

Summary of safety and performance – EX

This Summary of Safety and Performance (SSP) is intended to provide public access to an updated summary of the main aspects of the safety and performance of the device.

The SSP is not intended to replace the Instructions For Use as the main document to ensure the safe use of the device, nor is it intended to provide diagnostic or therapeutic suggestions to intended users or patients. The following information is intended for users/healthcare professionals.

1. Device identification and general information

1.1. Device trade name

EX (REF 1081EU)

1.2. Manufacturer

APIRO Diagnostics Kft.

Liget utca 3/2, HU-2040 Budaörs, Hungary

1.3. Manufacturer's single registration number (SRN)

HU-MF-000043501

1.4. Basic UDI-DI

59998629921081EU_1VW

1.5. European Medical Device Nomenclature (EMDN)

W01030299 - Haemostasis reagents – other

1.6. Risk class of device

Class C. Classification rules 3j and 3k

1.7. Year when the device was first CE-marked under Regulation (EU) 2017/746 covering the device

2025

1.8. Authorized representative

n/a

1.9. Notified Body

3EC International a.s. (2265)

2. Intended purpose and other indications

2.1. Intended purpose

The EX is a ready to use reagent for in-vitro diagnostic professional use, intended for examination of the extrinsic coagulation system in citrated blood during viscoelastometry analysis.

2.2. Indication(s) and target population(s)

Indicated to be used when an alteration of the extrinsic coagulation system in the blood of the adult patients suspected.

2.3. Indication whether it is a device for near-patient testing and/or a companion diagnostic

The EX assay is not intended for near-patient testing.

The EX assay is not intended for a companion diagnostics.

2.4. Limitations and/or contra-indications

The clotting time of the EX assay can be prolonged by anticoagulants such as direct factor Xa inhibitors or thrombin antagonists, and also by factors interfering with the polymerization of the blood clot (e.g. the presence of colloids). A high hematocrit can lead to reduced clot firmness in the EX assay.

3. Device description

3.1. Description of the device

An assay system for assessment of whole blood clotting using recombinant tissue factor (coagulation activator), an inhibitor of heparin (polybrene), calcium chloride for the recalcification of the citrated blood sample, a pipette tip and a reagent carrier. Intended for laboratory use.

3.2. Description of the components

The sales unit of the device contains 10 individually sealed single-use pouches containing one pipet tip with reagent each, providing a dry chemistry reagent composed of recombinant tissue factor, polybrene, calcium chloride, buffer and stabilizers. Each pouch contains one desiccant bag. Each individually sealed tip is used for one analysis, i.e. the sales unit of the device allows to perform 10 tests.

3.3. Previous generations or variants of the device

The current device generation is the first, thus there are no previous generations of the device.

3.4. Description of any accessories which are intended to be used in combination with the device

No accessories required.

3.5. Description of any other devices and products which are intended to be used in combination with the device

Device name	Device REF	Device type	Device manufacturer
ClotPro 6.0	111010	analyzer	enicor GmbH
Cups & Pins	112010	receptacles	enicor GmbH
QC1	113101	positive control	enicor GmbH
QC2	113102	negative control	enicor GmbH

4. Harmonised standards and CS applied

Following harmonized standards were applied during the development and lifecycle of the device:

EN ISO 13485:2016 + A11:2021 *Medical devices — Quality management systems — Requirements for regulatory purposes*

EN ISO 14971:2019 + A11:2021 *Medical devices — Application of risk management to medical devices*

EN ISO 15223-1:2021 *Medical devices — Symbols to be used with information to be supplied by the manufacturer — Part 1: General requirements*

Common specifications as defined in the IVDR have not been developed to date for the device.

5. Risks and warnings

5.1. Residual risks and undesirable effects

The following residual risks were identified during the risk management activities for the device:

- In case of an off-label use of the product, test results may be incorrectly interpreted by the user.
- In case of device handling errors, patient's coagulation may be incorrectly reflected.
- In case of the use of the expired product, patient's coagulation may be incorrectly reflected.
- In case of unacceptable transport and storage conditions, patient's coagulation may be incorrectly reflected.

No undesirable side-effects were identified during the post-market activities for the device.

5.2. Warnings and precautions

CAUTION: A use of the device outside of its intended purpose, may lead to the test results being incorrectly interpreted by the user.

CAUTION: Incorrect storage conditions may affect reagent stability and lead to wrong test results.

CAUTION: Do not use tips from defective pouches or from pouches missing the desiccant pack.

CAUTION: Intended for single use - do not reuse.

