SIEMENS Healthineers

INNOVANCE® Heparin
INNOVANCE HEPARIN

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Revision bar indicates update to previous version.

Intended Use

INNOVANCE HEPARIN is an in vitro diagnostic reagent for the quantitative, WHO-standardized determination of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) activity for monitoring patients under UFH or LMWH therapy in human sodium citrated plasma by means of automated, chromogenic methods.

Summary and Explanation

Heparin (UFH and LMWH) considerably accelerates the inactivation of thrombin and coagulation factor Xa (Xa) by antithrombin (AT). For this reason, UFH and LMWH preparations are widely used as prophylactic and therapeutic anticoagulants. The main clinical indications for UFH are in prevention and treatment of venous thromboembolism, in certain types of acute coronary syndrome, in thrombotic stroke and extracorporeal circulation. LMWH has been replacing UFH in many of the latter's traditional indications. Due to numerous influences the anticoagulant effect of an identical dose of heparin varies from patient to patient[1,2].

Quantification of UFH and LMWH allows reconciliation with therapeutic target ranges, and can be helpful in special patient populations, such as pregnant women, children, patients with gross over- or under-weight, or multi-morbid patients. Monitoring UFH by anti-Xa measurement allows specific quantification of UFH especially in case of prolonged base-line APTT, as frequently seen in patients with liver disease, lupus anticoagulants, after thrombolytic therapy, with congenital or acquired factor deficiencies or APTT prolongation in inflammatory syndromes[3,4].

Principles of the Procedure

INNOVANCE HEPARIN assay is a one stage chromogenic assay. The reagent kit consists of two components. One component (Reagent) contains Xa, the other (Substrate) a chromogenic substrate specific for Xa. Upon mixing of INNOVANCE HEPARIN REAGENT and INNOVANCE HEPARIN SUBSTRATE Xa converts the chromogenic substrate into two products, one of them is paranitroaniline. The formation of paranitroaniline can be quantified by the coagulation analyzer employing light absorption at a specific wave length (405 nm).

In the presence of a heparin containing sample the formation of paranitroaniline will be reduced in a time dependent manner. This is due to inhibition of Xa by the heparin/AT complex. This complex is formed in the patient's plasma and competes with the substrate conversion by Xa. The concentration of the complex is not only dependent on the concentration of heparin but also on the availability of the patient's endogenous antithrombin. By comparison to a reference curve the heparin activity of the sample can be quantified.

To reduce the influence from heparin antagonists, such as platelet factor 4 (PF4), dextran sulfate is included in the reaction mixture.

Reagents

Note: The INNOVANCE HEPARIN can be used on automated coagulation analyzers.
Siemens Healthineers 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® Heparin INNOVANCE HEPARIN			
REAGENT	Ready to use liquid containing: • FXa, bovine (~0.7 IU/mL) • TRIS • Sodium chloride • EDTA Na-salt • Bovine serum albumin • Dextran 500 • Preservative: • reaction mass of 5-chloro-2-methyl-2H-isothiazol-3-one / 2-methyl-2H-isothiazol-3-one (3:1) pH 8.0	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	2–8 °C: once opened, 8 weeks[a]
SUBSTRATE	Ready to use liquid containing: • Suc-Ile-Glu(piperidin-1-yl)-Gly-Arg-pNA.HCl (1.25 mg/mL) • Sodium acetate • Preservative: • reaction mass of 5-chloro-2-methyl-2H-isothiazol-3-one / 2-methyl-2H-isothiazol-3-one (3:1) pH 5.0	2–8 °C May be used up to the expiry date indicated on the label if stored unopened.	2–8 °C: once opened, 8 weeks[a]

[a] closed original 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 in which the user and/or patient is established.

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

INNOVANCE HEPARIN REAGENT, INNOVANCE HEPARIN SUBSTRATE
Hazardous ingredient: reaction mass of 5-chloro-2-methyl-2H-isothiazol-3-one / 2-methyl-2H-isothiazol-3-one (3:1).
May produce an allergic reaction.

