# FloMass Total Metanephrines in Urine

## Reagents for 100 assays

# Instruction Manual

REF **EUM18100**

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*


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


Batch code / Code du lot / Chargenbezeichnung / Código de lote / Codice del lotto / Código do lote / Número do lote / Lotnummer


Packing number / Numéro d'emballage / Packnummer / Número de envase / Numero confezioni / Número de embalagem / Número de embalagem / Emballagenummer


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
MRM: Multiple Reaction Monitoring
Q1: Quadrupole 1
Q3: Quadrupole 3
RT: Retention Time
S/N: Signal/Noise ratio
SPE: Solid Phase Extraction
TEM: Source Temperature

## 1.3 CLINICAL APPLICATION

FloMass Total Metanephrines in Urine is an in vitro diagnostic kit intended for the quantitative and simultaneous determination of 3 analytes in human urine sample (Table 1) using high performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS).

| ANALYTE |
|---|
| Metanephrine |
| Normetanephrine |
| 3-Methoxytyramine |

Table 1: Analytes measured by FloMass Total Metanephrines in Urine

Metanephrines (Metanephrine, Normetanephrine and 3-Methoxytyramine) are molecules obtained by Catecholamines metabolism (Epinephrine, Norepinephrine and Dopamine) and their amount is linked to pheochromocytoma or others neuroendocrine tumors [1-6].

# 2 PRINCIPLE OF THE METHOD

The kit is intended for the quantitative and simultaneous determination of total Metanephrines in human urine 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 |
|---|---|
| Metanephrine | Metanephrine $^{2}H_3$ |
| Normetanephrine | Normetanephrine $^{13}C$ $^{2}H_3$ |
| 3-Methoxytyramine | 3-Methoxytyramine $^{13}C$ $^{2}H_5$ |

Table 2: Analytes measured by kit EUM18100 and related internal standards

The analytes are isolated from urine samples by a combined method of hydrolysis and SPE column extraction [7-8].
Once extracted, analytes are chromatographically separated by a specific reverse phase column. Subsequently, they enter in ESI source where they are transferred into 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 by the third quadrupole for subsequent detection.
Measurement in MRM mode with HPLC chromatographic separation ensures high selective and sensitive analytes identification and quantification [1-8].

# 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 |
|---|---|---|---|
| EUM17011 | Mobile Phase A | 500 mL | Room temperature |
| EUM17012 | Mobile Phase B | 500 mL | Room temperature |
| EUM18021 | Hydrolyzing Reagent | 1.5 mL | Room temperature |
| EUM18022 | Complexing Reagent | 65 mL | Room temperature |
| EUM18023 | pH Corrector Reagent | 25 mL | Room temperature |
| EUM18024 | SPE Activating Reagent | 110 mL | Room temperature |

| CATALOG NUMBER | DESCRIPTION | QUANTITY | STORAGE |
|---|---|---|---|
| EUM18025 | SPE Conditioning Reagent | 110 mL | Room temperature |
| EUM18026 | SPE Washing Reagent | 110 mL | Room temperature |
| EUM18027 | SPE Eluting Reagent | 65 mL | Room temperature |
| EUM18031 | Internal Standard Mix | 2 x 1.0 mL | -20°C |
| EUM18061 | SPE Columns | 100 pcs | Room temperature |

Table 3: Components, description, quantity and storage of kit EUM18100

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 |
|---|---|---|---|
| EUM17041 | 7-Levels Calibrators | 2 x 7 x 1.0 mL | -20°C |
| EUM17051 | 2-Levels Unique Controls for Biological Amines | 2 x 2 x 2.0 mL | -20°C |
| EUM18062 | Hydrolysis tubes with caps | 100 pcs | Room temperature |
| EUM00C17 | Chromatographic Column | 1 pc | Room temperature |
| EUM00A14 | Precolumn | 4 pcs | Room temperature |
| EUM00A15 | Holder + precolumn | 1 pc | Room temperature |

Table 4: Accessories, description, quantity and storage of kit EUM18100

## *3.3 CONTROLS AND CALIBRATION OF ANALYTICAL SYSTEM*

Calibration should be done using 7-Levels Calibrators (EUM08041) 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 (EUM18051). Urinary matrix Quality Lyophilized controls in urinary matrix are useful to verify the accuracy and precision of the analytical procedures. For analytes concentrations, stability and accessories preparation, refer to package leaflet.

