Elecsys PTH

cobas®

REF		Σ	SYSTEM
09744436190	09744436500	100	**cobas e** 402 **cobas e** 801

English

System information

Short name	ACN (application code number)	Application
PTH	10204	18 minutes
PTHST	10205	9 minutes (STAT = Short Turn Around Time)

Intended use

Immunoassay for the in vitro quantitative determination of intact parathyroid hormone in human serum and plasma for the differential diagnosis of hypercalcemia and hypocalcemia. This assay can be used intraoperatively.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on **cobas e** immunoassay analyzers.

Summary

Parathyroid hormone (PTH) is a single-chain 84-amino-acid peptide produced by the parathyroid glands in response to decreased extracellular concentrations of ionized calcium. Its main role is to increase serum calcium levels by stimulating the release of calcium from bone and its renal re-absorption in the distal tubule. In the proximal tubule, PTH stimulates the synthesis of calcitriol which in turn increases intestinal absorption of calcium and exerts an endocrine feed-back on the secretion of PTH at the parathyroid level. PTH also decreases the renal re-absorption of phosphate in the proximal tubule, thereby decreasing serum phosphate.[1]

Parathyroid gland disorders lead to elevated or depressed blood calcium levels (hypercalcemia or hypocalcemia) brought about by a change in the secretion of PTH.

Detection of subfunctioning parathyroid glands (hypoparathyroidism) requires the use of a highly sensitive test in order to be able to measure PTH levels well below normal. Hyperfunctioning of the parathyroid glands results in an increased secretion of PTH (hyperparathyroidism). Primary causes are adenomas of the parathyroid glands. In secondary hyperparathyroidism the blood calcium level is low as a result of other pathological states (e.g. vitamin D deficiency).[2]

The determination of PTH intraoperatively during adenoma resection in the parathyroid glands has been reported for primary hyperparathyroidism,[3,4] secondary hyperparathyroidism relating to renal failure,[5,6] and tertiary hyperparathyroidism post renal transplant surgery.[7] Because PTH has a reported half-life of 3-5 minutes,[8] a significant drop in PTH levels after resection of the abnormal gland or glands enables the surgeon to assess whether all hyperfunctioning parathyroid tissue has been removed from the patient.[9]

The National Academy of Clinical Biochemistry recommends routine use of intraoperative PTH testing for patients undergoing surgery for primary hyperparathyroidism, both in initial surgeries and in reoperative procedures.[10]

The Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend that serum PTH concentration should be measured regularly in patients with Chronic Kidney Disease (CKD) and maintained within the target ranges that are defined according to the stage of CKD.[11,12]

The Elecsys assay for determining intact PTH employs a sandwich test principle in which a biotinylated monoclonal antibody reacts with the N-terminal fragment (1-37) and a monoclonal antibody labeled with a ruthenium complex[a)] reacts with the C-terminal fragment (38-84).

The antibodies used in this assay are reactive with epitopes in the amino acid regions 26-32 and 37-42.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

Test principle

Sandwich principle.

Total duration of assay: 18 minutes.

- 1st incubation: 30 µL of sample, a biotinylated monoclonal PTH-specific antibody, and a monoclonal PTH-specific antibody labeled with a ruthenium complex 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.

Total duration of assay: 9 minutes.

- During a 9 minute incubation, antigen in the sample (30 µL), a biotinylated monoclonal PTH-specific antibody, a monoclonal PTH-specific antibody labeled with a ruthenium complex and streptavidin-coated microparticles react to form a sandwich complex, which is bound to the solid phase.

For both assay applications:

- 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 II 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 **cobas** link.

Reagents - working solutions

The **cobas e** pack is labeled as PTH.

M Streptavidin-coated microparticles, 1 bottle, 7.2 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-PTH-Ab~biotin, 1 bottle, 7.0 mL:
Biotinylated monoclonal anti-PTH antibody (mouse) 2.3 mg/L; phosphate buffer 100 mmol/L, pH 7.0; preservative.

R2 Anti-PTH-Ab~$Ru(bpy)_3^{2+}$, 1 bottle, 7.0 mL:
Monoclonal anti-PTH antibody (mouse) labeled with ruthenium complex 2.0 mg/L; phosphate buffer 100 mmol/L, pH 7.0; preservative.

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.

