Dade® Actin® FSL Activated PTT Reagent

ACTIN FSL

Revision bar indicates update to previous version.

CE 0197

Intended Use

ACTIN FSL is an in vitro diagnostic reagent for the quantitative determination of activated partial thromboplastin time (APTT) as an aid to diagnosis, screening for hemostasis disorders and monitoring of unfractionated heparin in human sodium citrated plasma by means of automated, semi-automated and/or manual coagulometric methods.

For APTT testing no international reference preparation or method is available.

Summary and Explanation

ACTIN FSL is a liquid reagent based on purified soy and rabbit brain phosphatides with ellagic acid for plasma activation.

The APTT, a global screening procedure[1,2] used primarily to evaluate coagulation abnormalities in the intrinsic pathway, will also detect severe functional deficiencies in factors: FII, FV, FX, or fibrinogen. The APTT has also been widely advocated[3–6] as a means to monitor the effectiveness of unfractionated heparin therapy where the clotting time is prolonged in proportion to the level of heparin. In patients receiving oral anticoagulants, the circulating levels of factors: FII, FVII, FIX, and FX are depressed therefore the APTT can be expected to be prolonged. The presence of non-specific inhibitors, such as the lupus-like anticoagulant[1,7], may prolong the APTT but this effect is variable and generally recognized as being related more to the nature of the APTT reagent employed.

In summary, the APTT is a clinically important screening test with wide applicability for the diagnosis of coagulant disorders and therapeutic monitoring of both, hemorrhagic and thrombotic disease[8–11] and is specifically used

- In pre-surgery bleeding risk assessment
- In screening for bleeding disorders, e.g. in case of suspected intrinsic factor deficiency or inhibitors to intrinsic coagulation factors
- As an aid to diagnosis of lupus anticoagulants (inhibitors) in patients with thrombophilia
- For monitoring of therapy in patients receiving unfractionated heparin

Furthermore, ACTIN FSL can be used in combination with the respective factor: FVIII, FIX, FXI or FXII deficient plasma for the quantification of the coagulation factors: FVIII, FIX, FXI and FXII.

Principles of the Procedure

Factors of the intrinsic coagulation system are activated by incubating the plasma with the optimal amount of phospholipids and a surface activator. The addition of calcium ions triggers the coagulation process, and the clotting time is then measured.

Reagents

Note: ACTIN FSL can be used 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® Actin® FSL Activated PTT Reagent ACTIN FSL	Ready to use liquid containing: • mixture of purified soy phosphatides[a] and rabbit cephaline in 1.0×10^{-4} M ellagic acid • Preservative • Stabilizer • Buffer	2–8 °C May be used up to the expiry date indicated on the label if stored unopened. Do not freeze!	2–15 °C: once opened, 7 days[b]

[a] No standard potency has been established and accepted for purified soy phosphatides.
[b] closed original vial

If the reagent is left to stand, a green deposit may form consisting of ellagic acid and lipids. Before use, mix by inverting. Avoid contamination with plasma.

After use, store the closed container at 2 to 8 °C.

Signs of expiry:

- deviations from the normal laboratory value in the determination of normal plasma or controls

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

ACTIN FSL must be mixed gently by inversion (5 to 8 times) before use.

Specimen Collection and Handling

Collecting the Specimen

Mix nine parts of freshly collected patient blood with one part of 0.11 mol/L or 0.13 mol/L (3.2 % or 3.8 %) sodium citrate. It is recommended that blood specimens for plasma-based coagulation testing should be collected by venipuncture using a blood collection system that collects the specimen directly into a glass or plastic evacuated tube containing the appropriate additive.

Evacuated tubes containing the desired anticoagulant are commercially available and may be used with caution in blood coagulation studies. For special studies, syringe technique may be preferred.

Centrifuge the blood specimen at 1 500 × g for no less than 15 minutes at room temperature as soon as possible after collection.

Storing the Specimen

Store in an unopened tube at room temperature.

