15 minutes at +15 to +25 °C. Mix carefully once more before using.

Storage and Stability
If stored unopened at +2 to +8 °C, INNOVANCE® D-Dimer CONTROL 1 and INNOVANCE® D-Dimer CONTROL 2 can be stored and used up to the expiry date indicated on the label.

Stability after reconstitution

Temperature	INNOVANCE® D-Dimer Control 1 / INNOVANCE® D-Dimer Control 2
+15 to +25 °C	8 hours
+2 to +8 °C	7 days
≤ -18 °C**	4 weeks

** Must be frozen in the original containers. Do not refreeze after thawing.

INNOVANCE® D-Dimer Control 1 and INNOVANCE® D-Dimer Control 2 may be frozen in the original container and thawed again once after reconstitution. The previous storage time at +15 to +25 °C must not have exceeded 4 hours. The plasma must be well sealed and frozen as quickly as possible. Thawing must be completed at +37 °C within a maximum of 10 minutes. INNOVANCE® D-Dimer Control 1 and INNOVANCE® D-Dimer Control 2 should not stand for more than 4 hours at +15 to +25 °C after thawing. INNOVANCE® D-Dimer Control 1 and INNOVANCE® D-Dimer Control 2 must no longer be used if they contain visible clots.

Procedure
For quality control, INNOVANCE® D-Dimer Control 1 and INNOVANCE® D-Dimer Control 2 is used with the INNOVANCE® D-Dimer kit according to the Instructions for Use, or the Stratus® CS D-Dimer TestPak. The value obtained must be within the range as indicated in the lot-specific Table of Assigned Values.

Determination of assigned values
The target values were assigned by Siemens Healthcare Diagnostics by using INNOVANCE® D-Dimer Calibrator and the corresponding INNOVANCE® D-Dimer reagents, or the Stratus® CS DDMR CalPak and the corresponding Stratus® CS DDMR TestPak. The mean values of the series of determinations performed over several days with different instruments and reagent lots are indicated in the lot-specific Table of Assigned Values.

The range is a fixed interval that covers the systematic analytical deviations that may occur due to deviations in reagents or analyzers.
The method-dependent target values and ranges for each lot of INNOVANCE® D-Dimer Control 1 and INNOVANCE® D-Dimer Control 2 are provided in the accompanying Table of Assigned Values. If used as a precision control, the user should establish the target concentration and confidence limits during a preliminary phase. Due to performance variability, the use of methods other than those stated in the accompanying Table of Assigned Values is not recommended.

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CE

Edition April 2009

INNOVANCE® D-Dimer Kontrollen
INNOVANCE® D-Dimer CONTROLS

Schattierte Abschnitte - Aktualisierte Informationen gegenüber der Ausgabe Juni 2008

Anwendungsbereich
INNOVANCE® D-Dimer Kontrolle 1 und INNOVANCE® D-Dimer Kontrolle 2 dienen zur Bewertung der Präzision und analytischen Abweichung im normalen und pathologischen Bereich an Siemens und Sysmex® Systemen.

Reagenzien
Inhalt der Handelspackung
INNOVANCE® D-Dimer CONTROLS REF OPDY 03 mit
5 x ⟶ 1 ml INNOVANCE® D-Dimer CONTROL 1, Kontrolle 1
5 x ⟶ 1 ml INNOVANCE® D-Dimer CONTROL 2, Kontrolle 2
1 x Tabelle chargen- und methodenspezifischer Sollwerte und Bereiche.

Zusammensetzung
Die Kontrollplasmen INNOVANCE® D-Dimer Kontrolle 1 und INNOVANCE® D-Dimer Kontrolle 2 sind D-Dimer-enthaltende lyophilisierte Produkte auf Humanplasma-Basis.

Konservierungsmittel: 5-Chlor-2-methyl-4-isothiazol-3-on *und*
2-Methyl-4-isothiazol-3-on (< 1 mg/l)
Natriumazid (< 1 g/l)

Warnungen und Vorsichtsmaßnahmen
1. Nur zur *in-vitro*-diagnostischen Anwendung.
2. Enthält Natriumazid (< 1 g/l) als Konservierungsmittel. Natriumazid kann mit kupfer- oder bleihaltigen Abflussrohren explosive Verbindungen eingehen. Entsorgen Sie bitte ordnungsgemäß entsprechend den örtlichen Richtlinien.
3. INNOVANCE® D-Dimer Kontrolle 1 und INNOVANCE® D-Dimer Kontrolle 2 enthalten Komponenten humanen Ursprungs.
   Jede individuelle Blutspende wurde mit negativem Befund auf humane Immundefizienz-Viren (HIV) 1 und 2, Hepatitis B-Viren (HBV) und Hepatitis C-Viren (HCV) getestet. Die eingesetzten Teste entsprachen entweder den Anforderungen der EU Richtlinie über In-vitro-Diagnostika oder waren von der FDA zugelassen. Da kein Test mit völliger Sicherheit die Abwesenheit von Infektionserregern garantieren kann, sollten alle Produkte mit humanen Bestandteilen mit angemessener Sorgfalt behandelt werden.

Zusätzlich benötigte Materialien
INNOVANCE® D-Dimer
INNOVANCE® D-Dimer Kit, REF OPBP
Destilliertes Wasser
Pipetten
Gerinnungsmessgerät
Stratus® CS Acute Care* Diagnostic System:
DDMR TestPak, REF CDDMR
DDMR CalPak, REF CDDMR-C
DDMR DilPak, REF CDDMR-D
Stratus® CS STAT Flourometric Analyzer

Vorbereitung der Kontrollplasmen
INNOVANCE® D-Dimer CONTROL 1 und INNOVANCE® D-Dimer CONTROL 2 werden jeweils mit 1 ml destilliertem Wasser unter vorsichtigem Schütteln (ohne Schaumbildung) gelöst. Mindestens 15 Minuten bei +15 bis +25 °C stehen lassen. Vor Gebrauch noch einmal vorsichtig schütteln.

Haltbarkeit und Lagerungsbedingungen
INNOVANCE® D-Dimer CONTROL 1 und INNOVANCE® D-Dimer CONTROL 2 sind ungeöffnet bei +2 bis +8 °C zu lagern und bis zu dem auf dem Etikett angegebenen Verfallsdatum verwendbar.

