FloMass NOAC in Serum

Reagents for 100 assays

Instruction Manual

REF **EUM12100**

IVD **For *in vitro* diagnostic use**

CE

PROVIDE PERSONAL SOLUTIONS

B.S.N. S.r.l. | Biological Sales Network
Tel. +39.0374.351005
Via Coelli, 18 26012 Castelleone (CR)

contact@bsn-srl.it
bsn-srl.it

B.S.N. BIOLOGICAL SALES NETWORK S.R.L.
26012 Castelleone (CR) Italy - Via Coelli, 18
Tel. +39 0374 351005 - Fax +39 0374 57965 - e-mail: info@bsn-srl.it – bsn@postecert.it
Reg. Imprese / C.F. / P.IVA: 11317290150 - R.E.A. di Cremona n. 143395

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1 INTRODUCTION

1.1 IVD SYMBOLS

IVD	In vitro diagnostic medical device /Dispositif médical de diagnostique en vitro /In-Vitro-Diagnostikum / Producto sanitario para diagnóstico in vitro / Dispositivo medico-diagnostico in vitro / Dispositivo médico para in til in vitro diagnostik
LOT	Batch code / Code du lot / Chargenbezeichnung / Código de lote / Codice del lotto / Código do lote / Número do lote / Lotnummer
PN	Packing number / Numéro d'emballage / Packnummer / Número de envase / Numero confezioni / Número de embalagem / Número de embalagem / Emballagenummer
REF	Catalog number / Référence du catalogue / Bestellnummer / Número de catálogo / Numero di catalogo / Referência de catálogo / Código / Katalognummer
	Use by / Utiliser jusqu'au / Verwendbar bis / Fecha de caducidad / Utilizzare entro / Prazo de validade / Data limite de utilização / Holdbar til
	Temperature limitation / Limites de température / Temperaturbegrenzung / Limite de temperatura / Limiti di temperatura / Limites de temperatura / Limite de temperatura / Temperaturbegrænsning
	Add liquid / Ajout de liquide / Flüssigkeit zugeben / Añadir líquido / Aggiungi liquido / Adicionar líquido / Adicionar líquido / Tilføj væske
	Store in the dark / Conserver à l'abri de la lumière / Dunkel aufbewahren / Almacenar en ambiente oscuro / Conservare al buio / Armazenar no escuro / Guardar longe da luz / Opbevares mørkt
	Contains sufficient for <n> tests / Contenu suffisant pour "n" tests / Inhalt ausreichend für <n> Prüfungen / Contenido suficiente para <n> ensayos /Contenuto sufficiente per "n" saggi / Conteúdo suficiente para "n" ensaios / Conteúdo suficiente para <n> testes / Indeholder tilstrækkeligt til "n" test
	Consult instructions for use / Consulter les instructions d'utilisation / Gebrauchsanweisung beachten / Consulte las instrucciones de uso / Consultare le istruzioni per l'uso / Consulte as instruções de utilização / Consultar Instruções de uso / Se brugsanvisning
	Manufacturer / Fabricant / Hersteller / Fabricante / Fabbricante / Fabricante / Fabricado por / Producent
	This way up / Haut / Diese Seite oben / Este lado arriba / Questo lato in alto / Este lado para cima / Este lado para cima / Denne side op
	Recyclable / Recyclable / Recyclebar / Reciclable / Riciclabile / Reciclável / Reciclável / Genanvendeligt
	Brittle / Fragile / Zerbrechilich / Fragile / Fragil / Skrøbelig

1.2 ABBREVIATIONS

CAD: Collision Gas Pressure
CE: Collision energy
CLSI: Clinical and Laboratory Standards Institute
CUR: Curtain Gas
CV: Coefficient of Variation
CXP: Collision Exit Potential
DP: Desolvation Potential
EP: Entrance Potential
ESI: Electrospray Ionization
GS1: Gas 1
GS2: Gas 2
HPLC-MS/MS: High Performance Liquid chromatography-tandem mass spectrometry
IS: Ion Spray Voltage
LLOD: Lower Limit of Detection
LLOQ: Lower Limit of Quantification
M/Z: Mass/Charge ratio
MPA: Mobile Phase A
MPB: Mobile Phase B
MPC: Mobile Phase C
MRM: Multiple Reaction Monitoring
PP: Polypropylene
Q1: Quadrupole 1
Q3: Quadrupole 3
RT: Retention Time
S/N: Signal/Noise ratio
TDM: Therapeutic Drug Monitoring
TEM: Source temperature