If immediate testing is to be done, the plasma may remain on the packed cells. Otherwise plasma should be separated from the cells. To separate the plasma, use a plastic transfer pipette, remove plasma to a plastic tube. Do not store on ice. Nonheparinized plasma should be tested within 4 hours of blood collection.

Plasma containing unfractionated heparin should be centrifuged within 1 hour of blood collection, stored at room temperature and tested within 4 hours.

Platelet-poor plasma may be frozen at ≤ −20 °C for ≤2 weeks in a non frost-free freezer. Frozen plasma should be rapidly thawed at 37 °C, gently mixed and tested immediately. Samples should not stand at 37 °C for more than five minutes.

Please refer to CLSI document H21-A5[13] for detailed information on sample preparation and storage.

Procedure

Materials Provided

REF	Contents		
B4219-1	Dade® Actin® FSL Activated PTT Reagent ACTIN FSL	10 ×	2 mL
B4219-2	Dade® Actin® FSL Activated PTT Reagent ACTIN FSL	10 ×	10 mL

Materials Required but not Provided

Item	Description
REF ORHO37	$CaCl_2$ SOLUTION, Calcium Chloride Solution, (0.025 mol/L)
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 B4224-50	Ci-Trol HEPARIN CONTROL 1, Dade® Ci-Trol® Heparin Control, Low
REF B4224-60	Ci-Trol HEPARIN CONTROL 2, Dade® Ci-Trol® Heparin Control, High
–	For blood collection, use sodium citrate (0.11 mol/L or 0.13 mol/L / 3.2 % or 3.8 %), or Standard commercial blood collection systems
–	Distilled or deionized water without preservatives
–	Plastic tubes

Item	Description
–	Pipettes for precise measurement of 0.1 mL
Coagulation analyzers[c], 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] 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 $CaCl_2$ SOLUTION at 37 °C		
Pre-warm 0.1 mL ACTIN FSL for 1 minute at 37 °C. (Mix before use)		
Pipet into coagulation tubes as follows:		
	Test Sample	Control Plasma
ACTIN FSL (pre-warmed)	0.1 mL	0.1 mL
Plasma	0.1 mL	–
Control Plasma	–	0.1 mL
	Mix well. Incubate at 37 °C for 3 minutes.	
$CaCl_2$ SOLUTION (pre-warmed)	0.1 mL	0.1 mL
	Simultaneously with addition of $CaCl_2$ SOLUTION start stopwatch, mix well. After 20 seconds start to observe for clot formation.	

Note: Incubation times exceeding 5 minutes may cause loss of FV and FVIII and are not recommended.
Each laboratory should determine the optimal heating-activation time for its particular assay system.

Monitoring of Unfractionated Heparin Therapy with APTT

When using the APTT for this purpose, the factors influencing the test should be kept in mind. General considerations are listed below.

A. Time of collection is important since the *in-vivo* half-life of unfractionated heparin is approximately 1.5 hours[5]. When it is administered, it has an immediate anticoagulant effect but its efficacy decreases rapidly with time. This is especially apparent with intermittent single intravenous injections.

B. The anticoagulant used for sample collection can alter test results.

C. Platelet factor 4, a heparin neutralizing factor in platelet alpha-granules, can be released by platelet aggregation or damage. To prevent this occurrence *in-vitro*, the specimen should be collected with a minimum of trauma. Cold temperatures are known to induce platelet aggregation and release platelet factor 4; therefore, centrifugation at room temperature is recommended for heparin studies.

D. Using the APTT to monitor unfractionated heparin therapy is time-dependent. Delay in testing samples will result in prolonged APTT determinations. Therefore, it is imperative that the testing on all samples be performed as soon as possible.

E. Increased contact activation times may result in prolonged APTT in plasma containing heparin. There is great variability of the APTT in heparinized plasma with different lengths of activation time. It is imperative that the optimal heating-activation time of the ACTIN FSL-plasma mixture be rigidly standardized[14].

