IVD CAPSULE D-Dimer - Instructions for Use (IFU)

REF P02.00050

English

Intended use

The **IVD CAPSULE D-Dimer** is a single use, rapid in vitro diagnostic test for the quantitative measurement of D-Dimer in human sodium citrate anticoagulated venous whole blood. The **IVD CAPSULE D-Dimer** is intended to be used, in conjunction with clinical pretest probability, in the aid in the diagnosis of venous thromboembolism (VTE) including deep vein thrombosis (DVT), pulmonary embolism (PE) and disseminated intravascular coagulation (DIC), in patients suspected of DVT, PE or DIC (according to CLSI H59-A [1]).

D-Dimer testing is often ordered in the primary care and emergency room (ER) with symptoms of a serious condition (e.g., chest pain and difficulty in breathing).

The **IVD CAPSULE D-Dimer** is to be used with the **abioSCOPE** 2.0 in vitro diagnostic test system. The system is intended for professional use in clinical laboratory settings, in hospitals and point of care (PoC) locations including near-patient testing.

Summary

D-Dimer is formed by the breakdown of cross-linked fibrin degradation products, and its presence in human plasma is a well-established marker indicative of fibrinolytic activity. D-Dimer analysis is critical for the exclusion of thromboembolic events such as deep vein thrombosis (DVT), pulmonary embolism (PE) and disseminated intravascular coagulation (DIC) [2]. Elevated D-dimer levels are present in conditions associated with increased coagulation activation, such as during DVT, PE and DIC as mentioned earlier, but D-Dimer is also increased in numerous other conditions including acute aortic dissection, obstetrical complications, third trimester pregnancy, surgery or polytrauma. Therefore, this test is used predominantly as an exclusion test in patients suspected of DVT or PE in combination with a pre-test probability [1, 3-5].

Test principle

The blood sample is mixed with a solution composed of fluorescently labelled antibodies specific to human D-Dimer. The blood sample, now containing the D-Dimer-antibody complex, is loaded onto the capsule of the kit.

Patient material is passively drawn through the capsule by capillary action and passes through a built-in separator that excludes red blood cells and particles from the measurement area.

After passing through the separator, the D-Dimer-antibody complex is captured by antibodies immobilized on the capsule's read-out area.

The quantity of captured D-Dimer is proportional to the fluorescence generated by the fluorophore conjugated to the detection antibody. Therefore, the measured fluorescence signal is proportional to the concentration of D-Dimer within the sample. The **abioSCOPE** automatically calculates the concentration of each sample and displays it on the instrument screen. D-Dimer concentrations are expressed in fibrinogen equivalent unit (FEU) which corresponds to the concentration of fibrinogen initially present in the sample that leads to the measured level of D-Dimer. The equivalence between these two measurement units is approximately 2 ng/ml FEU = 1 ng/ml of D-Dimer.

Reagents

Each assay contains one vial with 100 µl of the **abioMIX** reagent. The **abioMIX** reagent is composed of a fluorescently labelled anti-human D-Dimer antibody, dissolved in a phosphate buffered saline solution supplemented with bovine serum albumin, Tween-20 and ProClin300 preservative (Table 1).

Ingredient	Concentration
Fluorescently labelled anti-human D-Dimer antibody	4.50 µg/ml
Bovine serum albumin	0.1% (w/v)
Tween 20 (CAS number 005-64-5)	1% (v/v)
ProClin 300 (CAS number 55965-84-9)	0.04% (v/v)

Table 1| Composition of the **abioMIX** reagent.

Materials included

- 1x D-Dimer capsule
- 1x vial of **abioMIX** reagent
- 1x capillary blood collector (**abioPIPETTE**)
- 1x desiccant bag
- 1 x printed Instructions for Use (IFU)

Sample collection and handling

Venous whole blood is collected in designated trisodium citrate blood tubes by venous puncture and anticoagulated according to the manufacturer's protocol, in conformity with the recommendations for haemostasis tests. Prepare a trisodium citrate anti-coagulated blood tube. Turn the plunger clockwise by one quarter to activate the provided **abioPIPETTE**. Outside the test tube press on the **abioPIPETTE**'s plunger and maintain the pressure. Insert the **abioPIPETTE** into the tube. Release the plunger to completely fill the **abioPIPETTE** with blood and then remove it. 50 µl of blood are loaded.

