BSN
Biological Sales Network

FloMass Biogenic Amines in Plasma

Reagents for 100 assays

Instruction Manual

REF **EUM23100**

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

CE

PROVIDE PERSONAL SOLUTIONS

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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, SPE loading
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 Biogenic Amines in Plasma is an in vitro diagnostic kit intended for the quantitative and simultaneous determination of eight analytes in human plasma samples (Table 1) using high performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS).

ANALYTE
Adrenaline
Noradrenaline
Dopamine
Metanephrine
Normetanephrine
3-Methoxytyramine
Serotonine
L-DOPA

Table 1: Analytes measured by EUM23100 FloMass Biogenic Amines in Plasma

Catecholamines (Adrenaline, Noradrenaline and Dopamine) are neurotransmitters produced by the adrenal gland. Once released in the body, they induce physiological changes including an increase in heart rate and blood pressure. The release of these molecules also involves bronchodilation, tachypnea and reduction of insulin resulting in the release of glucagon which is converted into blood glucose.
However, their excessive production in the blood can be a symptom of pheochromocytoma, neuroblastoma and, occasionally, of other neuroectodermal tumors.
Serotonin is a neurotransmitter produced at the gastrointestinal level, mainly involved in the sleep/wake cycle, hunger/satiety, intestinal motility, mood, memory and libido. It is also considered the molecule that regulates good mood and for this reason it is also known as the "happiness hormone".
A lack of serotonin leads to fibromyalgia, a disease characterized by pain and perennial muscle tension, at the origin of stiffness and difficulty in movements. An excess of serotonin instead leads to serotonin syndrome, characterized by headache, agitation, confusion, tremors, muscle twitching, chills, tachycardia, sweating, nausea and diarrhea.
L-DOPA is the precursor of Dopamine, from which all the other Biogenic Amines are then produced through the enzymatic activity of the organism. It is also administered to mitigate the effects of Parkinson's disease, as this disease leads to a progressive decrease in dopamine production due to the degradation of neurons present in the “substantia nigra” [1-7].

2 PRINCIPLE OF THE METHOD

The kit is intended for the quantitative and simultaneous determination of Biogenic Amines in human plasma samples using high performance liquid chromatography 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 standards marked with stable isotopes are added (Table 2).

ANALYTE	INTERNAL STANDARD
Adrenaline	Adrenaline $^{2}H_{6}$
Noradrenaline	Noradrenaline $^{2}H_{6}$
Dopamine	Dopamine $^{2}H_{4}$
Metanephrine	Metanephrine $^{2}H_{3}$
Normetanephrine	Normetanephrine ^{13}C $^{2}H_{3}$
3-Methoxytyramine	3-Methoxytyramine ^{13}C $^{2}H_{5}$
Serotonin	Serotonin $^{2}H_{4}$
L-DOPA	L-DOPA $^{2}H_{3}$

Table 2: Analytes measured by kit EUM23100 and related internal standards

The sample preparation involves a step to functionalize molecules improving the ionization yield. This ensures greater applicability of the method even on high-range spectrometers. Next step involves a precipitation step to eliminate the proteins contained in the plasma.
Given the resulting high salinity and a small quantity of residual proteins of the treated sample, chromatography is performed preceded by an on-line SPE to ensure sample cleanliness. Then, analytes are automatically transferred to an analytical column where they are separated. 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 into 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 chromatographic separation ensures high selective and sensitive analytes identification and quantification [1-6,8,9].