F. Different test systems (i.e., manual, photo-optical, etc.) exhibit variable heparin sensitivity. Interchanging of test systems should be avoided.

G. Baseline data on the APTT of each patient before the start of therapy should be established where feasible to determine the respective patient APTT as it relates to the laboratory normal range established for the test in that laboratory.

H. Studies have shown variability in original estimates of the quality of unfractionated heparin from different sources and different manufacturers. *In-vivo* reactivity varies with the type of heparin administered, the metabolism of the individual and other co-administrated medications[5,12].

I. Because the APTT can vary with technique, method, equipment, reagent lot and heparin used, each laboratory must establish its own therapeutic ranges, or verify them whenever one or more of the aforementioned variables is changed. This can be done by simultaneously determining the APTT and the heparin concentration for samples from patients receiving heparin therapy. A doseresponse curve can be calculated from the data using regression analysis, and the APTT range corresponding to a heparin concentration of 0.3 to 0.7 U/mL (by a factor FXa inhibition assay) can be derived[4,5,12].

The correlation between APTT clotting times and heparin levels are generally low in *ex-vivo* specimens yielding r^2 values of < 0.5 in many cases. Less than 50 % of the variation in APTTs in heparinized plasma is explained by differences in the heparin concentration in *ex-vivo* plasmas[12,35].

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
Heparin monitoring:	Ci-Trol HEPARIN CONTROL 1 Ci-Trol HEPARIN CONTROL 2

Two controls (one in the normal range and one in the pathological/therapeutical range) must be measured at the start of the test run, after each change of reagent vial, and at least once during an 8-hour shift. The control material should be prepared and processed in the same manner as the patient samples. Each laboratory should establish its own confidence intervals for the controls. This interval is generally ±2 to ±2.5 standard deviations (SD) from the mean control value. If the control values are outside of the confidence interval, the controls, reagents and instrument must be checked. Before reporting the patient values, it is recommended that all steps should be documented that were taken to identify and rectify the problem. New control ranges should be defined for each new lot of reagents or controls.

Results

Results of the activated partial thromboplastin time testing should be reported as the APTT in seconds. These results should be related to the normal range for APTT testing in each laboratory. It is suggested that the patient results be reported to the clinician in conjunction with the normal range. Control values for the reagent test system should never be used in place of a normal range. Furthermore, the reporting of APTT results in terms of an upper normal only may result in incorrect interpretation. Shortened APTT results may also indicate some abnormal condition in the patient's coagulation system. Additional studies at the manufacturer indicate that ACTIN FSL exhibits a dose response relationship to *in-vitro* heparin levels.

Limitations

APTT testing encompasses the entire clotting process from contact activation to fibrin formation and is therefore more susceptible to variations than specific individual tests. The control and use of APTT is therefore subject to inherent limitations. Control of plasma sample conditions is strictly emphasized. Studies have shown that sample decomposition may occur more rapidly in stored samples that are not refrigerated. Extremely small plasma volumes (prior to testing) are to be avoided since pH changes in the plasma from physiological conditions may be encountered. Such changes may lead to the decomposition of plasma components of the blood coagulation system. It should be noted that APTT testing may be affected by a number of commonly administered drugs. Decrease in time of APTT determination in conjugated estrogen therapy in males and oral contraceptive administration in females has been reported[15,16]. Increase in the APTT has been

seen in diphenylhydantoin, heparin, warfarin, naloxone and radiographic agent administration[17,18]. Therapeutic doses of hirudin or other direct thrombin inhibitors may prolong clotting times[19].

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

In addition, the choice of anticoagulant (i.e. citrate vs. oxalate) and the condition of the specimen (e.g. hemolyzed, lipemic, parenteral feeding, etc.) may affect results[12,20,21].