Stabilität nach Rekonstitution

Temperatur	INNOVANCE® D-Dimer Kontrolle 1 / INNOVANCE® D-Dimer Kontrolle 2
+15 bis +25 °C	8 Stunden
+2 bis +8 °C	7 Tage
≤ -18 °C**	4 Wochen

** In Originalgefäß einfrieren und nach dem Auftauen nicht erneut einfrieren.

INNOVANCE® D-Dimer Kontrolle 1 und INNOVANCE® D-Dimer Kontrolle 2 kann nach Rekonstitution im Originalgefäß einmal eingefroren und wieder aufgetaut werden. Die vorhergehende Standzeit bei +15 bis +25 °C darf nicht mehr als 4 Stunden betragen haben. Das Plasma muss gut verschlossen und möglichst schnell eingefroren werden.

Das Auftauen ist bei +37 °C in max. 10 Minuten zu vollziehen. INNOVANCE® D-Dimer Kontrolle 1 und INNOVANCE® D-Dimer Kontrolle 2 sollen nach dem Auftauen nicht länger als 4 Stunden bei +15 bis +25 °C stehen. Sind Gerinnsel sichtbar, sind INNOVANCE® D-Dimer Kontrolle 1 und INNOVANCE® D-Dimer Kontrolle 2 nicht mehr zu verwenden.

Testdurchführung

Zur Qualitätskontrolle wird INNOVANCE® D-Dimer Kontrolle 1 oder INNOVANCE® D-Dimer Kontrolle 2 mit dem INNOVANCE® D-Dimer Kit oder Stratus® CS D-Dimer Test Pak nach Vorschrift der jeweiligen Gebrauchsanweisung verwendet. Der erhaltene Wert muss innerhalb des in der chargenspezifischen Sollwertetabelle angegebenen Bereichs liegen.

Werteermittlung

Die Sollwerte wurden von Siemens Healthcare Diagnostics unter Verwendung vom INNOVANCE® D-Dimer Kalibrator und den entsprechenden INNOVANCE® D-Dimer Reagenzien bzw. vom Stratus® CS DDMR CalPak und entsprechendem Stratus® CS DDMR TestPak ermittelt und sind die Mittelwerte einer Reihe von Bestimmungen, erhoben an mehreren Tagen mit verschiedenen Geräten und Reagenzchargen. Diese Werte sind in der chargenspezifischen Sollwertetabelle zu finden.

Der Bereich ist ein fester Bereich, der die systematischen analytischen Abweichungen abdeckt, die durch Abweichungen von Reagenz oder Analysengerät entstehen können.

Die methodenabhängigen Sollwerte und Bereiche für jede Charge INNOVANCE® D-Dimer Kontrolle 1 und INNOVANCE® D-Dimer Kontrolle 2 sind der beigefügten Sollwertetabelle zu entnehmen. Bei der Verwendung als Präzisionskontrolle sollten in einer Vorperiode Kontrollwert und Kontrollgrenzen vom Anwender ermittelt werden. Aufgrund von veränderter Leistung wird empfohlen, keine anderen Methoden zu verwenden, als die, die in der beiliegenden Sollwertetabelle zu finden sind.

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Ausgabe April 2009

INNOVANCE® D-Dimer Contrôles
INNOVANCE® D-Dimer CONTROLS

Paragraphes surlignés - informations mises à jour par rapport à l'édition de Juin 2008

Domaine d'utilisation

Les contrôles INNOVANCE® D-Dimer Control 1 et INNOVANCE® D-Dimer Control 2 sont des contrôles dosés, destinés à l'évaluation de la précision et du biais analytique, dans les domaines normal et thérapeutique, pour la détermination des D-dimères avec les systèmes Siemens et Sysmex®.

Réactifs

Contenu des conditionnements

Contrôles INNOVANCE® D-Dimer CONTROLS REF OPDY 03 comprenant

5 x ⟶ 1 ml d'INNOVANCE® D-Dimer CONTROL 1, contrôle 1

5 x ⟶ 1 ml d'INNOVANCE® D-Dimer CONTROL 2, contrôle 2

1 x tableau de valeurs spécifiques au lot et à la méthode et de domaines de valeurs acceptables.

Contenu

Les contrôles INNOVANCE® D-Dimer contrôle 1 et INNOVANCE® D-Dimer contrôle 2 sont des produits à base de plasma humain lyophilisés contenant des d-dimères.

Conservateurs : 5-chloro-2-methyl-4-isothiazole-3-one *et*
2-methyl-4-isothiazole-3-one (< 1 mg/l)
azide de sodium (< 1 g/l)

Mises en garde et précautions d'emploi

1. Réactifs réservés à un usage de diagnostic *in-vitro*.
2. Contient de l'azite de sodium (< 1 g/l) comme conservateur. L' azite de sodium peut réagir avec les tuyaux d'évacuation en cuivre ou en plomb et former des composés explosifs. L'évacuer conformément aux réglementations locales.
3. Les contrôles INNOVANCE® D-Dimer contrôle 1 et INNOVANCE® D-Dimer contrôle 2 contiennent des composants d'origine humaine.
   Chaque donneur ou donneur d'unité a été testée avérée négative pour le virus d'immunodéficience humaine (HIV) 1 et 2, virus de l'hépatite B (HBV) et virus de l'hépatite C (HCV) en utilisant soit un test en conformité avec la directive diagnostique in vitro en vigueur en Europe ou les tests approuvés par le FDA. Comme aucun test connu ne peut offrir l'assurance complète de l'absence des agents infectieux, tous les produits dérivés humains devraient être manipulés avec les précautions appropriées.

Matériel et autres réactifs nécessaires

INNOVANCE® D-Dimer
Coffret INNOVANCE® D-Dimer, REF OPBP
Eau distillée
Pipettes
Automate de coagulation
Système de diagnostic Stratus® CS Acute Care* :
DDMR TestPak, REF CDDMR
DDMR CalPak, REF CDDMR-C
DDMR DilPak, REF CDDMR-D
Automate de détection fluorimétrique Stratus® CS STAT

Préparation des plasmas de contrôle

Dissoudre les contrôles INNOVANCE® D-Dimer CONTROL 1 et INNOVANCE® D-Dimer CONTROL 2 avec 1 ml d'eau distillé chacun et agiter doucement (sans former de mousse). Laisser reposer pendant au moins 15 minutes entre +15 et +25 °C. Agiter doucement encore une fois avant utilisation.