Test procedures

1. Use the **abioPIPETTE** filled with 50 µl of venous whole blood that was collected according to "**Sample collection and handling**".
2. Pick up the **abioMIX** vial and flick it to move the **abioMIX** down to the bottom before use. Pierce the cap with the tip of the filled **abioPIPETTE** without pushing the plunger and insert it fully into the vial. Next, push on the **abioPIPETTE**'s plunger to dispense the entire blood

sample into the **abioMIX** reagent vial. Hold the pressure on the plunger of the **abioPIPETTE** and remove the **abioPIPETTE.** The plunger can be released outside of the vial.

3. Tap the vial at least 10 times on a hard surface to mix thoroughly the blood-**abioMIX** solution and proceed immediately to the next step (***note****: a well-mixed sample will have a homogenous color*).
4. Outside the vial, push down the plunger completely and hold the pressure. Insert the **abioPIPETTE** as far as possible into the vial. Release the plunger to completely fill the **abioPIPETTE** with the mix and remove the **abioPIPETTE**. Press the plunger gently to deposit the mixture evenly on the entire surface of the membrane (white area) in the center of the capsule. The mixture should be dispensed slowly to allow the solution to wick into the capsule. Ensure that the pipette tip does not scrape the membrane.
5. Fold the lid over to close the capsule. Hold the capsule only by the edges. Be careful not to touch the bottom side of the capsule.
6. To start the measurement, touch the button "measure" on the **abioSCOPE** reader. The tray will open automatically.
7. Place the capsule onto the tray according to the guided capsule position on the screen, then touch the button "close tray".

To measure the sample, refer to the **abioSCOPE** 2.0 User Manual.

Storage and stability

The **IVD CAPSULE D-Dimer** has a shelf life of 5 months when refrigerated (at 2°C to 8°C), as indicated by the expiration date printed on the label. Allow the **IVD CAPSULE D-Dimer** to warm up to room temperature before opening and use it immediately after.

The blood sample mixed with the **abioMIX** reagent should be immediately loaded onto the D-Dimer capsule and the filled capsule immediately measured.

Sample stability

It is preferred to analyse the samples as soon as possible after venous punction. Whole blood samples must be stored at room temperature (20 to 25 °C) before measurement.

Traceability and calibration

IVD CAPSULE D-Dimer is calibrated by the manufacturer using a purified preparation of human D-Dimer in trisodium citrate anticoagulated plasma supplemented with red blood cells. Each lot of **IVD CAPSULE D-Dimer** is calibrated using a weighted 5 parameter logistic curve fit data reduction method. The instrument automatically reads in the lot-specific calibration data that are embedded within the capsule's chip, eliminating the need for calibration by the user. D-Dimer values assigned to the calibration material are directly traceable to the highest available reference material, so that results for a given measurand is comparable across methods and laboratories.

Quality control

The **abioSCOPE** evaluates internal controls at power-on and after insertion of the capsule. If controls fail, the **abioSCOPE** displays a specific error message.

It is recommended to use external reference material for quality control. Contact the manufacturer for assistance and follow the applicable local regulations and guidelines.

The **IVD CAPSULE D-Dimer** is calibrated to measure human D-Dimer in sodium citrate anticoagulated whole blood samples. Quality control results obtained with external reference material that differs in terms of sample matrix (e.g., serum or plasma) should by analysed with caution.

The control intervals should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined target range provided by the manufacturer of the reference material. Each laboratory should establish corrective measures to be taken if values fall outside of the defined ranges.