1.3 CLINICAL APPLICATION

FloMass NOAC in Serum is an in vitro diagnostic kit intended for the quantitative and simultaneous determination of 4 direct acting oral anticoagulants (DOAC) in human serum samples (Table 1) using high performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS).

ANALYTE
Apixaban
Edoxaban
Rivaroxaban
Dabigatran

Table 1: Analytes measured by FloMass NOAC in Serum

The development of NOACs represented an important progress in therapy for the prevention of arterial and venous thromboembolism. In effect, these drugs are replacing the use of warfarin, a molecule characterized by several limitations such as the delayed onset of action, the narrow therapeutic window, the several drug interactions with other drugs or foods, the variable and unpredictable response, the influence of genetic polymorphism of CYP2C9 and VKORC1 and the need of frequent monitoring of coagulation. [1-3]
The "direct oral anticoagulants" DOACs or "new oral anticoagulants" NOACs are represented by Edoxaban, Rivaroxaban, Apixaban (inhibitors of coagulation factor Xa) and by Dabigatran (direct thrombin inhibitor).
Although NOACs show many advantages, the reduction in hepatic metabolism and impairment of renal function can cause an increase in the plasma concentration of the drug, inducing the risk of bleeding and developing a thromboembolic episode.
Since it appears that there is a direct association between the plasmatic NOAC concentration and the anticoagulant effect, it is possible to predict the existence of therapeutic plasma concentration ranges where the risk of these effects is lower.
TDM (Therapeutic Drug Monitoring) is generally recommended for drugs with large pharmacokinetic variability, drugs with a narrow therapeutic index, and drugs that have no clear association between drug concentration and therapeutic effect and/or adverse reaction.
Since all these points fit to NOACs, a targeted dosage is necessary for a good TDM and optimization of therapy. [3-5]

2 PRINCIPLE OF THE METHOD

The kit is intended for the quantitative and simultaneous determination of Apixaban, Dabigatran, Edoxaban and Rivaroxaban in human serum samples using high performance liquid chromatography technique coupled with tandem mass spectrometry (HPLC-MS/MS).
At the beginning of the preparatory phase, to normalize the sample preparation and instrumental variability, the internal standard marked with stable isotopes are added (Table 2).
Then, an extraction of the analytes is performed via protein precipitation with specific solvent addition. After centrifugation, the supernatant is separated and injected in the chromatographic system.

ANALYTE	INTERNAL STANDARD
Apixaban	Apixaban $^{13}C,^{2}H_8$
Edoxaban	Edoxaban $^{2}H_6$
Rivaroxaban	Apixaban $^{13}C,^{2}H_8$
Dabigatran	Dabigatran $^{13}C_6$

Table 2: Analyte measured by kit EUM12100 and related internal standard

Once extracted, analytes are chromatographically separated by a specific column. Subsequently, they enter in ESI source where they are transferred to the gas phase and ionized. Then ions enter in the triple quadrupole mass spectrometer, where they are measured in MRM mode.
Thus, only selected ions with a defined mass/charge ratio (m/z) are isolated in the first quadrupole and subsequently transferred in to the collision cell where they are fragmented by impact with an inert gas (nitrogen or argon). Among the fragments, only those with a defined m/z ratio are isolated in the third quadrupole for subsequent detection.
Measurement in MRM mode with HPLC separation ensures high selective and sensitive analyte identification and quantification.

3 COMPONENTS AND ACCESSORIES

3.1 KIT CONTENTS

Components for sample preparation included in the kit are shown in Table 3.

