INNOVANCE® D-Dimer

Revision bar indicates update to previous version.

CE 0197

Intended Use

INNOVANCE® D-Dimer is an in vitro diagnostic reagent for the quantitative, non-standardized determination of cross-linked fibrin degradation products (D-dimers) for exclusion of deep vein thrombosis (DVT) and pulmonary embolism (PE) in conjunction with a clinical pretest probability (PTP) assessment model in outpatients suspected of DVT or PE in human sodium citrated plasma by means of automated, immunoturbidimetric methods.

In addition, INNOVANCE® D-Dimer can be used as an aid in diagnosis and monitoring of hypercoagulable states in patients at risk or with signs of disseminated intravascular coagulopathy (DIC) or other disorders associated with a hypercoagulability.

Summary and Explanation

D-dimer is a global indicator of coagulation activation and fibrinolysis and, therefore, an indirect marker of thrombotic activity. This specific cross-linked fibrin degradation product is formed through the sequential action thrombin, activated FXIII, and plasmin. First, thrombin, generated when coagulation is activated, converts fibrinogen to fibrin and activates FXIII. Second, FXIIIa covalently cross-links D-domains in adjacent fibrin monomers. Third, plasmin (formed on the fibrin surface by plasminogen activation) cleaves substrate fibrin at specific sites, and when it cleaves fibrin cross-linked by FXIIIa, it generates D-dimer. Thus, lysis of cross-linked fibrin results in a mixture of smaller and larger fibrin degradation products containing D-dimer, the structure formed by cross-linked adjacent D-domains[1–3].

D-dimer is cleared through the kidneys and the reticuloendothelial system and has a plasma half-life of approximately 8 hours. Low levels of D-dimer can be found circulating under normal physiologic conditions, while pathologically elevated levels can be found in any condition associated with enhanced fibrin formation and fibrinolysis, such as venous thromboembolism, disseminated intravascular coagulopathy (DIC), cancer, surgery, pregnancy, inflammatory diseases and others[1].

The major diagnostic application of D-dimer testing is in the exclusion of thromboembolic events, such as deep vein thrombosis (DVT) or pulmonary embolism (PE) and has been implemented into guidelines for diagnosis and management of DVT and PE[2–4]. D-dimer testing is recommended for exclusion of DVT and PE in conjunction with a clinical pretest probability (PTP) assessment model in outpatients suspected of VTE. The use of an age-adjusted D-dimer cutoff in outpatients older than 50 years (e.g. age-adjusted cutoff = age (years) x 0.010 mg/L (using D-dimer assays with a cutoff of 0.500 mg/L) is considered as safe as the standard cutoff and increases the diagnostic utility of the test[5].

A general increase in D-dimer concentration resulting in a reduced specificity for exclusion of VTE is observed for the marker D-dimer in patients with recent surgery, trauma or thrombolytic therapy, in patients with cancer, aortic aneurysm, liver cirrhosis, sepsis or severe infections as well as in elderly patients and during pregnancy[1–3].

Persistently high values of D-dimer have consistently been shown to increase the risk for recurrent VTE once anticoagulation is stopped. Strategies that incorporate the assessment of D-dimer have the potential to identify subjects in whom anticoagulation should be continued or can be safely discontinued[6,7,8,9].

D-dimer levels can be helpful for the diagnosis of DIC. Scoring systems have been developed that include determination of platelet count, fibrinogen level, and prothrombin time in addition to the D-dimer level. Such scoring systems are helpful, not only for the diagnosis of DIC, but also for monitoring its progression[2,3,10,11].

During uncomplicated pregnancy D-dimer levels increase with duration of gestation; highest levels are observed in the third trimester[12]. Use of D-dimer measurement may help to guide anticoagulant treatment in recurrent pregnancy loss associated with antiphospholipid syndrome[13].

In cancer patients D-dimer levels have been shown to be associated with the risk to develop thromboembolic complications, as well as with disease progression[14,15].

Further applications of D-dimer testing in preventive cardiology have been described in connection with coronary and carotid atherosclerosis, as well as aortic disease[16].

