Elecsys PTH (1-84)

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REF		Σ	SYSTEM
			cobas e 411
09005757190	09005757500	100	**cobas e** 601
			cobas e 602

English

System information

For **cobas e** 411 analyzer: test number 930
For **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number 273

Please note

The measured PTH (1-84) value of a patient's sample can vary depending on the testing procedure used. The laboratory finding must therefore always contain a statement on the PTH (1-84) assay method used. PTH (1-84) values determined on patient samples by different testing procedures cannot be directly compared with one another and could be the cause of erroneous medical interpretations. Therefore, the results reported by the laboratory to the physician should include: "The following results were obtained with the Elecsys PTH (1-84) assay. Results from assays of other manufacturers cannot be used interchangeably."

The performance characteristics for this assay have not been established for pediatric specimens.

Intended use

Immunoassay for the in vitro quantitative determination of biointact parathyroid hormone, PTH (1-84) 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) 1-84 is the full-length 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]

PTH (1-84) has a half-life of only a few minutes and is cleaved into various fragments and cleared very rapidly from the circulation.[2]

Parathyroid gland disorders lead to elevated or depressed blood calcium levels (hypercalcemia or hypocalcemia) caused 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.[3]

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).[3]

PTH measurement is routinely prescribed in patients with chronic renal failure to identify renal osteodystrophy subtypes and adapt treatment, and in non-renal patients to explore any disorder of calcium-phosphate metabolism.[4]

Measurement of PTH (1-84) in patients with chronic kidney disease (CKD)

PTH levels serve as surrogates for bone histology in patients with end-stage renal disease (ESRD), and they are an essential guide to ongoing clinical management, particularly during the treatment of secondary hyperparathyroidism with vitamin D sterols.[5]

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 CKD beginning with CKD stage 3 (stage 2 for children).[6] When the PTH concentration is above the target values, drugs that decrease PTH secretion such as active vitamin D compounds or calcimimetic agents may be given and the doses are then adapted according to the evolution of the PTH concentration. By contrast, if the PTH concentration is below the target range, any treatment that may decrease PTH secretion is stopped to avoid adynamic bone disease and associated extra-skeletal calcifications.[7] Low PTH levels induced by high dialysate calcium levels were found to be associated with an increased risk of cardiovascular death.[8]

The Elecsys PTH (1-84) assay is a third generation PTH assay[4] as it specifically measures the biologically intact molecule of PTH, PTH (1-84). This can be of advantage in chronic renal failure patients as it was shown that fragments of PTH (i.e. PTH 7-84) accumulate in patients on dialysis presumably due to reduced excretion.[9] However, the proportion of these fragments increases as glomerular filtration rate (GFR) falls, suggesting that this relationship might vary with the severity of renal failure.[10]

Since then, several studies have demonstrated that, in animal or cellular models, PTH (7-84) exerts effects that are opposite to those of PTH (1-84) (decrease in serum calcium and phosphate, inhibition of bone resorption), and is produced by the parathyroid glands in response to an increase in serum calcium levels.[11]

Also the ratio between PTH (1-84) and PTH (7-84) was proposed as a predictor for the severity of secondary hyperparathyroidism in dialysis patients.[12]

Clinical investigations in intraoperative use

The determination of PTH intraoperatively during adenoma resection in the parathyroid glands has been reported for primary hyperparathyroidism,[13,14] secondary hyperparathyroidism relating to renal failure,[15,16] and tertiary hyperparathyroidism post renal transplant surgery.[17]

Because PTH has a reported half-life of 3-5 minutes,[18] a significant drop in PTH levels after resection of the abnormal gland enables the surgeon to assess the completeness of resection and whether all hyperfunctioning parathyroid tissue has been removed from the patient.[19]

The National Academy of Clinical Biochemistry recommended routine use of intraoperative PTH testing for patients undergoing surgery for primary hyperparathyroidism, both in initial surgeries and in reoperative procedures.[20]

Selective measurement of the biologically intact PTH (1-84) molecule may be advantageous during parathyroid surgery, as there is evidence that PTH (1-84) decreases more rapidly than "non-1-84" PTH immediately after parathyroidectomy.[4]

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

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

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 50 µL of sample, a biotinylated monoclonal PTH-specific antibody, and 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.
- 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.