CATALOG NUMBER	DESCRIPTION	QUANTITY	STORAGE
EUM12011	Mobile Phase A	1 L	Temperatura ambiente
EUM12012	Mobile Phase B	600 mL	Temperatura ambiente
EUM12013	Mobile Phase C	250 mL	Temperatura ambiente
EUM12021	Precipitant Solution	25 mL	Temperatura ambiente
EUM12031	Internal Standard	0.6 mL	-20°C

Table 3: Components, description, quantity and storage of kit EUM12100

The kit consists of reagents for 100 assays.
The expiry date of the intact kit is shown on the external product label. Follow storage conditions given on the product label of each component of the kit and keep it away from light and/or heat.

3.2 KIT SUPPORT ACCESSORIES

CATALOG NUMBER	DESCRIPTION	QUANTITY	STORAGE
EUM12041	7-Levels Calibrators, lyophil.	2 x 7 x 1.0 mL	-20°C
EUM12051	3-Levels Controls, lyophil.	2 x 3 x 1.0 mL	-20°C
EUM00C12	Chromatographic Column	1 pc	Room Temperature

Table 4: Accessories, description, quantity and storage of kit EUM12100

3.3 CONTROLS AND CALIBRATION OF ANALYTICAL SYSTEM

Calibration should be done using 7-Levels Calibrators (EUM12041) containing the analytes. Calibrators should follow patient samples preparation (Chapter 7). A new calibrator series should be prepared for each analytical run.
BSN supplies quality control sets at three different concentration levels (EUM12051).
Lyophilized controls in human serum matrix are useful to verify the accuracy and precision of analytical procedures and to determine the analytes in the matrix.
For analyte concentrations, stability and accessories preparation, refer to package leaflet.

3.4 CHROMATOGRAPHIC SYSTEM

The kit has been validated using analytical column (EUM00C12).

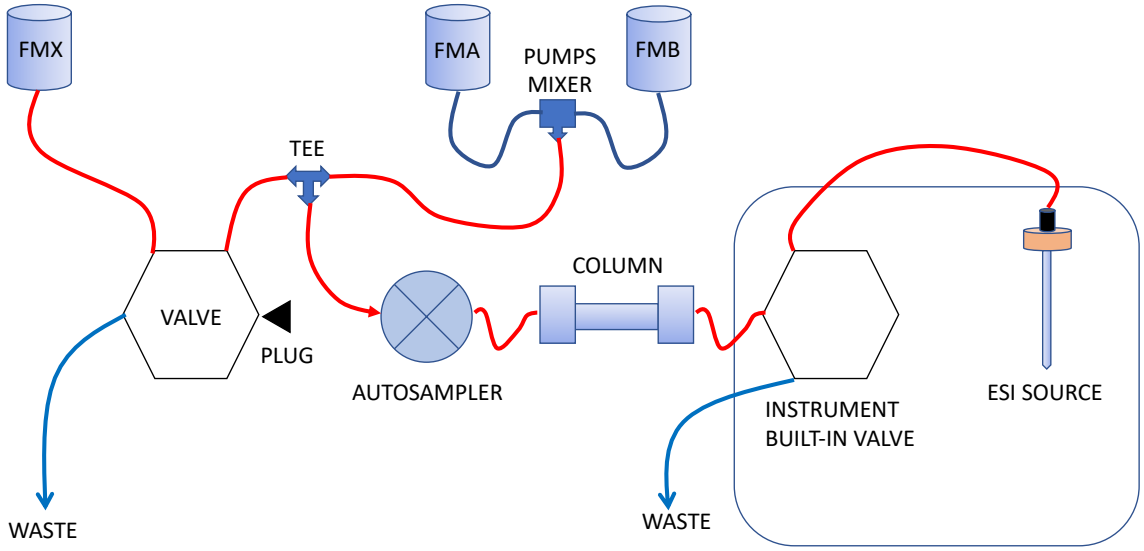

Figure 1: Arrangment of HPLC instrument

Stress tests on column showed that it is possible to carry out approximately 500 analysis in matrix with a single precolumn. It is recommended to perform some blank injections before each run and verify the backpressure values.

4 REQUIRED INSTRUMENTS

The kit requires a HPLC system with a tandem mass spectrometer and dedicated software. Triple quadrupole mass spectrometer should be of medium or medium-high level.