Warnings and precautions

- For in vitro diagnostic use.
- The **IVD CAPSULE D-Dimer** must be kept refrigerated until use.
- Do not freeze.
- Allow the **abioMIX** reagent vial to reach room temperature before use.
- This product requires the handling of human specimens. It is recommended that all human-sourced material is considered potentially infectious. Universal precautions that apply to the user's facility should be applied for handling and disposal of materials during and after testing [6].
- Do not use reagents after the expiry date printed on the box.
- Do not use the diagnostic kit if the pouch is damaged.
- Incubation of the specimen in the **abioMIX** for more than 5 minutes may impact test results.
- If the whole blood sample is not immediately analysed, it is important to homogenize the sample (i.e., ensure the resuspension of the blood cells) before performing the test.
- The **abioSCOPE** 2.0 should be regularly cleaned and decontaminated (see the User Manual)

Reagent deterioration

The following observations indicate reagent deterioration:

- Presence of turbidity in the **abioMIX** vial.

- Consistently high or low values from assay kits from the same batch.

In such cases the kit should not be used.

Limitations

- Test results should be interpreted within the complete clinical picture. Definitive diagnosis and/or clinical decision should not be based solely on the results of any single diagnostic test but made after all clinical and laboratory findings are evaluated.
- Clinically elevated total protein level may interfere with test results.
- Grossly haemolytic, icteric, or grossly lipemic specimen may interfere with test results at clinically elevated concentrations.
- All assay materials are single-use and cannot be re-used or transferred to another kit.

The user shall report any serious incident that has occurred in relation to the device to the manufacturer and the relevant national competent authority.

Expected values

The mean D-Dimer concentration range in adults was measured in 516 randomly selected normal subjects at 306 +/- 130 ng/ml FEU [7].

It is recommended that each laboratory determine its own reference values.

Measuring range: 212 - 1000 ng/ml FEU

The linear range of the assay was determined by diluting a pool of samples with clinically elevated D-Dimer levels in a pool of samples with low D-Dimer levels to obtain concentrations spanning the entire assay range (212 to 1000 ng/ml FEU of D-Dimer). Regression analysis demonstrated that the assay response was linear with a slope of 0.97 and an intercept of 15.93 in this range. The analytical sensitivity study demonstrated a limit of blank (LoB) of 77 ng/ml FEU, a limit of detection (LoD) of 109 ng/ml FEU and a limit of quantification (LoQ) of 212 ng/ml FEU.

D-Dimer concentrations below 212 ng/ml FEU are reported as "< 212 ng/ml FEU", and values above 1000 ng/ml FEU are reported as "> 1000 ng/ml FEU".

Linearity was established in accordance with the recommendation of the CLSI document EP06, 2nd edition [8], and the LoB, LoD and LoQ with EP17-A2 [9].

The **IVD CAPSULE D-Dimer** showed no high-dose effect ("prozone effect", "Hook effect") at concentrations below 43500 ng/ml FEU (this was the highest tested D-Dimer concentration) for trisodium citrate anticoagulated whole blood.

Precision

The between-day precision was measured with 1 run of 4 replicates per day, for 20 days, on 3 samples covering the assay reportable range of the **IVD CAPSULE D-Dimer** on the **abioSCOPE** 2.0 (Table 3).

D-Dimer level	Mean value [ng/ml FEU]	Between-day CV
Level 1	319	6%
Level 2	603	0%
Level 3	1051	0%

Table 3| Summary of the 20 days precision study.

The between-lot precision was measured with 3 lots of IVD CAPSULE D-Dimer, 5 replicates per day, for 5 days, on 3 samples covering the assay reportable range of the **IVD CAPSULE D-Dimer** on the **abioSCOPE** 2.0 (Table 4).

D-Dimer level	Mean value [ng/ml FEU]	Between-lot CV
Level 1	220	5%
Level 2	382	1%
Level 3	671	2%

Table 4| Summary of the between-lot precision study.

The between-device precision was measured on 3 different **abioSCOPE** with 1 lot of **IVD CAPSULE D-Dimer**, 5 replicates, on 3 samples covering the assay reportable range of the **IVD CAPSULE D-Dimer** on the **abioSCOPE** 2.0 (Table 5).