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
EUM22011	Mobile Phase A	500 mL	Room Temperature
EUM22012	Mobile Phase B	300 mL	Room Temperature
EUM22013	Mobile Phase C SPE Loading	1000 mL	Room Temperature
EUM23021	Diluting Solution	6 mL	Room Temperature*
EUM23022	Precipitant Solution	1.2 mL	Room Temperature**
EUM23023	Buffer Solution	30 mL	Room Temperature*
EUM23024	Reagent Solution	6 mL	Room Temperature*
EUM23031	Internal Standard Mix for Biogenic Amines in Plasma	150 µL	-20°C

Table 3: Components, description, quantity and storage of kit EUM23100

*After opening, keep the solutions in tightly closed vial. Store at 2-8°C.
**Store the solution exclusively at Room Temperature

The kit consists of reagents for 100 assays.
The expiry date of the intact kit is shown on the external product label. Follow the 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
EUM23041	7-Levels Calibrators, lyophil.	2 x 7 x 1.0 mL	-20°C
EUM23051	2-Levels Controls, lyophil.	2 x 2 x 1.0 mL	-20°C
EUM00C22	Chromatographic Column	1 pc	Room Temperature
EUM00S02	Loading Column	1 pc	Room Temperature
EUM00P01	Green Peek	1 pc	Room Temperature
EUM23026	Washing Solutions A and B	2 x 5 mL	Room Temperature

Table 4: Accessories, description, quantity and storage of kit EUM23100

3.3 CONTROLS AND CALIBRATION OF ANALYTICAL SYSTEM

Calibration should be done using 7-Levels Calibrators (EUM23041) 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 two different concentration levels (EUM23051).

Lyophilized controls in urinary matrix are useful to verify the accuracy and precision of the analytical procedures and for the proper determination of analytes in matrix. For analytes concentrations, stability and accessories preparation, refer to package leaflet.

3.4 CHROMATOGRAPHIC SYSTEM

The kit has been validated using analytical column (EUM00C22) coupled to the loading column (EUM00S02).

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-high level.

4.1 REQUIRED HPLC MODULES

1. Binary pump able to support a backpressure of 400 bar or more
2. Additional pump
3. Autosampler with at least 100 µL loop and cooling function (8°C)
4. Column thermostating chamber (45°C) with 6-way switching valve
5. Red peek tubes, fittings Peek in order to make connections using switching valve in column thermostating chamber
6. Degasser for modules 1 and 2

4.2 REQUIRED EQUIPMENT AND MATERIALS FOR SAMPLE PREPARATION

1. Centrifuge (10000-12000 rpm) for 1.5- or 2-mL vials
2. Vortex for vials
3. Pipettes and tips
4. 1.5- or 2-mL PP vials
5. Autosampler vials with plastic adapter for 200 µL
6. Orbital shaker
7. Chemical hood
8. Freezer that can reach -20 °C

5 HPLC-MS/MS SYSTEM CONDITIONS

Ionization: ESI positive mode
MS/MS: specific MRM
Injection Volume: 50-95 µL (variable according to instrumental sensitivity)
Running Time: 12 min
Column Heater: 45 °C
Analytical Column Flow: 0.3 mL/min
Depth of injection: 3 mm from the cuvette bottom
Autosampler thermostatation: 15 °C

Chromatographic gradient

TIME (min)	%MPB	FMC Flow (mL/min)	Valve
0.00	20	0.30	0
0.10		1.50	
1.95		1.50	
1.96		0.30	
2.00			1
2.05	20		
2.10		0.30	
2.15		0.15	
8.00	45		
8.25	95		
9.80		0.15	
9.95		0.30	
10.00			0
10.25	95		
10.30	2		
11.90		1.50	
11.95	20		
12.00	stop		

Table 5: Chromatographic gradient of kit EUM23100

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

Backpressure: using a flow rate of 0.3 mL/min, precolumn-column system backpressure should not exceed 150 bar.

Column storage: in order to preserve analytical or loading columns once detached from instrument, it is necessary to leave them in the initial conditions of the chromatographic gradient and insert them in the suitable package closing firmly with caps.

Loading Column Washing: to increase the lifespan of the column and improve the chromatography performance it is advisable to use Washing Solutions A and B (EUM23026), applying the chromatographic washing method described in the technical data sheet associated with the solutions.

