

Elecsys BRAHMS PCT

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| REF | | Σ | SYSTEM |
|-------------|-------------|----------|--|
| 09318712190 | 09318712500 | 100 | cobas e 411 cobas e 601 cobas e 602 |

English

System information

For **cobas e 411** analyzer: test number 2610

For **cobas e 601** and **cobas e 602** analyzers: Application Code Number 580

Intended use

Immunoassay for the in vitro quantitative determination of procalcitonin (PCT) in human serum and plasma. PCT is a marker of host response to bacterial infection. The Elecsys BRAHMS PCT assay is indicated as an aid to be used in conjunction with clinical evaluation for:

- the early detection of clinically relevant bacterial infections
- the assessment of the degree of severity and the prognosis of the outcome of systemic bacterial infection, sepsis, and septic shock
- identifying patients that benefit from antibiotic treatment
- monitoring of antibiotic therapy
- assessing the success of antibiotic therapy

in patients with suspected or confirmed bacterial infection.

The electrochemiluminescence immunoassay "ECLIA" is intended for use on **cobas e** immunoassay analyzers.

Summary

Sepsis presents a tremendous challenge to the healthcare system with an in-hospital mortality rate of up to 26 %.¹ The treatment goal in sepsis is to administer effective antimicrobial therapy as soon as possible as earlier recognition of sepsis and intervention improve patient outcome.^{2,3} Lower respiratory tract infections (LRTIs) are a leading cause of sepsis and account for approximately 16 % of global sepsis-related deaths.⁴ Respiratory tract infections (RTIs) are a common cause of antibiotic overtreatment with antibiotics prescribed for approximately 50-60 % of patients with suspected acute RTIs^{5,6,7} and up to 70 % of patients with suspected LRTIs, despite the vast majority having a viral etiology.^{8,9,10} This inappropriate use of antibiotics is believed to be a primary cause of the spread of antibiotic-resistant bacteria.¹¹ Antibiotic stewardship programs, involving promotion of the appropriate administration of antibiotics, are essential to combat the increase of antibiotic-resistant microorganisms.

PCT is a precursor protein of the hormone calcitonin produced by parafollicular cells (C cells) of the thyroid and neuroendocrine cells of the lung and the intestine.^{12,13} PCT is undetectable in the blood of healthy individuals, but is produced ubiquitously in response to endotoxin or mediators released following bacterial infections.^{14,15}

PCT serum concentrations are elevated in clinically relevant bacterial infections and can further increase correlating to the severity of infection.^{14,16,17,18} Successful control of the underlying bacterial infection by the host immune system or antibiotic therapy results in a decrease of PCT concentration, with a half-life of 24 hours.^{14,16,17} The measurable decline of PCT levels can be used to guide the discontinuation of antibiotic therapy.¹⁹

Depending on the clinical setting, PCT cut-off values can be used to guide antibiotic therapy decisions alongside other clinical and laboratory parameters.²⁰ In the low and moderate acuity setting (primary care/emergency department/medical ward), PCT concentrations ≤ 0.25 µg/L aid in identification of patients in which bacterial infection is unlikely and antibiotic therapy should be discouraged.¹⁹ PCT concentrations > 0.25 µg/L aid in identification of patients with a probable bacterial infection for which antibiotic therapy is recommended.

Several randomized controlled trials and meta-analyses have demonstrated that the use of PCT-guided initiation or discontinuation of antibiotic therapy in patients with acute RTIs significantly reduces antibiotic consumption without compromising patient outcome.^{21,22,23,24,25,26} Safe reduction of antibiotic consumption through PCT guidance was confirmed in routine clinical practice without increased risk of complications.²⁷

The utility of PCT for guiding antibiotic therapy decisions has similarly been shown for sepsis with beneficial patient outcome.^{28,29,30,31,32,33} A patient-level meta-analysis confirmed that PCT guidance can also be used in

patients with impaired kidney function, for which PCT use was associated with shorter antibiotic treatment duration and lower mortality rates.³³

The use of PCT to guide antibiotic therapy duration is recommended in International guidelines. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) 2018 guidelines support the use of diagnostic tests, such as PCT, as part of sepsis management to guide antibiotic duration and dosing.³⁴ The 2011 European Respiratory Society (ERS) support the use of PCT to guide shorter treatment duration in patients with community acquired pneumonia.³⁵ PCT is also listed in the World Health Organization Model List of Essential In Vitro Diagnostics to guide antibiotic therapy or discontinuation in sepsis and LRTI (for use only in tertiary care facilities and above).³⁶

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: Antigen in the sample (30 µL), a biotinylated monoclonal PCT-specific antibody, and a monoclonal PCT-specific antibody labeled with a ruthenium complex^{a)} react to form a sandwich complex.
- 2nd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.
- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the reagent barcode or e-barcode.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex (Ru(bpy)₃²⁺)

Reagents - working solutions

The reagent rackpack (M, R1, R2) is labeled as PCTX.