Reagents - working solutions

The reagent rackpack is labeled as PTH (1-84).

Elecsys PTH (1-84)

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M Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-PTH-Ab~biotin (gray cap), 1 bottle, 7 mL:
Biotinylated monoclonal anti-PTH antibody (mouse) 2.0 mg/L; phosphate buffer 100 mmol/L, pH 7.0; preservative.

R2 Anti-PTH-Ab~Ru(bpy)$_3^{2+}$ (black cap), 1 bottle, 7 mL:
Monoclonal anti-PTH antibody (mouse) labeled with ruthenium complex 1.0 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 dust/fume/gas/mist/vapours/spray.

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

All information required for correct operation is read in from the respective reagent barcodes.

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:	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	84 days
on the analyzers	56 days

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.

K_2-EDTA, K_3-EDTA and Li-heparin plasma as well as Li-heparin plasma tubes containing separating gel.

Because of the short half-life of PTH, it is recommended that, when serum is needed, the blood must be centrifuged immediately.

Preference should be given to K_2-EDTA or K_3-EDTA plasma, as it is stable longer than serum.

Criterion: Slope 0.9-1.1 + coefficient of correlation ≥ 0.95 and within a bias ≤ ± 25 % at medical decision point 1 (15 pg/mL) and within a bias ≤ ± 12 % at medical decision point 2 (57 pg/mL).

Serum: Stable for 7 hours at 20-25 °C, 24 hours at 2-8 °C, 6 months at -20 °C (± 5 °C). Freeze only once.

Plasma: Stable for 24 hours at 20-25 °C, 48 hours 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, 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.

Materials required (but not provided)

- REF 05608554190, PTH (1-84) CalSet, for 4 x 1.0 mL
- REF 05618860190, PreciControl Varia, for 4 x 3.0 mL
- REF 11732277122, Diluent Universal, 2 x 16 mL sample diluent or REF 03183971122, Diluent Universal, 2 x 36 mL sample diluent
- 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

Elecsys PTH (1-84)

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- REF 03004899190, PreClean M, 5 x 600 mL detection cleaning solution
- 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.

cobas e 601 and **cobas e** 602 analyzers: PreClean M solution is necessary.

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.

Calibration

Traceability: This method has been standardized against the WHO international standard 95/646.

Every Elecsys 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 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 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 12 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

For quality control, use PreciControl Varia.

In addition, other suitable control material can be used.

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.

Calculation

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

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	≤ 1130 µmol/L or ≤ 66 mg/dL
Hemoglobin	≤ 0.062 mmol/L or ≤ 100 mg/dL
Intralipid	≤ 1500 mg/dL
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL
Rheumatoid factors	≤ 1200 IU/mL
IgG	≤ 2.8 g/dL
IgA	≤ 1.6 g/dL
IgM	≤ 0.8 g/dL
Albumin	≤ 12 g/dL

Criterion: Recovery within ± 12 % of initial value for samples > 25 pg/mL or ± 3 pg/mL for samples ≤ 25 pg/mL.

The assay is affected by hemolysis > 100 mg/dL. Do not analyze samples that show visible signs of hemolysis.

There is no high-dose hook effect at PTH (1-84) concentrations up to 30000 pg/mL (3180 pmol/L).

Pharmaceutical substances

In vitro tests were performed on 18 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 (alendronate)	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.

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

5.50-2300 pg/mL or 0.583-244 pmol/L (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 5.50 pg/mL (< 0.583 pmol/L). Values above the measuring range are reported as > 2300 pg/mL (> 244 pmol/L).

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 3.50 pg/mL

Limit of Detection = 5.50 pg/mL

Limit of Quantitation = 10 pg/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 ≥ 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 %.

Elecsys PTH (1-84)

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Dilution

Samples with PTH (1-84) concentrations above the measuring range can be diluted with Diluent Universal. The recommended dilution is 1:2 (either automatically by the analyzers, or manually). The concentration of the diluted sample must be ≥ 1000 pg/mL (≥ 106 pmol/L).

After manual dilution, multiply the result by the dilution factor.

After dilution by the analyzers, the software automatically takes the dilution into account when calculating the sample concentration.

Expected values

Normal values in apparently healthy individuals

The normal value range was determined in a clinical study using 596 samples from apparently healthy individuals. The reference population was selected according to normal clinical chemistry parameters, normal hematology results, no vitamin D intake and normal calcium values as determined by flame photometry. The values given are only indicative and may vary from other published data.

