«УТВЕРЖДЕНО»/Approved

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Дата/Data:
10.03.2020

ppa. Dr. Bernhard Ciommer
Director Global RA & QA Compliance

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ИНСТРУКЦИЯ ПО ПРИМЕНЕНИЮ
Instructions of use

Набор реагентов B·R·A·H·M·S PlGF plus KRYPTOR для автоматического иммунофлуоресцентного количественного определения PlGF (ПлФР, плацентарный фактор роста) в сыворотке человека и ЭДТА-плазме

B·R·A·H·M·S PlGF plus KRYPTOR reagent kit is an automatic immunofluorescence assay for the quantitative determination of PlGF (Placental Growth Factor) in human serum and EDTA plasma

Производства / Manufacturer

B·R·A·H·M·S GmbH (Б·Р·А·М·С ГмбХ)
Neuendorfstr. 25, 16761 Hennigsdorf, Germany, Германия

2020

[illegible]	[illegible]
[illegible]	[illegible]
Кофеин	[illegible]
[illegible]	[illegible]
Этанол	[illegible]
Фенилэфрин	18 мг/л
Гентамицин	10 мг/л
[illegible]	[illegible]
Фенобарбитал	[illegible]
Альбендазол	15 мг/л
Метопролол	5 мг/л
Железо	150 мг/дл
Дифенгидрамин	0,2 г/л

Правильность/линейность

Линейность рассчитана в соответствии с методическими рекомендациями CLSI EP6-A (Оценка линейности процедур количественного измерения), при разведении с рекомбинантным ПНФР линейность теста наблюдалась от предела количественного определения до 7 000 пг/мл.

Образцы пациентов не подлежат разведению.

Специфичность/хук эффект высоких концентраций

Для концентраций до 500 000 пг/мл "хук эффект" отсутствует.

Погрешность / Воспроизводимость для коэф. [illegible] одного исследования

Эти результаты были получены с использованием образцов, содержащих различные концентрации веществ, в соответствии с методическими рекомендациями CLSI EP5-A2 (Оценка точности методов количественного измерения)

Диапазон концентраций (пг/мл)	[illegible]
8,69	14,6 %
17,2	7,6 %
47,3	3,1 %
411	[illegible]

Погрешность / Воспроизводимость [illegible]

[illegible]

[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]

Instruction	
Sample volume	[illegible]
Incubation time	[illegible]
Results [illegible]	[illegible]
Conversion factor	[illegible]
Direct measuring range	[illegible]
Measuring range with automatic dilution	not applicable
Sample type	serum, EDTA plasma
Stability on board	[illegible]
[illegible]	[illegible]
Calibration stability	[illegible]
Assay principle	[illegible]

[illegible]	• If the assay is carried out within 48 hours of blood collection, store samples at 2...8 °C. If not, samples shall be aliquoted and stored frozen (−20 °C). • Glycated and hepatic plasma should not be used. • It is possible to use both K2 and K3 EDTA plasma only for plasma assays. • Place the sample in a tube suited for use on GRAHAM SKERPLOK compact PLUS/KRYPTOR (90...100 × 17 mm diameter). Do not use primary tube. • The sample tube must contain a minimum volume which will vary depending on the diameter of the sample tube. A 12 mm diameter tube will require an additional 150 µL of sample. • FIGL concentrations in patients' samples are not expected to exceed the [illegible] • [illegible]

Conditions of preliminary sample processing
• Serum and EDTA (K2 or K3) plasma can be used. When centrifuging of whole blood samples (2000 × g for at room temperature), the serum should be centrifuged [illegible] stability. The sample should be [illegible] hours after collection (2...8 °C) and up to [illegible] days from blood collection and up to [illegible] days. If [illegible] within 24 hours, the [illegible] be frozen at −20 °C. • Repeated freezing/thawing steps are not recommended.

[illegible]

[illegible]

Reference Range

Normal non pregnant subjects.

A study of 100 presumably healthy [illegible] samples were found below 16.7 pg/mL [illegible] 16.7 pg/mL.

Normal Values during pregnancy

A continuous study of the Fetal Medicine Foundation in UK [illegible] serum samples of pregnant women, reveals the following results using the BRAHMS PlGF plus KRYPTOR assay:

Gestational age (completed weeks)	n	5th percentile (pg/mL)	Median (pg/mL)	95th percentile (pg/mL)
5	59	9.3	17.1	28.9
6	100	11	[illegible]	[illegible]
10	150	16.7	[illegible]	153.0
11	83	19.0	32.1	61.0
12	231	21.3	42.3	96.7
13	122	25.2	54.7	100.9
14	13	34.2	61.6	132.6

Note: It is recommended that each laboratory establish its own reference ranges based on representative patient collectives and/or test the validity of the manufacturer's commercial test kit data. The values above have been established on serum and are given only as an example.