- M** Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative.
- R1** Anti-PCT-Ab~biotin (gray cap), 1 bottle, 9 mL: Biotinylated monoclonal anti-PCT antibody (mouse) 2.0 µg/mL; phosphate buffer 95 mmol/L, pH 7.5; preservative.
- R2** Anti-PCT-Ab~Ru(bpy)₃²⁺ (black cap), 1 bottle, 9 mL: Monoclonal anti-PCT antibody (mouse) labeled with ruthenium complex 5.6 µg/mL; phosphate buffer 95 mmol/L, pH 7.5; preservative.
- PCT Cal1** PCT calibrator 1 (white cap; lyophilized), 1 bottle for 4 mL: PCT (recombinant) approximately 0.10 ng/mL in a human serum matrix; preservative.
- PCT Cal2** PCT calibrator 2 (black cap; lyophilized), 1 bottle for 4 mL: PCT (recombinant) approximately 54 ng/mL in a human serum matrix; preservative.
- PC PCT1** PreciControl PCT 1 (beige cap; lyophilized), 2 bottles each for 4 mL: PCT (recombinant) approximately 0.50 ng/mL in a human serum matrix; preservative.
- PC PCT2** PreciControl PCT 2 (brown cap; lyophilized), 2 bottles each for 4 mL: PCT (recombinant) approximately 10 ng/mL in a human serum matrix; preservative.

Calibrators:

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The exact lot-specific calibrator values are encoded in the barcoded labels of the test-specific reagent.

Controls:

cobas e 602 analyzers: The controls will be handled automatically by the analyzers. The exact lot specific target values and ranges are available both as an electronic barcode and as a value sheet provided via the **cobas** link.

All other analyzers: The controls are not barcode labeled and must be run as external controls. All values and ranges must be entered manually. Please refer to section "QC" in the operator's manual or to the online help of the instrument software. Non-barcode labeled controls: Only one target value and range for each control level can be entered on the analyzer. Different reagent lots with different control target values and ranges cannot be used in parallel in the same run. The exact lot specific target values and ranges are printed on the enclosed (or electronically available) value sheet included in the reagent kit. Please ensure that the correct values are used.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:

Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:

Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:



Warning

H317 May cause an allergic skin reaction.

H412 Harmful to aquatic life with long lasting effects.

Prevention:

P261 Avoid breathing dust.

P273 Avoid release to the environment.

P280 Wear protective gloves.

Response:

P333 + P313 If skin irritation or rash occurs: Get medical advice/attention.

P362 + P364 Take off contaminated clothing and wash it before reuse.

Disposal:

P501 Dispose of contents/container to an approved waste disposal plant.

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

All human material should be considered potentially infectious. All products derived from human blood are prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV. The testing methods use assays that have been approved or cleared by the FDA or that are in compliance with the legal rules of the European Union (IVDR 2017/746/EU, IVDD 98/79/EC, Annex II, List A). However, as no testing method can rule out the potential risk of infection with absolute certainty, the material should be handled with the same level of care as a patient specimen. In the event of exposure, the directives of the responsible health authorities should be followed.^{37,38}

Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).

Reagent handling

The reagents in the kit (M, R1 and R2) are ready-for-use and are supplied in bottles compatible with the system.

Calibrators:

Carefully dissolve the contents of 1 bottle by adding exactly 4 mL of distilled or deionized water and allow to stand closed for 15 minutes to reconstitute. Mix carefully, avoiding foam formation. Transfer the reconstituted calibrators into empty labeled snap-cap bottles.

Unless the entire volume is necessary for calibration on the analyzer, transfer aliquots of the freshly reconstituted calibrators into empty snap-cap bottles (CalSet Vials). Attach the supplied labels to these additional bottles. Store the aliquots at -20 °C (± 5 °C) for later use. Perform **only one** calibration procedure per aliquot.