4.1 REQUIRED HPLC MODULES

1. Binary pump able to support a backpressure of 200 bar or more
2. Isocratic auxiliary pump
3. Autosampler with cooling function (10°C)
4. Column Heater (30°C)
5. Degasser

4.2 REQUIRED EQUIPMENT AND MATERIALS FOR THE SAMPLE PREPARATION

1. Centrifuge (13000 rpm) for 1.5- or 2-mL vials
2. Vortex
3. Pipettes and tips
4. 1.5- or 2-mL PP vials
5. Autosampler vials with plastic adapter for 200 µL
6. Chemical hood

5 HPLC-MS/MS SYSTEM CONDITIONS

Ionization: ESI positive mode
MS/MS: specific MRM
Injection volume: 1-10 µL (variable according to instrumental sensitivity)
Running time: 5 min
Column heater: 30°C

Chromatographic gradient

TIME (min)	%MPA	%MPB	TOTAL FLOW (mL/min)	HPLC VALVE	MPC FLOW (mL/min)	MASS SPEC VALVE
0.00	98	2	0.45	0	0.02	A
0.05			0.45			
0.10			1.50			B
0.75			1.50			
0.79			0.45			
0.80	98	2				A
1.30	5	95				
2.51			0.45			
2.52			0.00			
2.53					0.02	
2.54					1.00	
2.55				1		

TIME (min)	%MPA	%MPB	TOTAL FLOW (mL/min)	HPLC VALVE	MPC FLOW (mL/min)	MASS SPEC VALVE
3.30				0		
3.31					1.00	
3.32					0.02	
3.33			0.00			
3.34			1.50			
3.35	5	95				
3.36	98	2				
5.00	98	2	1.50	0	0.02	A

Table 5: Chromatographic gradient of kit EUM12100

Column conditioning: column should be conditioned for 5 min at chromatography gradient initial condition. Then run 3 blank injections (MPA only) using the gradient as above.

Backpressure: at a flow rate of 0.45 mL/min, chromatographic system backpressure should not exceed 150 bar.

Column storage: in order to preserve the column once detached from instrument, it is necessary to wash it with water/methanol (50:50) solution and insert it in the suitable package closing firmly with caps.

