Elecsys Cortisol III

cobas®

REF		Σ	SYSTEM
07682808190	07682808500	300	**cobas e** 402 **cobas e** 801

English

System information

Short name	ACN (application code number)
CORT 3 U	10248

Intended use

Immunoassay for the in vitro quantitative determination of cortisol in human urine. The determination of cortisol is used for the recognition and treatment of functional disorders of the adrenal gland.

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

Summary

Cortisol is quantitatively the major glucocorticoid product of the adrenal cortex.[1] The main reason to measure cortisol is to diagnose human diseases which are caused by the overproduction of cortisol in Cushing's syndrome, deficiency of adrenal steroid excretion in Addison's disease, and for therapy monitoring in Cushing's syndrome and in Addison's disease.[1] Cortisol plays an important role in the regulation of many essential physiological processes, including energy metabolism, maintenance of electrolyte balance and blood pressure, immunomodulation and stress responses, cell proliferation as well as cognitive functions. The major fraction of cortisol circulates bound to plasma proteins as corticosteroid binding globulin and albumin.[2] The biologically active free fraction comprises only 2-5 % of the total hormone concentration.[1,2]

Certain psychiatric disorders (depression, anxiety disorder), poorly controlled diabetes mellitus, and alcoholism can be associated with mild hypercortisolism and may produce test results suggestive of Cushing's syndrome.[3] Low levels of cortisol are seen in patients with rare adrenal enzyme defects and after long-lasting stress.

Initial testing for Cushing's syndrome is recommended with one of the following tests: urinary free cortisol (UFC) in 24 hours, late-night salivary cortisol or dexamethasone suppression test.[3]

Cortisol which is excreted into urine without alteration, is referred to as UFC. Usually there is a direct proportional relationship between UFC and the unbound and hence biologically active cortisol in the blood.[4] One of the advantages of measuring UFC is that cortisol excretion in urine collected over a 24-hour period is not subject to the diurnal rhythm of cortisol secretion, which allows an integrated assessment to differentiate between healthy individuals and patients with Cushing's syndrome.[3]

The secretion of cortisol is mainly controlled by the hypothalamic-pituitary-adrenal axis (HPA). When cortisol levels in the blood are low, a group of cells in a region of the brain called the hypothalamus release corticotropin-releasing hormone (CRH) which causes the pituitary gland to secrete another hormone, adrenocorticotropic hormone (ACTH), into the bloodstream. High levels of ACTH are detected in the adrenal glands and stimulate the secretion of cortisol, causing blood levels of cortisol to rise. As the cortisol levels rise, they start to block the release of CRH from the hypothalamus and ACTH from the pituitary.[2]

Normally, the highest cortisol secretion happens in the second half of the night with peak cortisol production occurring in the early morning. Following this, cortisol levels decline throughout the day with lowest levels during the first half of the night.[5] Therefore the circadian variations of cortisol secretion and the influence of stress have to be considered for the sampling conditions in serum, plasma and saliva.[3]

The Elecsys Cortisol III assay makes use of a competitive test principle using a monoclonal antibody which is specifically directed against cortisol. Endogenous cortisol which has been liberated from binding proteins with danazol competes with the exogenous cortisol derivative in the test which has been labeled with a ruthenium complex[a)] for the binding sites on the biotinylated antibody.

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

Test principle

Competition principle. Total duration of assay: 18 minutes.

- 1st incubation: By incubating the sample (6 µL) with a cortisol-specific biotinylated monoclonal antibody, immunocomplexes are formed, the amount of which is dependent upon the analyte concentration in the provided sample.
- 2nd incubation: After addition of streptavidin-coated microparticles and a cortisol-derivative labeled with a ruthenium complex, the still-vacant sites of the biotinylated antibodies become occupied, with formation of an antibody-hapten complex. The entire 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.

Reagents - working solutions

The **cobas e** pack is labeled as CORT 3.

M Streptavidin-coated microparticles, 1 bottle, 12.4 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-cortisol-Ab~biotin, 1 bottle, 21.0 mL:
Biotinylated monoclonal anti-cortisol antibody (mouse) 18 ng/mL; danazol 20 µg/mL; MES[b)] buffer 100 mmol/L, pH 6.0; preservative.

R2 Cortisol-peptide~$Ru(bpy)_3^{2+}$, 1 bottle, 21.0 mL:
Cortisol derivative (synthetic), labeled with ruthenium complex, 5 ng/mL; danazol 20 µg/mL; MES buffer 100 mmol/L, pH 6.0; preservative.

b) MES = 2-morpholino-ethane sulfonic acid

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.

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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 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.

Collect 24-hour urine in clean containers without preservatives and measure the volume (L/24 h).

24-hour urine can be used directly, no extraction is required.

Before measurement, transfer the sample to a container compatible for use on the analyzer.

Centrifuge samples containing precipitates before performing the assay.

Homogenize and centrifuge frozen samples prior to measurement.

Stable for 24 hours at 20-25 °C, 4 days at 2-8 °C, 3 months at -20 °C (± 5 °C). Freeze only once.