Please note for **cobas e 602** analyzers: Both the vial labels, and the additional labels (if available) contain 2 different barcodes. Please turn the vial cap 180° into the correct position so that the barcode between the yellow markers can be read by the system. Place the vial on the analyzer as usual.

Controls:

Carefully dissolve the contents of 1 bottle by adding exactly 4 mL of distilled or deionized water and allow to stand closed for 15 minutes to reconstitute. Mix carefully, avoiding foam formation. Unless the entire volume is necessary for quality control on the analyzer, transfer aliquots of the reconstituted controls into empty snap-cap bottles (Control vials for the **cobas e 602** analyzers). Attach the supplied labels to these additional bottles. For all other analyzers transfer aliquots into appropriate tubes for storage. When measuring non-barcoded controls, use only recommended sample tubes "cup on tube" or "cup on rack". Store the aliquots at -20 °C (± 5 °C) for later use. Perform **only one** control procedure per aliquot.

Note: Do not combine bottles from different lots. Use only control bottles out of one lot with each other.

Please note: Both the vial labels and additional labels contain a barcode for the **cobas e 602** analyzers only. Place the vial on the analyzer as usual.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the Elecsys reagent kit **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

| Stability of the reagent rackpack | |
|-----------------------------------|----------------------------------|
| unopened at 2-8 °C | up to the stated expiration date |
| after opening at 2-8 °C | 12 weeks |
| on the analyzers | 4 weeks |

| Stability of the calibrators and controls | |
|---|----------------------------------|
| lyophilized calibrators/controls | up to the stated expiration date |
| reconstituted calibrators/controls on the analyzers | 2 hours (use only once) |
| reconstituted calibrators/controls at -20 °C (± 5 °C) | 3 months (freeze only once) |

Store the calibrators and controls **upright** in order to prevent the solution from adhering to the snap-cap.

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

Serum collected using standard sampling tubes or tubes containing separating gel.

Li-heparin, K₂-EDTA and K₃-EDTA plasma.

Plasma tubes containing separating gel can be used.

Criterion: Slope 0.9-1.1 + intercept within ± 0.06 ng/mL + coefficient of correlation ≥ 0.95.

Stable for 24 hours at 20-25 °C, 48 hours at 2-8 °C, 13 months at -20 °C (± 5 °C). Freeze only once.

Frozen samples can lead to a lower recovery of up to 8 %.

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The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge samples containing precipitates before performing the assay.

Do not use samples and controls stabilized with azide.

Ensure the samples, calibrators and controls are at 20-25 °C prior to measurement.

Due to possible evaporation effects, samples, calibrators and controls on the analyzers should be analyzed/measured within 2 hours.

Materials provided

See "Reagents – working solutions" section for reagents.

- 2 x 8 bottle labels (calibrators)
- 2 x 14 bottle labels (controls)
- 6 empty labeled snap-cap bottles

Materials required (but not provided)

- [REF](#) 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles
- [REF](#) 03142949122, ControlSet Vials, 2 x 56 empty snap-cap bottles
- General laboratory equipment
- **cobas e** analyzer

Additional materials for the **cobas e** 411 analyzer:

- [REF](#) 11662988122, ProCell, 6 x 380 mL system buffer
- [REF](#) 11662970122, CleanCell, 6 x 380 mL measuring cell cleaning solution
- [REF](#) 11930346122, Elecsys SysWash, 1 x 500 mL washwater additive
- [REF](#) 11933159001, Adapter for SysClean
- [REF](#) 11706802001, AssayCup, 60 x 60 reaction cups
- [REF](#) 11706799001, AssayTip, 30 x 120 pipette tips
- [REF](#) 11800507001, Clean-Liner

Additional materials for **cobas e** 601 and **cobas e** 602 analyzers:

- [REF](#) 04880340190, ProCell M, 2 x 2 L system buffer
- [REF](#) 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- [REF](#) 03023141001, PC/CC-Cups, 12 cups to prewarm ProCell M and CleanCell M before use
- [REF](#) 03005712190, ProbeWash M, 12 x 70 mL cleaning solution for run finalization and rinsing during reagent change
- [REF](#) 12102137001, AssayTip/AssayCup, 48 magazines x 84 reaction cups or pipette tips, waste bags
- [REF](#) 03023150001, WasteLiner, waste bags
- [REF](#) 03027651001, SysClean Adapter M

Additional materials for all analyzers:

- [REF](#) 11298500316, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

Resuspension of the microparticles takes place automatically prior to use. Read in the test-specific parameters via the reagent barcode. If in exceptional cases the barcode cannot be read, enter the 15-digit sequence of numbers.