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

Not to be used for the determination of the activity or concentration of anticoagulants other than UFH and LMWH (e.g. heparinoids, synthetic pentasaccharides, direct factor Xa inhibitors). Danger of under- or overdosing resulting in thrombotic events or bleedings, respectively.

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 Siemens Healthineers on request.

Preparing Reagents

Reagents (Reagent and Substrate) are liquid and ready to use. Before use unscrew and remove caps. Place the reagents on the analyzer and start measurement.

All kit components are lot-specific. The combination with components from other lots may lead to incorrect results.

Specimen Collection and Handling

Specimen type: Platelet poor citrated human plasma.

Collecting the Specimen

To obtain platelet poor citrated human plasma, carefully mix 1 part sodium citrate solution (0.11 mol/L, 3.2 %) with 9 parts venous blood, avoiding the formation of foam. An evacuated tube system or a syringe may be used. Centrifuge the blood tube as soon as possible for at least 15 minutes at 1 500 to 2 500 × g. After centrifugation the number of platelets in the plasma should be < 10 000/µL.

Storing the Specimen

Plasma can be stored either on cells or siphoned from the cellular components in a closed tube at room temperature. Siphoned plasma can also be stored at ≤ –18 °C. For storage at ≤ –18 °C freeze plasma within 4 hours of blood collection.

Stability of the samples:

15 to 25 °C	(plasma stored on cells)	4 hours
15 to 25 °C	(plasma siphoned from cells)	4 hours
≤ –18 °C	(plasma siphoned from cells)	3 days
≤ –74 °C	(plasma siphoned from cells)	6 months

Preparing frozen Specimen
Frozen plasma should be thawed within 10 minutes at 37 °C and homogenized by carefully mixing without foam formation. Then carry out the determination of heparin activity within 2 hours.

Please refer to CLSI Guide-line H21-A5 for further details[5]. The manufacturer's instructions for the sampling equipment must also be observed.

Procedure

Materials Provided

REF	Contents		
OPOA03	INNOVANCE® Heparin INNOVANCE HEPARIN		
	INNOVANCE® Heparin Reagent INNOVANCE HEPARIN REAGENT	5 ×	3.2 mL
	INNOVANCE® Heparin Substrate INNOVANCE HEPARIN SUBSTRATE	5 ×	4.0 mL

Materials Required but not Provided

Item	Description
REF OPOB03	INNOVANCE HEPARIN CALIBRATOR, INNOVANCE® Heparin Calibrator
REF OPOC03	INNOVANCE HEPARIN UF CONTROL 1, INNOVANCE® Heparin UF Control 1
REF OPOD03	INNOVANCE HEPARIN UF CONTROL 2, INNOVANCE® Heparin UF Control 2
REF OPOE03	INNOVANCE HEPARIN LMW CONTROL 1, INNOVANCE® Heparin LMW Control 1
REF OPOF03	INNOVANCE HEPARIN LMW CONTROL 2, INNOVANCE® Heparin LMW Control 2
REF B4234-25	OV BUFFER, Dade® Owren's Veronal Buffer
REF OQUB19	Cleaner SCS (on BCS® XP System only)
Coagulation analyzers[b], such as:	• Atellica® COAG 360 System • BCS® XP System • SYSMEX CA-660 System • SYSMEX CS-2000i/CS-2100i System • SYSMEX CS-2500 System • SYSMEX CS-5100 System • SYSMEX CN-3000/CN-6000 System

[b] 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.

Refer also to the Reference Guide (Application Sheets).

Test Procedure

Pipetting of samples and reagents as well as mixing and processing is performed automatically by the analyzer. For details refer to the Instruction Manual and Reference Guide (Application Sheet).