Principles of the Procedure

Polystyrene particles covalently coated with a monoclonal antibody (8D3)[19] 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 on automated coagulation analyzers. Sysmex provides Reference Guides (Application Sheets) for several coagulation analyzers. The Reference Guides (Application Sheets) contain analyzer/assay specific handling and performance information which may differ from that provided in these Instructions for Use. In this case, the information contained in the Reference Guides (Application Sheets) supersedes the information in these Instructions for Use. Please also consult the instruction manual of the instrument manufacturer!

Reagent	Description	Storage	Stability
INNOVANCE® D-Dimer			
REAGENT	Lyophilized reagent containing: • polystyrene particles coated with monoclonal antibody to D-dimer, mouse[a] (reconstituted: 0.1 g/L) • Albumin, human (reconstituted: 0.5 g/L) • Buffers, preservatives	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	2–8 °C: reconstituted, 4 weeks[b]; ≤ –18 °C[c]: reconstituted, 4 weeks[b]
BUFFER	Ready to use liquid containing: • buffers/stabilizers, preservatives	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	2–8 °C: once opened, 4 weeks[b]; ≤ –18 °C[c]: once opened, 4 weeks[b]
SUPPLEMENT	Ready to use liquid containing: • heterophilic blocking reagent (0.63 g/L) • Buffers, preservatives	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	2–8 °C: once opened, 4 weeks[b]; ≤ –18 °C[c]: once opened, 4 weeks[b]

Reagent	Description	Storage	Stability
DILUENT	Ready to use liquid containing: • Buffers, preservatives	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	2–8 °C: once opened, 4 weeks[b]; ≤ –18 °C[c]: once opened, 4 weeks[b]
CALIBRATOR	Lyophilized reagent containing: • human plasma • D-dimer preparation, human[d] (reconstituted: 5.0 mg/L FEU) • buffers/stabilizers, preservatives	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	15–25 °C: reconstituted, 4 hours[b]
EMPTY VIAL			

[a] antibody concentration may vary from lot to lot
[b] closed original vial
[c] Do not refreeze after thawing. Follow the freeze and thaw instructions in section "Preparing Reagents".
[d] nominal value per vial

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

Warnings and Precautions

For *in-vitro* diagnostic use only.

For laboratory professional use.

According to EU regulation 2017/746, any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the EU Member State through your local distribution representative in which the user and/or patient is established.

Safety data sheets (MSDS/SDS) available upon request.

Danger! INNOVANCE D-Dimer REAGENT
Hazardous ingredient: Imidazole (4.81 % [w/w]).
H315: Causes skin irritation. **H318**: Causes serious eye damage. **H360D**: May damage the unborn child.

P201: Obtain special instructions before use. **P264**: Wash hands thoroughly after handling. **P280**: Wear protective gloves/protective clothing/eye protection/face protection. **P308 + P313**: IF exposed or concerned: Get medical advice/attention. **P305 + P351 + P338**: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. **P310**: Immediately call a POISON CENTER or doctor/physician.

Danger! INNOVANCE D-Dimer DILUENT
Hazardous ingredient: Imidazole (0.332 % [w/w]).
H360D: May damage the unborn child.
P201: Obtain special instructions before use. **P280**: Wear protective gloves/protective clothing/eye protection/face protection. **P308 + P313**: IF exposed or concerned: Get medical advice/attention.

Warning! INNOVANCE D-Dimer CALIBRATOR
Hazardous ingredient: Sodium azide (0.806 % [w/w]), reaction mass of 5-chloro-2-methyl-2H-isothiazol-3-one / 2-methyl-2H-isothiazol-3-one (3:1) (0.00878 % [w/w]).
H317: May cause an allergic skin reaction. **H412**: Harmful to aquatic life with long lasting effects. **P261**: Avoid breathing dust. **P280**: Wear protective gloves/protective clothing/eye protection/face protection. **P273**: Avoid release to the environment. **P302 + P352**: IF ON SKIN: Wash with plenty of soap and water. **P333 + P313**: If skin irritation or rash occurs: Get medical advice/attention. **P362 + P364**: Take off contaminated clothing and wash it before reuse. **P501**: Dispose of contents and container in accordance with all local, regional, and national regulations.

