SIEMENS Healthineers

INNOVANCE® D-Dimer

Revision bar indicates update to previous version.

Intended Use

For the quantitative determination of cross-linked fibrin degradation products (D-dimers) in human plasma on Siemens Healthineers and SYSMEX Coagulation Systems. The INNOVANCE® D-Dimer assay is intended for use in conjunction with a non-high clinical pre-test probability (PTP) assessment model to exclude deep vein thrombosis (DVT) and pulmonary embolism (PE).

Summary

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 weight (e.g. DD 195 kD, DD/E 228 kD DXXD 693 kD, YXD/DXY 850kD) containing the D and E domain[1]. An association between a certain mixture or molecular weight 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, DIC, acute aortic dissection, myocardial infarction, malignant diseases, obstetrical complications, third trimester of pregnancy, surgery or polytrauma[3-8]. However, in the context of venous thromboembolism, 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].

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

- 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

Principles of the Procedure

Polystyrene particles covalently coated with a monoclonal antibody (8D3)[10] 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 Healthineers 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.

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]
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	Ready to use liquid containing:		

[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

Warnings and Precautions

For *in-vitro* diagnostic use only.

For laboratory professional use.

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

CAUTION!
Federal (USA) law restricts this device to sale by or on the order of licensed healthcare professionals.


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.

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.

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. Mix carefully 2. Avoid foam formation 3. BUFFER only: resuspend potential precipitates by gently swirling. Any residual precipitates after resuspension do not impact test results 4. 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 same 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 same 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 noted on the vial label using the framed free space		

Specimen Collection and Handling:

- Recommended specimen types: citrated platelet poor plasma.
- To obtain plasma, carefully mix 1 part sodium citrate solution (0.11 mol/L) with 9 parts venous blood, avoiding the formation of foam. An evacuated tube system or syringe may be used.
- Centrifuge the blood tube after blood collection for 15 minutes at 1 500 x g to 2 500 x g. Please refer to CLSI guideline H21-A5[11] for further details.
- The manufacturer’s instructions for the sampling equipment must also be observed.
- Clarify highly lipemic plasma once more by centrifugation at approximately 15 000 x g for 10 minutes.

Stability of the 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. Do not refreeze.

Preparation of Frozen Samples

- Preparation of frozen plasma aliquots should be performed in accordance with CLSI guideline H21-A5[11]; ensure that platelet poor plasma is utilized (platelet count < 10 000/µL).
- Freeze plasma within 4 hours of blood collection at ≤ –18 °C.
- Thaw frozen plasma at 37 °C for 10 minutes and homogenize by carefully mixing without foam formation. Then carry out the D-dimer determination within 2 hours. Do not refreeze.
- For specific handling information on the various analyzers, please consult the respective Reference Guides (Application Sheets).
- Clarify specimens with turbid plasma by centrifugation at approximately 15 000 x g for 10 minutes.

Procedure

Materials Provided

INNOVANCE® D-Dimer Kit REF OPBP 09

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 11

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

Materials Required but not Provided

INNOVANCE® D-Dimer Controls REF OPDY 09
INNOVANCE® D-Dimer Sample Diluent REF OPBR 03
Coagulation analyzer
Distilled water
Pipettes

Test Steps

- Sampling, reagent delivery, mixing, and processing are automatically performed by the coagulation analyzer. For details of this processing, refer to the respective Operator's Guide.

Calibration

Calibrate each lot of INNOVANCE® D-Dimer kit using the INNOVANCE® D-Dimer CALIBRATOR provided with the same kit. Use the analyzer specific values for the INNOVANCE® D-Dimer CALIBRATOR as detailed in the enclosed Table of Analytical Values in mg/L FEU (Fibrinogen Equivalent Units).

Calibration Material	INNOVANCE® D-Dimer CALIBRATOR
Calibration Scheme	6 levels, n = 2 per level
Units	mg/L (FEU)

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	See below "A new calibration is required"
A new calibration is required:	• For each new lot of INNOVANCE® D-Dimer Kit. 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

Quality Control

- INNOVANCE® D-Dimer Controls must be tested at least every eight hours around patient sample testing on each testing day, after each calibration 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 the example below:

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):	1 250 µg/L FEU or 1 250 ng/mL FEU

Measuring Range (Reportable 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 Procedure

The D-dimer method was evaluated for interference and cross-reactivity according to CLSI guideline EP7-A2[12]. For interference the bias is the difference in the results between the control sample (without the interferent) and the test sample (contains the interferent) expressed in percent.