Performing Calibration

Calibration Material:	INNOVANCE HEPARIN CALIBRATOR. For preparation, please follow the procedure described in the chapter "Preparing Reagents" in the Instructions for Use of INNOVANCE HEPARIN CALIBRATOR.
Calibration Scheme:	5 levels. Two determinations per level.
Units:	IU/mL
Typical Calibration Levels:	The heparin activities of INNOVANCE HEPARIN CALIBRATOR 1-5 are provided in the respective Table of Analytical Values.
A new calibration is required:	• for each new reagent lot of INNOVANCE HEPARIN. • 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

Low range:	INNOVANCE HEPARIN UF CONTROL 1
	INNOVANCE HEPARIN LMW CONTROL 1
High range:	INNOVANCE HEPARIN UF CONTROL 2
	INNOVANCE HEPARIN LMW CONTROL 2

Follow government regulations or accreditation requirements for quality control frequency. If not specified otherwise analyze two levels (low range and high range) of the adequate quality control material (INNOVANCE® Heparin UF Controls for determination of UFH containing plasmas, INNOVANCE® Heparin LMW Controls for determination of LMWH containing plasmas) at start of the test run, with each calibration, upon reagent vial changes and at least every eight hours on each day of testing.

Each laboratory should determine its own quality control ranges, either by means of the target values and ranges provided by the manufacturer of the controls or by means of control values determined in the laboratory. The measured values obtained must be within the range 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. Please also refer to Kitchen et al[6] for out of range results.

Results

Results are given in IU/mL.

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

Limitations

The endogenous heparin neutralizer PF4 may erroneously decrease reported results for Heparin. Exogenous Xa inhibitors (Apixaban, Danaparoid, Fondaparinux and Rivaroxaban) may erroneously increase results.

Turbidity and particles in the samples may interfere with the assay. Therefore, samples containing particles must be centrifuged prior to testing. Lipemic or turbid samples which cannot be clarified by centrifugation (10 minutes at approximately 15 000 × g) must be excluded from the assay.

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.

Siemens Healthineers 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 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.

Expected Values

Therapeutic Range

To ensure an optimal heparin therapy with minimum risk of bleeding or thromboembolic complications please refer to the recommendations made by the heparin manufacturer for heparin activity.

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 HEPARIN.

Measuring Range

0.10 to 1.50 IU/mL

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

The limit of quantitation is below the lower limit of the assay range (0.10 IU/mL) and was determined according to CLSI guideline EP17-A2[7] using UFH and LMWH containing plasmas (Total error of 0.085 IU/mL).

Precision

Precision studies were conducted with the BCS® XP System as described in the CLSI guideline EP05-A2[8], using INNOVANCE HEPARIN UF CONTROL 1, INNOVANCE HEPARIN UF CONTROL 2, INNOVANCE HEPARIN LMW CONTROL 1, INNOVANCE HEPARIN LMW CONTROL 2 and 6 plasma pools.

			Repeatability		Within-Device/Lab Precision	
Sample	n	Mean [IU/mL]	SD[c] [IU/mL]	CV[d] [%]	SD[c] [IU/mL]	CV[d] [%]
Plasma pool 1 containing UFH	80	0.16	0.010	–	0.012	–
Plasma pool 1 containing LMWH	80	0.17	0.009	–	0.013	–
INNOVANCE HEPARIN UF CONTROL 1	80	0.30	0.008	–	0.010	–
INNOVANCE HEPARIN LMW CONTROL 1	80	0.46	0.023	–	0.026	–
INNOVANCE HEPARIN UF CONTROL 2	80	0.63	–	1.30	–	1.64
Plasma pool 2 containing LMWH	80	0.66	–	1.50	–	1.95
INNOVANCE HEPARIN LMW CONTROL 2	80	1.01	–	1.13	–	1.63
Plasma pool 3 containing LMWH	80	1.07	–	1.14	–	1.59
Plasma pool 4 containing LMWH	80	1.31	–	1.03	–	1.21
Plasma pool 2 containing UFH	80	1.40	–	0.72	–	1.05

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

Reproducibility was assessed based on externally conducted studies, including site, laboratory, operator and lot variability factors.

