Elecsys C-Peptide

cobas®

REF		Σ	SYSTEM
07027168190* 07027168214*	07027168500	100	**cobas e** 402 **cobas e** 801

* Some kits shown may not be available in all countries.

English

System information

Short name	ACN (application code number)
CPEPTID	10081

Intended use

Immunoassay for the in vitro quantitative determination of C-peptide in human serum, plasma and urine.

The assay is intended for use as an aid in the diagnosis and treatment of patients with abnormal insulin secretion.

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

Summary

C-peptide is a single chain 31-amino acid (AA 33-63) polypeptide connecting the insulin A chain with the B chain in the proinsulin molecule. It has a molecular weight of approximately 3021 Da.[1,2]

The proteolytic cleavage of the precursor proinsulin results in the two molecules insulin and C-peptide. Both are secreted in equimolar amounts and released into circulation via the portal vein. As half of the insulin, but almost none of the C-peptide is extracted in the liver, C-peptide has a longer half-life (about 35 minutes) than insulin. 5 to 10 times higher concentration of C-peptide persist in the peripheral circulation, and these levels fluctuate less than insulin. C-peptide is removed from the circulation by the kidneys and degraded, with a fraction excreted unchanged in the urine. The concentration in urine is about 10-20 fold higher than in serum.[3]

In the past, C-Peptide has been considered biologically inactive. However, recent studies have demonstrated that it is capable of eliciting molecular and physiological effects suggesting that C-peptide is in fact a bioactive peptide.[4] There is evidence that C-peptide replacement, together with insulin administration, may prevent the development or retard the progression of long-term complications in type 1 diabetes.[5,6,7,8,9,10]

Measurements of C-peptide, insulin and glucose are used as an aid in the differential diagnosis of hypoglycemia (factitious hypoglycemia and hypoglycemia caused by hyperinsulinism) to ensure an appropriate management and therapy of the patients. To quantify the endogenous insulin secretion, C-peptide is measured basally, after fasting and after stimulation and suppression tests.[3] Due to high prevalence of endogenous anti-insulin antibodies C-peptide concentrations reflect the endogenous pancreatic insulin secretion more reliably in insulin-treated diabetics than the levels of insulin itself.[2,11] Measurements of C-peptide may therefore be an aid in the assessment of a residual β-cell function in the early stages of type 1 diabetes mellitus and for the differential diagnosis of latent autoimmune diabetes of adults (LADA) and type 2 diabetes.[2,11,12,13,14]

C-peptide measurements are also used to assess the success of islet transplantation and for monitoring after pancreatectomy.[2,13,15,16]

Urinary C-peptide is measured when a continuous assessment of β-cell function is desired, to determine the Urinary C-peptide Creatinine Ratio (UCPCR), in patients with unstable glycemic control, in insulin-dependent diabetes mellitus, or when frequent blood sampling is not practical (e.g. in children).[2,3,17]

Although testing for C-peptide is not required for the routine monitoring of diabetes, it is a valuable tool for the individual therapeutic decisions which are essential for an optimal long-term metabolic control.[3,18]

Elevated C-peptide levels may also result from renal insufficiency and obesity.[3,18]

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 12 µL of sample, a biotinylated monoclonal C-peptide-specific antibody, and a monoclonal C-peptide-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 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.

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

Reagents - working solutions

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

M Streptavidin-coated microparticles, 1 bottle, 5.8 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-C-peptide-Ab~biotin, 1 bottle, 9.9 mL:
Biotinylated monoclonal anti-C-peptide antibody (mouse) 1 mg/L, phosphate buffer 50 mmol/L, pH 6.0; preservative.

R2 Anti-C-peptide-Ab~$Ru(bpy)_3^{2+}$, 1 bottle, 9.9 mL:
Monoclonal anti-C-peptide antibody (mouse) labeled with ruthenium complex 0.4 mg/L; phosphate buffer 50 mmol/L, pH 6.0; 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.

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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 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.

Criterion: Slope 0.9-1.1 + coefficient of correlation ≥ 0.95.

24-hour urine (must be prediluted 1:10 with Diluent MultiAssay before measurement).

Stability of the 24-hour urine (after collection), serum and plasma samples: 4 hours at 15-25 °C, 24 hours at 2-8 °C, 30 days 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 heat-inactivated samples.