Normal values during second and third trimester of pregnancy

From EDTA plasma samples collected from 347 singleton pregnancies with a normal pregnancy outcome, levels of sFlt-1 and PlGF were determined in parallel and the sFlt-1/PlGF ratio were calculated [25]

sFlt-1/PlGF ratio (pg/pg)

Gestational age (completed weeks)	n	5th percentile (pg/mL)	Median (pg/mL)	95th percentile (pg/mL)
14-19	21	764	1515	2945
20-24	60	639	1349	4443
25-28	66	612	1111	3955
29-33	44	699	1195	5797
34-36	39	1074	2572	8492

[illegible]

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

Gestational age (completed weeks)	n	5th percentile (pg/mL)	Median (pg/mL)	95th percentile (pg/mL)
14-19	21	[illegible]	101	318
20-24	60	[illegible]	271	868
25-28	66	[illegible]	453	1000
29-33	44	[illegible]	507	1152
34-36	39	[illegible]	170	702
37-delivery	117	[illegible]	131	750

[illegible]

Gestational age (completed weeks)	n	5th percentile	Median	95th percentile
14-19	21	5	14	26
20-24	60	1	4	17
25-28	66	1	3	9
29-33	46	1	4	35
34-36	39	[illegible]	17	158
37-delivery	117	[illegible]	20	131

Clinical sensitivity and specificity

In an external study using the [illegible] and the [illegible] PROTEOR [illegible] in parallel [illegible] [illegible] and 20 patients with preeclampsia [illegible] [illegible] ratio of 95 was applied to calculate sensitivity and specificity [illegible] calculated at 95 % and the specificity at 88 %.

All pregnancies were singleton pregnancies. Preeclampsia was defined as new onset of hypertension and proteinuria after 20 weeks of gestation. A preeclamptic pregnancy was defined as early onset if clinical signs appeared before 34 weeks of gestation.

Assay Performance

Detection Limit

The Limit of Detection (LoD), and Limit of Quantitation (LoQ) [illegible] EP17-A2 guideline (Protocols for Determination of Limits of Detection and Limits of Quantitation). The LOD has been assessed as being 0.94 pg/ml. The LOQ has been assessed as being 1.6 pg/ml.

Sensitivity

[illegible]

[illegible]

The limit of quantitation (LOQ) [illegible] (imprecision and bias) ≤ 20 %. The LOQ is determined in accordance with the CLSI EP17-A2 guideline (Protocols for Determination of Limits of Detection and Limits of Quantitation). It has been assessed as being 6.94 pg/ml.

Specificity

The antibodies used in this assay are specific for [illegible] PlGF-1.

The cross reactivity is determined in accordance with the CLSI EP7-A2 guideline (Interference Testing in Clinical Chemistry). The following substances were added to serum with PlGF concentrations of 12 pg/ml., 35 pg/ml. or 480 pg/ml. and found not to interfere at the concentrations indicated below:

Tested substance	Tested concentration	Observed cross reactivity
PlGF-2 (glycosylated)	10 000 pg/ml	13%
PlGF-3	10 000 pg/ml	2%
VEGF-165	10 000 pg/ml	[illegible]
VEGF/PlGF heterodimer	10 000 pg/ml	[illegible]

The interference testing is performed in accordance with the CLSI EP7-A2 guideline (Interference Testing in Clinical Chemistry). The following substances were added to serum with PlGF concentrations of 12 pg/mL, 35 pg/mL or 480 pg/ml. and found not to interfere at the concentrations indicated below:

Tested substance	Tested concentration
Paracetamol	200 mg/L
Acetylsalicylic Acid	652 mg/L
Ascorbic acid	30 mg/mL
Caffeine	59 mg/L
Calcium	200 mg/L
Ethanol	5.5 (v/v)
Uric acid	15 pg/ml
[illegible]	[illegible] mg/l
Heparin	3000 I.U.
Ibuprofen	500 mg/L
L-Methyldopa	15 mg/L
Metoprolol	5 mg/L
[illegible]	150 µg/dL
Hydralazin	0.2 g/l

Accuracy / Linearity

The linearity is determined in accordance with the CLSI EP6-A guideline (Evaluation of the Linearity of Quantitative Measurement Procedures), based on dilution with a constant PlGF. The linearity of the assay is demonstrated from the LOQ up to 7 000 pg/ml. Undiluted sample cannot be diluted.