Sample activity	Combined sites		Combined assay lots	
	SD[c] [IU/mL]	CV[d] [%]	SD[c] [IU/mL]	CV[d] [%]
≤ 0.50 IU/mL	≤ 0.029	–	≤ 0.005	–
> 0.50 IU/mL	–	≤ 6.59	–	≤ 2.09

[c] SD: Standard Deviation
[d] CV: Coefficient of Variation

Method Comparison

A study was performed with fresh and frozen samples to compare the INNOVANCE HEPARIN assay on the BCS® XP System to the HEMOSIL Liquid Anti-Xa assay on the ACL TOP for the measurement of heparin. The results from the Passing-Bablock regression analysis are summarized in the following table:

n	Activity range of plasma samples investigated	Correlation Coefficient	Regression equation
313 (UFH and LMWH containing plasma samples)	0.10–1.47 IU/mL	0.981	y = 1.10 x + 0.01 IU/mL
162 (only UFH containing plasma samples)	0.10–1.39 IU/mL	0.987	y = 1.12 x – 0.03 IU/mL
151 (only LMWH containing plasma samples)	0.10–1.47 IU/mL	0.981	y = 1.09 x + 0.05 IU/mL

Interference

The INNOVANCE HEPARIN assay was evaluated for interference on the BCS® XP System according to CLSI guideline EP07-A2[9].

Following concentrations of listed endogenous substances were found to cause no interference up to the indicated concentrations:

Substance	No Interference up to...
Bilirubin (not conjugated)	60 mg/dL
Bilirubin (conjugated)	40 mg/dL
Hemoglobin (free)	549 mg/dL
Triglycerides	807 mg/dL

Note: The values cited for specific performance characteristics of the assay represent typical results and are not to be regarded as specifications for INNOVANCE HEPARIN.

Standardization

Assay calibration is perfomed with calibrator plasmas which are traceable to the WHO (World Health Organization) International Standards for UFH and LMWH.

Technical Assistance

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

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Current Version of Application Sheets

INNOVANCE HEPARIN can be used in combination with various automated coagulation analyzers. Siemens Healthineers provides Reference Guides/Application Sheets for the coagulation analyzers listed in section "Materials Required but not Provided", page 4 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.

References

1. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):e24S-e43S.
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3. Kitchen S, Gray E, Mackie I, et al. Measurement of non-coumarin anticoagulants and their effects on tests of Haemostasis: Guidance from the British Committee for Standards in Haematology. Br J Haematol. 2014;166(6):830-41.
4. Kitchen S. Problems in laboratory monitoring of heparin dosage. Br J Haematol 2000;111(2):397-406.
5. CLSI. Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays and Molecular Hemostasis Assays. Approved Guideline – Fifth Edition. CLSI document **H21-A5** [ISBN 1-56238-657-3]. CLSI, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898 USA, 2008.
6. Kitchen S, Preston FE, Olson JD. Internal quality control in the hemostasis laboratory. In: Kitchen S, Olson JD, Preston FE, editors. Quality in Laboratory Hemostasis and Thrombosis. 2nd ed. Wiley-Blackwell; 2013. P.57-64.
7. CLSI. Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition. CLSI document **EP17-A2** [ISBN 1-56238-795-2]. CLSI, 950 West Valley Road, Suite 2500, Wayne, PA 19087-1898 USA, 2012.
8. NCCLS. Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second Edition. NCCLS document **EP5-A2** [ISBN 1-56238-542-9]. NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2004
9. CLSI. Interference testing in clinical chemistry; Approved Guideline–Second Edition. CLSI document **EP7-A2** [ISBN 1-56238-584-4]. Clinical Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2005.

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		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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