RESPONSE BIOMEDICAL

INSTRUCTIONS FOR USE

RAMP® D-dimer

C1106-2.5

WARNING!

For *in vitro* diagnotic use only

Failure to follow RAMP® test procedures may result in invalid and/or erroneous results. Read the entire Instructions For Use prior to performing test.

INTENDED USE

The RAMP® D-dimer test is a quantitative immunochromatographic test indicated for use as an *in vitro* diagnostic product used in the quantification of the fibrin degradation product (FDP) D-dimer in human EDTA anti-coagulated whole blood.

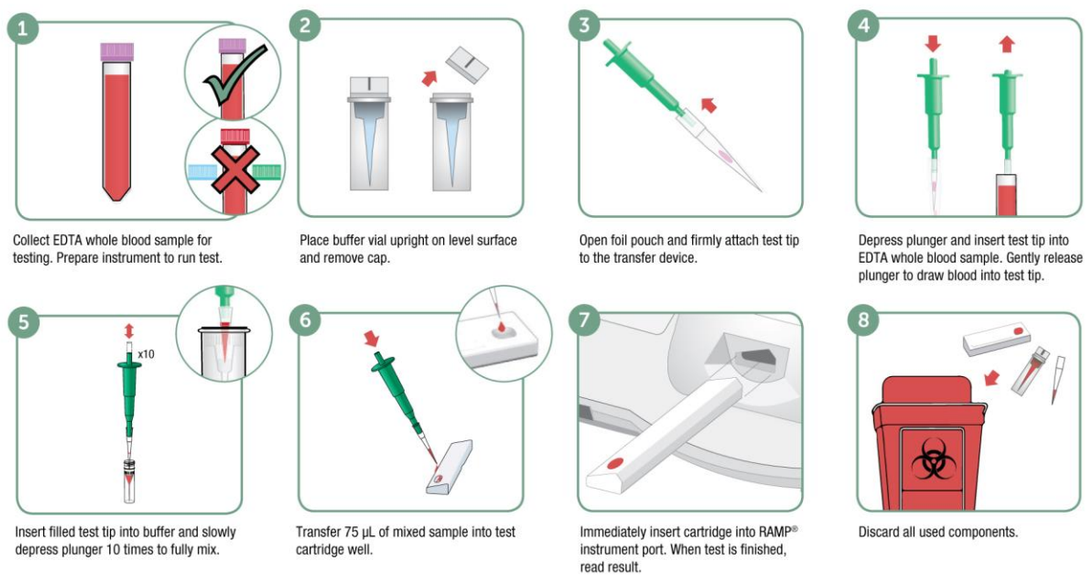
WWW.RESPONSEBIO.COM | SPEED. PRECISION. ACCURACY.

IVD

24-HOUR TECHNICAL SUPPORT
Tel: 1-866-525-7267 (toll free) Tel: 1-604-219-6119 (int'l)
Email: techsupport@responsebio.com

RESPONSE CORPORATE OFFICE
Tel: 1-888-591-5577 (toll free) Tel: 1-604-456-6010 (int'l)
Email: customersupport@responsebio.com

Running a test



SUMMARY AND EXPLANATION

D-dimer is a fibrin degradation product (FDP), a small protein fragment that is present in the blood after a blood clot is degraded by fibrinolysis. It is so named because it contains two cross-linked D fragments of the fibrinogen protein. As a result, D-dimer is considered to be a marker of coagulation activation and therefore D-dimer is present in the circulation as part of the normal wound healing process, but it is also valuable as a diagnostic marker for Disseminated Intravascular Coagulation (DIC) and as an aid to the rule-out of Venous Thromboembolism (VTE), a spectrum of diseases that include Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) [1 to 5].

The level of D-dimer in the blood is usually increased during thromboembolism as the intrinsic lytic system attempts to breakdown the intravascular clot. [3] Plasma D-dimer levels are elevated in a number of thrombotic states, including DVT, PE, malignant neoplasm, myocardial infarction, trauma, recent surgery, and hepatic insufficiency. [6] This limits the test's specificity for any one given disease, preventing it from becoming a screening test for the presence of PE and DVT. A negative test, however, has been found to have a high negative predictive value and is clinically useful as a predictor of the absence of both DVT and PE. [7] Also, in situations when the patient presents at a time when the full range of diagnostic tests is not available, a negative D-dimer test may allow the patient to be discharged until further tests can be completed, avoiding hospital admission.

TEST PRINCIPLE

The RAMP® D-dimer test is a quantitative immunochromatographic test for the determination of D-dimer in EDTA whole blood. Mixed EDTA whole blood is applied into the sample well of the test cartridge. The red blood cells are retained in the sample pad and the separated plasma migrates along the strip. Fluorescent-dyed particles coated with anti-D-dimer antibodies bind to D-dimer, if present in the sample. As the sample migrates along the strip, D-dimer bound particles are captured at the detection zone and excess fluorescent-dyed particles are captured at the control zone.