[illegible]

[illegible]

Precision/Reproducibility [illegible]

This was evaluated using samples of different concentrations in accordance with the CLSI EP5-A2 guideline (Evaluation of Precision Performance of Quantitative Measurement Methods)

Concentration range (pg/mL)	Within-assay CV %
8.69	[illegible]
17.2	7.6 %
47.3	3.1 %
411	1.7 %

Precision/Reproducibility [illegible]

This was evaluated using samples of different concentrations in accordance with the CLSI EP5-A2 guideline (Evaluation of Precision Performance of Quantitative Measurement Methods)

Concentration range (pg/mL)	Between-assay CV %
7.49	16.4 %
17.2	8.1 %
47.3	6.6 %
928	4.0 %

Interfering Factors

[illegible] Chemistry). The following substances [illegible] pg/mL to 400 pg/mL and found no [illegible] interference indicated below.

Factor	Description
Free unconjugated bilirubin	No significant effect up to 250 mg/l
Hemoglobin	No significant effect up to 5 g/l
Human serum albumin	No significant effect up to 50 g/l
Triglycerids	No significant effect up to 20 g/l

Traceability

An International PIGF - Reference Preparation is not available. Therefore the assay is calibrated using a reference preparation of recombinant human PlGF, as the best available standard. Traceability [illegible]

[illegible]

[illegible]

Product	[illegible]
Contaminated packaging	[illegible]
Pollutes	Remove pollutes with absorbing paper All materials used for cleaning up must be disposed of as infectious laboratory waste.

Manufacturer's authorized representative:

Thermo Fischer Scientific Joint Stock Company (Thermo Fisher Scientific JSC)

73, Kubinskaya St., Letter A, Bldg 1, St. Petersburg 198207

Tel.: (812) 703-42-15, facsimile: (812) 703-42-16

Email

Warranties

The Manufacturer guarantees the conformity of the characteristics of the product stated in the operating documentation, subject to use in accordance with the instructions and intended use provided by the manufacturer.

For all questions, technical advice and support please contact the manufacturer's authorized representative in the Russian Federation:

Thermo Fischer Scientific Joint Stock Company (Thermo Fisher Scientific JSC), Russia

73, Kubinskaya St., Letter A, Bldg 1, St. Petersburg 198207

Tel.: (812) 703-42-15, facsimile: (812) 703-42-16

Email: info.tp.spb@thermofisher.com

Bibliography

Analyte

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[illegible] of values [illegible]
[illegible]

[illegible]
In vitro diagnostic medical devices [illegible]
[illegible]
(ISO 18153:2009)

8. EN ISO 18113-2:2011
In vitro diagnostic medical devices – Information supplied by the manufacturer (labelling) – Part 2: In vitro diagnostic reagents for professional use
(ISO 18113-2:2009)

9. EN ISO 23640:2015
Evaluation of stability of in vitro diagnostic reagents
(ISO 23640:2011)

10. IEC 62366:2015 / EN 62366-1:2015
Medical devices – Part 1: Application of usability engineering to medical devices (IEC 62366:2007 + CORR:2014)

[illegible]

[illegible]

[illegible]

1. Dr. Bernhard [illegible]
   born January 28, 1964,
   domiciled in D-13593 Berlin
   Pottkamgasse 27,

   Dr. Jörg-Markus Paul
   born August 02, 1967,
   domiciled in D-13503 Berlin
   Reinerswalder Steig 22,

both commercially domiciled in 16767 Hennigsdorf, [illegible],
acknowledged their signatures before me.

The identity of the deponents is personally known to me.

At the same time I certify according to § 21 BeurkG to the respectively certified extract from the statement of the Register of Companies of the District Court of Neuruppin dated March 09, 2020 that with HRB-Nr. 8872 NP H.R.A.I M S GmbH domiciled in Hennigsdorf is registered and that Dr. Bernhard Clommer as well as Dr. Jörg Markus Paul are registered as management team members and are both authorised to represent the company.

Berlin, in the business premises of the notary [illegible]
Berliner Straße 32, D-13467 Berlin

March 10, 2020 [illegible] /2020

Bismarck
Notary in Berlin
Federal Republic of Germany