Stabilités et conditions de conservation

S'ils sont conservés fermés, entre +2 et +8 °C, les contrôles INNOVANCE® D-Dimer CONTROL 1 et INNOVANCE® D-Dimer CONTROL 2 peuvent être conservés et utilisés jusqu'à la date d'expiration indiquée sur l'étiquette.

Stabilité après reconstitution

Température	INNOVANCE® D-Dimer contrôle 1 / INNOVANCE® D-Dimer contrôle 2
+15 et +25 °C	8 heures
+2 et +8 °C	7 jours
≤ -18 °C**	4 semaines

** Congeler dans les conteneurs d'origine. Ne jamais recongeler un produit décongelé.

Les contrôles INNOVANCE® D-Dimer contrôle 1 et INNOVANCE® D-Dimer contrôle 2 peuvent être congelés dans leur conteneur d'origine et décongelés à nouveau une fois après reconstitution. La durée de conservation préalable entre +15 et +25 °C ne doit pas avoir dépassé 4 heures. Le plasma doit être bien scellé et congelé aussi vite que possible. La décongélation doit être réalisée à +37 °C dans un délai de 10 minutes au maximum. Les contrôles INNOVANCE® D-Dimer contrôle 1 et INNOVANCE® D-Dimer contrôle 2 ne doivent pas reposer pendant plus de 4 heures entre +15 et +25 °C après la décongélation. Les contrôles INNOVANCE® D-Dimer contrôle 1 et INNOVANCE® D-Dimer contrôle 2 ne doivent plus être utilisés s'ils contiennent des caillots visibles.

Procédure

À des fins de contrôle de qualité, les contrôles INNOVANCE® D-Dimer Control 1 et INNOVANCE® D-Dimer Control 2 sont utilisés avec le coffret INNOVANCE® D-Dimer, conformément à la notice d'utilisation, ou le coffret Stratus® CS D-Dimer TestPak. La valeur obtenue doit être comprise dans le domaine de valeurs mentionné dans le Tableau des valeurs théoriques spécifique du lot.

Détermination des valeurs théoriques

Les valeurs cibles ont été attribuées par Siemens Healthcare Diagnostics en utilisant le calibrateur INNOVANCE® D-Dimer Calibrator et les réactifs INNOVANCE® D-Dimer correspondants , ou le Strastus CS DDMR CalPak et le Stratus CS DDMR TestPak correspondant. Les moyennes des séries de déterminations effectuées sur plusieurs jours avec différents instruments et différents lots de réactifs sont mentionnées dans le Tableau des valeurs théoriques spécifique du lot.

Le domaine de valeurs acceptables est un intervalle fixe qui couvre les écarts analytiques systémiques pouvant se produire en raison d'écarts de réactifs ou d'analyseurs.

Les valeurs cibles dépendant de la méthode et les domaines de valeurs acceptables de chaque lot de contrôles INNOVANCE® D-Dimer contrôle 1 et INNOVANCE® D-Dimer contrôle 2 sont présentés dans le Tableau de valeurs théoriques joint. En cas d'utilisation comme contrôle de précision, l'utilisateur doit établir la concentration cible et les limites de confiance au cours d'une phase préliminaire. En raison de possibles variations des performances, l'utilisation de méthodes autres que celles stipulées dans le Tableau des valeurs théoriques joint n'est pas recommandée.

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Édition Avril 2009

INNOVANCE® D-Dimer Controlli
INNOVANCE® D-Dimer CONTROLS

Vedere sezioni ombreggiate - informazioni aggiornate rispetto all'edizione attuale da Giugno 2008

Uso Previsto

INNOVANCE® D-Dimer controllo 1 e INNOVANCE® D-Dimer controllo 2 sono controlli dosati per la valutazione di precisione e di deviazione analitica nell'intervallo normale e patologico per la determinazione del D-dimero su sistemi Siemens e Sysmex®

Reagenti

Materiali forniti

INNOVANCE® D-Dimer CONTROLS REF OPDY 03 con

5 x ⟶ 1 mL INNOVANCE® D-Dimer CONTROL 1, controllo 1

5 x ⟶ 1 mL INNOVANCE® D-Dimer CONTROL 2, controllo 2

1 x tabella di valori assegnati lotto- e metodo-specifici e intervalli di accettabilità.

Contenuto

INNOVANCE® D-Dimer controllo 1 e INNOVANCE® D-Dimer controllo 2 sono prodotti liofilizzati a base di plasma umano contenenti D-Dimero.

Conservanti: 5-cloro-2-metil-4-isotiazol-3-one *e*
2-metil-4-isotiazol-3-one (< 1 mg/L)
sodio azide (< 1 g/L)

Avvertenze e Precauzioni

1. Per uso diagnostico *in-vitro*.
2. Contiene sodio azide (< 1 g/L) come conservante. La sodio azide può reagire con le tubazioni in rame o piombo nelle linee di scarico formando composti esplosivi. Provvedere allo smaltimento in modo appropriato e secondo le normative locali.
3. INNOVANCE® D-Dimer controllo 1 e INNOVANCE® D-Dimer controllo 2 contengono componenti di origine umana.

   Ogni donatore o unità di sangue da donatore è stato analizzato e trovato negativo per il virus dell'immunodeficienza umana (HIV) 1 e 2, per il virus dell'epatite B (HBV) e per il virus dell'epatite C (HCV) utilizzando test conformi alla Direttiva per Diagnostici In Vitro in ambito europeo oppure test approvati dalla FDA. Poiché nessun test noto può garantire la totale assenza di agenti infettivi, tutti i prodotti di derivazione umana devono essere manipolati con adeguate precauzioni.

Altri materiali richiesti, ma non forniti

INNOVANCE® D-Dimer

Kit INNOVANCE® D-Dimer, REF OPBP
Acqua distillata

Pipette

Analizzatore per coagulazione

Sistema diagnostico Stratus® CS Acute Care*:
DDMR TestPak, REF CDDMR
DDMR CalPak, REF CDDMR-C
DDMR DilPak, REF CDDMR-D
Analizzatore fluorimetrico Stratus® CS STAT

Preparazione dei Plasmi di Controllo

Sciogliere INNOVANCE® D-Dimer CONTROL 1 e INNOVANCE® D-Dimer CONTROL 2 con 1 mL di acqua distillata ed agitare bene (evitare formazione di schiuma). Lasciar riposare per almeno 15 minuti da +15 a +25 °C. Agitare bene ancora una volta prima dell'uso.