The RAMP® instrument then measures the amount of fluorescence emitted by the complexes bound at the detection zone and at the control zone. Using a ratio between the two fluorescence values, a quantitative reading is calculated. For further information on the use of the instrument, refer to the RAMP® Operator's Manual.

REAGENTS

- The RAMP® test kit contains all the reagents necessary for the quantification of D-dimer in EDTA whole blood.
- The sample buffer contains phosphate buffer, animal protein, surfactant, and ProClin® 300 / ProClin® 950 as preservatives.

WARNINGS AND PRECAUTIONS

- For in vitro diagnostic use.
- For use by qualified personnel per local, state, or Federal regulations or accrediting agency requirements.
- Read the entire instructions for use (IFU) prior to use. Directions should be read and followed carefully, or invalid or erroneous results may occur.
- Do not interchange or mix components of different RAMP® tests, RAMP® lots or components from other manufacturers.
- Do not use the kit, or any kit component, past the indicated expiry date.
- Do not use any visibly damaged components.
- Do not insert a cartridge on which blood or any other fluid is spilled, into the instrument.
- Disposal of all waste materials should be in accordance with local guidelines.
- Exercise standard precautions required for handling all laboratory reagents and patient samples.
- The device contains material of animal origin and should be handled as a potential biohazard.
- The sample buffer provided contains ProClin®, a potential skin sensitizer. Avoid spilling or splashing reagents containing ProClin® on skin or clothing. In case of contact, thoroughly flush with water.

STORAGE AND STABILITY

Store at 2 to 8°C (35 to 46°F). Do not freeze.

Stability

Unopened at 2 to 8°C (35 to 46°F)	Up to the stated expiration date
When stored at 18 to 25°C (64 to 77°F)	14 days

SAMPLE COLLECTION & PREPARATION

- Use ONLY EDTA Whole Blood (Plastic K2EDTA tubes are recommended). Other sample types and anticoagulants have not been evaluated.
- Avoid blood samples that show gross hemolysis as these may interfere with the test and cause erroneous results. If this occurs, another blood sample should be obtained and tested.
- Testing must be completed within 2 hours of phlebotomy. However, if this is not possible, the EDTA whole blood can be stored for up to 2 days at 2 to 8°C. If stored, allow blood samples to equilibrate to 18 to 25°C for at least 15 minutes prior to use.

MATERIALS PROVIDED

- 25 pouches, each containing 1 RAMP® test cartridge and 1 test tip
- 25 RAMP® buffer vials
- 1 transfer device for 75 µL
- 1 lot card
- 1 instructions for use (IFU)

MATERIALS REQUIRED (BUT NOT PROVIDED)

- REF: C1100 RAMP® Reader instrument; or
- REF: C2100 RAMP® 200 instrument control module, and
- REF: C3100 RAMP® 200 instrument test module
- REF: C2003 RAMP® Cardiac Controls (optional)
- Optional accessories such as RAMP® printer and/or barcode scanner
- Specimen collection tubes: EDTA (Venous Whole Blood)

Use only the listed RAMP® instruments approved for use with this test.

LOT CARD CALIBRATION

Each RAMP® test kit includes a lot card that is individually packaged in an anti-static pouch. The lot card provides information specific to the kit test cartridge lot, including lot number, expiration date, and standard curve information. For further details on loading lot-specific information, see the RAMP® instrument Operator's Manual. No additional calibration beyond insertion of the lot card is necessary. This operation is required only once per test kit lot.

For each new lot, remove the lot card from its pouch and insert it into the lot card slot on the instrument. Once the lot card has been uploaded, return to its pouch and do not discard. Avoid touching the contacts at the end of the lot card.

PROCEDURE

Prior to sample preparation allow all components to come to room temperature for at least 15 minutes.

- Keep the test cartridge and test tip in the sealed foil pouch until ready for use. Once opened, test cartridges and test tips must be used or discarded within 60 minutes.
- The test cartridge, test tip, and buffer vial should be discarded after a single-use. Do not reuse.