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

Caution
INNOVANCE D-Dimer REAGENT, INNOVANCE D-Dimer SUPPLEMENT, INNOVANCE D-Dimer CALIBRATOR
This device contains material of animal origin and should be handled as a potential carrier and transmitter of disease.

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

Dispose of hazardous or biologically contaminated materials according to the practices of your institution. Discard all materials in a safe and acceptable manner and in compliance with all government requirements.

Summary of Safety and Performance (SSP) is available in the European database on medical devices (see Eudamed public website: https://ec.europa.eu/tools/eudamed). In case Eudamed is not available, SSP can be delivered by the manufacturer on request.

Preparing Reagents

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 "Reagents", page 2.

Instructions for the preparation of the kit components

Instructions	REAGENT	BUFFER SUPPLEMENT / DILUENT	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

Instructions	REAGENT	BUFFER SUPPLEMENT / DILUENT	CALIBRATOR
Freeze and thaw	1. Use the original container or the empty vial provided with the kit 2. Follow storage instructions in section "Reagents", page 2 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		n/a
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			

Specimen Collection and Handling

Collecting the Specimen

- 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 after blood collection for 15 minutes at 1500 to 2500 × g. Please refer to CLSI guideline H21-A5[20] for further details. The manufacturer's instructions for the sampling equipment must also be observed.
- Clarify turbid plasma once more by centrifugation at ~15000 × g for 10 minutes.

Storing the Specimen

Stability of the samples:

15 to 25 °C	4 hours
2 to 8 °C	24 hours
≤ –18 °C	4 weeks[e]

[e] If frozen within 4 hours of blood collection.

Preparation of Frozen Samples

- Preparation of frozen plasma aliquots should be performed in accordance with CLSI guideline H21-A5[20]; ensure that platelet poor plasma is utilized (platelet count <10000/µL).
- Freeze plasma within 4 hours of blood collection at ≤ –18 °C.
- Thaw frozen plasma within 10 minutes at 37 °C and homogenize by gentle mixing without foam formation.
- Clarify specimens with turbid plasma by centrifugation at ~15000 × g for 10 minutes.
- Carry out the D-dimer determination within 2 hours. Do not refreeze the specimen.

Procedure

Materials Provided

REF	Contents		
OPBP03	INNOVANCE® D-Dimer		
	INNOVANCE® D-Dimer reagent INNOVANCE D-Dimer REAGENT	3 × →	4 mL
	INNOVANCE® D-Dimer buffer INNOVANCE D-Dimer BUFFER	3 ×	5 mL
	INNOVANCE® D-Dimer supplementary reagent INNOVANCE D-Dimer SUPPLEMENT	3 ×	2.6 mL
	INNOVANCE® D-Dimer Sample Diluent INNOVANCE D-Dimer DILUENT	3 ×	5 mL
	INNOVANCE® D-Dimer Calibrator INNOVANCE D-Dimer CALIBRATOR	2 × →	1 mL
	Empty vial EMPTY VIAL	1 ×	12 pcs.
OPBP07	INNOVANCE® D-Dimer		
	INNOVANCE® D-Dimer reagent INNOVANCE D-Dimer REAGENT	6 × →	4 mL
	INNOVANCE® D-Dimer buffer INNOVANCE D-Dimer BUFFER	6 ×	5 mL
	INNOVANCE® D-Dimer supplementary reagent INNOVANCE D-Dimer SUPPLEMENT	6 ×	2.6 mL
	INNOVANCE® D-Dimer Sample Diluent INNOVANCE D-Dimer DILUENT	6 ×	5 mL
	INNOVANCE® D-Dimer Calibrator INNOVANCE D-Dimer CALIBRATOR	2 × →	1 mL

Materials Required but not Provided

Item	Description
REF OPDY03	INNOVANCE D-Dimer CONTROLS, INNOVANCE® D-Dimer Controls
REF OPBR03	INNOVANCE D-Dimer DILUENT, INNOVANCE® D-Dimer Sample Diluent
–	Distilled or deionized water without preservatives
–	Plastic test tubes
–	Pipettes for precise measurement of 0.1 mL
Coagulation analyzers[f], such as:	• Automated Blood Coagulation Analyzer CA-600 series (CA-600 series) • AUTOMATED BLOOD COAGULATION ANALYZER CS-2500 (CS-2500 System) • AUTOMATED BLOOD COAGULATION ANALYZER CS-5100 (CS-5100 System)

[f] Availability of analyzers may vary by country.