Conservazione e Stabilità

Se conservati chiusi da +2 a +8 °C, INNOVANCE® D-Dimer CONTROL 1 e INNOVANCE® D-Dimer CONTROL 2 possono essere utilizzati fino alla data di scadenza indicata sull'etichetta.

Stabilità dopo ricostituzione

Temperatura	INNOVANCE® D-Dimer controllo 1 / INNOVANCE® D-Dimer controllo 2
da +15 a +25 °C	8 ore
da +2 a +8 °C	7 giorni
≤ -18 °C**	4 settimane

** Congelare nei contenitori originali. Non ricongelare dopo scongelamento.

INNOVANCE® D-Dimer controllo 1 e INNOVANCE® D-Dimer controllo 2 possono essere congelati nei contenitori originali e scongelati una volta dopo ricostituzione. Il tempo di permanenza da +15 a +25 °C non deve aver superato le 4 ore. Il plasma deve essere ben sigillato e congelato il più rapidamente possibile. Lo scongelamento deve essere completato a +37 °C entro un massimo di 10 minuti. INNOVANCE® D-Dimer controllo 1 e INNOVANCE® D-Dimer controllo 2 non devono restare per più di 4 ore da +15 a +25 °C dopo scongelamento. INNOVANCE® D-Dimer controllo 1 e INNOVANCE® D-Dimer controllo 2 non devono essere utilizzati se contengono coaguli visibili.

Procedura

Per il controllo di qualità, INNOVANCE® D-Dimer controllo 1 e INNOVANCE® D-Dimer controllo 2 vengono utilizzati con il kit INNOVANCE® D-Dimer secondo le Istruzioni per l'Uso. Oppure Stratus® CS D-Dimer TestPak. Il valore ottenuto deve rientrare negli intervalli di riferimento della Tabella dei Valori Assegnati specifica per ciascun lotto.

Determinazione dei valori assegnati

I valori target sono stati assegnati da Siemens Healthcare Diagnostics utilizzando INNOVANCE® D-Dimer Calibratore e i corrispondenti reagenti INNOVANCE® D-Dimer, oppure Stratus® CS DDMR CalPak e l'equivalente Stratus® CS DDMR TestPak. I valori medi delle determinazioni in serie eseguite nell'arco di più giorni con diversi strumenti e lotti di reagenti sono indicati nella Tabella dei Valori Assegnati specifica per ciascun lotto.

L'intervallo di accettabilità è un intervallo definito che copre la deviazione analitica sistematica che può verificarsi a causa di deviazioni a carico dei reagenti o degli analizzatori.

I valori target e gli intervalli di accettabilità per ogni lotto di INNOVANCE® D-Dimer controllo 1 e INNOVANCE® D-Dimer controllo 2 vengono forniti nella Tabella dei Valori Assegnati allegata. Se utilizzati come controllo di precisione, l'Utilizzatore deve definire la concentrazione target ed i limiti di confidenza in fase preliminare. Data la variabilità delle prestazioni, si sconsiglia l'uso di metodi diversi da quelli indicati nella Tabella dei Valori di Assegnati allegata.

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Edizione Aprile 2009

INNOVANCE® D-Dimer Controles
INNOVANCE® D-Dimer CONTROLS

Observe las secciones resaltadas - Es Información actualizada de la edición anterior desde de junio 2008

Uso previsto

INNOVANCE® D-Dimer Control 1 e INNOVANCE® D-Dimer Control 2 son controles valorados para la evaluación de la precisión y exactitud en los rangos normal y patológico, para la determinación de D-dímero con los sistemas Siemens y Sysmex®.

Reactivos

Materiales suministrados

INNOVANCE® D-Dimer CONTROLS REF OPDY 03 contiene

5 x ⟶ 1 ml INNOVANCE® D-Dimer CONTROL 1, control 1

5 x ⟶ 1 ml INNOVANCE® D-Dimer CONTROL 2, control 2

1 x tabla de valores asignados e intervalos de aceptación, específicos de procedimiento y de lote.

Contenido

INNOVANCE® D-Dimer control 1 e INNOVANCE® D-Dimer control 2 son productos basados en plasma humano liofilizado que contienen D-dímero.

Conservantes: 5-cloro-2-metil-4-isotiazol-3-ona *y*
2-metil-4-isotiazol-3-ona (< 1 mg/l)
azida sódica (< 1 g/l)

Advertencias y precauciones

1. Para uso diagnóstico *in-vitro*.
2. **Contiene azida de sodio (< 1 g/l) como conservante. La azida de sodio puede reaccionar** con tuberías de cobre o de plomo en los conductos de drenaje y formar compuestos explosivos. Elimine este producto de forma apropiada conforme a la normativa local.
3. INNOVANCE® D-Dimer control 1 e INNOVANCE® D-Dimer control 2 contienen componentes de origen humano.

   Cada donante o unidad de donación, ha sido analizada para detectar la presencia del virus de inmunodeficiencia humana 1 y 2 (VIH), virus de la hepatitis B (VHB) y virus de la hepatitis C (VHC), utilizando las técnicas aprobadas por la directiva de diagnósticos in-vitro de la UE o FDA. Para la elaboración del producto se han utilizado únicamente las donaciones con resultados negativos. Como no hay ninguna prueba que ofrezca la completa seguridad de ausencia de agentes infecciosos, todos los productos obtenidos a partir de material de origen humano, deben ser manipulados con las debidas precauciones.

Materiales adicionales necesarios, pero no suministrados

INNOVANCE® D-Dimer

INNOVANCE® D-Dimer kit, REF OPBP

Agua destilada

Pipetas

Analizador de coagulación

Sistema de diagnóstico Stratus® CS Acute Care*:
DDMR TestPak, REF CDDMR
DDMR CalPak, REF CDDMR-C
DDMR DilPak, REF CDDMR-D
Analizador fluorimétrico Stratus® CS STAT

Preparación de los Plasmas control

Disolver INNOVANCE® D-Dimer CONTROL 1 e INNOVANCE® D-Dimer CONTROL 2 con 1 ml de agua destilada en cada uno y mezclar suavemente (sin formación de espuma). Dejar reposar un mínimo de 15 minutos entre +15 y +25 °C. Volver a mezclar cuidadosamente una vez más antes de su uso.