CAUTION: Any serious incident that has occurred as a result of the use of the device has to be reported to the manufacturer and the competent authority of the Member State in which the user and/or patient is established.

CAUTION: Failure to comply with these instructions for use may result in device handling errors leading to wrong test results.

CAUTION: Human blood samples should be handled with care, following general precautions recommended for bio-hazardous materials.

CAUTION: General precautions (e.g., wear gloves and minimize skin exposure to specimens and reagents) should be followed when handling all materials.

NOTE: Dispose of waste according to local regulations.

NOTE: A material safety data sheet is available upon request.

CAUTION: Collect a venous blood sample according to the recommended procedures using a blood collection tube with 3.2% sodium citrate. Samples should be analyzed within 3 hours from blood collection. Store the blood at room temperature. Always ensure blood collection tubes are filled to the indicated fill volume to avoid excessive citrate levels.

CAUTION: Do not use the expired product. The use of the expired product may lead to wrong test results.

5.3. Other relevant aspects of safety, including a summary of any field safety corrective action (FSCA including FSN)

No FSCA or FSN were issued for the device to date.

6. Summary of performance evaluation and post-market performance follow-up (PMPF)

6.1. Summary of scientific validity of the device

The EX assay is a functional whole-blood based assay to be used on viscoelastometry analyzers. Coagulation is activated by a combination of recombinant tissue factor, calcium chloride and polybrene as a heparin antagonist.

Viscoelastometry (Volod 2022, Heubner 2022) allows for the detection of whole blood formation in whole blood, and thus detects coagulation initiation (by the clotting time, CT), blood clot firmness (by the maximum clot firmness, MCF, or related parameters, such as the A20, amplitude 20 minutes after CT) and clot stability or fibrinolysis (by the maximum lysis, ML).

Volod O, Bunch CM, Zackariya N, Moore EE, Moore HB, Kwaan HC, Neal MD, Al-Fadhl MD, Patel SS, Wiarda G, Al-Fadhl HD, McCoy ML, Thomas AV, Thomas SG, Gillespie L, Khan RZ, Zamlut M, Kamphues P, Fries D, Walsh MM. *Viscoelastic Hemostatic Assays: A Primer on Legacy and New Generation Devices. J Clin Med. 2022 Feb 7;11(3):860.*

Heubner L, Mirus M, Vicent O, Güldner A, Tiebel O, Beyer-Westendorf J, Fries D, Spieth PM. *Point of care coagulation management in anesthesiology and critical care. Minerva Anesthesiol. 2022 Jul-Aug;88(7-8):615-628.*

The use of a combination of recombinant tissue factor, calcium chloride and polybrene is commonly used in viscoelastometry tests such as the ex-tem® or EX-test assays (Volod 2022) (tem® is a registered trademark by CA Casyso, Switzerland). Such assays allow to determine coagulation activation, clot formation and clot stability or fibrinolysis, which can support the patient management during coagulopathy, and is often used together with other viscoelastometry assays (tissue-factor triggered viscoelastometry with fibrinolysis inhibition, viscoelastometry with platelet inhibition) (Heubner 2022).

Several studies (for example Dirkmann 2014, Saito 2020, Thaler 2025) confirm the detection of fibrinolysis using TF-triggered viscoelastometry.

Dirkmann D, Görlinger K, Peters J. *Assessment of early thromboelastometric variables from extrinsically activated assays with and without aprotinin for rapid detection of fibrinolysis. Anesth Analg. 2014 Sep;119(3):533-542.*

Saito T, Hayakawa M, Honma Y, Mizugaki A, Yoshida T, Katabami K, Wada T, Maekawa K. *Relationship Between Severity of Fibrinolysis Based on Rotational Thromboelastometry and Conventional Fibrinolysis Markers. Clin Appl Thromb Hemost. 2020 Jan-Dec;26.*

Thaler S, Zorn A, Aster I, Koliogiannis D, Renz BW, Guba M, Groene P. *Hyperfibrinolysis Detection During Liver Transplantation Using Viscoelastometry. Clin Transplant. 2025 May;39(5):e70179.*

The detection of elevated INRs by the clotting time of TF-triggered viscoelastometry was reported by Schmidt et al (Schmidt 2015) and Yoshii et al (Yoshii 2022).

