Summary of safety and performance – TPA

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

TPA (REF 1021EU)

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

59998629921021EU_1TG

1.5. European Medical Device Nomenclature (EMDN)

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 TPA is a ready to use reagent for in-vitro diagnostic professional use, intended for detection of tranexamic acid in citrated blood during viscoelastometry analysis.

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

Indicated to be used when the presence of tranexamic acid in the blood of the adult patients suspected to be exposed to tranexamic acid is suspected.

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

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

The TPA assay is not intended for a companion diagnostics.

2.4. Limitations and/or contra-indications

The TPA assay should not be used for patients that have been exposed to epsilon-amino-caproic acid or aprotinin, as these drugs could lead to false-positive results.

The mechanism of the TPA assay is not specific to tranexamic acid. Other antifibrinolytic drugs such es epsilon-amino-caproic acid and aprotinin can also block TPA-triggered fibrinolysis in viscoelastometry and lead to false-positive results in the TPA assay. Endogenous inhibition of fibrinolysis can also block fibrinolysis in the TPA assay and therefore lead to false-positive results.

3. Device description

3.1. Description of the device

An assay system for assessment of whole blood clot formation with fibrinolysis activation, triggered using recombinant tissue factor (coagulation activator) and recombinant tissue plasminogen activator (fibrinolysis activator). It contains an inhibitor of heparin (polybrene). It also contains calcium chloride for the recalcification of the citrated blood sample. 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, recombinant tissue plasminogen activator, polybrene (a heparin antagonist), 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 [10].

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 the sample according to the recommended procedures [11][12]. Samples should be analyzed within 3 hours from blood collection. 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 TPA assay is a functional whole-blood based test for the detection of tranexamic acid on viscoelastometry analyzers. Viscoelastometry is a standard method for the measurement of blood coagulation in whole blood. This method continuously records blood coagulation by the mechanical stability of the blood clot (clot firmness), which allows not only to detect the clot formation, but also its stability or fibrinolysis.

Viscoelastometry is widely used worldwide and its applications have been summarized for example in Volod 2022.

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.

The reagent of the TPA assay consists on a combination of the following active components:

1. recombinant tissue factor: activator of blood coagulation via the extrinsic pathway
2. calcium chloride: used to recalcify the citrated blood sample
3. polybrene (Hexadimethrine bromide): heparin antagonist
4. recombinant plasminogen activator (TPA): used to stimulate fibrinolysis.

Components 1-3 are established standard components in viscoelastography (see Volod 2022, table 2).

The use of TPA-augmented viscoelastometry for the detection of tranexamic acid was introduced previously by the TPA-test by enicor GmbH, Munich, Germany. In several publications the successful use of this assay to detect tranexamic acid was reported:

- *Yoshii R, Takahashi Y, Tanaka KA, Kawajiri H, Sawa T, Amaya F, Ogawa S. Point-of-care testing for tranexamic acid efficacy: a proof-of-concept study in cardiac surgical patients. Br J Anaesth. 2024 Jun;132(6):1211-1218.*
- *Tran A, Katz D. Variability of fibrinolytic activity in pregnant patients exposed to tissue plasminogen activator: an in vitro study utilizing rotational thromboelastometry. Int J Obstet Anesth. 2024 Aug;59:103994.*
- *Coupland LA, Pai KG, Pye SJ, Butorac MT, Miller JJ, Crispin PJ, Rabbolini DJ, Stewart AHL, Aneman A. Protracted fibrinolysis resistance following cardiac surgery with cardiopulmonary bypass: A prospective observational study of clinical associations and patient outcomes. Acta Anaesthesiol Scand. 2024 Jul;68(6):772-780.*
- *Dibiasi C, Ulbing S, Bancher-Todesca D, Ulm M, Gratz J, Quehenberger P, Schaden E. Concentration-effect relationship for tranexamic acid inhibition of tissue plasminogen activator-induced fibrinolysis in vitro using the viscoelastic ClotPro® TPA-test. Br J Anaesth. 2024 Feb;132(2):343-351.*
- *Kammerer T, Groene P, Sappel SR, Peterss S, Sa PA, Saller T, Giebl A, Scheiermann P, Hagl C, Schäfer ST. Functional Testing for Tranexamic Acid Duration of Action Using Modified Viscoelastometry. Transfus Med Hemother. 2021 Mar;48(2):109-117.*
- *Groene P, Sappel SR, Saller T, Nitschke T, Sa PA, Paulus A, Chappell D, Schäfer ST. Functional testing of tranexamic acid effects in patients undergoing elective orthopaedic surgery. J Thromb Thrombolysis. 2021 May;51(4):989-996.*

Also previously the combination of tissue factor and recombinant t-PA was reported to be sensitive to the fibrinolysis inhibition by tranexamic acid:

- *Godier A, Parmar K, Manandhar K, Hunt BJ. An in vitro study of the effects of t-PA and tranexamic acid on whole blood coagulation and fibrinolysis. J Clin Pathol. 2017 Feb;70(2):154-161.*
- *Rozen L, Faraoni D, Sanchez Torres C, Willems A, Noubouossie DC, Barglazan D, Van der Linden P, Demulder A. Effective tranexamic acid concentration for 95% inhibition of tissue-type plasminogen activator induced hyperfibrinolysis in children with congenital heart disease: A prospective, controlled, in-vitro study. Eur J Anaesthesiol. 2015 Dec;32(12):844-50.*

In summary both experimental studies as well as the published experiences with the TPA-test by enicor GmbH show that the diagnostic strategy of the TPA assay is scientifically sound.

6.2. Summary of performance data from the equivalent device

In the TPA-test by enicor GmbH the following performance data were summarized in the instructions for use:

Precision was determined with blood of a healthy donor, tested with and without the addition of 10 µg TXA/mL on 4 ClotPro analyzers in 6 channels each (n=24).

	Reproducibility (inter-channel / inter-device)		
	Mean	SD	CV
Citrated blood:			
ML [%]	94.5	0.5	0.5%
LT [sec]	198.5	25.1	12.7%
Citrated blood + TXA:			
ML [%]	17.0	3.6	20.9%
LT [sec]	>3500		

In a study investigating patient samples under tranexamic acid (TXA) treatment (n=208 from 42 patients undergoing orthopedic surgery (Groene 2021) the following fibrinolytic response was found in relation to the determined TXA concentrations (mean±SD, range in parentheses):

TXA [µg/mL]	ML [%]	LT [sec]	n
0-1	96.4 ±0.7 (94.5 – 98)	394 ±176 (206 - 1289)	75
1-4	39.1 ±14.5 (22.5 – 98)	1248 ±923 (382 - 4500)	45
4-7	55.2 ±33.8 (11.5 - 98)	3366 ±1219 (1279 - 4500)	25
7-10	30.8 ±23.9 (5.5 – 96.5)	4209 ±733 (2149 - 4500)	26
>10	11.9 ±6.8 (2.5 – 36.5)	>4500	37

This shows that above a TXA concentration of 10 µg/mL a completely or almost completely blocked fibrinolytic response was recorded, while fibrinolysis was normal or close to normal at very low TXA

concentrations of <1 µg/mL. Between 1 and 10 µg/mL a concentration- dependent decrease of fibrinolysis was recorded, with a significant variability between different samples.

Groene P, Sappel SR, Saller T, Nitschke T, Sa PA, Paulus A, Chappell D, Schäfer ST. Functional testing of tranexamic acid effects in patients undergoing elective orthopaedic surgery. J Thromb Thrombolysis. 2021 May;51(4):989-996

In addition to the above information from the instructions for use of the TPA-test the successful use to detect tranexamic acid was published in the following publications:

- *Yoshii R, Takahashi Y, Tanaka KA, Kawajiri H, Sawa T, Amaya F, Ogawa S. Point-of-care testing for tranexamic acid efficacy: a proof-of-concept study in cardiac surgical patients. Br J Anaesth. 2024 Jun;132(6):1211-1218.*
- *Tran A, Katz D. Variability of fibrinolytic activity in pregnant patients exposed to tissue plasminogen activator: an in vitro study utilizing rotational thromboelastometry. Int J Obstet Anesth. 2024 Aug;59:103994.*
- *Coupland LA, Pai KG, Pye SJ, Butorac MT, Miller JJ, Crispin PJ, Rabbolini DJ, Stewart AHL, Aneman A. Protracted fibrinolysis resistance following cardiac surgery with cardiopulmonary bypass: A prospective observational study of clinical associations and patient outcomes. Acta Anaesthesiol Scand. 2024 Jul;68(6):772-780.*
- *Dibiasi C, Ulbing S, Bancher-Todesca D, Ulm M, Gratz J, Quehenberger P, Schaden E. Concentration-effect relationship for tranexamic acid inhibition of tissue plasminogen activator-induced fibrinolysis in vitro using the viscoelastic ClotPro® TPA-test. Br J Anaesth. 2024 Feb;132(2):343-351.*
- *Kammerer T, Groene P, Sappel SR, Peterss S, Sa PA, Saller T, Giebl A, Scheiermann P, Hagl C, Schäfer ST. Functional Testing for Tranexamic Acid Duration of Action Using Modified Viscoelastometry. Transfus Med Hemother. 2021 Mar;48(2):109-117.*

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

The effect of fibrinolysis inhibitors on the TPA assay is detected by the lysis time (LT).

The reference range for the lysis time (LT) is 135-270 sec.

This was determined in a clinical study including 123 healthy individuals, aged 18.9 - 79.2 years, 51.2% female and 48.8% male, by the calculation of the 95% central interval (2.5° percentile – 97.5° percentile).