Example of chromatogram

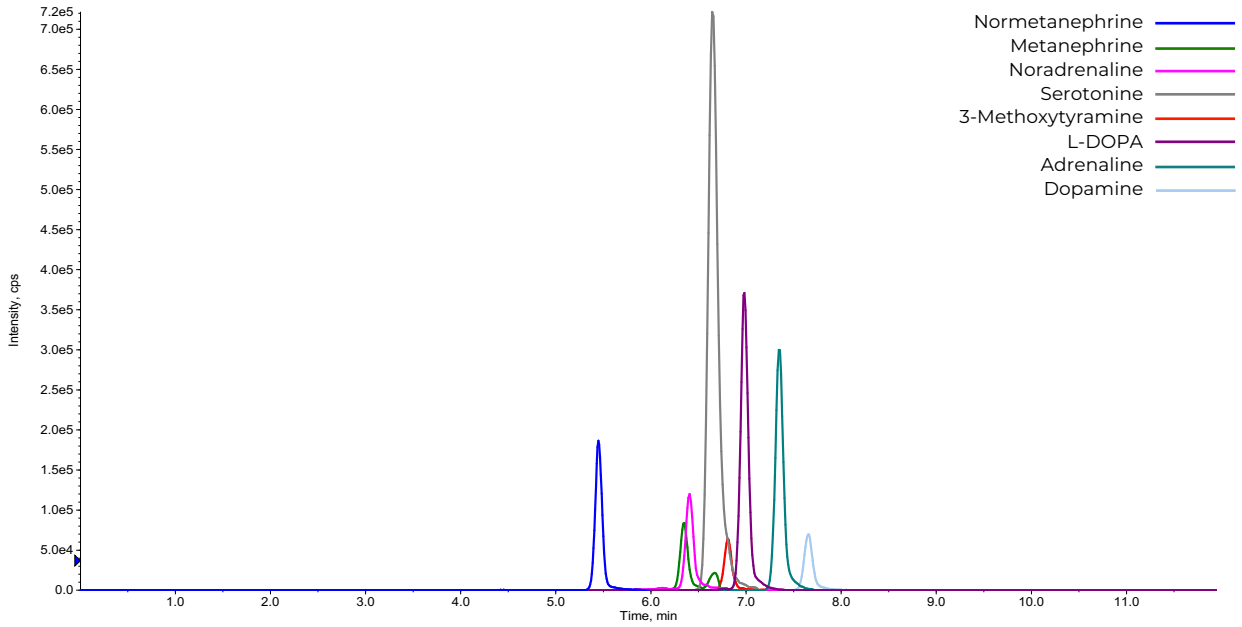

Figure 1: Example of chromatogram identified using kit EUM23100

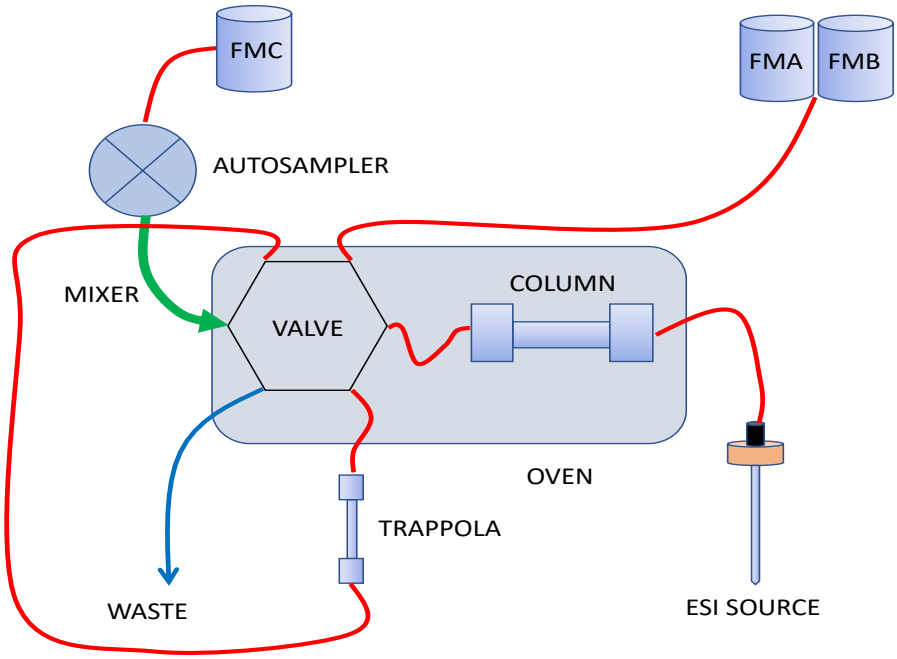

Figure 2: Plumbing configuration

6 SOURCE PARAMETERS AND TRANSITIONS

6.1 SOURCE PARAMETERS

Source parameters used in MS Method of kit EUM23100 with a Sciex series X500 triple quadrupole mass spectrometer are shown below.

Curtain Gas (CUR): 30 psi
Collision Gas Pressure (CAD): Medium
Ion Spray Voltage (IS): 5500 V
Temperature (TEM): 450°C
Gas 1 (GS1): 50 psi
Gas 2 (GS2): 40 psi

6.2 TRANSITIONS

Monitored (1) and confirm (2) transitions and the MS parameters for each analyte using a HPLC Shimadzu Nexera combined with the Sciex 6500 triple quadrupole mass spectrometer are shown in Table 6. ESI positive mode.

ANALYTE	TR	Q1	Q3	DP	EP	CE	CXP
Adrenaline 1	7.3	334.2	222.1	100	6	30	14
Adrenaline 2	7.3	334.2	278.1	100	6	20	14

ANALYTE	TR	Q1	Q3	DP	EP	CE	CXP
Adrenaline IS	7.3	340.2	228.1	100	6	30	14
Noradrenaline 1	6.4	320.2	264.2	90	6	15	14