N = 596	PTH (1-84) range	
	pg/mL	pmol/L
Mean	31.3	3.32
2.5th percentile	14.9	1.58
97.5th percentile	56.9	6.03

The subgrouping of the above cohort according to the vitamin D (25-OH) level shows the inverse relationship between the concentrations of PTH (intact) and PTH (1-84) and vitamin D (25-OH).

N	Vitamin D (25-OH)	PTH (intact) median		PTH (1-84) median	
	ng/mL	pg/mL	pmol/L	pg/mL	pmol/L
339	≤ 20	41.4	4.39	32.2	3.41
157	> 20 and < 30	37.0	3.92	29.0	3.07
100	≥ 30	33.0	3.50	24.9	2.64

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

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								
			Repeatability			**Intermediate precision**		
Sample	Mean		SD		CV	SD		CV
	pg/mL	pmol/L	pg/mL	pmol/L	%	pg/mL	pmol/L	%
HS* 1	7.05	0.747	0.538	0.0570	7.6	0.802	0.0850	11.4
HS 2	13.9	1.47	0.604	0.0640	4.3	0.853	0.0904	6.1
HS 3	49.0	5.19	0.561	0.0595	1.1	0.973	0.103	2.0
HS 4	1041	110	8.94	0.948	0.9	16.2	1.72	1.6
HS 5	2053	218	25.2	2.67	1.2	34.3	3.64	1.7
PC** Varia 1	39.7	4.21	0.480	0.0509	1.2	0.671	0.0711	1.7
PC Varia 2	125	13.3	2.11	0.224	1.7	2.18	0.231	1.8

* HS = Human serum

** PC = PreciControl

cobas e 601 and **cobas e** 602 analyzers								
			Repeatability			**Intermediate precision**		
Sample	Mean		SD		CV	SD		CV
	pg/mL	pmol/L	pg/mL	pmol/L	%	pg/mL	pmol/L	%
HS 1	9.52	1.01	0.408	0.0432	4.3	0.475	0.0504	5.0
HS 2	18.0	1.91	0.462	0.0490	2.6	0.585	0.0620	3.2
HS 3	56.1	5.95	0.828	0.0878	1.5	0.922	0.0977	1.6
HS 4	1120	119	10.5	1.11	0.9	13.1	1.39	1.2
HS 5	2167	230	26.9	2.85	1.2	27.3	2.89	1.3
PC Varia 1	41.4	4.39	0.678	0.072	1.6	0.775	0.0822	1.9
PC Varia 2	128	13.6	1.88	0.199	1.5	2.00	0.212	1.6

Method comparison

a) A comparison of the Elecsys PTH (1-84) assay, REF 05608546190 (y) with the Elecsys PTH assay, REF 11972103122 (x) gave the following correlations (pg/mL):

Number of samples measured: 1347

Passing/Bablok[21]	Linear regression
y = 0.668x + 3.02	y = 0.555x + 10.2
τ = 0.927	r = 0.987

The sample concentrations were between 9.38 and 2514 pg/mL (0.994 and 266 pmol/L).

b) A comparison of the Elecsys PTH (1-84) assay, REF 09005757190 (y) with the Elecsys PTH (1-84) assay, REF 05608546190 (x) gave the following correlations (pg/mL):

Number of samples measured: 100

Passing/Bablok[21]	Linear regression
y = 1.03x + 0.745	y = 1.03x + 0.380
τ = 0.986	r = 1.00

The sample concentrations were between 5.57 and 2123 pg/mL (0.590 and 225 pmol/L).

Analytical specificity

- ≤ 0.1 % cross-reactivities: Osteocalcin, β-CrossLaps (collagen-fragment), and bone-specific alkaline phosphatase
- ≤ 0.1 % cross-reactivities: PTH (1-34), PTH (7-84)
- For the N-terminal PTH related peptide (PTH-RP) no cross-reactivity was found in an epitope scan with the monoclonal antibody reactive with PTH N-terminal fragment used in this assay.

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Elecsys PTH (1-84)

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For further information, please refer to the appropriate operator’s manual for the analyzer concerned, the respective application sheets, the product information 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.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see dialog.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

CE 0123

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