1. Prepare RAMP® instrument for test cartridge. Refer to the RAMP® Operator's Manual for detailed instructions on Starting a Test.
2. Ensure that the EDTA whole blood sample is well mixed by gentle inversion.
3. Uncap the buffer vial and place upright on a clean, dry level surface; or in a holder.
4. Open a test pouch and remove the test cartridge and tip. Place the test cartridge on a clean, level surface. Firmly attach the test tip to the supplied transfer device.
5. Before inserting the test tip into the sample, fully depress the transfer device plunger.
6. Insert tip into sample and fully release plunger. The test tip should fill with 75 µL of blood.
7. Immediately transfer the filled test tip into the buffer vial close to, but not touching, the bottom.
8. Mix sample slowly by fully pressing and releasing the plunger 10 times; while keeping the tip submerged in the buffer for optimal mixing and to minimize air bubbles.
9. Once mixing is complete, draw 75 µL of sample into the test tip by releasing the plunger one final time and immediately dispense liquid into the sample well of the test cartridge. Small droplets may remain in the tip; this is expected.
10. Immediately insert the test cartridge fully into the instrument and press until firm resistance is felt.
11. The instrument will draw the cartridge in and test development will begin.
12. The instrument will analyze the cartridge and report the result in approximately 15 minutes.
13. Record the result, if required. For additional information on printing and/or uploading results, please refer to the Operator's Manual.
14. Remove the used test cartridge and discard all used test components according to local biohazard procedures. DO NOT reuse.

For additional information on the general operation and troubleshooting of the instrument, please refer to the RAMP® Operator's Manual.

QUALITY CONTROL

Refer to the RAMP® Operator's Manual for full details on quality control operation and troubleshooting.

SYSTEM QUALITY CONTROL

The RAMP® instrument has error checking and self-diagnostic functions (Internal Quality Control (IQC)) that assure system integrity. These include algorithms and measurements used to confirm acceptable operator technique, sample handling, and test performance. Frequency of IQC may be programmed at desired intervals.

Valid results are displayed only after all performance requirements have been met.

PROCEDURAL CONTROLS

- Each RAMP® test has built-in controls. Test cartridges have a control zone that is scanned as part of the test protocol to ensure proper sample flow.
- Control limits for each lot of test cartridges are established during the manufacturing process and are incorporated in the test-specific lot parameters. If a control result does not meet specifications, the sample result is not reported and a message is displayed.

LIQUID QUALITY CONTROL (LQC)

- It is recommended that quality control materials be run with the RAMP® test in conformance with federal, state and local requirements for quality control testing.
- While the running of commercial control materials are recommended, it is not a requirement to use, or assure, performance of the RAMP® test unless specified by local regulations or institutional requirements.
- To run a LQC sample, follow the instructions under the "Procedure" section in this IFU. Treat the control as a whole blood sample.

TEST RUN MESSAGES

When the RAMP® instrument is unable to continue a specific task it will emit an audio alarm and display a message. Refer to the RAMP® Operator's Manual 'Troubleshooting Guide' section for a full description of all messages. If repeated tests give unexpected results, contact Response Biomedical Technical Support for assistance

LIMITATIONS

- For diagnostic purposes, the patient's medical history, clinical examination and other findings should always be assessed in conjunction with the RAMP® test results. A test result that is inconsistent with the clinical signs and symptoms should be interpreted with caution.
- Factors such as technical or procedural errors or the presence of substances in blood specimens other than those that have been evaluated (see Interference section of this IFU), may interfere with the RAMP® test and cause erroneous results.
- As with any immunoassay, patient specimens may contain heterophilic antibodies that may result in either falsely elevated or depressed results. Presence of these antibodies may be due to elevated levels of rheumatoid factor, treatment with mouse monoclonal antibodies for diagnostic or therapeutic purposes, or other undetermined factors. The RAMP® test has been formulated to reduce the effects of heterophilic antibodies, but complete elimination of heterophilic interference from all samples cannot be guaranteed.

TEST CUT-OFF AND EXPECTED VALUES

The RAMP® D-dimer Expected Values (reference range) study was conducted at one clinical site and included 91 apparently healthy individuals (49 women and 42 men). The normal range for the RAMP® D-dimer test (determined as the 95th percentile of these results) includes values ≤ 386 ng/mL FEU. No statistically significant bias due to gender or ethnicity was observed in this study. Each laboratory should investigate the transferability of the expected values to its own patient population and, if necessary, determine its own reference ranges.

PERFORMANCE CHARACTERISTICS

MEASUREMENT RANGE

100 to 5000 ng/mL FEU.

D-dimer levels in excess of 5000 ng/mL are reported as greater than (>) 5000 ng/mL FEU, values less than 100 ng/mL should be reported as (<) 100 ng/mL FEU.

HOOK EFFECT

No high dose hook effect was observed for the RAMP® D-dimer test up to the highest level tested (~250,000 ng/mL FEU).

DETECTION LIMIT

To determine the Limit of Blank (LoB), 60 replicates of a blank material were tested. The LoB, estimated as the non-parametric determination of the 95th percentile of all 60 replicates, was determined to be <100 ng/mL FEU.