Noradrenaline 2	6.4	320.2	152.1	90	6	35	14
Noradrenaline IS	6.4	326.2	270.2	90	6	15	14
Dopamine 1	7.6	322.2	266.2	70	6	25	14
Dopamine 2	7.6	322.2	137.1	70	6	50	14
Dopamine IS	7.6	326.2	141.1	70	6	50	14
Metanephrine 1	6.3	292.2	180.1	90	6	30	14
Metanephrine 2	6.3	292.2	236.1	90	6	20	14
Metanephrine IS	6.3	295.2	183.1	90	6	30	14
Normetanephrine 1	5.4	278.2	166.1	70	6	25	14
Normetanephrine 2	5.4	278.2	222.1	70	6	15	14
Normetanephrine IS	5.4	282.2	226.1	70	6	15	14
3-Methoxytyramine 1	6.8	280.2	151.1	60	6	30	14
3-Methoxytyramine 2	6.8	280.2	224.1	60	6	20	14
3-Methoxytyramine IS	6.8	286.2	157.1	60	6	30	14
Serotonin 1	6.6	290.2	160.1	70	6	20	14
Serotonin 2	6.6	290.2	216.1	70	6	25	14
Serotonine IS	6.6	294.2	164.1	70	6	20	14
L-DOPA 1	7.0	366.2	152.1	60	6	40	14
L-DOPA 2	7.0	366.2	208.1	60	6	22	14
L-DOPA IS	7.0	369.2	155.1	60	6	40	14

Table 6: Detected transitions, retention times and potentials using HPLC Shimadzu + 6500 Sciex mass spectrometer

7 SAMPLE PREPARATION

Calibrators and controls follow the same sample preparation.

