Dade® Innovin®

Revision bar indicates update to previous version.

CE 0197

Intended Use

Dade® Innovin® is an in vitro diagnostic reagent for the quantitative determination of prothrombin time (PT) as an aid to diagnosis, screening for hemostasis disorders and monitoring of oral anticoagulation therapy with vitamin K antagonists in human sodium citrated plasma by means of automated, semi-automated and/or manual coagulometric methods.

For monitoring vitamin K antagonist anticoagulation therapy PT is reported in WHO-standardized INR (International Normalized Ratio).

Summary and Explanation

Dade® Innovin® Reagent is prepared from purified recombinant human tissue factor produced in E. coli, combined with synthetic phospholipids (thromboplastin), calcium, buffers and stabilizers. The reagent initiates clotting via the extrinsic and common pathways in a global screening test, the prothrombin time (PT).

The PT is a clinically important test for the detection of coagulation abnormalities and can be used[1–3]:

- for monitoring of oral anticoagulant therapy in patients receiving vitamin K antagonists,
- in pre-surgery bleeding risk assessment,
- in screening for bleeding disorders like suspected extrinsic factor deficiency,
- as aid in diagnosis for hemostasis disorders like liver disease or DIC
- to derive the fibrinogen concentration (when in the normal range) from the PT by photo-optical coagulation analyzers.

Dade® Innovin® Reagent is manufactured using recombinant human tissue factor and synthetic phospholipids which do not contain any other clotting factors such as prothrombin, FVII and FX. Therefore, it is highly sensitive to factor deficiencies and oral anticoagulant treated patient plasma samples. The sensitivity of Dade® Innovin® Reagent is very similar to the first WHO human brain reference thromboplastin. Dade® Innovin® Reagent is insensitive to therapeutic levels of heparin. The high sensitivity of Dade® Innovin® Reagent to coagulation factors and its insensitivity to therapeutic heparin make it beneficial in monitoring oral anticoagulant therapy with vitamin K antagonists. In addition, its high sensitivity (i.e. the responsiveness of the reagent to moderately depleted factor activity) allows differentiation of abnormal plasmas, even in the mildly pathological range[4,5].

Furthermore, Dade® Innovin® Reagent can be used in combination with the respective factor FII, FV, FX or FVII deficient plasma for the quantification of the coagulation factors: FII, FV, FX and FVII.

Principles of the Procedure

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

Reagents

Note: Dade® Innovin® can be used manually or 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
Dade® Innovin®	Lyophilized reagent containing: • Thromboplastin: recombinant human tissue factor (reconstituted: ~100–200 µg/L[a]) with synthetic phospholipids • Calcium • Heparin neutralizer • Buffer • Stabilizer: • BSA	2–8 °C May be used up to the expiry date indicated on the label if stored unopened. Do not freeze!	2–8 °C: reconstituted, 10 days[b]; 15–25 °C: reconstituted, 5 days[b]; 37 °C: reconstituted, 24 hours[b]

[a] depending on specific activity
[b] closed original vial

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

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.

Caution
This device contains material of animal origin and should be handled as a potential carrier and transmitter of disease.

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

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

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

Note: Do not use distilled water containing preservatives.

Specimen Collection and Handling

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

Centrifuge the blood specimen at 1 500 × g for no less than 15 minutes at room temperature.

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

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

Procedure

Materials Provided

REF	Contents	
B4212-40	Dade® Innovin®	10 × → 4 mL
B4212-50	Dade® Innovin®	10 × → 10 mL
B4212-100	Dade® Innovin®	12 × → 20 mL

Materials Required but not Provided

Item	Description
REF ORKE41 REF 291070 REF B4244-10	CONTROL N, Control Plasma N, or Dade® Ci-Trol® 1, or Ci-Trol CONTROL 1, Dade® Ci-Trol® Coagulation Control Level 1, as control for the normal range
REF OUPZ17 REF 291071 REF B4244-20	CONTROL P, Control Plasma P, or Dade® Ci-Trol® 2, or Ci-Trol CONTROL 2, Dade® Ci-Trol® Coagulation Control Level 2, as control for the pathological/therapeutical range
REF 291072 REF B4244-30	Dade® Ci-Trol® 3, or Ci-Trol CONTROL 3, Dade® Ci-Trol® Coagulation Control Level 3, as control for the pathological/therapeutical range
REF OPAT03	PT-Multi CALIBRATOR (Refer to the Instructions for Use for details on use)
REF ORKL17	STANDARD PLASMA, Standard Human Plasma, or fresh normal plasma[6] for determining the mean normal PT (MNPT)[c]
–	For blood collection, use sodium citrate 0.11 mol/L or 0.13 mol/L (3.2 % or 3.8 %)
–	Distilled or deionized water without preservatives
–	Plastic test tubes
	Plastic transfer pipettes

Item	Description
–	Pipettes for precise measurement of 20.0 mL, 10.0 mL, 1.0 mL, 0.50 mL, 0.20 mL and 0.10 mL
Coagulation analyzers[d], 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)

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

[d] 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.