Please note that the applications on other analyzers can be validated by the instrument manufacturer in accordance with the requirements of the REGULATION (EU) 2017/746 under their responsibility as long as the intended purpose and performance are not modified.

Performing 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 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 8 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

The measuring range depends on the individual application of the assay due to instrument related conditions. Application specific performance data are listed in the respective Reference Guides of the instruments.

A typical calibrated measuring range is 0.17 to 4.40 mg/L FEU (e.g. BCS® XP System). Samples with an initial result outside the measuring range may be diluted with DILUENT. The BCS® XP Systems automatically performs a sample dilution, resulting in an extended measuring range of up to 35.2 mg/L FEU.

Limitations

The following substances were found as interfering with the INNOVANCE® D-Dimer method above the levels of concentration given below:

Cholesterol above 315 mg/dL (8.1 mmol/L), Dextrane 40 above 1800 mg/dL. Lipoglycopeptide antibacterial drugs (such as oritavancin) may interfere with D-dimer assays. Oritavancin has been shown to elevate D-dimer concentrations up to 72 hours after its administration[17].

Turbidity and particles in the samples may interfere with the determination. Therefore, samples containing particles must be centrifuged for 10 minutes at approx. 15000 × 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.

In a representative study, fibrinogen degradation products (X, Y, D and E) were tested according to CLSI guideline EP7-A2 with the following cross-reactivity: Fibrinogen degradation products 2.0 to 20.0 mg/L with ≤2.5 % cross-reactivity. Note: % cross-reactivity = apparent Ddimer concentration minus true concentration divided by concentration of the cross-reactant multiplied by 100. The cross-reactivity observed resulted in an increase of apparent D-dimer concentrations.

The manufacturer has validated use of these reagents on various analyzers to optimize product performance and meet product specifications. Please note that the applications on other analyzers can be validated by the instrument manufacturer in accordance with the requirements of the REGULATION (EU) 2017/746 under their responsibility as long as the intended purpose and performance are not modified. User defined modifications are not supported by the manufacturer as they may affect performance of the system and assay results. It is the responsibility of the user to validate modifications to these instructions or use of the reagents on analyzers other than those included in Application Sheets or these Instructions for Use.

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

DVT clinical diagnosis should not be based on the result of INNOVANCE® D-Dimer alone.

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[18].

Patients with subsegmental/peripheral PE or distal DVT may have a normal INNOVANCE® D-Dimer result[21,22].

Exclusionary claim of PE in patients with high PTP scores has not been established.

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

Expected Values

In a study of ostensibly healthy individuals using a specific lot of INNOVANCE® D-Dimer, the following values were obtained:

	n	90th Percentile
BCS®/BCS® XP System	150	0.55 mg/L FEU

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.

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[23].

Performance Characteristics

Note

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

Specificity and crossreactivity

In a representative study, fibrinogen degradation products (X, Y, D and E) were tested according to CLSI guideline EP7-A2[25] 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[21]. The cross-reactivity observed resulted in an increase of apparent D-dimer concentrations.

Precision

Precision studies were conducted with the BCS®/BCS® XP System, as described in the CLSI guideline EP5-A2[24], 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.

Sample	n	Mean [mg/L FEU]	Repeatability CV [%]	Within-Device/Lab Precision CV [%]
INNOVANCE D-Dimer CONTROL 1	80	0.3	4.1	4.3
INNOVANCE D-Dimer CONTROL 2	80	2.6	1.4	2.2
Normal plasma pool	80	0.2	7.8	7.9
Plasma pool (low)	80	0.8	3.4	4.5
Plasma pool (high)	80	3.6	1.5	2.6

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

The reproducibility was assessed by the manufacturer for INNOVANCE® D-Dimer based on publicly available proficiency testing information in 2019/2020. The overall reproducibility median CV % was found to be <15 % (normal samples) and <12 % (pathological samples) including lot, instrument, laboratory and operator variability factors.