The following substances interfere with the INNOVANCE® D-Dimer method above the concentrations given below:

Substance Tested	Substance Concentration	S. I. Units
Cholesterol	315 mg/dL	8.1 mmol/L
Dextrane 40	1 800 mg/dL	-

In a representative study, fibrinogen degradation products (X, Y, D und E) were tested according to CLSI guideline EP7-A2[12] with the following cross-reactivity:

Cross-reactant	concentration	% cross-reactivity
Fibrinogen degradation products	2.0 to 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. The cross-reactivity observed resulted in an increase of apparent D-dimer concentrations.

- Turbidity and particles in the samples may interfere with the determination. Therefore, samples containing particles must be centrifuged for 10 minutes at approximately 15 000 x g again prior to testing.
- Lipemic samples or samples that contain particles, which cannot be clarified by centrifugation (10 minutes at approximately 15 000 x g) must not be used.
- Due to matrix effects, inter-laboratory survey samples 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 falsely elevated or depressed results. 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 Healthineers 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 Healthineers as they may affect performance of the system and assay results. It is the responsibility of the user to validate modifications to these instructions or use of the reagents on analyzers other than those included in Siemens Healthineers Application Sheets or these instructions for use.
- Results of this test 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.
- Patients with subsegmental/peripheral PE or distal DVT may have a normal INNOVANCE® D-Dimer result[13,14].
- Exclusionary claim of PE in patients with high PTP scores has not been established.

Expected Values

Less than 0.59 mg/L FEU for normal healthy subjects.

In a study with 150 apparently healthy, 18 to 62 year old adults (60 females and 90 males) from Central Europe, a 90th percentile of 0.59 mg/L FEU was obtained for the BCS®/BCS® XP System.

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, size and age of the thrombus. Therefore, a thromboembolic event cannot be diagnosed with certainty on the basis of the reference range[15].

Specific Performance Characteristics

The following data represent typical performance for the BCS®/BCS® XP System.

Precision[16,a)]

Material	Mean (mg/L FEU)	Precision (n = 80) CV (%)	
		Repeatability	Within-device/lab
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

a) CLSI guideline EP5-A2 was used. During each day of testing, two separate runs, with two test samples, for each test material, were analyzed for 20 days.

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

Comparative Method[17,b)]

Comparative Method	Regression Statistics Slope	Intercept (mg/L FEU)	Correlation Coefficient	n
Stratus® CS DDMR	0.951	0.059	0.97	318[c)]
VIDAS D-DIMER EXCLUSION	1.11	-0.075	0.96	265[d)]

b) CLSI guideline EP9-A2 was used. The method used to fit the linear regression line was Passing-Bablok.

c) The range of D-dimer values in the correlation studies was 0.18 to 4.39 mg/L FEU.

d) The range of D-dimer values in the correlation studies was 0.17 to 4.17 mg/L FEU.

Clinical Performance of the INNOVANCE® D-Dimer assay to exclude DVT

The INNOVANCE® D-Dimer assay was evaluated on the BCS®/BCS® XP System in a multi- center study to validate the exclusion of DVT using fresh specimens collected from 455 consecutive patients presenting to the emergency department with suspected DVT. Of these 455 patients, 29 were excluded for a total of 426 patients available for final analysis.

All patients were evaluated using the Wells' rules to estimate a likely or unlikely pre-test probability (PTP) of DVT[18]. Patient specimens were tested with the INNOVANCE® D-Dimer assay and results were compared to a cut-off value of 0.50 mg/L (FEU). A D-dimer result < 0.50 mg/L (FEU) was considered negative and a D-dimer result ≥ 0.50 mg/L (FEU) was considered positive.

Patients with a positive D-dimer result were evaluated by imaging methods, e.g. compression ultrasound and/or venography. Patients with a negative D-dimer, as well as those with negative imaging results, were followed for three months to evaluate potential development of DVT. All patients were subject to imaging at the physicians' discretion.

The overall prevalence of DVT in those patients available for final analysis was 21.8 % (93/426). The following instrument-specific sensitivity, specificity and negative predictive value (NPV) with upper and lower 95 % confidence limits (CL) were obtained with the INNOVANCE® D-Dimer clinical cut-off of 0.50 mg/L (FEU).