Estabilidad y almacenaje

INNOVANCE® D-Dimer CONTROL 1 e INNOVANCE® D-Dimer CONTROL 2 se pueden utilizar hasta la fecha de caducidad indicada en la etiqueta, si se conservan sin abrir entre +2 y +8 °C

Estabilidad después de la reconstitución

Temperatura	INNOVANCE® D-Dimer control 1 / INNOVANCE® D-Dimer control 2
+15 a +25 °C	8 horas
+2 a +8 °C	7 días
≤ -18 °C**	4 semanas

** Debe ser congelado en los recipientes originales. No congelar de nuevo después de su descongelación.

INNOVANCE® D-Dimer control 1 e INNOVANCE® D-Dimer control 2 después de la reconstitución pueden ser congelados en el recipiente original y descongelarse de nuevo.,si el tiempo de conservación entre +15 y +25 °C previo a la congelación no ha superado 4 horas. El frasco del plasma debe estar bien tapado y ser congelado tan rápido como sea posible. La descongelación debe realizarse a +37 °C en menos de 10 minutos como máximo. INNOVANCE® D-Dimer control 1 e INNOVANCE® D-Dimer control 2 no deben permanecer durante más de 4 horas entre +15 y +25 °C después de la descongelación. INNOVANCE® D-Dimer control 1 e INNOVANCE® D-Dimer control 2 no deben utilizarse si contienen coágulos visibles.

Procedimiento

Para el control de calidad, INNOVANCE® D-Dimer Control 1 e INNOVANCE® D-Dimer Control 2 se utilizan con el kit INNOVANCE® D-Dimer de acuerdo con las Instrucciones de utilización, o bien con el Stratus® CS D-Dimer TestPak. El valor obtenido ha de estar dentro del margen indicado en la tabla de valores asignados del lote en cuestión.

Determinación de valores asignados

Los valores objetivo fueron asignados por Siemens Healthcare Diagnostics utilizando el INNOVANCE® D-Dimer Calibrator y los correspondientes reactivos INNOVANCE® D-Dimer, o bien el Stratus® CS DDMR CalPak y el correspondiente Stratus® CS DDMR TestPak. Los valores medios de la serie de determinaciones realizadas a lo largo de varios días con distintos instrumentos y lotes de reactivos, vienen indicados en la tabla de valores asignados para cada lote en cuestión.

El intervalo de aceptación es un intervalo fijo que cubre las desviaciones analíticas sistemáticas que pueden ocurrir debido a desviaciones en los reactivos o analizadores.

Los valores objetivo dependientes del procedimiento y los intervalos de aceptación para cada lote de INNOVANCE® D-Dimer control 1 e INNOVANCE® D-Dimer control 2 se proporcionan en la tabla de valores asignados adjunta. Si se utilizan como un Control de la precisión, el usuario debe establecer la concentración objetivo y los límites de confianza durante una fase preliminar. Debido a la variabilidad de rendimiento, no se recomienda seguir otros métodos distintos a los que figuran en la tabla adjunta de valores asignados.

INNOVANCE y Stratus son marcas comerciales de Siemens Healthcare Diagnostics.

* Acute Care es una marca comercial of Siemens Healthcare Diagnostics.

Sysmex es una marca comercial de SYSMEX CORPORATION.

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Edición Abril 2009

INNOVANCE® D-Dimer Controlos
INNOVANCE® D-Dimer CONTROLS

Secções sombreadas - Informações actualizadas versus a edição de Junho de 2008

Campo de aplicação

INNOVANCE® D-Dimer controlo 1 e INNOVANCE® D-Dimer controlo 2 são controlos preparados para avaliação da precisão e desvio analítico no intervalo normal e patológico para a determinação de D-dímero nos sistemas Siemens e Sysmex®.

Reagentes

Conteúdo da embalagem

INNOVANCE® D-Dimer CONTROLS REF OPDY 03 com

5 x ⟶ 1 ml INNOVANCE® D-Dimer CONTROL 1, controlo 1

5 x ⟶ 1 ml INNOVANCE® D-Dimer CONTROL 2, controlo 2

1 x tabela de valores atribuídos e intervalos de aceitação específicos para lote e para método.

Conteúdo

INNOVANCE® D-Dimer controlo 1 e INNOVANCE® D-Dimer controlo 2 são produtos à base de plasma humano liofilizado contendo D-dímero.

Conservantes: 5-cloro-2-metil-4-isotiazolo-3-ona *e*
2-metil-4-isotiazolo-3-ona (< 1 mg/l)
azida de sódio (< 1 g/l)

Advertências e medidas de precaução

1. Para utilização de diagnóstico *in-vitro*.
2. Contém azida de sódio (< 1 g/l) como conservante. A azida de sódio pode reagir com os tubos de cobre ou de chumbo das canalizações de esgotos formando compostos explosivos. Elimine este produto de forma correcta e de acordo com as regulamentações locais.
3. INNOVANCE® D-Dimer controlo 1 e INNOVANCE® D-Dimer controlo 2 contêm componentes de origem humana.
   Cada doador ou unidade de doação foi testada para detectar a presença de vírus de imunodeficiências humana 1 e 2 (VIH), vírus de hepatite B (VHB) e vírus de hepatite C (VHC) de acordo com as técnicas aprovadas pelas directivas de diagnóstico in-vitro da EU ou FDA. Para a elaboração deste produto foram utilizadas unicamente as unidades com resultados negativos. Como não existe nenhum teste que ofereça a garantia completa de ausência de agentes infecciosos, todos os materiais obtidos a partir de material de origem humana deverão ser manipulados com as devidas precauções.

Materiais adicionais necessários mas não fornecidos

INNOVANCE® D-Dimer
Kit INNOVANCE® D-Dimer, REF OPBP
Água destilada
Pipetas
Analisador de coagulação

Sistema de diagnóstico Stratus® CS Acute Care*:
DDMR TestPak, REF CDDMR
DDMR CalPak, REF CDDMR-C
DDMR DilPak, REF CDDMR-D
Analisador fluorimétrico Stratus® CS STAT

Preparação dos plasmas de controlo

Reconstituir INNOVANCE® D-Dimer CONTROL 1 e INNOVANCE® D-Dimer CONTROL 2 com 1 ml de água destilada cada e agitar cuidadosamente (sem formar espuma). Deixar em repouso durante pelo menos 15 minutos a +15 - +25 °C. Agitar cuidadosamente mais uma vez antes de usar.