### *3.4 CHROMATOGRAPHIC SYSTEM*

The kit has been validated using analytical column (EUM00C17) coupled to the precolumn (EUM00A14) and its holder (EUM00A15).
Stress tests on column showed that it is possible to carry out approximately 200-250 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-high level.

### *4.1 REQUIRED HPLC MODULES*

1. Binary pump able to support a backpressure of 400 bar or more
2. Autosampler with cooling function (10°C)
3. Column oven (50°C)
4. Degasser

### *4.2 REQUIRED EQUIPMENT AND MATERIALS FOR SAMPLE PREPARATION*

1. Centrifuge (10000-13000 rpm) for 1.5- or 2.0-mL vials
2. Vortex for vials
3. Pipettes and tips
4. 1.5- or 2.0-mL 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:** MRM specific
**Injection Volume:** 1 µL (variable according to the instrumental sensitivity)
**Running Time:** 3.2 min
**Column Oven:** 45°C

**Chromatographic gradient**

| TIME (min) | %MPA | %MPB | FLOW (mL/min) |
|---|---|---|---|
| 0 | 98 | 2 | 1.2 |
| 0.35 | 98 | 2 | 1.2 |
| 1 | 75 | 25 | 1.2 |
| 1.2 | 5 | 95 | 1.2 |
| 2.15 | 5 | 95 | 1.2 |
| 2.16 | 98 | 2 | 1.2 |
| 3.2 | 98 | 2 | 1.2 |
| 3.21 | Stop | Stop | Stop |

Table 5: Chromatographic gradient of kit EUM18100

**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 1.2 mL/min, chromatographic system backpressure should not exceed 200 bar.