Prevention:

P261 Avoid breathing mist or vapours.

P272 Contaminated work clothing should not be allowed out of the workplace.

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

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

Reagent handling

The Elecsys PTH assay can be used for both the 9-minute application and the 18-minute application.

The reagents in the kit have been assembled into a ready-for-use unit that cannot be separated.

All information required for correct operation is available via the **cobas** link.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the **cobas e** pack **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability:	
unopened at 2-8 °C	up to the stated expiration date
on the analyzers	16 weeks

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, K_2-EDTA and K_3-EDTA plasma.

Plasma tubes containing separating gel can be used.

Because of the instability of PTH in unseparated serum, serum tubes should be centrifuged immediately. In contrast, PTH was found to be stable for > 24 hours at room temperature in whole blood anticoagulated with EDTA. Therefore, preference should be given to EDTA plasma.[13,14]

Criterion: Slope 0.9-1.1 + intercept within ≤ ± 2.4 pg/mL + coefficient of correlation ≥ 0.95.

Serum: Stable for 8 hours at 15-25 °C, 2 days at 2-8 °C, 6 months at -20 °C (± 5 °C).

Plasma: Stable for 2 days at 15-25 °C, 3 days at 2-8 °C, 6 months at -20 °C (± 5 °C).

Freeze only once.

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 and calibrators are at 20-25 °C prior to measurement.

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

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

- REF 08928487190, CalSet II PTH, for 4 x 1.0 mL
- REF 05618860190, PreciControl Varia, for 4 x 3.0 mL
- General laboratory equipment
- **cobas e** analyzer

Additional materials for **cobas e** 402 and **cobas e** 801 analyzers:

- REF 06908799190, ProCell II M, 2 x 2 L system solution
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 07485409001, Reservoir Cup, 8 cups to supply ProCell II M and CleanCell M
- REF 06908853190, PreClean II M, 2 x 2 L wash solution
- REF 05694302001, Assay Tip/Assay Cup tray, 6 magazines x 6 magazine stacks x 105 assay tips and 105 assay cups, 3 wasteliners
- REF 07485425001, Liquid Flow Cleaning Cup, 2 adaptor cups to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning Detection Unit
- REF 07485433001, PreWash Liquid Flow Cleaning Cup, 1 adaptor cup to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning PreWash Unit
- 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.

Place the cooled (stored at 2-8 °C) **cobas e** pack on the reagent manager. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the **cobas e** pack.

Calibration

Traceability: This method has been standardized against a commercial PTH test (RIA). The recovery of the NIBSC 95/646 (WHO) standard was assessed by testing dilutions in human serum covering the measuring range (40-4000 pg/mL) on 16 analyzers of the **cobas e** family. The mean recovery was 100 % ± 4 %.

The predefined master curve is adapted to the analyzer using the relevant CalSet.

Calibration frequency: Calibration must be performed once per reagent lot using fresh reagent (i.e. not more than 24 hours since the **cobas e** pack 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 12 weeks when using the same reagent lot
- after 28 days when using the same **cobas e** pack on the analyzer
- as required: e.g. quality control findings outside the defined limits

Quality control

Use PreciControl Varia 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 **cobas e** pack, 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.

Calculation

The analyzer automatically calculates the analyte concentration of each sample (either in pg/mL or pmol/L).

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Conversion factors: pg/mL x 0.106 = pmol/L
pmol/L x 9.43 = pg/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	≤ 1129 µmol/L or ≤ 66 mg/dL
Hemoglobin	≤ 0.155 mmol/L or ≤ 250 mg/dL
Intralipid	≤ 1500 mg/dL
Biotin	≤ 4920 nmol/L or ≤ 1200 ng/mL
Rheumatoid factors	≤ 1200 IU/mL
Albumin	≤ 70 g/L

Criterion: Recovery of ± 1.5 pg/mL of initial value for samples ≤ 15 pg/mL and within ± 10 % of initial value for samples > 15 pg/mL.

The assay is affected by hemolysis > 250 mg/dL. Do not analyze samples that show visible signs of hemolysis.

There is no high-dose hook effect at PTH concentrations up to 17000 pg/mL (1802 pmol/L).

In vitro tests were performed on 17 commonly used pharmaceuticals. No interference with the assay was found.