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 09290940190, CalSet Cortisol III Urine, for 4 x 1.0 mL
- REF 06687776190, PreciControl Cortisol Urine, for 4 x 1.0 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: The urine application of the Elecsys Cortisol III assay has been standardized by an isotope dilution-liquid chromatography-tandem mass spectrometry (ID-LC-MS/MS) based method. The method is traceable to the certified standard reference material SRM 921a Cortisol from the National Institute of Standards and Technology (NIST).

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 Cortisol Urine.

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 (either in nmol/L, µg/dL or µg/L).

Conversion factors:

nmol/L x 0.03625 = µg/dL

nmol/L x 0.3625 = µg/L

µg/dL x 27.586 = nmol/L

µg/L x 2.7586 = nmol/L

Manual calculation for urinary free cortisol, cortisol excretion over 24 hours (cortisol concentration/24 h): Multiply the analyzer results by the volume of the 24-hour urine (L/24 h). When the analyzer result is given in µg/dL, multiply it again by 10 in order to achieve a result given in µg/24 h.

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	≤ 0.621 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 2000 mg/dL

Compound	Concentration tested
Biotin	≤ 14735 nmol/L or ≤ 3600 ng/mL
Rheumatoid factors	≤ 1200 IU/mL
IgG	≤ 7.0 g/dL
IgA	≤ 1.6 g/dL
IgM	≤ 1.0 g/dL
Human serum albumin	≤ 4.9 g/dL
Creatinine	≤ 5 mmol/L
Glucose	≤ 5 mmol/L
NaCl	≤ 750 mmol/L
Urea	≤ 350 mmol/L

Criterion: For concentrations of 7.5-42 nmol/L the deviation is ≤ 4.2 nmol/L. For concentrations > 42-500 nmol/L the deviation is ≤ 10 %.

Pharmaceutical substances
In vitro tests were performed on 12 commonly used pharmaceuticals. No interference with the assay was found.

At concentrations corresponding to the daily therapeutic dose, the special drugs prednisolone and hydrocortisone caused elevated concentrations of cortisol.
For the special drug 6-methylprednisolone, no interference was observed for concentrations ≤ 0.157 mg/dL.

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

Special drugs

Drug	Concentration tested mg/dL
Amlodipine	0.008
Betamethasone	0.0345
Beclomethasone	0.000631
Budenoside	0.00063
Canrenone	0.075
Dexamethasone	1.20
Fludrocortisone	0.120
Fluticasone propionate	0.0003
HCT (hydrochlorothiazide)	0.113
Lisinopril	0.025
Losartan potassium	0.092
Metformin	1.20
Metoprolol	0.150
Mometasone	0.000045
Prednisone	0.010
Spironolactone	0.0555
Triamterene	0.059
Valsartan	1.17
Verapamil	0.160
Triamcinolone	0.003
Atorvastatin	0.075
Danazol	0.030
Diclofenac	2.40
β-Sitosterol	1.00

Drug interferences are measured based on recommendations given in CLSI guidelines EP07 and EP37 and other published literature. Effects of concentrations exceeding these recommendations have not been characterized.

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.

Pregnancy, contraceptives and estrogen therapy give rise to elevated cortisol concentrations.
During metyrapon tests, 11-deoxycortisol levels are elevated. Falsely elevated cortisol values may be determined due to cross-reactivity (see section "Analytical specificity").
Patients suffering from 21-hydroxylase deficiency exhibit elevated 21-deoxycortisol levels and this can also give rise to falsely elevated cortisol results.

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

7.50-500 nmol/L or 0.272-18.1 µg/dL (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 7.50 nmol/L (< 0.272 µg/dL). Values above the measuring range are reported as > 500 nmol/L (> 18.1 µg/dL).

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 4.00 nmol/L (0.145 µg/dL)

Limit of Detection = 7.50 nmol/L (0.272 µg/dL)

Limit of Quantitation = 10.0 nmol/L (0.363 µg/dL)

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 defined as the lowest amount of analyte in a sample that can be accurately quantitated with a total allowable error of ≤ 30 %.

Expected values

31.7-282 nmol/24 h (11.5-102 µg/24 h)

These values correspond to the 2.5th and 97.5th percentiles of results obtained from a total of 202 apparently healthy subjects examined, aged 18 years and older. Exclusion criteria were pregnancy, lactation, use of oral contraceptives, medication with cortisone/cortisol and without recent infection or vaccination (Roche study No. RD002296, 2022).