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

**Example of chromatogram**

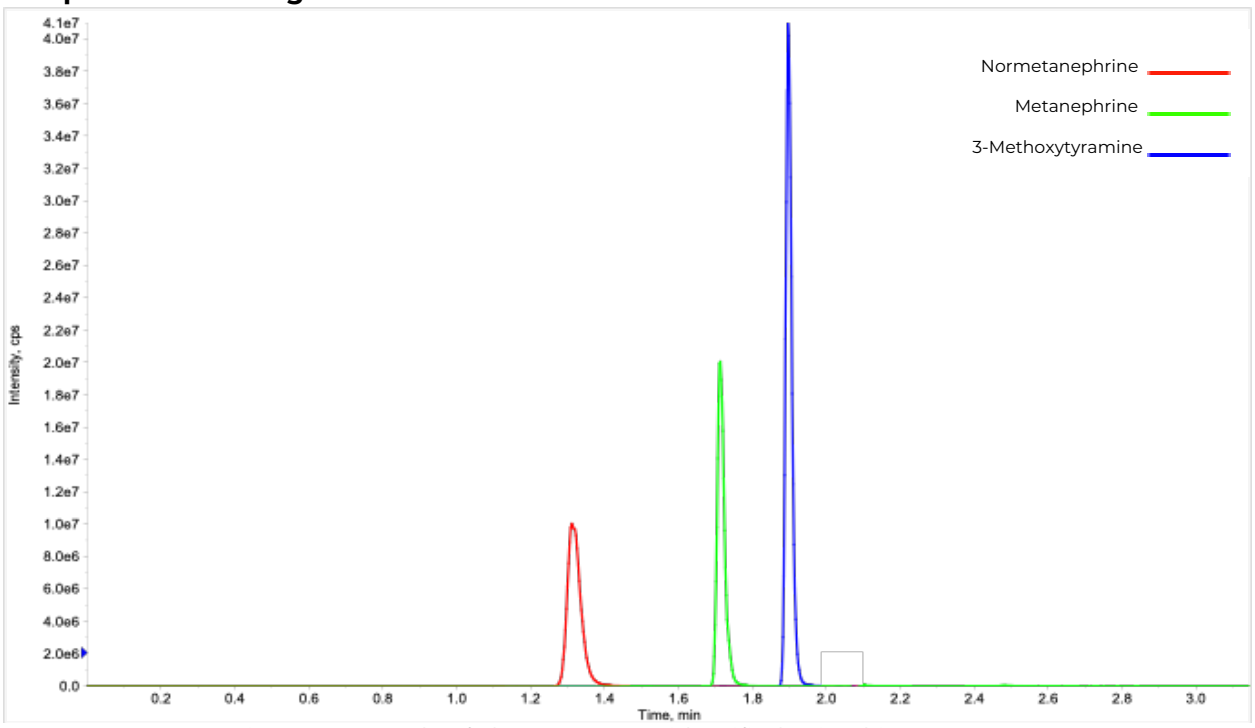


Figure 1: Example of chromatogram identified using kit EUM18100

# 6 SOURCE PARAMETERS AND TRANSITIONS

## *6.1 SOURCE PARAMETERS*

Source parameters used in MS Method of kit EUM18100 with a Sciex series X500 QTrap mass spectrometer are shown below.

**Curtain Gas (CUR):** 25 psi
**Collision Gas Pressure (CAD):** Medium
**Ion Spray Voltage (IS):** 5500 V
**Temperature (TEM):** 550°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 whid the Sciex series X500 QTrap mass spectrometer are shown in Table 6. ESI positive mode.

| ANALYTE | RT | Q1 | Q3 | DP | EP | CE | CXP |
|---|---|---|---|---|---|---|---|
| Metanephrine 1 | 1.7 | 180.1 | 165.1 | 60 | 10 | 26 | 10 |
| Metanephrine 2 | 1.7 | 180.1 | 148.1 | 60 | 10 | 26 | 10 |
| Normetanephrine 1 | 1.3 | 166.1 | 134.1 | 45 | 10 | 24 | 10 |
| Normetanephrine 2 | 1.3 | 166.1 | 121.1 | 45 | 10 | 25 | 10 |
| 3-Methoxytyramine 1 | 1.9 | 151.1 | 119.1 | 60 | 10 | 20 | 10 |
| 3-Methoxytyramine 2 | 1.9 | 151.1 | 91.0 | 60 | 10 | 28 | 10 |
| Metanephrine IS | 1.7 | 183.1 | 151.1 | 60 | 10 | 25 | 10 |
| Normetanephrine IS | 1.3 | 170.1 | 125.1 | 45 | 10 | 24 | 10 |
| 3- Methoxytyramine IS | 1.9 | 157.1 | 93.0 | 60 | 10 | 28 | 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. Pipette 200 µL of urine (if human, preserved with 0.1% HCl) in a hydrolysis tube with cap. Then add 10 µL of Hydrolyzing Reagent (EUM18021) and incubate at 90°C for 25 min
2. Prepare a mix with 600 µL of Complexing Reagent (EUM18022) + 20 µL of Internal Standard Mix (EUM18031) sufficient for the number of samples to be analyzed
3. After cooling, add 620 µL of the Mix solution obtained in step 2 of the procedure to each vial
4. Add 200 µL of pH Correcting Reagent (EUM18023)
5. Vortex for 30 sec
6. Condition the SPE Column (EUM18061) with 1 mL of SPE Activating Reagent (EUM18024) followed by 1mL of SPE Conditioning Reagent (EUM18025)
7. Load all the sample onto the SPE Column and allow it to elute without applying vacuum
8. Add 1 mL of SPE Washing Reagent (EUM18026) and apply full vacuum for 30 sec dehydrating the SPE Column
9. Elute the analytes with 600 µL of SPE Eluting Reagent (EUM18027), if necessary, apply vacuum
10. Transfer 200 µL of eluate to an autosampler vial
11. Inject 1-20 µL according to the instrumental sensitivity and analyze with HPLC-MS/MS technique

## 8 COLLECTION AND STORAGE OF SAMPLES

The kit is intended for the analysis of human urine samples collected following standard methods, such as those described in document GP16-A3 of the Clinical and Laboratory Standards Institute (CLSI) [9]. The measurement should be performed on 24 hours' urine samples without using any preserving agent.