Bring the cooled reagents to approximately 20 °C and place on the reagent disk (20 °C) of the analyzer. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the bottles.

Calibrators:

Place the reconstituted calibrators (in the system-compatible bottles with barcoded labels) in the sample zone.

All the information necessary for calibrating the assay is automatically read into the analyzer.

After calibration has been performed, discard the calibrators.

Analyze the controls PC PCT1 and PC PCT2. After the control procedure has been performed, discard the controls.

Calibration

Traceability: This method has been standardized against the BRAHMS PCT LIA assay.

Every Elecsys BRAHMS PCT reagent set has a barcoded label containing specific information for calibration of the particular reagent lot. The predefined master curve is adapted to the analyzer using PCT Cal1 and PCT Cal2.

Calibration frequency: Calibration must be performed once per reagent lot using fresh reagent (i.e. not more than 24 hours since the reagent kit was registered on the analyzer).

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Renewed calibration is recommended as follows:

- after 8 weeks when using the same reagent lot
- after 7 days when using the same reagent kit on the analyzer
- as required: e.g. quality control findings outside the defined limits

Quality control

Use PC PCT 1 and PC PCT 2 or other suitable controls for routine quality control procedures.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per reagent kit, and following each calibration.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

If necessary, repeat the measurement of the samples concerned.

Follow the applicable government regulations and local guidelines for quality control.

Note: The target values and ranges were determined and evaluated by Roche. They were obtained using the Elecsys BRAHMS PCT assay reagents and analyzers available at the time of testing.

cobas e 602 analyzers: Updated target values and ranges are available both as an electronic barcode and as a value sheet provided via the **cobas** link.

All other analyzers: The control values and ranges must be entered manually. Please refer to the corresponding section in the operator's manual.

Calculation

The analyzer automatically calculates the analyte concentration of each sample in ng/mL.

Limitations - interference

The effect of the following endogenous substances and pharmaceutical compounds on assay performance was tested. Interferences were tested up to the listed concentrations and no impact on results was observed.

Endogenous substances

| Compound | Concentration tested |
|--------------------|-------------------------------|
| Bilirubin | ≤ 428 µmol/L or ≤ 25 mg/dL |
| Hemoglobin | ≤ 0.559 mmol/L or ≤ 900 mg/dL |
| Intralipid | ≤ 1500 mg/dL |
| Biotin | ≤ 4912 nmol/L or ≤ 1200 ng/mL |
| Rheumatoid factors | ≤ 1500 IU/mL |

Criterion: For concentrations ≤ 0.1 ng/mL the deviation is ≤ 0.015 ng/mL. For concentrations > 0.1 ng/mL the deviation is ≤ 15 %.

There is no high-dose hook effect at PCT concentrations up to 1000 ng/mL.

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In vitro tests were performed on 18 commonly used and 7 special pharmaceuticals. No interference with the assay was found.

In rare cases, interference due to extremely high titers of antibodies to analyte-specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.

PCT levels can be increased in certain situations without infectious origin. These include, but are not limited to:³⁹

- prolonged or severe cardiogenic shock
- prolonged severe organ perfusion anomalies
- small cell lung cancer or medullary C-cell carcinoma of the thyroid
- early after major trauma, major surgical intervention, severe burns
- treatments which stimulate the release of pro-inflammatory cytokines
- neonates (< 48 h after birth)⁴⁰

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

Limits and ranges

Measuring range

0.02-100 ng/mL (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 0.02 ng/mL. Values above the measuring range are reported as > 100 ng/mL.

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 0.015 ng/mL

Limit of Detection = 0.02 ng/mL

Limit of Quantitation = 0.06 ng/mL

The Limit of Blank, Limit of Detection and Limit of Quantitation were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A2 requirements.

The Limit of Blank is the 95th percentile value from $n \geq 60$ measurements of analyte-free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low concentration samples. The Limit of Detection corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95 %).

The Limit of Quantitation is the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of ≤ 20 %.

Dilution

Samples with PCT concentrations above the measuring range can be diluted manually with PCT negative human serum or plasma. The recommended dilution is 1:4. The concentration of the diluted sample must be ≥ 20 ng/mL. After manual dilution, multiply the result by the dilution factor.