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 03184919190, C-Peptide CalSet, for 4 x 1.0 mL
- REF 05341787190, PreciControl Multimarker, for 6 x 2.0 mL
- REF 07299010190, Diluent MultiAssay, 36 mL sample diluent
- 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 the WHO International Reference Reagent for C-peptide of human insulin for immunoassay, IRR, code 84/510, established 1986, from the National Institute for Biological Standards and Control (NIBSC).[19]

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

For quality control, use PreciControl Multimarker.

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 **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 in nmol/L, ng/mL or pmol/L (selectable).

Conversion factors:

ng/mL (µg/L) x 0.33333 = nmol/L

ng/mL x 333.33 = pmol/L

nmol/L x 3.0 = ng/mL

pmol/L x 0.003 = 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	≤ 855 µmol/L or ≤ 50 mg/dL
Hemoglobin	≤ 0.186 mmol/L or ≤ 300 mg/dL
Intralipid	≤ 2000 mg/dL
Biotin	≤ 246 nmol/L or ≤ 60 ng/mL
Rheumatoid factors	≤ 1200 IU/mL

Criterion: For concentrations ≤ 0.5 ng/mL the deviation is ≤ 0.2 ng/mL of initial value. For concentrations > 0.5 ng/mL the deviation is ≤ 10 % of initial value.

Samples should not be taken from patients receiving therapy with high biotin doses (i.e. > 5 mg/day) until at least 8 hours following the last biotin administration.

There is no high-dose hook effect at C-peptide concentrations up to 60.0 nmol/L (180 ng/mL).

Pharmaceutical substances
In vitro tests were performed on 16 commonly used pharmaceuticals in serum and 12 commonly used pharmaceuticals in urine. 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.

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

Serum and plasma: 0.007-13.3 nmol/L or 0.02-40 ng/mL (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 0.007 nmol/L (< 0.02 ng/mL). Values above the measuring range are reported as > 13.3 nmol/L (> 40 ng/mL) (or up to 133 nmol/L or 400 ng/mL for 10-fold diluted samples).

Urine: 0.067-133 nmol/L or 0.2-400 ng/mL (defined by the 10 x Limit of Detection for serum/plasma and the 10 x maximum of the master curve for serum/plasma, thus taking into account the 1:10 predilution of urine samples with Diluent MultiAssay). Values below the Limit of Detection are reported as < 0.067 nmol/L (< 0.2 ng/mL). Values above the measuring range are reported as > 133 nmol/L (> 400 ng/mL) or retested in a higher dilution of the sample.

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Serum and plasma:

Limit of Blank = 0.003 nmol/L (0.01 ng/mL)

Limit of Detection = 0.007 nmol/L (0.02 ng/mL)

Limit of Quantitation = 0.050 nmol/L (0.15 ng/mL)

Urine:

Please refer to the values for serum/plasma, taking into account the mandatory 1:10 predilution of urine samples.

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

Serum and plasma: Although the necessity for dilutions is unlikely due to the high measuring range, samples with C-peptide concentrations above the measuring range can be diluted with Diluent MultiAssay. The recommended dilution is 1:10 (either automatically by the analyzers or manually). The concentration of the diluted sample must be ≥ 1.3 nmol/L (≥ 4 ng/mL).

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.

Urine: All urine samples must be prediluted 1:10 with Diluent MultiAssay before measurement (either automatically by the analyzers or manually).

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

Urine samples with C-peptide concentrations above the measuring range can be retested using a 1:20 or higher dilution with Diluent MultiAssay (either automatically by the analyzers or manually). The concentration of the diluted sample must be ≥ 1.3 nmol/L (≥ 4 ng/mL).

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

Expected values

Studies with the Elecsys C-Peptide assay were performed using serum samples from apparently healthy fasting males and females, and 24 h urine samples from apparently healthy individuals.

The following results were obtained:

	N	Median	5th-95th percentile	Unit
C-peptide in serum/plasma	96	1.96	1.1-4.4	ng/mL
		0.65	0.37-1.47	nmol/L
C-peptide in 24-hour urine	79	54.8	17.2-181	µg/24 h
		18.3	5.74-60.3	nmol/24 h

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

Serum and plasma:

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 402 and **cobas e** 801 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean nmol/L	SD nmol/L	CV %	SD nmol/L	CV %
Human serum 1	0.041	0.001	2.9	0.001	3.5
Human serum 2	0.337	0.003	0.9	0.008	2.3
Human serum 3	1.34	0.028	2.1	0.044	3.3
Human serum 4	6.37	0.128	2.0	0.211	3.3
Human serum 5	12.1	0.343	2.8	0.440	3.6
PC[b)] Multimarker 1	0.670	0.009	1.3	0.017	2.6
PC Multimarker 2	3.40	0.062	1.8	0.109	3.2

b) PC = PreciControl

cobas e 402 and **cobas e** 801 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean ng/mL	SD ng/mL	CV %	SD ng/mL	CV %
Human serum 1	0.124	0.004	2.9	0.004	3.5
Human serum 2	1.01	0.009	0.9	0.023	2.3
Human serum 3	4.01	0.084	2.1	0.133	3.3
Human serum 4	19.1	0.385	2.0	0.632	3.3
Human serum 5	36.4	1.03	2.8	1.32	3.6
PC Multimarker 1	2.01	0.027	1.3	0.052	2.6
PC Multimarker 2	10.2	0.186	1.8	0.327	3.2

Urine:

Elecsys C-Peptide

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Precision was determined using Elecsys reagents and human urine samples 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					
		Repeatability		**Intermediate precision**	
Sample	Mean nmol/L	SD nmol/L	CV %	SD nmol/L	CV %
Urine 1	0.357	0.020	5.5	0.022	6.2
Urine 2	3.37	0.128	3.8	0.160	4.8
Urine 3	12.8	0.231	1.8	0.277	2.2
Urine 4	63.7	0.917	1.4	2.46	3.9
Urine 5	130	2.55	2.0	3.14	2.4

cobas e 402 and **cobas e** 801 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean ng/mL	SD ng/mL	CV %	SD ng/mL	CV %
Urine 1	1.07	0.059	5.5	0.067	6.2
Urine 2	10.1	0.384	3.8	0.480	4.8
Urine 3	38.5	0.692	1.8	0.831	2.2
Urine 4	191	2.75	1.4	7.38	3.9
Urine 5	391	7.64	2.0	9.43	2.4

Method comparison

a) A comparison of the Elecsys C-Peptide assay, REF 07027168190 (**cobas e** 801 analyzer; y), with the Elecsys C-Peptide assay, REF 03184897190 (**cobas e** 601 analyzer; x), gave the following correlations (ng/mL):

Number of serum samples measured: 169

Passing/Bablok[20]	Linear regression
y = 1.00x - 0.002	y = 1.00x + 0.014
τ = 0.994	r = 1.00

The sample concentrations were between 0.091 and 39.0 ng/mL.

b) A comparison of the Elecsys C-Peptide assay, REF 07027168190 (**cobas e** 402 analyzer; y), with the Elecsys C-Peptide assay, REF 07027168190 (**cobas e** 801 analyzer; x), gave the following correlations (ng/mL):

Number of samples measured: 147

Passing/Bablok[20]	Linear regression
y = 0.971x - 0.004	y = 0.968x + 0.035
τ = 0.995	r = 1.00

The sample concentrations were between 0.036 and 38.2 ng/mL.

Analytical specificity

For the monoclonal antibodies used, the following cross-reactivities were found:

Substance	**Concentration tested µg/mL**	**Cross-reactivity %**
Proinsulin, human[c)]	0.10	28.6
Insulin, human[d)]	8.66	n. d.[e)]
Insulin, porcine[f)]	7.50	n. d.
Insulin, bovine[g)]	7.69	n. d.
Somatomedin[h)] (Insulin-like growth factor 1 - IGF-I)	1.0	n. d.
Human Growth Hormone[i)]	10.0	n. d.
Glucagon[j)]	10.0	n. d.

c) WHO preparation 09/296

d) WHO preparation 66/304

e) n. d. = not detectable

f) WHO preparation 83/515

g) WHO preparation 83/511

h) NIBSC code 02/254

i) NIBSC code 98/574

j) NIBSC code 69/194

The Elecsys C-Peptide assay uses two monoclonal antibodies specifically directed against human C-peptide. The antibodies show cross-reactivity with the C-chain of human proinsulin and presumably with partially processed proinsulins (split products). The concentrations of proinsulin and split products of fasting healthy subjects are 100 times lower than the C-peptide concentrations and therefore the cross-reactivity is of no clinical significance. In patients with insulinoma, the proinsulin concentrations are reported as up to 60-fold higher than those from fasting healthy subjects.[21,22]

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For further information, please refer to the appropriate 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.

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

Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
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