7.1 SAMPLE PREPARATION (CALIBRATOR AND/OR CONTROL)

1. Prepare a mix with 1 µL of Internal Standard Mix (EUM23031) + 49 µL of Diluting Solution (EUM23021) sufficient for the number of samples to be analyzed
2. Add 50 µL of plasma in a vial
3. Add 50 µL of Mix solution obtained in step 1 of the procedure and vortex for 5 sec
4. Add 250 µL of Buffer Solution (EUM23023)
5. Add 50 µL of Reagent Solution (EUM23024)
6. Put it in orbital shaker for 15 min at room temperature
7. Add 10 µL of Precipitant Solution (EUM23022)

8. Vortex for 5 sec
9. Incubate the tube at -20 °C for at least 10 min
10. Centrifuge at 12000 rpm for 10 min
11. Transfer all supernatant to an autosampler vial
12. Inject 50-95 µL and analyze with HPLC-MS/MS technique

8 COLLECTION AND STORAGE OF THE SAMPLES

The kit is indicated for the analysis of human plasma samples collected following standard methods, such as those described in documents H18-A3 and H01-A5 of Clinical and Laboratory Standards Institute (CLSI) [10,11]. It is recommended to draw blood with the patient in the supine position and immediately centrifuge the sample to separate plasma.

Stability of the samples:

- Cathecolamines (Adrenaline, Noradrenaline and Dopamine) remain stable for at least 24h if samples are stored at room temperature, for at least 48h if samples are stored at 2-8 °C and for at least one month if samples are stored at -20 °C [12].
- Metanephrines (Metanephrine, Normetanephrine and 3-Methoxytyramine) remain stable for at least 3 days if samples are stored at room temperature, for at least 7 days if samples are stored at 2-8 °C and for at least 3 months if samples are stored at -20 °C [13].
- Serotonin remains stable for at least 5h if samples are stored at room temperature, for at least 24h if samples are stored at 2-8 °C and for at least 3 months if samples are stored at -20 °C [14].
- L-DOPA remains stable for at least 7h if samples are stored at room temperature, for at least 24h if samples are stored at 2-8 °C and for at least 3 months if samples are stored at -20 °C [15].

8.1 EXPECTED VALUES AND RESULTS INTERPRETATION

Each laboratory should conduct a pilot study in order to determine the distribution of analytes concentrations in relation to its population. In order to establish the population dimension study, it is recommended to check CLSI document EP28-A3C [16].
Reference values and normal ranges are set according to the distribution.

8.2 REFERENCE RANGES

Catecholamines, free Metanephrines and Serotonin reference ranges in adults are listed in Table 7.

ANALYTE	REFERENCE VALUES
Adrenaline	< 200 ng/L
Noradrenaline	70.0 - 676 ng/L
Dopamine	< 30.0 ng/L
Metanephrine	10.0 – 90.0 ng/L
Normetanephrine	20.0 - 150 ng/L
3-Methoxytyramine	< 20.0 ng/L
Serotonin	40.0 - 200 µg/L
L-DOPA	1.00 – 7.00 µg/L

Table 7: Analytes reference values

Note: reference ranges are taken from selected and updated scientific literature. Their update corresponds to the date of revision of this document [5-7].
Reference ranges are not a recommendation by the manufacturer, but they can be used as guideline for own reference ranges of each clinical laboratory.

9 VALIDATION DATA

Validation data have been obtained with an HPLC-MS/MS system consisting of a HPLC Shimadzu Nexera coupled to a Sciex 6500 QTrap triple quadrupole mass spectrometer.
Refer to Paragraph 4.2 for the 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 (LOD) and quantification limit (LLOQ), which concentration provide a peak with S/N>3 and S/N>10 respectively, (Table 8).