Example of chromatogram

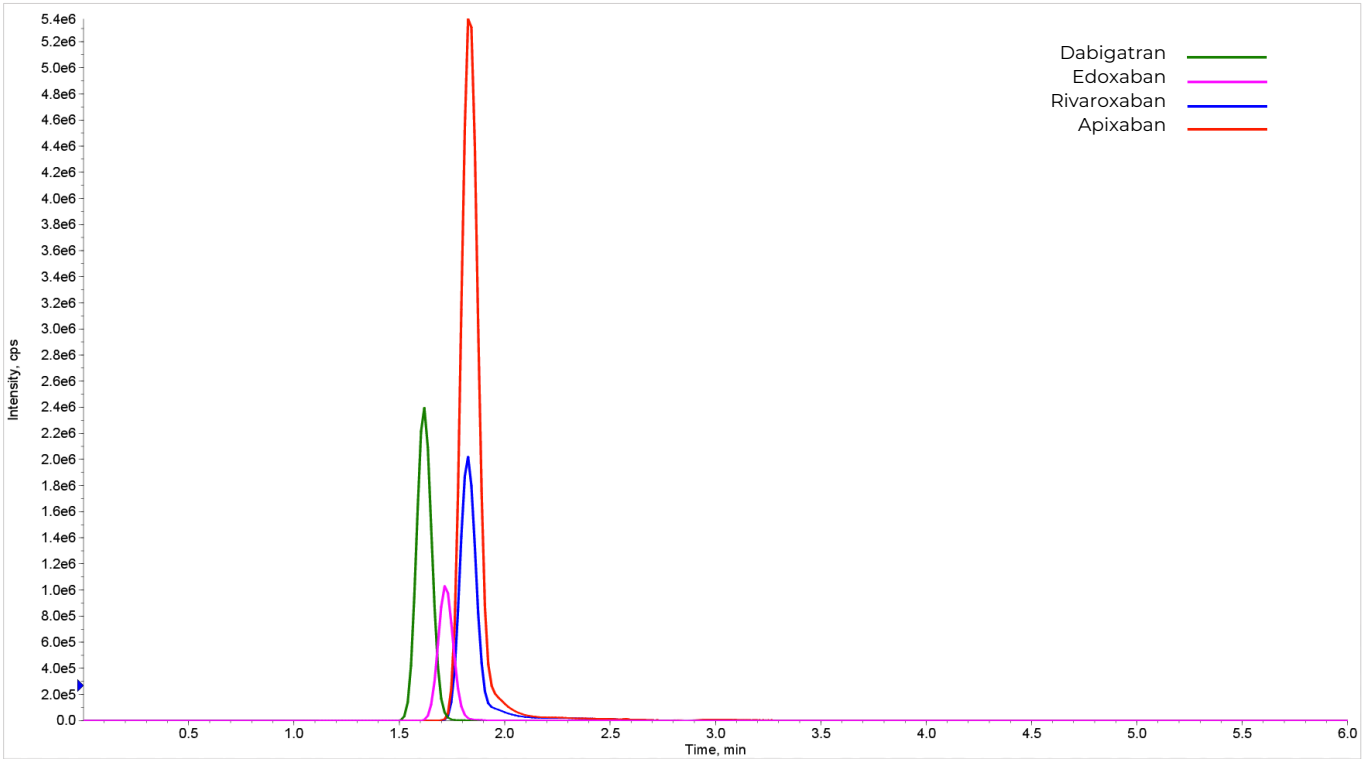

Figure 2: Example of chromatogram identified using kit EUM12100

6 SOURCE PARAMETERS AND TRANSITIONS

6.1 SOURCE PARAMETERS

Source parameters used in the MS method of EUM12100 kit with a Sciex series X500 triple quadrupole mass spectrometer are shown below.

Curtain Gas (CUR): 25 psi
Collision Gas Pressure (CAD): Medium
Ion Spray Voltage (IS): 5500 V
Temperature (TEM): 450°C
Gas 1 (GS1): 45 psi
Gas 2 (GS2): 50 psi

6.2 TRANSITIONS

Monitored transitions and the MS parameters for each analyte using a HPLC Shimadzu Nexera combined with the Sciex 4500 triple quadrupole mass spectrometer are shown in Table 6. ESI positive mode.

ANALYTE	TR	Q1	Q3	DP	EP	CE	CXP
Apixaban 1	1.82	460.2	443.3	110	10	34	10
Apixaban 2	1.82	460.2	199.2	110	10	46	10
Apixaban IS	1.82	469.2	452.2	110	10	34	10
Edoxaban 1	1.72	548.2	349.3	100	10	35	10
Edoxaban 2	1.72	548.2	366.2	100	10	28	10
Edoxaban IS	1.72	554.2	372.2	100	10	28	10
Rivaroxaban 1	1.80	436.1	145.0	100	10	40	10
Rivaroxaban 2	1.80	436.1	231.1	100	10	30	10
Dabigatran 1	1.62	472.1	289.0	100	10	40	10
Dabigatran 2	1.62	472.1	324.2	100	10	30	10
Dabigatran IS	1.62	478.1	295.0	100	10	40	10

Table 6: Detected transitions, retention times and potentials using HPLC Shimadzu + Sciex mass spectrometer

7 SAMPLE PREPARATION

Calibrators and controls follow the same sample preparation.

7.1 SAMPLE PREPARATION (CALIBRATOR/CONTROL)

1. Prepare a mix with 195 µL of Precipitant Solution (EUM12021) + 5 µL of Internal standard (EUM12031) sufficient for the number of samples to be analyzed
2. Resuspend 100 µL serum in a vial
3. Add 200 µL of Mix Solution obtained in step 1 of the procedure
4. Vortex for 30 sec
5. Incubate at room temperature for 10 min
6. Centrifuge at 12000 rpm for 10 min
7. Transfer supernatant into an auto samples vial
8. Inject 1-10 µL and analyze with HPLC-MS/MS technique

8 COLLECTION AND STORAGE OF THE SAMPLES

The kit is indicated for the analysis of human serum samples collected following standard methods such as those described in documents H18-A3 and H01-A5 of the Clinical and Laboratory Standards Institute (CLSI). [9,10] It is recommended to avoid using serum separator tubes because they can cause significant interferences with dosage system.