In a clinical study including 105 samples from 40 patients treated with tranexamic acid, the TPA assay was determined in citrated whole blood and the tranexamic acid concentration was determined in plasma after protein precipitation and phospholipid removal with liquid chromatography coupled to mass spectrometry [13]. Patients were 18.4 - 81.8 years old, 45.7% female and 54.3% male.

In all 69 patients with a TXA concentration ≥ 10 µg/mL maximum fibrinolysis was below 50% and therefore no lysis time was expressed. When no lysis time was reached, the lysis time was set as 3500 sec for the subsequent analysis.

When the patients treated with tranexamic acid (n=105) and the control group (reference patients, n=123) are analyzed together using a cut-off of ≥ 2100 sec for the lysis time, the sensitivity, specificity, positive predictive value and negative predictive values were as follows:

Sensitivity	100%
Specificity	81%
Positive predictive value (PPV)	70%
Negative predictive value (NPV)	100%
Positive likelihood ratio	5.3
Negative likelihood ratio	0

All individuals without exposure to tranexamic acid showed lysis times below the cut-off of 2100 sec. However, tranexamic acid at concentrations lower than 10 µg/mL already inhibited fibrinolysis in the sample.

The calculation of the lysis time (LT) in the TPA assay is based on the determination of the CT (clotting time), the MCF (maximum clot firmness) and the ML (maximum lysis).

The results for these parameters in the clinical trials were as follows:

Reference range (n=123):

	CT (sec)	MCF (mm)	ML (%)
2.5° percentile	22	17	91
97.5° percentile	50.8	41	96
mean	32.2	28.6	94.2
SD	7.2	6.9	2.7
min	20	9	71
max	58	47	97

Tranexamic acid study (n=105):

CT (sec)

	min	max	mean	SD
TXA 2.6 - 4.9µg/mL	21	55	36.9	11.1
TXA 5 - 9.6 µg/mL	27	58	40.3	8.2
TXA > 10 µg/mL	21	291	50.6	35.5

MCF (mm)

	min	max	mean	SD
TXA 2.6 - 4.9µg/mL	51	63	56.7	4.0
TXA 5 - 9.6 µg/mL	47	66	58.9	4.5
TXA > 10 µg/mL	43	71	59.2	5.4

ML (mm)

	min	max	mean	SD
TXA 2.6 - 4.9µg/mL	22	97	78.0	32.8
TXA 5 - 9.6 µg/mL	3	98	25.1	20.8
TXA > 10 µg/mL	0	18	6.5	4.3

Precision

In a precision study citrated blood with and without the addition of 10 µg tranexamic acid /mL was tested in 3 runs, on three analyzers, three operations and including 3 TPA reagent lots (54 determinations per sample). The resulting mean, standard deviation (SD) and coefficient of variation (CV) for the lysis time were as follows:

Citrated blood without the addition of tranexamic acid:

n	54
min	165 sec
max	285 sec
mean	206.7 sec
SD	24.0
CV	11.6%

Citrated blood with the addition of 10 µg/mL tranexamic acid:

All samples had fibrinolysis < 50% and therefore no lysis time.

n	54
mean	3500 sec
SD	0
CV	0%

The clot curve determined during the analysis should be smooth and not noisy. Repeat measurements with irregular curves.

6.4. Summary of performance data from other sources

There is no data of performance from other sources.

6.5. An overall summary of the 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 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

The TPA is a functional assay for the detection of tranexamic acid in a whole blood sample. The effect of tranexamic acid is quantified by the lysis time (LT), which is the time from the initiation of the clotting (CT = clotting time) until a fibrinolysis of 50% is detected. The LT is expressed in seconds.

In the clinical performance study for the TPA assay, it was found that using a pre-defined cut-off of 2100 sec for the LT a tranexamic acid concentration of >= 10 µg/L was detected with a sensitivity of 100% and a specificity of 81%.

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

There exists no international standard for recombinant tissue plasminogen activator (t-PA) as the primary active component of the TPA assay for the detection of tranexamic acid. Therefore, Apiro is using a tightly controlled pharmaceutical preparation as the source for the recombinant t-PA, therefore ensuring the stability of this crucial component of the assay.

In the clinical study the tranexamic acid (TXA) concentration was measured in plasma samples after using liquid chromatography coupled to mass spectrometry according to an analytical method validated following the EMA guideline on bioanalytical method validation (EMEA / CHMP / EWP / 192217 / 2009 Rev.1 Corr.2) at the MasSpecLab, UFR Simone Veil- Santé in Montigny le Bretonneux, France, working group Prof. Stanislas Grassin-Delyle. The method is linear in the range 1.0-1000.0 µg/mL, accuracy is between 88.4 and 96.6% and precision <3.0%.

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	2025-09-05	Initial version	☒ yes – validation language: English ☐ no