The latter is particularly true of optical instrumentation measurements of the APTT. Blood clotting factor deficiencies which should produce prolonged clotting times may be compensated for or made to appear normal by elevated levels of one or more different clotting factors. Similarly, the presence of active intermediates which would tend to reduce the clotting time may also mask conditions that would normally lead to prolongation of the APTT. Mild or minor deficiencies in several factors may have an additive effect on increasing the APTT. ACTIN FSL may provide variable APTT results in samples containing the lupus-like anticoagulant. The APTT assay is a functional test which screens for global coagulation disorders of the endogenous coagulation system. It is common knowledge that a low concentration of coagulation factors: FII, FV, FX and high concentration of fibrin(ogen) degradation products also have influence on the assay[22].

Therapeutic doses of direct thrombin inhibitors or direct Xa inhibitors may prolong APTT clotting times[23–27].

Unexpected abnormal APTT results should always be followed by additional coagulation studies to determine the source of abnormal results.

Action of heparin as an anticoagulant is related to its ability in conjunction with a plasma cofactor to interfere with several aspects of the coagulation mechanism, thus retarding the rate of fibrin formation (see "Monitoring of Unfractionated Heparin Therapy with APTT", page 4). Heparinase (Dade® Hepzyme®) can be used as a heparin neutralizer in plasma to rule out heparin contamination in coagulation testing[28]. Low levels of Antithrombin III can decrease the responsiveness of patients to heparin therapy. Antithrombin III slowly forms an inactive complex with the coagulant serine proteases, thrombin and factors: FIXa, FXa, FXIa and FXIIa. Heparin greatly accelerates this inactivation and this forms the basis for the therapeutic effect of these naturally occuring polysaccharide compounds. The test will not detect qualitative or quantitative platelet disorders, isolated factor FVII and factor FXIII deficiencies or vascular disorders. APTT values for patient samples containing non-specific lupus-like anticoagulants are prolonged using ACTIN FSL.

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

Reference intervals vary from laboratory to laboratory depending on the population served and the technique, method, equipment and reagent lot used. Therefore, each laboratory must establish its own reference intervals or verify them whenever one or more of the aforementioned variables are changed.

In a study of ostensibly healthy individuals using a specific lot of ACTIN FSL, the following values were obtained:

			90 % Reference Interval	
	n	Median [s]	5th Percentile [s]	95th Percentile [s]
CA-1500 System	111	27.3	25.0	31.3
BCS® System	111	28.6	25.3	33.8

Reference ranges for other populations such as pediatric groups should also be established where warranted.

Note: CLSI Document C28-A2 (cited in H47-A)[29,30] states that a parametric approach (mean ±2 SD) can be applied. The assumption of this approach (Gaussian normal distribution) must however be checked.

The APTT has been reported to show variable sensitivity to the presence of lupus-like inhibitors[31]. Using ACTIN FSL, the APTT exceeded the normal range in 74 % of 65 patient plasma samples with positive tissue thromboplastin inhibition (TTI) tests[32].

Performance Characteristics

ACTIN FSL has been carefully prepared to perform according to the results and within the limits described when used in the determination of activated partial thromboplastin time and in other coagulation procedures requiring an activated partial thromboplastin reagent.

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 ACTIN FSL

According to CLSI H47-A2, the APTT reagent/instrument combination used should provide abnormally prolonged results for plasmas that have less than 30 % factor activity of the coagulation factors: FVIII, FIX and FXI. 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[33].

Heparin Sensitivity

For determination of heparin sensitivity 54 samples from patients receiving unfractionated heparin were analyzed. By comparing the APTT obtained with ACTIN FSL and the Heparin activity measured with Berichrom Heparin a correlation coefficient r = 0.718 was observed on the CS-2100i instrument. Each individual laboratory hospital should determine its own therapeutic heparin range using the ex vivo method according the CLSI guidelines (H57- A2).