**Stability of the samples:** urinary Catecholamines and their metabolites are stable at acid pH. Metanephrines are more stable than catecholamines. In the dark, urine samples are stable for 24 hours at room temperature, for 7 days at 2-8°C and several months if stored at -20°C [10,11].
Metanephrines values are influenced by feeding and stress. Patients should avoid smoking, drinking alcohol, intaking caffeine and Tyramine rich foods (bananas, fruit juices, tomatoes, potatoes, beans, red wine) 8-12 hours before 24 hours urine collection [6].

### 8.1 EXPECTED VALUES AND RESULTS INTERPRETATION

Each laboratory should conduct a pilot study in order to determine the distribution of analytes concentration in relation to its population. In order to establish the population dimension study, it is recommended to check CLSI document EP28-A3C [12].
Reference values and normal ranges are set according to the distribution.

### 8.2 REFERENCE RANGES

Total Metanephrines reference ranges in adults are listed in Table 7, classified by gender.

| ANALYTE | ADULT MALES (µg/24 h) | ADULT FEMALES (µg/24 h) |
|---|---|---|
| Metanephrine | 44 - 261 | 30 - 180 |
| Normetanephrines | 100 - 560 | 100 - 560 |
| 3-Methoxytyramine | < 306 | < 242 |

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 [13].
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 in order 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 7).

| ANALYTE | LLOD (ng/mL) | LLOQ (ng/mL) | LINEARITY (ng/mL) |
|---|---|---|---|
| Metanephrine | 0.200 | 0.600 | 0.600 – 8000 |
| Normetanephrine | 0.400 | 1.50 | 1.50 – 16000 |
| 3-Methoxytyramine | 0.300 | 1.10 | 1.10 – 8000 |

Table 8: LOD, LOQ and linearity

## 9.2 RECOVERY

Increasing amount of standard has been added to 3 real human urine pools in order to evaluate the analytical recovery characteristics. Three different levels of enriched urine (low, medium, 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 (%) |
|---|---|---|---|
| Metanephrine | 96.7 | 85.9 | 101.3 |
| Normetanephrine | 98.7 | 93.5 | 101.9 |
| 3-Methoxytyramine | 98.5 | 93.6 | 106.1 |

Table 9: Average, minimum and maximum recovery values

## 9.3 PRECISION

Average concentration values (ng/mL) measured in the real urine pool (endogenous) and in 2 pools enriched with increasing concentrations of analytes (medium and high levels) 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) for each sample.
Inter-assay precision has been determined assaying 3 repetitions in 8 analytical series (n=24) for 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 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Endo | Medium | High | Endo | Medium | High | Endo | Medium | High | Endo | Medium | High |
| Metanephrine | 82.0 | 481 | 1690 | 2.1% | 2.6% | 2.0% | 3.4% | 3.3% | 3.2% | 4.0% | 4.2% | 3.8% |
| Normetanephrine | 147 | 1031 | 3709 | 3.2% | 2.4% | 2.0% | 4.1% | 3.5% | 2.9% | 5.2% | 4.3% | 3.5% |
| 3-Methoxytyramine | 84.5 | 468 | 1703 | 1.7% | 1.8% | 1.5% | 3.6% | 3.0% | 3.6% | 4.0% | 3.5% | 3.9% |

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 instruction. 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 system, HPLC systems and columns, which may require further development of the method, has not been validated.
- Do not use the kit after expiration date of its components.