ANALYTE	UNIT OF MEASURE	LOD	LLOQ	LINEARITY
Adrenaline	ng/L	0.446	1.49	1.49 – 10000
Noradrenaline	ng/L	1.81	6.02	6.02 – 40000
Dopamine	ng/L	0.350	1.17	1.17 – 4000
Metanephrine	ng/L	0.623	2.08	2.08 – 4000
Normetanephrine	ng/L	0.530	1.77	1.77 – 10000
3-Methoxytyramine	ng/L	0.173	0.578	0.578 – 2000
L-DOPA	µg/L	0.014	0.046	0.046 – 500
Serotonin	µg/L	0.376	1.25	1.25 – 10000

Table 8: LOD, LLOQ and linearity

9.2 RECOVERY

Increasing amount of standard has been added to 3 real plasma pools in order to evaluate the analytical recovery characteristics. Three different levels of enriched serum (low, medium and high level) 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 (%)
Adrenaline	99.8	95.1	102.3
Noradrenaline	102.2	93.0	108.9
Dopamine	99.8	92.2	102.6
Metanephrine	97.8	91.4	104.4
Normetanephrine	98.0	93.7	101.3
3-Methoxytyramine	94.2	89.1	103.2
L-DOPA	100.5	95.3	104.4
Serotonin	101.8	95.8	105.1

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 (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) for each sample.

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

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	UNIT OF MEASURE	AVERAGE CONC.			CV% INTRA			CV% INTER			CV% TOTAL		
		Low	Medium	High	Low	Medium	High	Low	Medium	High	Low	Medium	High
Adrenaline	ng/L	197	501	1477	2.0%	2.4%	2.4%	5.5%	9.0%	4.5%	5.9%	9.3%	5.1%
Noradrenaline	ng/L	799	2046	6123	2.5%	2.0%	2.4%	4.2%	3.5%	4.9%	4.9%	4.1%	5.5%
Dopamine	ng/L	78.0	201	592	3.5%	3.5%	2.7%	10.3%	3.7%	3.9%	10.9%	5.1%	4.7%
Metanephrine	ng/L	81.6	198	584	4.1%	4.3%	2.5%	6.2%	4.4%	4.8%	7.5%	6.1%	5.4%
Normetanephrine	ng/L	195	486	1443	2.7%	2.2%	1.9%	4.2%	12.3%	4.4%	5.0%	12.5%	4.8%
3-MT	ng/L	35.8	92.2	282	3.2%	4.1%	1.8%	5.8%	3.2%	5.0%	6.6%	5.2%	5.3%
L-DOPA	µg/L	10.0	25.1	74.5	2.9%	2.6%	2.2%	4.4%	3.5%	4.2%	5.3%	4.4%	4.7%
Serotonin	µg/L	202	518	1543	1.8%	1.2%	1.6%	3.6%	3.5%	4.0%	4.0%	3.7%	4.3%

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 the 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.

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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).

COMPONENT	CODE	CERTIFICATION
FloMass Ammine Biogene in Plasma	EUM23100	CE-IVD marked medical device according to Annex III
Mobile Phase A	EUM22011	CE-IVD marked medical device according to Annex III
Mobile Phase B	EUM22012	CE-IVD marked medical device according to Annex III
Mobile Phase C	EUM22013	CE-IVD marked medical device according to Annex III
Diluting Solution	EUM23021	CE-IVD marked medical device according to Annex III
Precipitant solution	EUM23022	CE-IVD marked medical device according to Annex III
Buffer Solution	EUM23023	CE-IVD marked medical device according to Annex III
Reagent Solution	EUM23024	CE-IVD marked medical device according to Annex III
Internal Standard Mix for Biogenic Amines in Plasma	EUM22031	CE-IVD marked medical device according to Annex III
Biogenic Amines Calibrators	EUM23041	CE-IVD marked medical device according to Annex III
Biogenic Amines Control	EUM23051	CE-IVD marked medical device according to Annex III
Chromatographic Column	EUM00C22	CE-IVD marked medical device according to Annex III
Loading Chromatographic Column	EUM00S02	CE-IVD marked medical device according to Annex III
Green Peek	EUM00P01	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.

This declaration is valid five years from the date of issue.

Castelleone (CR), 6 May 2022 Director