Stability of the samples: analytes keep their own values for 24 h if stored at room temperature, for 4-5 days at 2-8°C, or till 2 months at -20°C. Extracted sample are stable for 4-5 days at 2-8°C. [1,2]

8.1 EXPECTED VALUES AND RESULTS INTERPRETATION

Each laboratory should conduct a pilot study in order to determine the distribution of analyte concentrations in relation to its population. In order to establish the population dimension study, it is recommended to check CLSI document EP28-A3C. [11]
Reference values and normal ranges are set according to the distribution.

8.2 EXPECTED VALUES AND RESULTS INTERPRETATION

Therapeutic ranges of each NOAC are listed in Table 7 [12,13].

DRUG	DOSAGE/ TREATED DISEASE	PEAK RANGE (ng/mL)	TROUGH RANGE (ng/mL)
Dabigatran	150 mg	117 – 275	61 – 143
Rivaroxaban	20 mg	22 – 535	6 – 239
Apixaban	2.5 mg/VTE prevention	41 – 146	23 – 109
	2.5 mg/Ictus prevention	69 – 221	34 – 162

DRUG	DOSAGE/ TREATED DISEASE	PEAK RANGE (ng/mL)	TROUGH RANGE (ng/mL)
	5 mg/Ictus prevention	91 – 321	41 – 230
	2.5 mg/DVT treatment	30 – 153	11 – 90
	5 mg/DVT treatment	59 – 302	22 – 177
Edoxaban	30 mg	55 - 115	15 – 45
	60 mg	120 - 240	19 – 62

Table 7: Therapeutic ranges: peak and valley concentration. VTE: Venous thromboembolism; DVT: deep vein thrombosis

9 VALIDATION DATA

Validation data have been obtained with an HPLC-MS/MS system consisting of a HPLC Shimadzu Nexera coupled to a Sciex 4500 QTrap triple quadrupole mass spectrometer.
Refer to Paragraph 4.2 for materials and equipment used in the sample preparation.

9.1 LINEARITY, DETECTION LIMITS AND QUANTIFICATION

A linear regression analysis of real values concentration has been completed to evaluate linearity of calibration curve for each analytic session.
Linearity range of acceptability corresponds to $R^2 \geq 0.98$. All values obtained are higher than the above-mentioned value.
Detection limit (LLOD) and quantification limit (LLOQ), which concentration provide a peak with S/N>3 and S/N>10 respectively, are reported in the table below (Table 8).

ANALYTE	LLOD (ng/mL)	LLOQ (ng/mL)	LINEARITY (ng/mL)
Apixaban	0.060	0.210	0.210 – 1000
Edoxaban	0.090	0.310	0.310 – 1000
Rivaroxaban	0.060	0.210	0.210 – 1000
Dabigatran	0.120	0.410	0.410 – 1000

Table 8: LLOD, LLOQ and linearity

9.2 RECOVERY

Increasing amount of standard has been added to 3 real human serum pools in order to evaluate the analytical recovery characteristics. Three different levels of enriched serum (low, medium and high) have been obtained.

Recovery = (Measured quantity on enriched matrix - Measured quantity on non-enriched matrix) / Added quantity

Average recovery range of acceptability = ±20%, all the values obtained are higher than the above-mentioned value.

ANALYTE	AVERAGE RECOVERY (%)	MIN RECOVERY (%)	MAX RECOVERY (%)
Apixaban	97.6	90.0	106.8
Edoxaban	104.6	90.9	116.7
Rivaroxaban	95.5	81.3	106.4
Dabigatran	98.3	82.5	111.8

Table 9: Average, minimum and maximum recovery values

9.3 PRECISION

Average concentration values (ng/mL) measured in 3 pools enriched with increasing concentrations of analytes (low, medium and high level) are reported in Table 10.
Precision has been evaluated as intra-assay, inter-assay and total coefficient of variation.