Estabilidade e condições de conservação

Se for conservado, não aberto, a +2 - +8 °C, INNOVANCE® D-Dimer CONTROL 1 e INNOVANCE® D-Dimer CONTROL 2 podem ser conservados e utilizados até à data de validade indicada no rótulo.

Estabilidade após reconstituição

Temperatura	INNOVANCE® D-Dimer controlo 1 / INNOVANCE® D-Dimer controlo 2
+15 a +25 °C	8 horas
+2 a +8 °C	7 dias
≤ -18 °C**	4 semanas

** Tem que ser congelado nos recipientes originais. Não voltar a congelar depois de descongelar.

INNOVANCE® D-Dimer controlo 1 e INNOVANCE® D-Dimer controlo 2 podem ser congelados no recipiente original e descongelados novamente uma vez após reconstituição. O tempo de conservação anterior a +15 - +25 °C não poderá ser superior a 4 horas. O plasma tem que ser bem selado e congelado o mais rapidamente possível. O descongelamento deve ser concluído a +37 °C num período máximo de 10 minutos. INNOVANCE® D-Dimer controlo 1 e INNOVANCE® D-Dimer controlo 2 não devem permanecer durante mais de 4 horas a +15 - +25 °C depois de descongelados. INNOVANCE® D-Dimer controlo 1 e INNOVANCE® D-Dimer controlo 2 não podem ser utilizados se tiverem coágulos visíveis.

Execução do teste

Para o controlo de qualidade, INNOVANCE® D-Dimer controlo 1 e INNOVANCE® D-Dimer controlo 2 são utilizados em conjunto com o kit INNOVANCE® D-Dimer de acordo com as instruções ou o Stratus® CS D-Dimer TestPak. O valor obtido deve estar dentro do intervalo, conforme indicado na tabela de valores atribuídos específica do lote.

Determinação de valores atribuídos

Os valores-alvo foram atribuídos pela Siemens Healthcare Diagnostics utilizando o calibrador INNOVANCE® D-Dimer e os reagentes INNOVANCE® D-Dimer correspondentes ou o Stratus® CS DDMR CalPak e o Stratus® CS DDMR TestPak correspondente. Os valores médios da série de determinações executadas ao longo de vários dias com diferentes instrumentos e lotes de reagentes são indicados na tabela de valores atribuídos específica do lote.

O intervalo de aceitação é um intervalo fixo que cobre os desvios analíticos sistemáticos que possam ocorrer devido a desvios em reagentes ou analisadores.

Os valores-alvo e intervalos de aceitação dependentes do método para cada lote de INNOVANCE® D-Dimer controlo 1 e INNOVANCE® D-Dimer controlo 2 são fornecidos na tabela de valores atribuídos fornecida. Se utilizada como um controlo de precisão, o utilizador deve estabelecer a concentração-alvo e limites de confiança durante uma fase preliminar. Devido à variabilidade do desempenho, não é recomendada a utilização de métodos diferentes dos indicados na tabela de valores atribuídos fornecida.

INNOVANCE e Stratus são marcas comerciais da Siemens Healthcare Diagnostics.

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Sysmex é uma marca comercial da SYSMEX CORPORATION.

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Edição Abril 2009

Symbols Key / Symbolschlüssel / Explication des Symboles / Interpretazione simboli / Clave de los Símbolos / Chave dos Símbolos

2	Do not reuse / Nicht zur Wiederverwendung / Ne pas réutiliser / Non riutilizzare / No reutilizar / Não reutilizar
EXP CCYY-MM-DD	Use By / Verwendbar bis / Utiliser jusque / Utilizzare entro / Fecha de caducidad / Prazo de validade
LOT	Batch Code / Chargenbezeichnung / Code du lot / Codice del lotto / Código de lote / Código do lote
REF	Catalogue Number / Bestellnummer / Référence du catalogue / Numero di catalogo / Número de catálogo / Referência de catálogo
	Caution, consult accompanying documents / Achtung, Begleitdokumente beachten / Attention voir notice d'instructions / Attenzione, vedere le istruzioni per l'uso / Atención, ver instrucciones de uso / Atenção, consulte a documentação incluída
	Manufacturer / Hersteller / Fabricant / Fabbricante / Fabricante / Fabricante
EC REP	Authorized Representative in the European Community / Bevollmächtigter in der Europäischen Gemeinschaft / Mandataire dans la Communauté européenne / Mandatario nella Comunità Europea / Representante autorizado en la Comunidad Europea / Representante autorizado na Comunidade Europeia
Σ	Contains sufficient for <n> tests / Inhalt ausreichend für <n> Tests / Contenu suffisant pour "n" tests / Contenuto sufficiente per "n" saggi / Contenido suficiente para <n> ensayos / Conteúdo suficiente para "n" ensaios
IVD	*In Vitro* Diagnostic Medical Device / *In Vitro* Diagnostikum / Dispositif médical de diagnostic *in vitro* / Dispositivo medico-diagnostico *in vitro* / Producto sanitario para diagnóstico *in vitro* / Dispositivo médico para diagnóstico *in vitro*
	Temperature Limitation / Temperaturbegrenzung / Limites da température / Limiti di temperatura / Límite de temperatura / Limites de temperatura
	Consult Instructions for Use / Gebrauchsanweisung beachten / Consulter les instructions d'utilisation / Consultare le istruzioni per l'uso / Consulte las instrucciones de uso / Consulte as instruções de utilização
NON STERILE	Non-sterile / Nicht steril / Non stérile / Non sterile / No estéril / Não estéril
CE	CE Mark / CE Zeichen / Marquage CE / Marchio CE / Marca CE
CONTENTS	Contents / Inhalt / Contenu / Contenuto / Contenido / Conteúdo
⟶	Reconstitution Volume / Rekonstitutionsvolumen / Volume de reconstitution / Volume di ricostituzione / Volumen de reconstitución / Volume de reconstituição
LEVEL	Level / Konzentration / Niveau / Livello / Nivel / Nível

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Pathromtin® SL

Intended Use

Reagent for the determination of the activated partial thromboplastin time (APTT) in citrated human plasma.