Schmidt DE, Holmström M, Majeed A, Näslin D, Wallén H, Ågren A. *Detection of elevated INR by thromboelastometry and thromboelastography in warfarin treated patients and healthy controls. Thromb Res. 2015 May;135(5):1007-11.*

Yoshii R, Sawa T, Kawajiri H, Amaya F, Tanaka KA, Ogawa S. *A comparison of the ClotPro system with rotational thromboelastometry in cardiac surgery: a prospective observational study. Sci Rep. 2022 Oct 14;12(1):17269.*

The use of viscoelastometry in the context of coagulopathy is supported by various international guidelines:

Rossaint R, Afshari A, Bouillon B, Cerny V, Cimpoesu D, Curry N, Duranteau J, Filipescu D, Grottke O, Grønlykke L, Harrois A, Hunt BJ, Kaserer A, Komadina R, Madsen MH, Maegele M, Mora L, Riddez L, Romero CS, Samama CM, Vincent JL, Wiberg S, Spahn DR. *The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition. Crit Care. 2023 Mar 1;27(1):80.*

Kietaibl S, Ahmed A, Afshari A, Albaladejo P, Aldecoa C, Barauskas G, De Robertis E, Faraoni D, Filipescu DC, Fries D, Godier A, Haas T, Jacob M, Lancé MD, Llau JV, Meier J, Molnar Z, Mora L, Rahe-Meyer N, Samama CM, Scarlatescu E, Schlimp C, Wikkelsø AJ, Zacharowski K. *Management of severe peri-operative bleeding: Guidelines from the European Society of Anaesthesiology and Intensive Care: Second update 2022. Eur J Anaesthesiol. 2023 Apr 1;40(4):226-304.*

Casselmann FPA, Lance MD, Ahmed A, Ascari A, Blanco-Morillo J, Bolliger D, Eid M, Erdoes G, Haumann RG, Jeppsson A, van der Merwe HJ, Ortman E, Petricevic M, Weltert LP, Milojevic M; EACTS/EACTAIC/EBCP Scientific Document Group. *2024 EACTS/EACTAIC Guidelines on patient blood*

management in adult cardiac surgery in collaboration with EBCP. *Eur J Cardiothorac Surg.* 2025 May 6;67(5):ezae352.

Curry NS, Davenport R, Pavord S, Mallett SV, Kitchen D, Klein AA, Maybury H, Collins PW, Laffan M. The use of viscoelastic haemostatic assays in the management of major bleeding: A British Society for Haematology Guideline. *Br J Haematol.* 2018 Sep;182(6):789-806.

6.2. Summary of performance data from the equivalent device

2 equivalent devices have been identified: The EXTEM assay (Werfen) and the EX-test (enicor).

Precision data for the EXTEM assay is provided in the 510k of the widely used ROTEM sigma device. In K201440 the results of the 510k evaluations for the ROTEM sigma device are summarized.

https://www.accessdata.fda.gov/cdrh_docs/pdf20/k201440.pdf

For the EXTEM CT within-laboratory precision CV values of 6.8% - 13.6% are reported. For A5, A10, A20 and MCF within-laboratory precision CV values of 1.4% - 5.0% are reported.

Van Haeren et al (Van Haeren 2025) report a comparison between 2 generations of the EXTEM assay. In the comparison for EXTEM A10 parameter, at the “baseline” timepoint, a Deming regression with a slope of 1.01 and an intercept of 0.0 is reported and a correlation coefficient of 0.8536 (Passing-Bablok) (supplementary data). At the “heparinised timepoint the slope was 0.935 and the intercept was 8 and the correlation coefficient 0.9401. At the “post protamine” timepoint the slope was 0.949, the intercept was 6.3 and the correlation coefficient 0.8208.

van Haeren MMT, Breel JS, Schenk J, Eberl S, Hamer HM, Hollmann MW, Vlaar APJ, Müller MCA, Hermanns H; collaborators. Comparison of ROTEM® Delta and ROTEM® Sigma transfusion algorithm performance in thoracic aortic surgery: a single-centre prospective observational cohort study. *Br J Anaesth.* 2025 Feb;134(2):317-327.

Frick et al (Frick 2025) report a comparison between 2 generations of the EXTEM assay. In the comparison for EXTEM A10 parameter, a Deming regression with a slope of 0.84 and an intercept of 9.3 is reported, as well as a correlation coefficient (Pearson) of 0.937. In the comparison for EXTEM MCF parameter, a Deming regression with a slope of 0.92 and an intercept of 5.7 is reported, as well as a correlation coefficient (Pearson) of 0.957.

Frick R, Washburn B, Plocher D, Zoller JK, Gillihan J, Dombrowski M, Eby C, Farnsworth CW. Comparison of 2 thromboelastography methods using patient and control samples. *Res Pract Thromb Haemost.* 2025 Mar 30;9(3):102843.