Intra-assay precision has been determined assaying 10 replicates (n=10) of each sample.
Inter-assay precision has been determined assaying 3 repetitions in 8 analytical series (n=24) of each sample.

Total CV% = $(CV\%Intra^2 + CV\%Inter^2)^{1/2}$

Range of acceptability used for each variation coefficient are reported below.
Range of acceptability CV% Intra-assay = 10%
Range of acceptability CV% Inter-assay = 20%
Range of acceptability CV% Total = 20%

Obtained results respect the imposed ranges of acceptability.

ANALYTE	AVERAGE CONC. (ng/mL)			CV% INTRA			CV% INTER			CV% TOTAL		
	Low	Medium	High	Low	Medium	High	Low	Medium	High	Low	Medium	High
Apixaban	1.32	22.3	268	4.1%	4.2%	4.1%	10.3%	5.8%	4.0%	11.0%	7.2%	5.7%
Edoxaban	5.60	29.1	308	6.0%	4.2%	4.5%	5.7%	12.7%	10.0%	8.3%	13.4%	11.0%
Rivaroxaban	2.54	23.8	284	3.3%	5.2%	5.1%	14.3%	10.5%	8.8%	14.7%	11.7%	10.2%
Dabigatran	2.08	21.0	271	7.2%	2.3%	4.3%	13.4%	4.1%	3.0%	15.2%	4.7%	5.2%

Table 10: Intra-assay, inter-assay and total precision

10 GENERAL LIMITATIONS

- Kit must be used with the calibrators and the internal standard indicated in the kit instructions. The use of other standards or materials with this kit has not been validated.

- The use of other mobile phases, solutions or reagents other than those indicated in Paragraph 3.1 “KIT CONTENTS” has not been validated.
- The kit has been validated with configuration described in Chapter 9 “VALIDATION DATA”. The use of other triple quadrupole systems, HPLC systems and columns, which may require further development of the method, has not been validated.
- Do not use the kit after the expiry date of its components.

11 REFERENCES

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ANNEX 1: EC DECLARATION OF CONFORMITY

BSN Srl as Manufacturer and the only responsible for in-vitro diagnostic medical devices placed on the market under his own name, declares that these products meet all the provisions of the Legislative Decree n. 332 of the 8th September 2000, directive of in vitro diagnostic medical device 98/79/EC (in particular with regard to annex I) and subsequent amendments and additions. According to article 9 of the Legislative Decree 332/2000 and similar, this device belongs to the fourth class of devices, GENERIC IN VITRO DIAGNOSTIC MEDICAL DEVICES (all the other in vitro diagnostic medical devices except those in annex II and self-diagnostic tests).

NOME	CODIFICA	ORGANISMO DI CERTIFICAZIONE
FloMass NOAC in Serum	EUM12100	CE-IVD marked medical device according to Annex III
Mobile Phase A	EUM12011	CE-IVD marked medical device according to Annex III
Mobile Phase B	EUM12012	CE-IVD marked medical device according to Annex III
Mobile Phase C	EUM12013	CE-IVD marked medical device according to Annex III
Precipitant Solution	EUM12021	CE-IVD marked medical device according to Annex III
Internal Standard Mix for NOAC in Serum	EUM12031	CE-IVD marked medical device according to Annex III
7-Levels Calibrators, lyophil	EUM12041	CE-IVD marked medical device according to Annex III
3-Levels Controls, lyophil.	EUM12051	CE-IVD marked medical device according to Annex III
Chromatographic column	EUM00C12	CE-IVD marked medical device according to Annex III

Quality assurance system complying with the following directive:
UNI CEI EN ISO 13485:2016
UNI EN ISO 9001:2015

This declaration becomes invalid if modifications are introduced without B.S.N. Srl consent.
It is declared that the product is placed on the market in non-sterile package.

It is declared that B.S.N. Srl will keep all documents referred to in Annex III of the European Directive 98/79/EC at the disposal of the competent authorities for a 5-year period from the last date of production of the kit.

After the placing on the market of the product in question, it is declared that the Manufacturer has notified the competent authority of the application of post-market surveillance as requested from the European Directive 98/79/CE.

Castelleone (CR), 22 April 2022 Director