To determine the Limit of Detection (LoD), 5 replicates each of 12 low level clinical EDTA whole blood specimens were tested over 8 runs. The LoD was calculated to be <100 ng/mL FEU.

PRECISION

Repeatability and precision estimates were obtained using three levels of frozen control materials and three lots of RAMP® D-dimer tests. Controls were evaluated at three levels across the reportable range of the RAMP® D-dimer test (mean concentrations of 363, 656 and 4044 ng/mL FEU, respectively) and were tested in duplicate over 12 days, two runs per day. The RAMP® D-dimer test demonstrated Within-Run (Repeatability) %CVs ranging from 3.6% to 9.0% and Total Precision %CVs ranging from 4.3% to 11.0%.

INTERFERENCE

None of the following factors has been found to influence the RAMP® D-dimer test

- Hemolysis (hemoglobin to 200 mg/dL)
- Bilirubinemia (conjugated bilirubin to 5 mg/dL; unconjugated bilirubin to 15 mg/dL)
- Hyperlipidemia (cholesterol to 500 mg/dL; triglycerides to 500 mg/dL)
- Gamma (γ)-globulins (to 60 mg/dL)

However it is recommended not to use samples that appear to be clearly hemolyzed, lipemic or icteric and to collect a new sample if possible.

45 commonly used pharmaceutical compounds were evaluated for potential interference in the RAMP® D-dimer test. Compounds were evaluated by spiking different concentrations of each individual potential interferent into EDTA whole blood with D-dimer added to provide levels of ~400 and ~3,000 ng/mL FEU. Drugs and metabolites were tested at three times the Maximum Recommended Therapeutic Dose (MRTD); anticoagulants were tested at five times the MRTD. The pharmaceutical compounds tested are listed in the following table. No interference with the RAMP® D-dimer test was found.

Pharmaceutical Compounds

Acebutolol	Cyclosporin A	Nicotine
Acetaminophen	Diclofenac	Nicotinic Acid
Acetylsalicylic Acid	Digoxin	Nifedipine
Albuterol (Salbutamol)	Enalapril	Oxytetracycline
Allopurinol	Erythromycin	Plasminogen
Ambroxol	Fluoxetine	Propranolol
Ampicillin	Furosemide	Quinidine
Ascorbic Acid	Heparin	Simvastatin
Atorvastatin	Ibuprofen	Sulfamethoxazole
Caffeine	Indapamide	Tetracycline
Captopril	Lisinopril	Theophylline
Cefoxitin	Lovastatin	Triamterene
Chlorothiazide	Methyldopa	Trimethoprim
Clopidogrel	Milrinone	Verapamil
Cocaine	Nadolol	Warfarin

ANALYTICAL SPECIFICITY

No cross-reactivity was observed for fibrinogen (up to 1 mg/mL). Elevated concentrations of fragment D and fragment E, as may be present during thrombolytic therapy, may lead to elevated measurement values.

REFERENCES

[1]. Garcia-Berrocoso et al. 2010. Curr Cardiol Rev. 6(3):194

[2]. Brown. 2011. Ann Emerg Med. 58(4):375-6

[3]. Sakamoto et al. 2011. Hellenic J Cardio. 52:123-7

[4]. Sun et al. 2011. Br J Neurosurg. 25(3):363-8

[5]. Ghanavatian et al. 2011. Clin Lab. 57(9-10):771-6

[6]. Arch Pathol Lab Med. 1993. 117(10): 977-80

[7]. J Vasc Surg. 1999. 30(5):794-803

GLOSSARY OF SYMBOLS

EC REP Authorized Representative in European Community	LOT Batch Code	REF Catalogue Number
Caution	CE Mark	Consult Instructions for Use
Contains Sufficient for <n>Tests	Do Not Reuse	IVD In vitro Diagnostic Medical Device
Harmful, Irritant	Manufacturer	Temperature Limit
Use-by Date		

PRODUCT SUPPORT / ASSISTANCE

When the RAMP® instrument is unable to continue a specific task it will emit an audio alarm and display message. Refer to Operator's Manual 'Troubleshooting Guide' section for a full description of all Messages. If repeated tests give unexpected or inconsistent results, contact Response Biomedical Corp. Technical Support.

If you have any questions regarding the use of this product please contact Response Biomedical Corp. Technical Support:

- Within US or Canada (+1.866.525.7267)
- Outside US or Canada (+1.604.219.6119)
- By email at techsupport@responsebio.com

MANUFACTURER

RESPONSE BIOMEDICAL

Response Biomedical Corp.
1781 – 75th Avenue W
Vancouver, BC, Canada V6P 6P2
T. +1.604.456.6010
T. +1.888.591.5577 (Toll-free North America)
E. customersupport@responsebio.com

2014-03, V 2.5, English

REF C1106