Summary and Explanation

Pathromtin® SL Reagent enables rapid screening for disorders of the intrinsic coagulation system and sensitively detects Factors VIII and IX as well as the contact factors. In conjunction with deficient plasmas it enables the individual factors of the intrinsic system to be quantified and permits diagnosis of hemophilia. In addition it can be used for monitoring therapy with unfractionated heparin[1].

The use of the APTT as a screening test for coagulation disorders is indicated particularly prior to surgical interventions as this allows potential hemophiliacs to be diagnosed and given special therapeutic protection.

The presence of non-specific inhibitors such as the lupus-like anticoagulant may prolong the APTT, but this effect is variable and generally recognized as being related more to the nature of the APTT reagent employed[2].

Principle of the Method

Incubation of plasma with the optimal quantity of phospholipids and a surface activator leads to activation of factors of the intrinsic coagulation system. The addition of calcium ions triggers the coagulation process; the time to formation of a fibrin clot is measured.

Reagents

Note

Pathromtin® SL can be used manually or on automated coagulation analyzers.
Siemens Healthcare Diagnostics 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 such a 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!

Materials provided

10 x 5 mL, REF OQGS 29

20 x 5 mL, REF OQGS 35, REF 10484200

Composition

Pathromtin® SL Reagent: Silicon dioxide particles (1.2 g/L), plant phospholipids (0.25 g/L), sodium chloride, HEPES, pH 7.6

Preservative: Sodium azide (< 1 g/L)

Warnings and Precautions

For *in-vitro*-diagnostic use.

Contains sodium azide (< 1 g/L) as a preservative. Sodium azide can react with copper or lead pipes in drain lines to form explosive compounds. Dispose of properly in accordance with local regulations.

Preparation of the Reagents

Pathromtin® SL Reagent must be gently inverted (5 to 8 times) to mix before first use and must be used at room temperature (15 to 25 °C). Every 24 hours of use, the reagent must be inverted to resuspend any sediment.

Calcium Chloride Solution 0.025 mol/L: warm to 37 °C.

Storage and Stability

Stored unopened at 2 to 8 °C Pathromtin® SL Reagent may be used by the expiry date given on the label. Once opened Pathromtin® SL Reagent must be used within 2 weeks (store at 2 to 25 °C).

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

Materials required but not provided

- Calcium Chloride ($CaCl_2$) Solution 0.025 mol/L
- Control Plasma N, or Dade® Ci-Trol® Level 1 as control for the normal range
- Control Plasma P, or Dade® Ci-Trol® Level 2, or Dade® Ci-Trol® Level 3 as control for the pathological/therapeutic range
- Pipettes for precise measurement of 0.1 mL
- Plastic test tubes
- Coagulation analyzer

Specimen Collection and Preparation

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. Immediately centrifuge for no less than 15 minutes at 1500 x g, remove the supernatant plasma and keep at 15 to 25 °C until use in the test (max. 4 hours). In the US please refer to the CLSI Document H21-A5, entitled "Collection, Transport and Processing of Blood Specimens for Coagulation Testing and Performance of Coagulation Assays"[3].

Procedure

Manual Testing:

Pipette into a test tube pre-warmed to 37 °C:

Citrated plasma	100 µL
Pathromtin® SL Reagent	100 µL
Incubate for 2 minutes at 37 °C	
Calcium Chloride Solution (37 °C!)	100 µL

On adding the Calcium Chloride Solution start the stopwatch or timer on the coagulation analyzer and measure the coagulation time.

Monitoring of Unfractionated Heparin Therapy with APTT

When using the APTT for this purpose, the factors influencing the test should be kept in mind. General considerations are listed below.

A. Time of collection is important since the *in-vivo* half-life of unfractionated heparin is approximately 1.5 hours[4]. When it is administered, it has an immediate anticoagulant effect but the degree of this effect decreases rapidly with time. This is especially apparent with intermittent single intravenous injections.
B. The anticoagulant used for sample collection can alter test results.
C. Platelet factor 4, a heparin neutralizing factor in platelet alpha-granules, can be released by platelet aggregation or damage. To prevent this occurrence *in-vitro*, the specimen should be collected with a minimum of trauma. Cold temperatures are known to induce platelet aggregation and release platelet factor 4; therefore, centrifugation at room temperature is recommended for heparin testing.
D. Using APTT to monitor unfractionated heparin therapy is time-dependent. Delay in testing samples will result in prolonged APTT determinations. Therefore, it is imperative that the testing on all samples be performed as soon as possible.
E. Increased contact activation times may result in prolonged APTT in plasma containing heparin. It is imperative that the optimal heating-activation time of the Pathromtin® SL-plasma mixture be rigidly standardized[5].
F. Different test systems (i.e. manual, photo-optical, etc.) will exhibit variable heparin sensitivity. Interchanging of test systems should be avoided.
G. Baseline data on the APTT of each patient before the start of therapy should be established where feasible to determine the respective patient APTT as it relates to the reference range established for the test in that laboratory.
H. Studies have shown variability in original estimates of the quality of unfractionated heparin from different sources and different manufacturers. *In-vivo* reactivity varies with the type of heparin administered, the metabolism of the individual and other coadministrated medications[4,6].
I. Because the APTT can vary with technique, method, equipment, reagent lot and heparin used, each laboratory must establish its own therapeutic ranges, or verify them whenever one or more of the aforementioned variables is changed. This can be done by simultaneously determining the APTT and the heparin concentration for samples from patients receiving heparin therapy. A dose response curve can be calculated from the data using regression analysis, and the APTT range corresponding to a heparin concentration of 0.3 to 0.7 U/mL (by a factor Xa inhibition assay) can be derived[4,6,7].

Internal Quality Control

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

Pathological range: Control Plasma P, or Dade® Ci-Trol® Level 2, or Dade® Ci-Trol® Level 3

Two controls (one in the normal range and one in the pathological/therapeutic range) must be measured at the start of the test run, after each change of reagent vial, and at least once during an 8-hour shift. The control material should be prepared and processed in the same manner as the patient samples. Each laboratory should establish its own confidence intervals for the controls. This interval is generally ± 2 to ± 2.5 standard deviations from the mean control value. If the control values are outside of the confidence interval, the controls, reagents and instrument must be checked. Before reporting the patient values, it is recommended that all steps should be documented that were taken to identify and rectify the problem. New control ranges should be defined for each new lot of reagents or controls.