D-Dimer level	Mean value [ng/ml FEU]	Between-device CV
Level 1	261	7%
Level 2	426	4%
Level 3	671	5%

Table 5| Summary of the between-device precision study.

For practical reasons, the precision studies mentioned above were performed with trisodium citrate plasma samples. The within device precision of trisodium citrate anticoagulated whole blood and matching plasma has been verified and found to be similar.

The repeatability of the **IVD CAPSULE D-Dimer** on the **abioSCOPE** 2.0 has been evaluated with 10 sodium citrate anticoagulated venous whole blood samples covering the range of D-Dimer concentrations from 211 to 1046 ng/ml FEU. All samples were measured 10 times in a row on **1 abioSCOPE** with 1 lot of **IVD CAPSULE D-Dimer**. Imprecision values ranged from 10% to 20%.

All the precision studies were designed, executed, and analysed in accordance with the recommendations of the CLSI document EP05-A3, 3rd edition [10].

Analytical selectivity

The substances listed below were tested for interference. Each substance was tested at a clinically elevated concentration, on three D-Dimer samples covering the low, intermediate (near the medical decision point) and high range of the assay. Analytical

selectivity was established in accordance with the recommendation of the CLSI document EP07, 3rd edition [11] and its supplement EP37, 1st edition [12].

No interference was observed on the three D-Dimer samples at these concentrations (bias within +/- 10%) (Table 6).

Substance	Highest doses tested
Albumin	60 g/l
Hemoglobin	10 g/l
Free bilirubin	40 mg/dl
Conjugated bilirubin	40 mg/dl
D-Dimer	43500 ng/ml FEU (reported as '> 1000 ng/ml FEU')
Rheumatoid factor	100 IU/ml
Heparin, lithium	3 U/ml
Heparin, sodium	3 U/ml
Acethylsalicylic acid	3 mg/dl
Warfarin	7.50 mg/dl
Dalteparin sodium (anti-factor Xa)	5 IU/ml

Table 6| Test substances (endogenous and exogenous) and their concentrations.

An underestimation of 12% of the D-Dimer concentration has been observed on high level D-Dimer samples (> 800 ng/ml FEU) containing fibrinogen above 10 g/l. No interference was observed at this fibrinogen concentration for samples containing low or intermediate D-Dimer levels.

A clinically elevated immunoglobulin G (IgG) concentration (2000 mg/dl) might lead to an overestimation of the D-Dimer concentration on samples containing low D-Dimer levels (250 ng/ml FEU). No significant bias was observed at this IgG concentration for samples containing more than 400 ng/ml FEU of D-Dimer.

The following substances were found to bias test results by more than 10% (Table 7).

Substance	Concentration
Human anti-mouse antibodies (HAMA)	490 ng/ml
Triglycerides	500 mg/dl

Table 7| Substances that showed a significant bias at the tested concentration.

Although precautions have been taken to minimize interference caused by endogenous and exogenous substances, erroneous results caused by interferences can be observed. For diagnostic purposes, the results should always be compared to the patient's medical history, clinical signs, and other findings.

Method comparison

The IVD CAPSULE D-Dimer on the **abioSCOPE** 2.0 demonstrated a good comparability with the reference laboratory method VIDAS® D-Dimer Exclusion™ II, bioMérieux. 105 paired samples (sodium citrate venous whole blood on abioSCOPE 2.0 and corresponding venous plasma on reference method) were assessed on both methods in single replicate according to recommendation of CLSI document EP09-C, 3rd edition [13].

The Table 8 summarizes the study results.

abioSCOPE 2.0 versus VIDAS®	
Non-Weighted Deming linear regression	
Slope (95% CI)	1.19 (0.99 to 1.39)
Intercept (95% CI)	-14 (-89 to 60)

Table 8 | Comparison of methods Linear regression statistics were applied to the entire data set covering a range of value (on the **abioSCOPE** 2.0) of 222 to 930 ng/ml FEU (n = 105).

References

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CE marking according to the Directive 98/79/EC

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Near-patient testing.