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IVD

CEPHEN™ LS

REF CK521K R 6 vials x 1 mL
REF CK522K R 6 vials x 2.5 mL

English, revision: 07-2025

INTENDED USE:

Clotting method for the *in vitro* quantitative determination of activated Partial Thromboplastin Time (aPTT) in human citrated plasma, using an automated method. This method is an aid to diagnosis, used for the screening of patients who are suspected of coagulation disorders. Combined with CEPHEN™, this method is an aid to diagnosis for the presence of Lupus Anticoagulant (LA) in patients with antiphospholipid syndrome (APS) suspicion.
This device of *in vitro* diagnostic use is intended for professional use in the laboratory.

SUMMARY AND EXPLANATION:

Technical: [1]
Measurement of the plasma recalcification time, in presence of the standardized aPTT reagent (phospholipids and activator), on human citrated plasma, as a global screening test to explore the activity of the coagulation Factors (II, V, X, VIII: C, IX, XI, XII) and Fibrinogen.[1]
Clinical: [1-9]
The aPTT is a screening test to assess

- Abnormality of intrinsic or common coagulation pathway factors.
- Abnormalities or acquired deficiencies due to an excessive consumption of the coagulation factors, hepatic disorders…
- Coagulation inhibitors such as LA or auto-antibodies against coagulation factors.

CEPHEN™ LS has a higher sensitivity to LA than CEPHEN™.

PRINCIPLE:

CEPHEN™ LS is an activated Partial Thromboplastin Time (aPTT) reagent.
Activation of intrinsic pathway on citrated plasma is induced by activator (micronized silica) and mixture of vegetable soybean and synthetic-phospholipids, and the clotting time (CT) is measured in presence of calcium.[1]

REAGENTS:

R **aPTT**, activator (micronized silicate) at approximately 1 g/L and mixture of vegetable soybean and synthetic-phospholipids, liquid form. Contains preservatives and stabilizers.

The product is classified as non-hazardous and is not subject to labeling according to EC Regulation No. 1272/2008 [CLP].

WARNINGS AND PRECAUTIONS:

- Waste should be disposed of in accordance with applicable local regulations.
- Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.
- 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 or on request to HYPHEN BioMed).

REAGENT PREPARATION:

R Reagent is ready to use; homogenize while avoiding formation of foam and load it directly on the analyzer following Application Guide instruction.

The reagent can be opalescent, with possible presence of whitish to greyish siliceous sediments, which disappear after shaking.

STORAGE AND STABILITY:

Unopened reagents should be stored at 2-8°C in their original packaging. Under these conditions, they can be used until the expiry date printed on the kit.

R Reagent stability after opening, free from any contamination or evaporation, and stored closed, is of:

- **90 days** at 2-8°C.
- **Stability on board of the analyzer: see the specific Application Guide.**

REAGENTS AND MATERIALS REQUIRED BUT NOT PROVIDED:

Reagents:

- Distilled water.
- Calcium Chloride 0.025M (AR001B/AR001K/AR001L).

Specific controls plasma:

Product Name	Reference
BIOPHEN™ Normal Control Plasma	223201
BIOPHEN™ Abnormal Control Plasma	223301
EASYPLASMA™ Control Set	225601
CI TROL 1 / CI TROL 2 / CI TROL 3*	291070 (SMN :10873821) / 291071 (SMN :10873822) / 291072 (SMN :10873823)
CONTROL PLASMA N*	ORKE415 (SMN :10873873)
CONTROL PLASMA P*	OUPZ175 (SMN :10873890)

*Target assigned value available for Sysmex branded control on CS-series and CN-series

- For LA exploration:

Product Name	Reference
CEPHEN™	CK511K / CK512K / CK515K / CK515L
LA Control Plasma	SC081K / SC082K / SC083K

- Automatic analyzer for clotting assays such as: CS-series, STA-R® family, ACL-TOP® family, CN-series.
- Laboratory material.

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 is not modified.

TRACEABILITY:

There is no metrological calibration for aPTT[7] and LA assays; for more information refer to Instructions for Use of above controls.