Lupus Sensitivity[34]

By testing 97 samples with a confirmed lupus anticoagulant with ACTIN FSL, a median APTT of 42.9 s was determined; for 17 of the 97 samples the APTT did not exceed the 99th percentile of the normal control group in that study, demonstrating a high sensitivity of ACTIN FSL for the presence of lupus anticoagulant:

Sensitivity of ACTIN FSL

APTT Reagent	Sensitivity (%) 97.5th percentile cut-off	Sensitivity (%) 99th percentile cut-off
ACTIN FSL	95.9	82.5

Precision

Precision studies using the methodologies listed in this insert show that properly performed APTT tests should result in a standard deviation (SD) which corresponds to a coefficient of variation (CV) of less than 3 % in the normal range. The precision depends on instrument related conditions.

Application specific performance data are listed in the respective Reference Guides of the instruments.

The reproducibility was assessed by the manufacturer for APTT with Dade® Actin® FSL Activated PTT Reagent based on publicly available proficiency testing information in 2019. The overall reproducibility median CV% was found to be <8 % including lot, instrument, laboratory and operator variability factors.

Technical Assistance

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

Current Version of Application Sheets

ACTIN FSL 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

1. Kamal AH, Tefferi A, Pruthi RK. How to interpret and pursue an abnormal prothrombin time, activated partial thromboplastin time, and bleeding time in adults. Mayo Clin Proc. 2007;82:864-73.
2. Leung LLK. Perioperative evaluation of bleeding diathesis. Hematology Am Soc Hematol Educ Program. 2006;457-61.
3. Eikelboom JW, Hirsh J. Monitoring unfractionated heparin with the aPTT: Time for a fresh look. Thromb Haemost. 2006;96:547-52.
4. Bates SM, Johnston M, Hirsh J, et al. Use of a fixed activated partial thromboplastin time ratio to establish a therapeutic range for unfractionated heparin. Arch Intern Med. 2001;161:385-91.
5. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin. The seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126:188S-203S.
6. Marlar RA, Clement B, Gausman J. Activated partial thromboplastin time monitoring of unfractionated heparin therapy: Issues and recommendations. Semin Thromb Hemost. 2017;43:253-60.
7. Teruya J, West AG, Suell MN. Lupus Anticoagulant Assays. Questions answered and to be answered. Arch Pathol Lab Med. 2007;131:885-9.
8. Fritsma GA, Dembitzer FR, Randhawa A, et al. Recommendations for appropriate activated partial thromboplastin time reagent selection and utilization. Am J Clin Pathol. 2012;137:904-8.
9. Kershaw G. Performance of Activated Partial Thromboplastin Time (APTT): Determining Reagent Sensitivity to Factor Deficiencies, Heparin, and Lupus Anticoagulants. Methods Mol Biol. 2017;1646:75-83.
10. Levy JH, Szlam F, Wolberg AS, et al. Clinical use of the activated partial thromboplastin time and prothrombin time for screening: a review of the literature and current guidelines for testing. Clin Lab Med. 2014;34:453-77.
11. Kumano O, Ieko M, Naito S, et al. APTT reagent with ellagic acid as activator shows adequate lupus anticoagulant sensitivity in comparison to silica-based reagent. J Thromb Haemost. 2012;10:2338-43.
12. Olson JD, Arkin CF, Brandt JT, et al. College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy: laboratory monitoring of unfractionated heparin therapy. Arch Pathol Lab Med. 1998;122:782-98.