Method Comparison

A study was performed on a BCS® XP System 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:

INNOVANCE® D-Dimer	n	Concentration[g]	Slope	Intercept	Correlation Coefficient
Stratus® CS DDMR	1067	0.17–35.2 mg/L FEU	1.036	0.023 mg/L FEU	0.978
Commercially available assay	1417	0.17–35.2 mg/L FEU	1.312	0.172 mg/L FEU	0.961

[g] Concentration range of plasma samples investigated

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.

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.

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
Atellica® COAG 360 System	0.50	98.9 / 94.8	36.6 / 33.0	99.5 / 97.6	586[h]
CA-1500 System	0.50	99.4 / 98.0	39.3 / 36.9	99.5 / 98.7	1425
CA-560 CA-660 System	0.50	99.4 / 98.0	37.8 / 35.4	99.5 / 98.6	1425

LCL = lower 95 % confidence limit. The study design is described in the respective publications[26,27].

For the CS-2500 and CS-5100 System specific values, please see system specific Reference Guides (Application Sheets). The performance data for the exclusion of DVT and PE with the CS-2500 and CS-5100 systems were evaluated according to CLSI guideline H59-A[34].

[h] Different study populations were used both for the CS* System and the Atellica® COAG 360 System.

Interference

- The D-dimer method was evaluated for interference according to CLSI guideline EP7-A2[25].
- 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[28].

Substance tested (BCS®/BCS® XP System)	Substance concentration	S.I. units	D-dimer concentration	Bias[i] [%]	D-dimer concentration	Bias[i] [%]
Hemoglobin (hemolysate)	200 mg/dL	124 µmol/L	0.29 mg/L	3.4	2.43 mg/L	1.2
Bilirubin (not conjugated)	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

[i] 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 to 0.55 mg/L.

Substance	Test concentration	S.I. units
Acetaminophen	20 mg/dL	1 324 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
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)[29]	5 IU/mL	n.a.
Dextrane 40	1 800 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	1 770 µmol/L
Furosemide	6.0 mg/dL	181 µmol/L
Gentamicin	12 mg/dL	251 µmol/L
Heparin, ammonium-[30]	3 U/mL	n.a.
Heparin, lithium-[30]	3 U/mL	n.a.
Heparin, sodium-[30]	3 U/mL	n.a.
Ibuprofen	50 mg/dL	2 425 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[31]	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

Substance	Test concentration	S.I. units
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[32]	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

In a study with an application on the BCS® XP System, 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[33] 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.

Technical Assistance

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

Current Version of Application Sheets

INNOVANCE® D-Dimer can be used in combination with various automated coagulation analyzers. Sysmex provides Reference Guides/Application Sheets for the coagulation analyzers listed in section "Materials Required but not Provided", page 6 under the dedicated link below:

sysmex-ifu.com/ag

As the manufacturer continuously monitors the product performance and safety, the users are required to ensure that they work with the correct revision of the instructions for the product lots in use. Please periodically review the availability of new electronic labeling revisions to ensure safe use of the product.

The IFU version number is visible on each product box label. Sysmex ensures that all products lots bearing the same IFU version number are compatible with the electronic labeling provided via sysmex-ifu.com.

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Definition of Symbols

The following symbols may appear on the product labeling:

	Do not reuse		Use By
LOT	Batch Code	REF	Catalogue Number
	Caution		Manufacturer
EC REP	Authorized representative in the European Community	CH REP	Authorized representative in Switzerland
	Contains sufficient for <n> tests		Biological Risks
IVD	*In Vitro* Diagnostic Medical Device		Temperature Limitation
	Consult instruction for Use		Non-sterile
CE	CE marking of conformity	CE 0197	CE marking of conformity with notified body ID number. Notified body ID number can vary.
CONTENTS	Contents	→	Reconstitution volume
LEVEL	Level		Keep away from sunlight and heat
WARNING	Warning	DANGER	Danger
RxOnly	Prescription device (US only)	UDI	Device Identification (UDI) barcode
REACH xx/xx/xx	REACH Authorization Number		

Legal Information

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