Expected values

Reference range

A study performed with the Elecsys BRAHMS PCT assay using 492 samples from apparently healthy males (245) and females (247) revealed the following normal value: 0.046 ng/mL (95th percentile).

Clinical cutoff

Note: The cutoffs indicated below may vary according to the clinical situation.

PCT serum concentrations are elevated in clinically relevant bacterial infections and continue to rise with the increasing severity of the disease. However, as an expression of individually different immune responses and different clinical situations, the same focus of infection may be associated with varying individual elevations in PCT concentrations. Therefore, clinicians should use the PCT results in conjunction with the patient's other laboratory findings and clinical signs, and interpret the concrete values in the context of the patient's clinical situation. The reference ranges are therefore given for orientational purpose only.

Diagnosis of systemic bacterial infection/sepsis^{*17,18,41}

*SIRS, Sepsis, Severe Sepsis, and Septic Shock were categorized according to the criteria of the consensus conference of the American College of Chest Physicians/Society of Critical Care Medicine⁴²

| ng/mL PCT | Analysis |
|-------------------|--|
| < 0.5 | Local bacterial infection is possible. Systemic infection (sepsis) is unlikely. Low risk for progression to severe systemic infection (severe sepsis). IMPORTANT: PCT levels < 0.5 ng/mL do not exclude an infection, because localized infections (without systemic signs) may be associated with such low levels. If the PCT measurement is done very early after bacterial insult (< 6 hours), values may still be low. In this case, PCT should be re-assessed 6-24 hours later. |
| ≥ 0.5 to < 2 | Systemic infection (sepsis) is possible, but various conditions are known to induce PCT as well (see below). Moderate risk for progression to severe systemic infection (severe sepsis). The patient should be closely monitored both clinically and by re-assessing PCT within 6-24 hours. |
| ≥ 2 to < 10 | Systemic infection (sepsis) is likely, unless other causes are known. High risk for progression to severe systemic infection (severe sepsis). |
| ≥ 10 | Important systemic inflammatory response, almost exclusively due to severe bacterial sepsis or septic shock. High likelihood of severe sepsis or septic shock. |

Differential diagnosis of Lower Respiratory Tract Infections²¹

| ng/mL PCT | Analysis |
|---------------|--|
| < 0.1 | Indicates absence of bacterial infection. Use of antibiotics strongly discouraged, also in the presence of impaired pulmonary reserve in AECOPD. |
| 0.1 to 0.25 | Bacterial infection unlikely. The use of antibiotics is discouraged. |
| > 0.25 to 0.5 | Bacterial infection is likely. Antibiotic treatment is encouraged. |
| > 0.5 | Suggestive of the presence of bacterial infection. Antibiotic treatment is strongly encouraged. |

Antibiotic guidance in sepsis⁴³ and LRTI²²

Antibiotic therapy should be considered regardless of PCT result if the patient is clinically unstable, is at high risk for adverse outcome, has strong evidence of bacterial pathogen, or the clinical context indicates antibiotic therapy is warranted. If antibiotics are withheld, reassess if symptoms persist/worsen and/or repeat PCT measurement within 6-24 hours.

In order to assess treatment success and to support a decision to discontinue antibiotic therapy, follow up samples should be tested once every 1-2 days, based upon physician discretion taking into account the patients' evolution and progress. Antibiotic therapy may be adjusted using the discontinuation formula below:

- PCT_{Peak} : Highest observed PCT concentration
- $PCT_{Current}$: Most recent PCT concentration
- ΔPCT : Change in PCT concentration

ΔPCT : Calculate by using the following equation:

$$\Delta PCT = \frac{PCT_{Peak} - PCT_{Current}}{PCT_{Peak}} \times 100$$

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Antibiotic therapy may be discontinued if the $\Delta\text{PCT} > 80\%$ or if the $\text{PCT}_{\text{Current}}$ is:

- ≤ 0.25 ng/mL for LRTI patients
- ≤ 0.5 ng/mL for suspected or confirmed septic patients

Antibiotic therapy may be continued based on other clinical findings, such as:

- failure of a patient's condition to improve or apparent progression of radiologic severity upon chest x-ray or
- failure to control a local infection, or ongoing physiologic instability for patients with suspected or confirmed sepsis.