Results

The result is given in seconds.

Limitations of the Procedure

Interferences of APTT are described in bibliography references[8-10]. Therapeutic doses of hirudin or other direct thrombin inhibitors may prolong clotting times[11]. The choice of anticoagulant (i.e. oxalate instead of citrate) and the condition of the specimen (e.g. hemolyzed, lipemic, parenteral feeding, etc.) may affect results. The latter is particularly true of optical

instrumentation measurements of the APTT. Preactivation of the sample due to poor phlebotomy technique can lead to false results. Referencing the Sample Handling and Collection section of CLSI Document H21-A5 it is recommended that test tubes with non-wetable surfaces (e.g., plastic) be used rather than glass test tubes.

Siemens has validated use of these reagents on various analyzers to optimize product performance and meet product specifications. User defined modifications are not supported by Siemens 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 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

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.

In a study of ostensibly healthy individuals using a specific lot of Pathromtin® SL Reagent, the following values were obtained:

	Median	90 % Reference Interval	
		5^{th} Percentile	95^{th} Percentile
100 individuals Sysmex® CA-1500	30.9 s	26.4 s	37.5 s
111 individuals BCS® System	30.2 s	25.9 s	36.6 s

Reference ranges for other populations such as pediatric groups should also be established where warranted.

Specific Performance Characteristics

Precision

Using opto-densitometric detection, precision studies were run over a 5 day period, twice per day (n = 8 replicates per day), to total n = 40 for normal and pathological control plasmas as well as a heparin plasma pool. Intra-assay precision was calculated from the individual n = 4 precision values for the daily runs over the 5 days. Intra-assay precision ranged from 0.6 to 2.0 % CV, while the inter-assay precision ranged from 0.3 to 2.8 % CV.

Method Comparison

Results of a comparison of APTT determinations using Pathromtin® SL Reagent and another commercially available APTT reagent gave a correlation coefficient of 0.96 and a y-intercept of 2.1 s, and a slope of 0.99.

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Definition of Symbols

	Do not reuse	YYYY-MM-DD	Use By
LOT	Batch Code	REF	Catalogue Number
	Caution, consult accompanying documents		Manufacturer
EC REP	Authorized representative in the European Community	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 mark
CONTENTS	Contents	→	Reconstitution volume
LEVEL	Level		Keep away from sunlight and heat

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SIEMENS

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Standard Human Plasma

STANDARD PLASMA

For the calibration of coagulation and fibrinolysis tests

Intended Use

Standard Human Plasma is used for the calibration of the following tests:

1. Prothrombin time (PT)
2. Fibrinogen (Clauss method)
3. Coagulation factors II, V, VII, VIII, IX, X, XI, XII, XIII and VWF
4. Inhibitors: Antithrombin III, protein C, protein S, α_2-antiplasmin, C1 inhibitor
5. Total complement activity
6. Plasminogen

In addition, the stated sensitivity values for ProC® reagents are provided for calculating the normalized ratio for ProC® Global and ProC® Global/FV.

The percentage values given in the enclosed Table of Analytical Values relate to a pool of fresh citrated human plasma, which by definition, exhibits 100 % of the norm for all the factors. Coagulation factors and inhibitors for which a WHO Standard is available are referenced to this standard and the values are given in International Units (IU).

Reagents

Note

Standard Human Plasma can be used manually or on automated coagulation analyzers. Siemens Healthcare Diagnostics 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 such a case, the information contained in the Reference Guides (Application Sheets) supersedes the information in these Instructions for Use. In addition, please also consult the instruction manual of the instrument manufacturer.

Materials provided

STANDARD PLASMA **REF** ORKL 17

10 x → 1.0 mL, **STANDARD PLASMA**, Standard Human Plasma

Each pack of Standard Human Plasma contains a lot- and method-specific Table of Analytical Values.

Composition

Standard Human Plasma is obtained from pooled citrated plasma collected from selected healthy blood donors. Standard Human Plasma is stabilized with HEPES buffer solution (12 g/L) and lyophilized. To avoid contact activation of the coagulation system the preparation is supplied in siliconized vials.

Standard Human Plasma contains no preservative.

Warnings and Precautions

For *in-vitro* diagnostic use.

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 found to be in conformance with the In Vitro Diagnostic Directive in the EU or FDA approved tests. Because no known test can offer complete assurance of the absence of infectious agents, all human derived products should be handled with appropriate caution.

Preparation of the Calibrator

1. Reconstitute Standard Human Plasma by adding 1.0 mL distilled or deionized water.
2. Mix carefully to dissolve (without foam formation).
3. Let stand at 15 to 25 °C for at least 15 minutes.
4. Before use, again mix carefully.

Storage and Stability

Store Standard Human Plasma unopened at 2 to 8 °C and use by the expiry date given on the label.

Stability after reconstitution:

at 15 to 25 °C	4 hours
at ≤–20 °C	4 weeks

Reconstituted Standard Human Plasma should not be stored at 2 to 8 °C but can be frozen and thawed once. The reconstituted plasma must be frozen as rapidly as possible in a tightly closed container. 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.

Procedure

For establishing standard curves and/or determining a laboratory factor Standard Human Plasma is used with the corresponding reagents in accordance with the assay protocol in the relevant Instructions for Use.

Internal Quality Control

The accuracy of the standard curve should be assessed by running appropriate controls, which are listed in each related reagent Instructions for Use.

If the controls exhibit systematic deviations from the assigned ranges of the lot- and method-specific Table of Analytical Values, a new standard curve must be established.

Limitations of the Procedure

The standard curve is valid for the respective lot of the reagent used and must be renewed if the lot is changed as well as after any change in experimental conditions.

Siemens has validated use of these reagents on various analyzers to optimize product performance and meet product specifications. User defined modifications are not supported by Siemens 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 Application Sheets or these instructions for use.

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	Do not reuse		Use By
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	Biological Risks	IVD	*In Vitro* Diagnostic Medical Device
	Temperature Limitation		Consult instruction for Use
	Non-sterile	CE	CE mark
CONTENTS	Contents	→	Reconstitution volume
LEVEL	Level		Keep away from sunlight and heat

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