# 11 REFERENCES

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**[2]** Whiting M.J. (2009): **Simultaneous measurement of urinary metanephrines and catecholamines by liquid chromatography with tandem mass spectrometric detection.** *Ann Clin Biochem* 46: 129–136

**[3]** Bourcier S., Benoist J., Clerc F., Rigal O., Taghi M., Hoppilliard Y. (2006): **Detection of 28 neurotransmitters and related compounds in biological fluids by liquid chromatography/tandem mass spectrometry.** *Rapid Commun. Mass Spectrom* 20: 1405–1421

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**[7]** Gabler J., Miller A., Wang S. (2011): **A simple liquid chromatography-tandem mass spectrometry method for measuring metanephrine and normetanephrine in urine.** *Clin Chem Lab Med* 49(7):1213–1216

**[8]** Clark Z.D., Frank E.L. (2011): **Urinary metanephrines by liquid chromatography tandem mass spectrometry: Using multiple quantification methods to minimize interferences in a high throughput method.** *Journal of Chromatography B,* 879:3673–3680

**[9]** Clinical and Laboratory Standards Institute (CLSI) (2009*):* **Urinalysis; Approved Guideline – Third Edition.** *CLSI document GP16-A3.* CLSI, Wayne, Pennsylvania 19087-1898, USA

**[10]** Roberts N.B., Higgins G., Sargazi M. (2010): **A study on the stability of urinary free catecholamines and free methyl-derivatives at different pH, temperature and time of storage.** *Clin Chem Lab Med*;48(1):81–87

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**[12]** Clinical and Laboratory Standards Institute (2010): ***Defining, Establishing and verifying reference intervals in the clinical laboratory – Approved Guideline Third Edition*** CLSI Document EP28-A3C

**[13]** Ross G.A., Newbould, E.C., Thomas J., Boulouxl P.M.G., Besser G.M., Perretti D., Grossman A. (1993): **Plasma and 24 h-urinary catecholamine concentrations in normal and patient populations.** *Ann C/in Biochem* 30: 38-44

# ANNEX 1: EC DECLARATION OF CONFORMITY

B.S.N. 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 point 9 of Legislative Decree 332/2000 and subsequent amendments, the in vitro diagnostic medical device belongs to the fourth category of devices, that is GENERIC IN VITRO MEDICAL-DIAGNOSTIC DEVICES.

| COMPONENT | CODE | CERTIFICATION |
|---|---|---|
| Mobile Phase A | EUM17011 | CE-IVD marked medical device according to Annex III |
| Mobile Phase B | EUM17012 | CE-IVD marked medical device according to Annex III |
| Hydrolyzing Reagent | EUM18021 | CE-IVD marked medical device according to Annex III |
| Complexing Reagent | EUM18022 | CE-IVD marked medical device according to Annex III |
| pH Corrector Reagent | EUM18023 | CE-IVD marked medical device according to Annex III |
| SPE Activating Reagent | EUM18024 | CE-IVD marked medical device according to Annex III |
| SPE Conditioning Reagent | EUM18025 | CE-IVD marked medical device according to Annex III |
| SPE Washing Reagent | EUM18026 | CE-IVD marked medical device according to Annex III |
| SPE Eluting Reagent | EUM18027 | CE-IVD marked medical device according to Annex III |
| Internal Standard Mix | EUM18031 | CE-IVD marked medical device according to Annex III |
| Calibrators in Urine, for Catecholamines, Metanephrines and Serotonin, lyophil. | EUM17041 | CE-IVD marked medical device according to Annex III |
| Controls in Urine for biogenic amines, lyophil. | EUM17051 | CE-IVD marked medical device according to Annex III |
| Hydrolysis tubes with caps | EUM18062 | CE-IVD marked medical device according to Annex III |
| Chromatographic Column | EUM00C17 | CE-IVD marked medical device according to Annex III |
| Precolumn | EUM00A14 | CE-IVD marked medical device according to Annex III |
| Holder + precolumn | EUM00A15 | CE-IVD marked medical device according to Annex III |

Quality assurance system complying following directives:

- ✓ 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 the 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 products 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), 29/04/2022 Direction