If clinical picture has not improved and PCT remains high, re-evaluate and consider treatment failure or other causes.

Recommendations for laboratory reports

It is suggested to report the numerical PCT values (individual or paired). For paired PCT values the report should also indicate if the $\Delta\text{PCT}(\%)$ was $\leq 80\%$ or $> 80\%$. The laboratory report should include a reference or a link to the Elecsys BRAHMS PCT assay Method Sheet for a guided interpretation of the test results.

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

Clinical performance

Clinical studies were conducted on samples from 283 ICU patients. The patients were classified into categories based on the ACCP/SCCM (American College of Chest Physicians/Society of Critical Care Medicine) consensus criteria on their first day of ICU admission: SIRS (systemic inflammatory response syndrome), sepsis, severe sepsis and septic shock.⁴⁴

The PCT values of the patients with SIRS ($n = 95$) or sepsis ($n = 71$) compared to patients with severe sepsis ($n = 60$) or septic shock ($n = 57$) were as follows:

Results with a cutoff at 0.5 ng/mL

| Elecsys BRAHMS PCT | Clinical classification | | |
|--------------------|-------------------------|--------------------------------|-------|
| | SIRS | Severe sepsis/ septic shock | Total |
| < 0.5 ng/mL | 63 | 5 | 68 |
| ≥ 0.5 ng/mL | 32 | 112 | 144 |
| Total | 95 | 117 | 212 |

Based on the above data the sensitivity was 96 %, the specificity 66 %, the positive predictive value 78 % and the negative predictive value 93 %.

| Elecsys BRAHMS PCT | Clinical classification | | |
|--------------------|-------------------------|--------|-------|
| | SIRS | Sepsis | Total |
| < 0.5 ng/mL | 63 | 25 | 88 |
| ≥ 0.5 ng/mL | 32 | 46 | 78 |
| Total | 95 | 71 | 166 |

Based on the above data the sensitivity was 65 %, the specificity 66 %, the positive predictive value 59 % and the negative predictive value 72 %.

Results with a cut-off at 2 ng/mL

| Elecsys BRAHMS PCT | Clinical classification | | |
|--------------------|-------------------------|--------------------------------|-------|
| | SIRS | Severe sepsis/ septic shock | Total |
| < 2 ng/mL | 88 | 18 | 106 |
| ≥ 2 ng/mL | 7 | 99 | 106 |
| Total | 95 | 117 | 212 |

Based on the above data the sensitivity was 85 %, the specificity 93 %, the positive predictive value 93 % and the negative predictive value 82 %.

| Elecsys BRAHMS PCT | Clinical classification | | |
|--------------------|-------------------------|--------|-------|
| | SIRS | Sepsis | Total |
| < 2 ng/mL | 88 | 55 | 143 |
| ≥ 2 ng/mL | 7 | 16 | 23 |
| Total | 95 | 71 | 166 |

Based on the above data the sensitivity was 23 %, the specificity 93 %, the positive predictive value 70 % and the negative predictive value 62 %.

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using Elecsys reagents, pooled human sera and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplicate each for 21 days ($n = 84$). The following results were obtained:

| cobas e 411 analyzer | | | | | |
|----------------------|---------------|---------------|---------|---------------------------|---------|
| Sample | Mean ng/mL | Repeatability | | Intermediate precision | |
| | | SD ng/mL | CV % | SD ng/mL | CV % |
| Human serum 1 | 0.049 | 0.004 | 8.2 | 0.006 | 12.8 |
| Human serum 2 | 0.507 | 0.007 | 1.4 | 0.020 | 3.9 |
| Human serum 3 | 1.72 | 0.021 | 1.2 | 0.064 | 3.7 |
| Human serum 4 | 30.9 | 0.563 | 1.8 | 1.30 | 4.2 |
| Human serum 5 | 92.2 | 1.88 | 2.0 | 3.99 | 4.3 |
| PreciControl PCT1 | 0.490 | 0.008 | 1.6 | 0.018 | 3.7 |
| PreciControl PCT2 | 9.93 | 0.105 | 1.1 | 0.326 | 3.3 |