In addition, the following special drugs were tested. No interference with the assay was found.

Special drugs

Drug	Concentration tested mg/L
Fosamax	210
Cinacalcet	108
Sevelamer	2880
Calcitriol	0.00103

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.

Caution should be used when interpreting a PTH test result that does not appear to correspond to the clinical picture. The Elecsys PTH assay may be affected by these autoantibodies in extreme cases, resulting in a falsely elevated result.

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

2.4-5000 pg/mL or 0.254-530 pmol/L (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 2.4 pg/mL (< 0.254 pmol/L). Values above the measuring range are reported as > 5000 pg/mL (> 530 pmol/L).

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 1.2 pg/mL (0.127 pmol/L)

Limit of Detection = 2.4 pg/mL (0.254 pmol/L)

Limit of Quantitation = 6.0 pg/mL (0.636 pmol/L)

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 ≥ 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

Not necessary due to the broad measuring range.

Expected values

The reference ranges were determined in apparently healthy adults of various ethnicities (68 % Caucasian, 29 % African American, 3 % of other race) having normal creatinine, calcium and phosphate levels during summer and winter seasons. Patient samples were measured at each of the 3 locations, with the 25-hydroxyvitamin D levels measured by the Elecsys Vitamin D total II assay, REF 07464215190 (study CIM RD002540).

	Median PTH concentration, pg/mL			
Season	25(OH)D concentration ≤ 20 ng/mL			
			Percentile (95 % CI)	
	n	Median	2.5th	97.5th
Summer	71	39.2	16.7	74.1
Winter	112	40.0	19.5	86.6
Total	183	39.8	19.5 (13.2-22.1)	86.4 (74.1-99.0)

	Median PTH concentration, pg/mL			
Season	25(OH)D concentration > 20 to < 30 ng/mL			
			Percentile (95 % CI)	
	n	Median	2.5th	97.5th
Summer	80	37.4	20.1	59.8
Winter	85	33.0	13.8	60.4
Total	165	35.3	17.0 (12.8-19.4)	60.4 (59.5-101.0)

	Median PTH concentration, pg/mL			
Season	25(OH)D concentration ≥ 30 ng/mL			
			Percentile (95 % CI)	
	n	Median	2.5th	97.5th
Summer	94	31.6	14.3	51.9
Winter	47	33.7	17.7	68.3
Total	141	31.9	17.9 (13.7-19.5)	58.6 (51.9-94.9)

	Median PTH concentration, pg/mL			
Season	Total			
			Percentile (95 % CI)	
	n	Median	2.5th	97.5th
Summer	245	35.0	18.1 (13.7-20.4)	71.5 (60.7-94.9)
Winter	244	35.8	17.2 (12.8-19.4)	77.0 (69.2-99.0)
Total	489	35.5	17.3 (14.3-19.4)	74.1 (68.8-86.6)

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

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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, samples 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 402 and **cobas e** 801 analyzers (18-minute application)								
			Repeatability			**Intermediate precision**		
Sample	Mean		SD		CV	SD		CV
	pg/mL	pmol/L	pg/mL	pmol/L	%	pg/mL	pmol/L	%
HS[b] 1	9.47	1.00	0.159	0.017	1.7	0.236	0.025	2.5
HS 2	15.2	1.61	0.266	0.028	1.7	0.346	0.037	2.3
HS 3	63.3	6.71	0.738	0.078	1.2	1.10	0.117	1.7
HS 4	2514	266	33.2	3.52	1.3	47.6	5.05	1.9
HS 5	4786	507	46.5	4.93	1.0	87.2	9.24	1.8
PC Varia 1[c]	58.6	6.21	0.594	0.063	1.0	1.11	0.118	1.9
PC Varia 2	178	18.9	1.76	0.187	1.0	2.84	0.301	1.6

b) HS = Human serum

c) PC = PreciControl

cobas e 402 and **cobas e** 801 analyzers (9-minute application)								
			Repeatability			**Intermediate precision**		
Sample	Mean		SD		CV	SD		CV
	pg/mL	pmol/L	pg/mL	pmol/L	%	pg/mL	pmol/L	%
HS 1	9.85	1.04	0.252	0.027	2.6	0.290	0.031	2.9
HS 2	15.4	1.63	0.277	0.029	1.8	0.332	0.035	2.2
HS 3	63.2	6.70	0.663	0.070	1.0	1.28	0.136	2.0
HS 4	2445	259	29.3	3.11	1.2	45.3	4.80	1.9
HS 5	4632	491	61.3	6.50	1.3	95.5	10.1	2.1
PC Varia 1	51.8	5.49	0.539	0.057	1.0	1.00	0.106	1.9
PC Varia 2	155	16.4	1.52	0.161	1.0	2.72	0.288	1.8