Corresponding lower and upper confidence limits (95 % CI[c]) of the 2.5th and 97.5th percentiles:

2.5th percentile	95 % CI of the 2.5th percentile	97.5th percentile	95 % CI of the 97.5th percentile	Unit
31.7	≤ 22.4-35.5	282	225-435	nmol/24 h
11.5	≤ 8.13-12.9	102	81.4-158	µg/24 h

c) CI = confidence interval

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, human 24 h urine and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory

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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 urine 1	10.9	0.341	3.1	0.492	4.5
Human urine 2	88.7	2.41	2.7	3.34	3.8
Human urine 3	236	5.46	2.3	6.90	2.9
Human urine 4	296	5.86	2.0	9.37	3.2
Human urine 5	453	9.39	2.1	14.5	3.2
PreciControl Urine 1	204	4.04	2.0	5.00	2.5
PreciControl Urine 2	374	8.98	2.4	11.3	3.0

cobas e 402 and **cobas e** 801 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean µg/dL	SD µg/dL	CV %	SD µg/dL	CV %
Human urine 1	0.394	0.0124	3.1	0.0178	4.5
Human urine 2	3.22	0.0873	2.7	0.121	3.8
Human urine 3	8.56	0.198	2.3	0.250	2.9
Human urine 4	10.7	0.212	2.0	0.340	3.2
Human urine 5	16.4	0.340	2.1	0.525	3.2
PreciControl Urine 1	7.39	0.147	2.0	0.181	2.5
PreciControl Urine 2	13.6	0.325	2.4	0.408	3.0

Method comparison

a) A comparison of the urine application of the Elecsys Cortisol III assay, REF 07682808190 (**cobas e** 801 analyzer; y), with ID-LC/MS (x), using only native 24 h-urine samples, gave the following correlations (nmol/L):

Number of samples measured: 187

Passing/Bablok[6]	Linear regression
y = 1.272x - 6.52	y = 1.351x - 8.01
τ = 0.888	r = 0.954

The sample concentrations were between 9.88 and 488 nmol/L or 0.358 and 17.7 µg/dL (Elecsys Cortisol III assay).

When compared to mass-spectrometry, increased results might be observed for native urine samples due to the presence of potential cross-reactants (see section "Analytical specificity").[7,8]

b) A comparison of the urine application of the Elecsys Cortisol III assay, REF 07682808190 (**cobas e** 801 analyzer; y), with ID-LC/MS (x), using only 24 h-urine samples spiked with synthetic cortisol, gave the following correlations (nmol/L):

Number of samples measured: 139

Passing/Bablok[6]	Linear regression
y = 1.017x - 7.53	y = 1.030x - 8.71
τ = 0.958	r = 0.996

The sample concentrations were between 9.53 and 484 nmol/L or 0.345 and 17.5 µg/dL (Elecsys Cortisol III assay).

c) A comparison of the urine application of the Elecsys Cortisol III assay, REF 07682808190 (**cobas e** 402 analyzer; y), with the urine application of the Elecsys Cortisol III assay, REF 07682808190 (**cobas e** 801 analyzer; x), gave the following correlations (nmol/L):

Number of samples measured: 122

Passing/Bablok[6]	Linear regression
y = 0.997x - 0.800	y = 1.020x - 2.96
τ = 0.984	r = 0.999

The sample concentrations were between 9.90 and 475 nmol/L or 0.359 and 17.2 µg/dL (**cobas e** 801 analyzer).

d) A comparison of the urine application of the Elecsys Cortisol III assay, REF 07682808190 (**cobas e** 801 analyzer; y), with a commercially available method (x), using native 24 h-urine samples, gave the following correlations (nmol/L):

Number of samples measured: 126

Passing/Bablok[6]	Linear regression
y = 1.049x - 21.9	y = 1.091x - 27.4
τ = 0.934	r = 0.991

The sample concentrations were between 19.2 and 488 nmol/L or 0.696 and 17.7 µg/dL (Elecsys Cortisol III assay).

Analytical specificity

For the urine application of the Elecsys Cortisol III assay, the following cross-reactivities (in %) were found at the respective cross-reactant concentration, tested with a cortisol concentration of approximately 17 nmol/L (0.6 µg/dL):

Cross-reactant	**Concentration tested µg/dL**	**Cross-reactivity %**
11-Deoxycorticosterone	100	0.174
11-Deoxycortisol	50	24.3
17α-Hydroxyprogesterone	1000	0.412
21-Deoxycortisol	100	2.33
Corticosterone	750	0.368
Cortisone	500	1.49
Androstenedione	100	n. d.[d)]
DHEAS	1000	n. d.
DHEA	1000	n. d.
Progesterone	1000	0.00930
Testosterone	1000	n. d.
Estradiol	1000	n. d.
Estriol	1000	n. d.
Estrone	1000	n. d.
Aldosterone	1000	n. d.
Pregnenolone	1000	n. d.
17α-Hydroxypregnenolone	1000	0.0417
11β-Hydroxyprogesterone	1000	0.0173
Pregnanetriol	1000	n. d.
6α-Hydroxycortisol	100	n. d.
6β-Hydroxycortisol	100	0.0698
Cortisol-21 glucuronide	1000	0.0301
Allotetrahydrocortisol	10	11.3
Cortisol-21-sulfate	1000	n. d.
β-Cortol	1000	n. d.
β-Cortolone	1000	n. d.
Pregnanediol	1000	n. d.
Tetrahydrocortisol	10	n. d.

d) n. d. = not detectable

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References

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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

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