Manual Testing

Pre-warm Dade® Innovin® at 37 °C		
Pipet into coagulation tubes as follows:		
	Test Sample	Control Plasma
Plasma	0.1 mL	–
Control Plasma	–	0.1 mL
	Mix well. Incubate at 37 °C for 1–2 minutes (max. 5 minutes).	
Dade® Innovin® (pre-warmed)	0.2 mL	0.2 mL
	Simultaneously with addition of Dade® Innovin® start stopwatch, mix well. After start to observe for clot formation.	

Internal Quality Control

Normal range: Dade® Ci-Trol® 1, Ci-Trol CONTROL 1, or CONTROL N

Pathological range: Dade® Ci-Trol® 2, Ci-Trol CONTROL 2, or Dade® Ci-Trol® 3, Ci-Trol CONTROL 3, or CONTROL P

Two levels of quality control material (normal and pathological range) must be measured at start of the test run, with each calibration, upon reagent vial changes and at least every 8 hours on each day of testing.

The control material should be prepared and processed in the same manner as the samples.

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

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

Results

Currently, various methods are used for reporting PT results. ISI (International Sensitivity Index) values for Dade® Innovin® Reagent are provided for the particular reagent/instrument combination; these enable the results to be reported in INR (International Normalized Ratio)[6]. Computation and use of the INR are described below. Monitoring of oral anticoagulant therapy with vitamin K antagonists should only be reported with PT results expressed as INR as recommended in official guidelines and in the literature[6]. Alternatively, the patient's PT (in seconds) together with the reference range (in seconds) can be used to report results.

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

Determination of INR (International Normalized Ratio)

Values using Dade® Innovin® Reagent

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

1. According to the joint recommendations of the World Health Organization (WHO)[6] and the International Committee on Thrombosis and Haemostasis, the PT results for patients on vitamin K antagonist oral anticoagulants should be reported as INR values. Reported INR results are independent of the reagents and methods used, and are specifically intended for assessing patients stabilized on longterm oral anticoagulant therapy.

   The INR is determined[6] according to the following equation:

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

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

   The ISI values for this thromboplastin reagent are determined in accordance with WHO recommendations.

2. Methods of INR calculation:

   a. Calculators with exponential functions:

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

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

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

   b. Conversion Table:

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

   c. Automatic:

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

Derived Fibrinogen

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

Limitations

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

Derived fibrinogen results within the reference range can be directly reported. Results outside the reference range should be re-measured by a standard fibrinogen determination method, e.g. Fibrinogen method with THROMBIN REAGENT or with Multifibren® U Reagent. Derived fibrinogen testing is not suitable in patients with dysfibrinogenemia[8] or patients with prolonged PT, e.g. under oral anticoagulation or with PT% below 25 % of Norm[9,10].

Lipoglycopeptide antibacterial drugs (such as oritavancin or telavancin) may interfere with PT based assays. Consult Instructions for Use of respective drugs.

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

Expected Values

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

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

		% Reference Interval	
	n	**2.5th Percentile**	**97.5th Percentile**
PT	158	9.9 seconds	11.8 seconds
Derived Fibrinogen	124	1.8 g/L	3.5 g/L

Therapeutic Ranges

Therapeutic ranges for INR may vary depending on the indication of oral anticoagulant therapy[15].

Performance Characteristics

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.

Sensitivity

Factor Sensitivity of Dade® Innovin®

According to CLSI H47-A2, the PT reagent/instrument combination used should provide abnormally prolonged results for plasmas that have less than 30 % factor activity of the coagulation factors: FII, FV, FVII and FX. CLSI H47-A2 recommends to determine sensitivity levels by serial dilution of normal plasma into deficient plasma. Sensitivity levels determined by this method should ideally be within 30 and 45 %. However, the factor sensitivity levels determined by this method is strongly dependent on deficient plasma used[16].

Precision

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

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

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

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

The reproducibility was assessed by the manufacturer for Dade® Innovin® based on publicly available proficiency testing information in 2018/2019. The overall reproducibility median CV% was found to be

- PT % <10 %
- PT seconds <5 %
- PT INR <5 %
- Derived Fibrinogen <10 %

including lot, instrument, laboratory and operator variability factors.

Interference

Many commonly administered drugs may affect the results obtained in prothrombin time testing[6]. This should be kept in mind especially when unusual or unexpected abnormal results are obtained. Unexpected abnormal results should be followed by additional coagulation studies to determine the source of the abnormality.

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

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

Inhibitors such as lupus anticoagulant may interfere with the prothrombin time and result for example in INRs that do not reflect the exact degree of anticoagulation[11].

Hirudin or other direct thrombin inhibitors in therapeutic dose result in prolonged prothrombin times[12,13].

Some blood collection tubes may contain Mg^{2+} ions, which have been shown to interfere with recombinant thromboplastins[14].

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

Technical Assistance

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

Current Version of Application Sheets

Dade® Innovin® 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 3 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.

References

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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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