Method comparison

a) A comparison of the Elecsys PTH assay (18-minute application), REF 08928428190 (**cobas e** 801 analyzer; y) with the Elecsys PTH assay (18-minute application), REF 07251068190 (**cobas e** 801 analyzer; x) gave the following correlations (pg/mL):

Number of samples measured: 145

Passing/Bablok[15]	Linear regression
y = 0.993x - 1.30	y = 0.995x - 1.47
τ = 0.981	r = 1.00

The sample concentrations were between 3.36 and 4844 pg/mL (0.356 and 513 pmol/L).

b) A comparison of the Elecsys PTH assay (9-minute application), REF 08928428190 (**cobas e** 801 analyzer; y) with the Elecsys PTH assay (18-minute application), REF 08928428190 (**cobas e** 801 analyzer; x) gave the following correlations (pg/mL):

Number of samples measured: 127

Passing/Bablok[15]	Linear regression
y = 0.968x + 0.223	y = 0.978x - 8.34
τ = 0.980	r = 0.999

The sample concentrations were between 2.76 and 4806 pg/mL (0.293 and 509 pmol/L).

c) A comparison of the Elecsys PTH assay (18-minute application), REF 08928428190 (**cobas e** 402 analyzer; y) with the Elecsys PTH assay (18-minute application), REF 08928428190 (**cobas e** 801 analyzer; x) gave the following correlations (pg/mL):

Number of samples measured: 147

Passing/Bablok[15]	Linear regression
y = 0.959x - 0.0054	y = 0.970x - 5.03
τ = 0.978	r = 0.999

The sample concentrations were between 2.60 and 4930 pg/mL (0.276 and 523 pmol/L).

Analytical specificity

The Elecsys PTH assay does not show any significant cross-reactivity with the following substances, tested with PTH concentrations of approximately 15 pg/mL and 60 pg/mL (maximum tested concentration):

Cross-reactant	**Concentration tested**
PTH fragment 1-34	5000 pg/mL
PTH fragment 1-37	5000 pg/mL
PTH-related protein 1-86	5000 pg/mL

The assay has a 93 % cross-reactivity to the PTH fragment 7-84.

Clinical investigations in intraoperative use

In 2006, the National Academy of Clinical Biochemistry published their Laboratory Medicine Practice Guidelines for point of care testing, entitled Evidence Based Practice for Point of Care Testing.[10] The guidelines recommend the use of intraoperative parathyroid hormone testing 1) for patients undergoing surgery for hyperparathyroidism, especially in minimally invasive or directed procedures, 2) for patients undergoing reoperation, and 3) as a replacement for traditional laboratory measurements of PTH during venous localization in order to help the angiography team guide sampling.

The guidelines further recommend for patients undergoing parathyroidectomy for hyperparathyroidism that baseline samples be obtained preoperation exploration and pre-excision of the gland, and that post-excision sampling be drawn at 5 and 10 minutes post resection with a 50 % reduction in PTH concentrations from the highest baseline level. The guidelines also caution that additional samples may be necessary.[10]

PTH testing during parathyroid surgery was conducted by several groups of investigators using the Elecsys PTH immunoassay.[4,5,6,7]

The overall sensitivity and specificity of the assay to demonstrate successful surgery as defined by postoperative reduction of calcium levels was 99.6 % and 93.7 %, respectively.

References

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For further information, please refer to the appropriate user guide or operator's manual for the analyzer concerned, the respective application sheets and the Method Sheets of all necessary components (if available in your country).

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

The Summary of Safety & Performance Report can be found here: https://ec.europa.eu/tools/eudamed

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see navifyportal.roche.com for definition of symbols used):

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume for reconstitution
GTIN	Global Trade Item Number
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

Additions, deletions or changes are indicated by a change bar in the margin.

CE 0123

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