CE 0197 UKCA

IVD

CEPHEN™

REF CK511K R 6 vials x 1 mL
REF CK512K R 6 vials x 2.5 mL
REF CK515K R 8 vials x 5 mL
REF CK515L R 12 vials x 5 mL

HYPHEN BioMed

Sales and Support:
CoaChrom Diagnostica GmbH
www.coachrom.com | info@coachrom.com
Tel: +43-1-236 222 1 | Fax: +43-1-236 222 111
Toll-free contact for Germany:
Tel: 0800-24 66 33-0 | Fax: 0800-24 66 33-3

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™LS, 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.
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 (Lupus Anticoagulant) or auto-antibodies against coagulation factors.

However, the CEPHEN™ reagent sensitivity to LA is intentionally less sensitive than most other routine aPTT reagents. In combination with CEPHEN™ LS, can be used for determination of presence of LA in patients with antiphospholipid syndrome (APS) suspicion (normalized ratio).

PRINCIPLE:

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

REAGENTS:

R **aPTT**, activator (micronized silicate) at approximately 1 g/L, vegetable soybean 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™ LS	CK521K / CK522K
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]; 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 the 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™ kits following local recommendations or guidelines.
- Results can be reported as a CT and as ratio, eg:
  APTT ratio = Sample (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…)
- For LA exploration, reagent must be used in combination with the high sensitive aPTT reagent: CEPHEN™ LS (CK521K/CK522K).
- Lot to lot variability measured on 3 lots is: %CV= 5%

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™ 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 moderate sensitivity to LA.
- 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 ratio) established on healthy adult subjects (n=120) on CS-series, (n=120) on CN-series, (n=120) on STA-R® family, (n=121) on ACL-TOP® family, was measured between 0.80 and 1.16, 0,81 and 1.23, 0.77 and 1.21, 0.84 and 1.19 (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™.
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 13% for all samples.
Precision: coefficient of variation (CV) for all samples is less than 2% for repeatability, less than 5% for reproducibility and less than 7% 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

Agreement

	ACL TOP® family			
Analyte	**n**	**Linear regression**	**r**	**Reference / comparison method**
aPTT ratio	106	y = 1.07x+0.05	0.905	HemosIL® SynthASil

Sensitivity/Specificity

	ACL TOP® family				
Analyte	**n**	**Sensitivity**	**Specificity**	**Area under the curve (ROC)**	
aPTT ratio	106	0.981	1.000	1.000	
Analyte	**n**	**PPV**	**NPV**	**LR+**	**LR-**
aPTT ratio	106	98.1%	98.1%	52.96	0.020

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

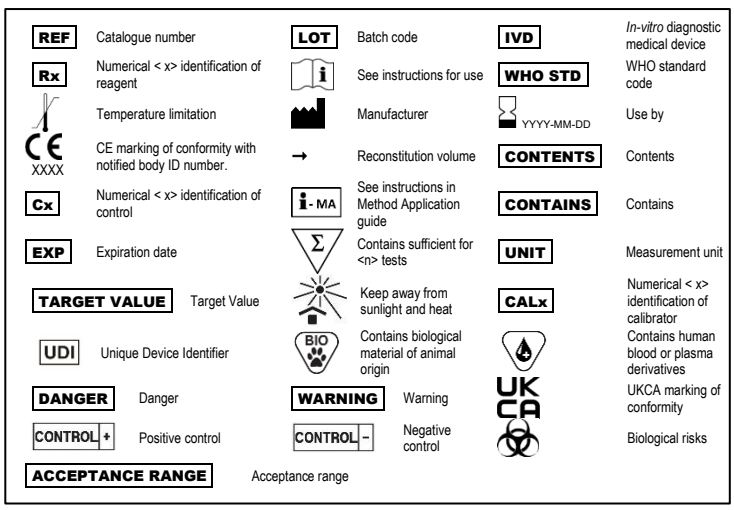
REFERENCES:

1. Kamal AH. *et al.* How to interpret and pursue an abnormal prothrombin time activated partial thromboplastin time, and bleeding time in adults. Mayo Clin Proc. 2007.
2. H60-A Document: "Laboratory Testing for the Lupus Anticoagulant; Approved Guideline". 2014.
3. Van Roessel S. *et al.* Accuracy of aPTT monitoring in critically ill patient treated with unfractionated heparin. The Journal of Medicine. 2014.
4. Gouin-Thibaut I. *et al.* Monitoring unfractionated heparin with APTT: A French collaborative study comparing sensitivity to heparin of 15 APTT reagents. Thrombosis Research 129. 2012.
5. CLSI document H47Ed3E: "One-Stage Prothrombin Time (PT) Test and Activated Partial Thromboplastin Time (APTT) Test", 3rd Edition, 2023.
6. Lawrie AS *et al.* Determination of APTT factor sensitivity- the misguiding guideline. Int J Lab Hematol. 2013.
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
10. CLSI Document H21-A5: "Collection, transport, and processing of blood specimens for testing plasma -based coagulation assays and molecular hemostasis assays; approved guideline". 2008
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:



HYPHEN BioMed
155 rue d'Eragny, 95000 Neuville-sur-Oise, France