Schmidt et al (Schmidt 2015) report a clinical study involving 107 patients on warfarin and 89 healthy controls. Compared with healthy controls, patients treated with warfarin had prolonged EXTEM clotting time ($p < 0.001$). Increased INR values correlated with EXTEM CT (Spearman $\rho = 0.87$). EXTEM CT had a sensitivity and specificity of 0.89 and 1.00, respectively, to detect elevated INR above 1.2 units, with a positive and negative predictive values (PPV and NPV) of 1.00 and 0.88, respectively.

Schmidt DE, Holmström M, Majeed A, Näslin D, Wallén H, Ågren A. Detection of elevated INR by thromboelastometry and thromboelastography in warfarin treated patients and healthy controls. *Thromb Res.* 2015 May;135(5):1007-11.

David et al (David 2016) report in trauma patients correlations of INR and EXTEM CT between 0.399 – 0.613 depending on the clinical group and timepoint, indicating that the agreement of INR and EXTEM CT depends on the clinical situation.

David JS, Durand M, Levrat A, Lefevre M, Rugeri L, Geay-Baillat MO, Inaba K, Bouzat P. Correlation between laboratory coagulation testing and thromboelastometry is modified during management of trauma patients. *J Trauma Acute Care Surg.* 2016 Aug;81(2):319-27.

6.3. Summary of performance data from conducted studies of the device prior to CE-marking

In a precision study citrated blood with and without hemodilution (50% using HES 6% in saline with 3.2% citrate) was tested in 3 runs, on three analyzers, three operations and including 3 EX reagent lots (54 determinations per sample). The resulting mean, standard deviation (SD) and coefficient of variation (CV) for the CT and A20 were as follows:

		citrated blood	hemodiluted blood
CT (sec)	mean ± SD	51.9 ± 4.7	114.5 ± 14.8
	CV	9.0%	12.9%
A20 (mm)	mean ± SD	58.3 ± 1.5	34.9 ± 2.2
	CV	2.5%	6.4%

To confirm the accuracy of the clot firmness parameters of the EX assay, its results were compared with a reference test, the EX-test assay by enicor (Heubner 2022).

Based on the parallel measurements of 103 samples from intensive care patients and healthy individuals, the slope, bias and correlation were calculated for the EX assay parameters (A5, A10, A20, MCF, ML) vs. the reference test (EX-test by enicor) according to CLSI EP09 (EP09c).

In the following table the Deming regression slope and bias (intercept) and, as a descriptive parameter, the Spearman correlation are shown. EXa: EX assay (Apiro), EXe: EX-test (Enicor)

Parameter	Slope	Bias	Spearman ρ
EXa-A5 vs EXe-A5	1.063	-3.583	0.923
EXa-A10 vs EXe-A10	1.057	-3.471	0.936
EXa-A20 vs EXe-A20	1.056	-3.480	0.94
EXa-MCF vs EXe-MCF	1.068	-4.280	0.947
EXa-ML vs EXe-ML	1.011	0.177	0.9

The determined agreement of the EX assay to the reference method compares very well with recent literature comparing different generations of viscoelastometry assays (van Haeren 2025, Frick 2025).

The reference range for the EX assay was determined in a clinical study including 121 healthy individuals, aged 19 - 79.3 years, 54.5% female and 45.5% male, and calculated of the 95% central interval:

Parameter	2.5 th percentile – 97.5 th percentile	Mean ± SD
CT (sec)	37 – 65	48.3 ± 10.2
A5 (mm)	40 – 57	47.6 ± 4.7
A10 (mm)	48 – 63	55.2 ± 4.2
A20 (mm)	53 – 66	59.6 ± 3.7
MCF (mm)	53 – 67	60.2 ± 3.7
ML (%)	2 – 12	5.9 ± 2.6

Detection of clotting factor deficiencies using the EX assay clotting time (CT)

The sensitivity and specificity of the EX assay clotting time for the detection of a factor deficiency of the extrinsic pathway was tested in a clinical study including patients suspected of a factor deficiency of the extrinsic pathway, due to the intake of vitamin K antagonists or a liver dysfunction.

The prothrombin time assay was used as a reference for the detection of a factor deficiency of the extrinsic pathway. A cut-off of INR \geq 1.5 was applied to detect a clinically relevant clotting factor deficiency, which is supported by international guidelines and recommendations.

The upper limit of the EX CT reference range was defined as the cut-off value for indicating an INR $>$ 1.5, i.e. an EX-CT $>$ 65 sec.