SPECIMEN COLLECTION AND PREPARATION:

Collection, preparation and storage of Platelet Poor Plasma (PPP) should be made according to laboratory or other validated methods[3-7]
The blood (9 volumes) should be carefully collected onto the trisodium citrate anticoagulant (1 volume) (0.109 mol/L, 3.2%) by clean venipuncture.
According to CLSI H21-A5[10] and studies[12]:

- Plasma should remain at room temperature for no longer than 4 hours.
- If assays will not be completed within 4 hours, plasma should be frozen at −20 °C or below.
- Plasma samples should be thawed at 37°C, only once.

PROCEDURE:

HYPHEN BioMed provides Application Guides for defined coagulation analyzer families. The Application Guides contain analyzer/assay specific handling and performance information and complement the information in these Instructions for Use.

QUALITY CONTROL:

The use of quality controls serves to validate method compliance, along with between-test assay homogeneity for a given batch of reagents.
Include quality controls with each series, as per good laboratory practice, in order to validate the test.
A new verification of the normal range must be carried out at least for each new lot of reagents or, after each important analyzer's maintenance, or when quality controls values are measured outside the acceptance range determined for the method. The clotting time obtained with the same reagent lot can vary slightly according to the instrument used and the clot detection sensitivity.
Each laboratory must define its acceptance ranges and verify the expected performance in its analytical system.

RESULTS:

- Determine mean and interval of normal range (CT expressed in seconds (s)) for each new lot of CEPHEN™ LS kits following local recommendations or guidelines.
- Results can be reported as a clotting time and as ratio, eg:
  APTT LS ratio = Sample CEPHEN™ LS (CT, s) / Mean of normals (CT, s).
- For LA exploration, reagent must be used in combination with the low sensitive aPTT reagent, CEPHEN™ (CK511K/CK512K/CK515K/CK515L).
  Normalized APTT ratio for LA = APTT LS ratio/ APTT ratio,
  Where APTT ratio = Sample CEPHEN™ (CT,s) / Mean of normals (CT, s).
- The results should be interpreted according to the patient's clinical and biological condition and other findings. Abnormal results should be investigated further (eg. Mixing studies, Factors assay, Lupus Anticoagulant assays, anticoagulant concentration …)
- Lot to lot variability measured on 3 lots is: %CV= 1%

LIMITATIONS:

- To ensure optimum test performance and to meet the specifications, the technical instructions validated by HYPHEN BioMed should be followed carefully.
- Any reagent presenting no limpid appearance or showing signs of contamination must be rejected.
- Any suspicious samples or those showing signs of activation must be rejected.
- The analyzer/CEPHEN™ LS combination used should provide abnormally prolonged results for plasmas having less than 30 % factor activity of the coagulation factors (FVIII, FIX and FXI)[5]. It is recommended to estimate/determine sensitivity levels by serial dilution of normal plasma pool into factor deficient plasma[5]. Estimated sensitivity levels should ideally be within 30 to 45 % (while strongly dependent on deficient plasma used)[6].
- Anticoagulant therapies and inhibitors of coagulation may affect aPTT results.
- Heparin sensitivity can present slight variations from lot to lot for a same reagent. The same anticoagulant plasmatic concentration (heparin) can produce variable prolongations of the aPTT, in particular for patients in intensive care units or resuscitation[3-5].
- This reagent has a high sensitivity to LA.
- aPTT values for patient samples containing non-specific Lupus-like anticoagulants may be prolonged.
- User defined modifications are not supported by HYPHEN BioMed 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 HYPHEN BioMed Application Guides or these Instructions for Use.

EXPECTED VALUES:

The reference interval (in aPTT LS ratio) established on healthy adult subjects (n=133) on CS-series, (n=132) on CN-series, (n=124) on STA-R® family, (n=124) on ACL-TOP® family, was measured between 0.86 and 1.26, 0.86 and 1.27, 0.86 and 1.18, 0.86 and 1.16 (Central 90%, 95th percentile). For LA exploration, the reference interval (in normalized ratio) established on healthy adult subjects (n=120) on CS-series, (n=120) on CN-series, (n=120) on STA-R® family, (n=123) on ACL-TOP® family, was measured between 0.68 and 1.34, 0.84 and 1.34, 0.84 and 1.34, 0.86 and 1.13 (Central 90%, 95th percentile). A normal range study was performed on each analyzer and is documented in the respective Application Guides of the analyzers. However, each laboratory has to determine its own normal range in its specific test conditions.