13. 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.
14. Hattersley PG, Hayse D. The effect of increased contact activation time on the activated partial thromboplastin time. Am J Clin Pathol. 1976;66:479-82.
15. Ambrus JL, Schimert G, Lajos TZ, et al. Effect of antifibrinolytic agents and estrogens on blood loss and blood coagulation factors during open heart surgery. J Med. 1971;2:65-81.
16. Prasad RN, Koh SC, Viegas OA, et al. Effects on hemostasis after two-year use of low dose combined oral contraceptives with gestodene or levonorgestrel. Clin Appl Thromb Hemost. 1999;5:60-70.
17. Solomon GE, Hilgartner MW, Kutt H. Coagulation defects caused by diphenylhydantoin. Neurology. 1972;22:1165-71.
18. Young DS, editor. Effects of Drugs on Clinical Laboratory Tests, 5th ed. Washington: AACC Press; 2000.
19. Greinacher A, Warkentin TE. The direct thrombin inhibitor hirudin. Thromb Haemost. 2008;99:819-29.
20. Soloway HB, Cox SP, Donahoo JV. Sensitivity of the activated partial thromboplastin time to heparin: effect of anticoagulant used for sample collection. Am J Clin Pathol. 1973;59:760-2.
21. Lippi G, Franchini M, Montagnana M, et al. Quality and reliability of routine coagulation testing: can we trust that sample? Blood Coag Fibrinolysis. 2006:17:513-9.
22. Thomas L, Chapter 16 in: Clinical Laboratory Diagnostics (Labor und Diagnose). 8th ed. TH Books; 2016.
23. Van Blerk M, Bailleul E, Chatelain B, et al. Influence of dabigatran and rivaroxaban on routine coagulation assays. A nationwide Belgian survey. Thromb Haemost. 2015 Jan;113(1):154-64. DOI: 10.1160/TH14-02-0161.
24. Greinacher A, Warkentin TE. The direct thrombin inhibitor hirudin. Thromb Haemost. 2008;99:819-29.
25. Funk DM. Coagulation assays and anticoagulant monitoring. Hematology / the Education Program of the American Society of Hematology. American Society of Hematology. Education Program. 2012;460-5. doi: 10.1182/asheducation-2012.1.460-465.
26. Harder S, Graff J, Klinkhardt U, et al. Transition from argatroban to oral anticoagulation with phenprocoumon or acenocoumarol: effects on prothrombin time, activated partial thromboplastin time, and Ecarin Clotting Time. Thromb Haemost. 2004;91:1137-45.
27. Kitchen S, Gray E, Mackie I, et al., BCSH committee. Measurement of noncoumarin anticoagulants and their effects on tests of Haemostasis: Guidance from the British Committee for Standards in Haematology. Br J Haematol. 2014;166:830–41. DOI: 10.1111/bjh.12975.
28. Harenberg J, Reichel T, Malsch R, et al. Multicentric evaluation of heparinase on aPTT, thrombin clotting time and a new PT reagent based on recombinant human tissue factor. Blood Coagul Fibrinolysis. 1996;7:453-458.
29. NCCLS. One-Stage Prothrombin Time (PT) Test and Activated Partial Thromboplastin Time (APTT) Test; Approved Guideline. NCCLS document **H47-A** [ISBN 1-56238-301-9]. NCCLS, 940 West Valley Road, Wayne, PA 19087, 1996
30. NCCLS. How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline—Second Edition. NCCLS document **C28-A2** [ISBN 1-56238-406-6]. NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, USA 2000
31. Mannucci PM, Canciani MT, Mari D, et al. The varied sensitivity of partial thromboplastin and prothrombin time reagents in the demonstration of the lupus-like anticoagulant. Scand J Haematol. 1979;22:423-32.
32. Schleider MA, Nachman RL, Jaffe EA, et al. A clinical study of the lupus anticoagulant. Blood. 1976;48:499-509.
33. Lawrie AS, Kitchen S, Efthymiou M, et al. Determination of APTT factor sensitivity- the misguiding guideline. Int J Lab Hematol. 2013;35:652-657.

34. Wissel T, Wagner C. Lupus anticoagulants sensitivity of Siemens APTT reagents. J Thromb Haemost. 2013;Suppl.2:1167.
35. Vandiver JW, Vondracek TG. Antifactor Xa Levels versus Activated Partial Thromboplastin Time for Monitoring Unfractionated Heparin. Pharmacotherapy. 2012;32(6):546–58.

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

Siemens Healthcare Diagnostics Products GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany
siemens-healthineers.com