Dade® Actin® FS Activated PTT Reagent

ACTIN FS

Revision bar indicates update to previous version.

CE 0197

Intended Use

ACTIN FS 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 FS is a liquid reagent based on purified soy 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 confirmation of lupus anticoagulants (inhibitors) in patients with thrombophilia
- For monitoring of therapy in patients receiving unfractionated heparin

Furthermore, ACTIN FS 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 FS 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® FS Activated PTT Reagent ACTIN FS	Ready to use liquid containing: • purified soy phosphatides[a] in 1.0×10^{-4} M ellagic acid • Buffer • Stabilizer • Preservative	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.

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.

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 FS 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[25,26]. 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 >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.

Non-heparinized plasma should be tested within 4 hours of blood collection.

Plasma containing unfractionated heparin should be centrifuged within one hour of blood collection, stored at room temperature and tested within 4 hours[27].

Platelet-poor plasma may be frozen at ≤ −20 °C for up to 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 > 5 minutes[28].

Please refer to CLSI document H21–A5[12] for detailed information on sample preparation and storage.

Procedure

Materials Provided

REF	Contents		
B4218-20	Dade® Actin® FS Activated PTT Reagent ACTIN FS	10 ×	2 mL
B4218-100	Dade® Actin® FS Activated PTT Reagent ACTIN FS	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 test tubes
–	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 FS for 1 minute at 37 °C. (Mix before use)		
Pipet into coagulation tubes as follows:		
	Test Sample	Control Plasma
ACTIN FS (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 the degree of this effect 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 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. It is imperative that the optimal heating-activation time of the ACTIN FS-plasma mixture be rigidly standardized[13].

F. Different test systems (i.e., manual, photo-optical, etc.) will 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 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[5,6].

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 dose-response 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 Xa inhibition assay) can be derived[4,5,6].

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.

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[14,15]. Increase in the APTT has been seen in diphenylhydantoin, heparin, warfarin, naloxone and radiographic agent administration[16,17]. Therapeutic doses of hirudin or other direct thrombin inhibitors may prolong clotting times[18].

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[6,19,20].

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 FS 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: FXII, FV, FX and high concentration of fibrin(ogen) degradation products also have influence on the assay[20].

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 (Hepzyme) can be used as a heparin neutralizer in plasma to rule out heparin contamination in coagulation testing[22].

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

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

			90 % Reference Interval	
	n	Median [s]	5th Percentile [s]	95th Percentile [s]
CA-1500 System	111	25.1	22.1	28.1
BCS® System	111	26.8	23.0	31.9

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

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.

Note: CLSI Document C28-A2 (cited in H47-A)[23,24] states that a parametric approach (mean ±2 SD) can be applied. The assumption of this approach (Gaussian normal distribution) must however be checked.

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 ACTIN FS

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[29].

Heparin Sensitivity

For determination of heparin sensitivity 83 samples from 18 patients receiving unfractionated heparin were analyzed. The therapeutic APTT range for unfractionated heparin therapy corresponding to the therapeutic anti-Xa range of 0.3 to 0.7 IU/mL was 60 to 100 s using the ACTIN FS on the CS-5100 System. Each individual laboratory hospital should determine its own therapeutic heparin range using the ex vivo method according the CLSI guidelines (H57-A2)[30].

Lupus Sensitivity

By testing 97 samples with a confirmed lupus anticoagulant with ACTIN FS, a median APTT of 37.1 s was determined; for 77 of the 97 samples the APTT did not exceed the 99th percentile of the normal control group in that study, demonstrating a low sensitivity of ACTIN FS for the presence of lupus anticoagulants[31].

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 4 % in the normal range. In additional clinical studies, duplicate determinations of an abnormal control plasma (clotting times of approximately 50 s) were performed over a period of 22 days. Results indicate that the APTT should agree within 4 % when performed properly.

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

The reproducibility was assessed by the manufacturer for APTT with Dade® Actin® FS Activated PTT Reagent based on publicly available proficiency testing information in 2018/2019. The overall reproducibility median CV% was found to be <5 % 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 FS 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.

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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		

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