PERFORMANCES:

Mathematical analyses are performed using a validated statistical software built in accordance with CLSI guidelines.
Performances studies were conducted as described in CLSI guidelines.
The following performance data represent typical results and are not to be regarded as specifications for CEPHEN™ LS.
All performances are documented in the respective Application Guides of the analyzers.

Analytical performances

Accuracy

Accuracy studies were assessed using laboratory controls and pooled plasmas.
Trueness: bias is less than 12% for all samples.
Precision: coefficient of variation (CV) for all samples is less than 4% for repeatability, less than 6% for reproducibility and less than 6% for within laboratory. Precision is documented in the respective Application Guides of the instruments.

Interfering substances

Interferences are defined by the analyzer system used and are documented in the respective Application Guides of the analyzers.

Clinical performances

For aPTT measurement:

Agreement

	ACL TOP® family			
Analyte	**n**	**Linear regression**	**r**	**Reference / comparison method**
aPTT LS ratio	106	y = 0.85x+0.32	0.775	HemosIL® SynthASil

Sensitivity/Specificity

	ACL TOP® family				
Analyte	**N**	**Sensitivity**	**Specificity**	**Area under the curve (ROC)**	
aPTT LS ratio	106	0.981	1.000	1.000	
Analyte	**n**	**PPV**	**NPV**	**LR+**	**LR-**
aPTT LS ratio	106	96.2%	98.1%	26.48	0.02

PPV: Predictive value of a positive result
NPV: Predictive value of a negative result
LR+ : Likelihood Ratio +
LR- : Likelihood Ratio –

For LA exploration:

Agreement

	ACL TOP® family		
Analyte	**n**	**Agreement**	**Reference / comparison method**
aPTT LS/aPTT ratio	137	97.8%	HemosIL® Silica clotting time

Sensitivity/Specificity

	ACL TOP® family				
Analyte	**N**	**Sensitivity**	**Specificity**	**Area under the curve (ROC)**	
aPTT LS/aPTT ratio	137	0.974	1.000	0.999	
Analyte	**N**	**PPV**	**NPV**	**LR+**	**LR-**
aPTT LS/aPTT ratio	137	98.7%	98.3%	59.22	0.01

PPV: Predictive value of a positive result
NPV: Predictive value of a negative result
LR+ : Likelihood Ratio +
LR- : Likelihood Ratio –

REFERENCES:

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7. Devreese KMJ. *et al.* Guidance from the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis. 2020.
8. Tripodi A. *et al.* Lupus anticoagulant detection in anticoagulated patients. Guidance from the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis. 2020.
9. Rasmussen *et al.* Unexpected, isolated activated partial thromboplastin time prolongation: A practical mini-review, Eur J Haematol. 2020
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11. Woodhams B. *et al.* Stability of coagulation proteins in frozen plasma. Blood coagulation and Fibrinolysis. 2001.
12. Ieko M. *et al.* Expert consensus regarding standardization of sample preparation for clotting time assays. Int J Hematol. 2020.

e-IFU (other languages) are available on www.hyphen-biomed.com.
For customer support and Application Guides, please contact your local provider or distributor (see www.hyphen-biomed.com).

Changes compared to the previous version.

The following symbols may appear on the product labeling:

REF	Catalogue number	LOT	Batch code	IVD	*In-vitro* diagnostic medical device
Rx	Numerical < x> identification of reagent		See instructions for use	WHO STD	WHO standard code
	Temperature limitation		Manufacturer	YYYY-MM-DD	Use by
CE XXXX	CE marking of conformity with notified body ID number.	→	Reconstitution volume	CONTENTS	Contents
Cx	Numerical < x> identification of control	i- MA	See instructions in Method Application guide	CONTAINS	Contains
EXP	Expiration date	Σ	Contains sufficient for <n> tests	UNIT	Measurement unit
TARGET VALUE	Target Value		Keep away from sunlight and heat	CALx	Numerical < x> identification of calibrator
UDI	Unique Device Identifier	BIO	Contains biological material of animal origin		Contains human blood or plasma derivatives
DANGER	Danger	WARNING	Warning	UK CA	UKCA marking of conformity
CONTROL +	Positive control	CONTROL –	Negative control		Biological risks
ACCEPTANCE RANGE	Acceptance range				

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