Based on the measurements of 105 patients with suspected clotting factor deficiencies and a control group (n=104, intensive care patients and healthy individuals) the following sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratio were determined:

Sensitivity	92.6%
Specificity	91 %
Positive predictive value (PPV)	0.781
Negative predictive value (NPV)	0.972
Positive likelihood ratio (LR+)	10.25
Negative likelihood ratio (LR-)	0.081

Detection of fibrinolysis

The ability of the EX assay to detect fibrinolysis was tested by the addition of increasing doses of t-PA to citrated blood. 4-fold determinations were performed. Means and standard deviations (SD) for the maximum lysis (ML) and maximum clot firmness (MCF) are shown below:

	t-PA (ng/ml)					
	0	100	200	300	400	600
ML (% , mean \pm SD)	3.25 \pm 0.5	3.75 \pm 0.5	97 \pm 0	96 \pm 0	96 \pm 0	95 \pm 0
MCF (mm, mean \pm SD)	56.8 \pm 1	56.5 \pm 1	48.8 \pm 1.3	39.8 \pm 0.5	34.3 \pm 0.5	28.8 \pm 1

This experiment shows that fibrinolysis is effectively detected using the EX assay. The dose-response detected matches well published viscoelastometry results (Faraoni 2015).

Faraoni D, Rozen L, Willems A, Torres CS, Pereira LM, Demulder A, Van der Linden P. Experimental model of hyperfibrinolysis designed for rotational thromboelastometry in children with congenital heart disease. Blood Coagul Fibrinolysis. 2015 Apr;26(3):290-7.

6.4. Summary of performance data from other sources

There is no data of performance from other sources.

6.5. An overall summary of performance and safety

The performance evaluation, including scientific validity, analytical performance, and clinical performance studies, has been conducted in accordance with the requirements of Annex XIII of the Regulation (EU) 2017/746 (IVDR). The evaluation confirms that the device meets the applicable GSPR as set out in Annex I of the IVDR.

The device demonstrates:

- Scientific validity for the intended analyte and clinical condition, supported by relevant scientific literature and established clinical practice;
- Analytical performance, including trueness, precision, specificity, sensitivity, linearity, and robustness, all validated through structured and statistically sound studies;
- Clinical performance, confirmed through clinical studies showing strong concordance with standard reference methods and demonstrating the clinical utility of the related products in their intended context.

Furthermore, all known and foreseeable risks have been systematically assessed and addressed through risk management and performance evaluation processes. The residual risks are mitigated to an acceptable level in accordance with the state of the art, and appropriate risk control measures are in place and communicated effectively to the user.

6.6. Ongoing or planned post-market performance follow-up

Post-market performance follow-up are planned to be performed every year.

7. Metrological traceability of assigned values

7.1. Explanation of the unit of measurement

Viscoelastometry is a functional method that continuously measures coagulation in whole blood, by detecting the elasticity (mechanical quality) of the blood clot during the coagulation process (Volod 2022). For historical reasons the blood clot firmness is expressed in millimeters (mm). The clotting time is the time from the start of the test until an amplitude of 2 mm is detected. It is expressed in sec. The clot firmness is quantified by the amplitude 5 min after CT (A5), amplitude 10 min after CT (A10), amplitude 20 min after CT (A20) and the maximum clot firmness (MCF). The clot stability or fibrinolysis is quantified by the maximum lysis parameter (in %).

Volod O, Bunch CM, Zackariya N, Moore EE, Moore HB, Kwaan HC, Neal MD, Al-Fadhl MD, Patel SS, Wiarda G, Al-Fadhl HD, McCoy ML, Thomas AV, Thomas SG, Gillespie L, Khan RZ, Zamlut M, Kamphues P, Fries D, Walsh MM. Viscoelastic Hemostatic Assays: A Primer on Legacy and New Generation Devices. J Clin Med. 2022 Feb 7;11(3):860.

7.2. Identification of applied reference materials and/or reference measurement procedures of higher order used by the manufacturer for the calibration of the device

For viscoelastometry as a functional whole blood method no international reference material or SI unit exists. The device was compared with a reference assay (EX-test) that is an accepted, ce marked method (Volod 2022, Heubner 2022).

8. Suggested profile and training for users

The device is intended to be used by:

- trained healthcare professionals
- trained laboratory professionals

The users are trained using standard strategies by trained personnel e.g. field service representatives of the local distributor. The training is performed using the instructions for use, and the viscoelastometry device and its documentation owned by the user.

9. Revision history

SSP revision number	Date issued	Change description	Revision validated by the Notified Body
1	2025-12-15	Initial version	<input checked="" type="checkbox"/> yes – validation language: English <input type="checkbox"/> no