| cobas e 601 and cobas e 602 analyzers | | | | | |
|---------------------------------------|---------------|---------------|---------|---------------------------|---------|
| Sample | Mean ng/mL | Repeatability | | Intermediate precision | |
| | | SD ng/mL | CV % | SD ng/mL | CV % |
| Human serum 1 | 0.045 | 0.006 | 13.3 | 0.007 | 16.2 |
| Human serum 2 | 0.495 | 0.013 | 2.7 | 0.021 | 4.2 |
| Human serum 3 | 1.71 | 0.032 | 1.9 | 0.058 | 3.4 |
| Human serum 4 | 31.4 | 0.324 | 1.0 | 0.990 | 3.2 |
| Human serum 5 | 93.0 | 1.52 | 1.6 | 3.39 | 3.6 |
| PreciControl PCT1 | 0.478 | 0.012 | 2.5 | 0.020 | 4.3 |
| PreciControl PCT2 | 10.0 | 0.113 | 1.1 | 0.305 | 3.0 |

Method comparison

A comparison of the Elecsys BRAHMS PCT assay, [REF] 08828644190 / 08828644200 / 09318712190 / 09318712200 (cobas e 601 analyzer; y), with the Elecsys BRAHMS PCT assay, [REF] 05056888200 / 05056888003 (cobas e 601 analyzer; x), using human serum gave the following correlations (ng/mL):

Number of samples measured: 150

| | |
|------------------------------|----------------------|
| Passing/Bablok ⁴⁵ | Linear regression |
| $y = 0.959x + 0.003$ | $y = 0.949x + 0.062$ |
| $r = 0.992$ | $r = 1.00$ |

The sample concentrations were between 0.031 and 89.7 ng/mL.

Analytical specificity

The Elecsys BRAHMS PCT assay did not show any significant cross reactions with the following substances, when tested with PCT

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concentrations of approximately 0.4 ng/mL and 1.5 ng/mL (max. tested concentration):

| Substances | Maximum tested concentration ng/mL |
|--------------------------------|---------------------------------------|
| Human katacalcin | 30 |
| Human calcitonin | 10 |
| Salmon calcitonin | 30000 |
| Eel calcitonin | 30000 |
| Human alpha-CGRP ^{b)} | 10000 |
| Human beta-CGRP | 10000 |

b) Calcitonin Gene-Related Peptide

Concordance with BRAHMS PCT LIA/BRAHMS PCT sensitive KRYPTOR

A comparison study was performed with the Elecsys BRAHMS PCT assay and the BRAHMS PCT LIA. Cutoff values of 0.5 ng/mL and 2 ng/mL have been evaluated.

| | BRAHMS PCT LIA | | |
|--------------------|----------------|-------------|-------|
| Elecsys BRAHMS PCT | < 0.5 ng/mL | ≥ 0.5 ng/mL | Total |
| < 0.5 ng/mL | 104 | 49 | 153 |
| ≥ 0.5 ng/mL | 6 | 370 | 376 |
| Total | 110 | 419 | 529 |

| | BRAHMS PCT LIA | | |
|--------------------|----------------|-----------|-------|
| Elecsys BRAHMS PCT | < 2 ng/mL | ≥ 2 ng/mL | Total |
| < 2 ng/mL | 266 | 10 | 276 |
| ≥ 2 ng/mL | 11 | 242 | 253 |
| Total | 277 | 252 | 529 |

The concordance between both assays was 90 % at the cutoff value of 0.5 ng/mL and 96 % at the cutoff-value of 2 ng/mL.

The Elecsys BRAHMS PCT assay was also compared to the BRAHMS PCT sensitive KRYPTOR. Cutoff values of 0.5 ng/mL and 2 ng/mL have been evaluated.

| | BRAHMS PCT sensitive KRYPTOR | | |
|--------------------|------------------------------|-------------|-------|
| Elecsys BRAHMS PCT | < 0.5 ng/mL | ≥ 0.5 ng/mL | Total |
| < 0.5 ng/mL | 183 | 20 | 203 |
| ≥ 0.5 ng/mL | 2 | 392 | 394 |
| Total | 185 | 412 | 597 |

| | BRAHMS PCT sensitive KRYPTOR | | |
|--------------------|------------------------------|-----------|-------|
| Elecsys BRAHMS PCT | < 2 ng/mL | ≥ 2 ng/mL | Total |
| < 2 ng/mL | 312 | 24 | 336 |
| ≥ 2 ng/mL | 1 | 260 | 261 |
| Total | 313 | 284 | 597 |

The concordance between both assays was 96 % at the cutoff value of 0.5 ng/mL and 96 % at the cutoff-value of 2 ng/mL.

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| | |
|------------|---|
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