All Patients

Instrument	DVT Patients (n)	Cut-off mg/L FEU	Sensitivity (CL) %	Specificity (CL) %	NPV (CL) %
BCS®/BCS® XP System	426	0.50	100.0 (96.1 – 100.0)	34.5 (29.4 – 39.9)	100.0 (96.8 – 100.0)

Patients with unlikely pre-test probability

Instrument	DVT Patients (n)	Cut-off mg/L FEU	Sensitivity (CL) %	Specificity (CL) %	NPV (CL) %
BCS®/BCS® XP System	267	0.50	100.0 (83.9 – 100.0)	37.0 (31.0 – 43.4)	100.0 (96.0 – 100.0)

CL = lower and upper 95 % confidence limits

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

Clinical Performance of the INNOVANCE® D-Dimer assay to exclude PE

The INNOVANCE® D-Dimer assay was evaluated on the BCS®/BCS® XP System in a multi-center study to validate the exclusion of PE using fresh specimens collected from 701 consecutive patients presenting to the emergency department with suspected PE. Of these 701 patients, 54 were excluded for a total of 647 patients available for final analysis.

All patients were evaluated using the Wells' rules to estimate a high, moderate or low pre-test probability (PTP) of PE[18]. Patient specimens were tested with the INNOVANCE® D-Dimer assay and results were compared to a cut-off value of 0.50 mg/L (FEU). A D-dimer result < 0.50 mg/L (FEU) was considered negative and a D-dimer result ≥ 0.50 mg/L (FEU) was considered positive.

Patients with a positive D-dimer result and/or a high PTP were evaluated by imaging methods, e.g. spiral CT and/or VQ scan. Patients with a negative D-dimer result and a low or moderate PTP (these patients underwent imaging at the physician's discretion), and patients with negative imaging results, were followed for three months to evaluate potential development of PE.

The overall prevalence of PE in those patients available for final analysis was 13.8 % (89/647). The following instrument-specific sensitivity, specificity and negative predictive value (NPV) with upper and lower 95 % confidence limits (CL) were obtained with the INNOVANCE® D-Dimer clinical cut-off of 0.50 mg/L (FEU).

All Patients

Instrument	PE Patients (n)	Cut-off mg/L FEU	Sensitivity (CL) %	Specificity (CL) %	NPV (CL) %
BCS®/BCS® XP System	647	0.50	98.9 (93.9 - 100.0)	39.6 (35.5 - 43.8)	99.6 (97.5 - 100.0)

Patients with low and moderate pre-test probability

Instrument	PE Patients (n)	Cut-off mg/L FEU	Sensitivity (CL) %	Specificity (CL) %	NPV (CL) %
BCS®/BCS® XP System	616	0.50	98.6 (92.5 - 100.0)	40.4 (36.3 - 44.7)	99.6 (97.5 - 100.0)

CL = lower and upper 95 % confidence limits

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

Interference

The INNOVANCE® D-Dimer method on BCS®/BCS® XP System was evaluated for interference according to CLSI guideline EP7-A2[12]. 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[20].

Interference

Substance tested (Instrument: BCS® Systems)	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	1 026 µmol/L	0.29 mg/L	-3.3	2.56 mg/L	0.8
Lipemia (Triglycerides)	600 mg/dL	6 840 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	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)[22]	5 IU/mL	n.a.
Diazepam	0.5 mg/dL	18 µmol/L
Digoxin	5 ng/mL	6.4 nmol
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[23]	3 U/mL	n.a.
Heparin, lithium[23]	3 U/mL	n.a.
Heparin, sodium[23]	3 U/mL	n.a.

Substance	Test Concentration	S. I. Units
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[24]	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	3 472 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
Creatinine	30 mg/dL	2 655 µmol/L
Albumin	6 g/dL	60 g/L
Rheumatoid Factors[25]	1 330 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[21] 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 and is 0.02 mg/L FEU.

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

Technical Assistance

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

siemens-healthineers.com

Current Version of Application Sheets

INNOVANCE® D-Dimer can be used in combination with various automated coagulation analyzers. Siemens Healthineers provides Reference Guides/Application Sheets for coagulation analyzers under the dedicated link below:

siemens-healthineers.com/rg

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

The IFU version number is visible on each product box label. Siemens Healthineers ensures that all products lots bearing the same IFU version number are compatible with the electronic labeling provided via siemens-healthineers.com/eIFU.

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Definition of Symbols

The following symbols may appear on the product labeling:

	Do not reuse		Use By
LOT	Batch Code	REF	Catalogue Number
	Caution		Manufacturer
EC REP	Authorized representative in the European Community		Contains sufficient for <n> tests
	Biological Risks	IVD	*In Vitro* Diagnostic Medical Device
	Temperature Limitation		Consult instruction for Use
NON STERILE	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

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