Elecsys Testosterone II

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REF		Σ	SYSTEM
			cobas e 411
08946353190	08946353500	100	**cobas e** 601
			cobas e 602

English

System information

For **cobas e** 411 analyzer: test number 111
For **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number 216

Intended use

Immunoassay for the in vitro quantitative determination of testosterone in human serum and plasma.

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

Summary

Testosterone measurements, performed with this assay, in human serum and plasma are used as an aid in diagnosis of clinical conditions characterized by low or high testosterone levels, such as hypogonadism, hyperandrogenism or androgen-secreting tumors.

Testosterone is one of the key androgen steroids produced in the Leydig cells of the testes. In men, testosterone secretion is regulated by luteinizing hormone (LH) and drives the development of primary and secondary sexual characteristics, spermatogenesis, musculoskeletal growth and erythropoiesis.[1]

In women, testosterone is mainly synthesized by the ovaries and adrenal glands. In addition to maintaining bone and skeletal muscle mass and function, testosterone in women maintains vulvovaginal health.[2,3]

Small percentages of testosterone are also produced peripherally through the conversion of androstenedione and dehydroepiandrosterone. Most of the circulating testosterone (97 to 98 %) is bound to carrier proteins, either specifically to sex hormone binding globulin (SHBG) or non-specifically to other blood proteins, such as albumin.[4] In women testosterone serum concentration is about 15-fold lower than in men.[2,5,6]

Decreased production of testosterone in males is caused by functional deficiency of the testes (hypogonadism) which is associated with impairment of primary and secondary male sexual development, as well as infertility.[7,8,9] Decreased production of testosterone can occur under certain circumstances, such as aging, certain medications, chemotherapy, hypothalamus-pituitary axis disorders.[1]

Increased production of androgens and specifically testosterone (hyperandrogenism) can occur in certain clinical conditions such as androgen-secreting tumors, in case of congenital adrenal hyperplasia, in women affected by Polycystic Ovary Syndrome (PCOS) or by idiopathic hyperandrogenemia.[10,11] Elevated testosterone levels can also be a consequence of elevation of SHBG due to hyperthyroidism, liver disease or to the use of medication with an estrogenic effect such as hormone contraceptives.[12]

The Elecsys Testosterone II assay is based on a competitive test principle using a high affinity monoclonal antibody (sheep) specifically directed against testosterone. Endogenous testosterone released from the sample by 2-bromoestradiol competes with the added testosterone derivative 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: 20 µL of sample are incubated with a biotinylated monoclonal testosterone-specific antibody. The binding sites of the labeled antibody become occupied by the sample analyte (depending on its concentration).
- 2nd incubation: After addition of streptavidin-coated microparticles and a testosterone derivate labeled with a ruthenium complex, 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 TESTO II.

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

R1 Anti-testosterone-Ab~biotin (gray cap), 1 bottle, 10 mL:
Biotinylated monoclonal anti-testosterone antibody (sheep) 40 ng/mL; releasing reagent 2-bromoestradiol; MES buffer 50 mmol/L, pH 6.0; preservative.

R2 Testosterone-peptide~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 9 mL:
Testosterone derivative, labeled with ruthenium complex 1.5 ng/mL; MES 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 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.

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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	12 weeks
on the analyzers	8 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- and K_3-EDTA plasma.

Criterion: Recovery within 80-120 % of serum value > 1 ng/mL, recovery of ± 0.2 ng/mL of serum value ≤ 1 ng/mL and slope 0.9-1.1 + bias at 0.5 ng/mL and 3.0 ng/mL ≤ 10 % + coefficient of correlation ≥ 0.95.

Stable for 1 week 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 heat-inactivated samples.

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 05202230190, Testosterone II CalSet II, for 4 x 1.0 mL
- REF 11731416190, PreciControl Universal, for 4 x 3.0 mL
- General laboratory equipment
- **cobas e** analyzer

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

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

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

- REF 04880340190, ProCell M, 2 x 2 L system buffer
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 03023141001, PC/CC-Cups, 12 cups to prewarm ProCell M and CleanCell M before use
- REF 03005712190, ProbeWash M, 12 x 70 mL cleaning solution for run finalization and rinsing during reagent change
- REF 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 is traceable to highly purified testosterone by weight via ID-GC/MS ("Isotope Dilution - Gas Chromatography/Mass Spectrometry").[13]

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 1 month (28 days) when using the same reagent lot
- after 7 days (when using the same reagent kit on the analyzer)
- as required: e.g. quality control findings outside the defined limits

Quality control

Use PreciControl Universal or other suitable controls for routine quality control procedures.

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

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

If necessary, repeat the measurement of the samples concerned.

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

Calculation

The analyzer automatically calculates the analyte concentration of each sample (either in ng/mL, ng/dL or nmol/L).

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Conversion factors: ng/mL x 3.47 = nmol/L
ng/mL x 100 = ng/dL
nmol/L x 0.288 = 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	≤ 513 µmol/L or ≤ 30 mg/dL
Hemoglobin	≤ 0.373 mmol/L or ≤ 600 mg/dL
Intralipid	≤ 800 mg/dL
Biotin	≤ 3600 ng/mL
Rheumatoid factors	≤ 1000 IU/mL

Criterion: Recovery within ± 10 % of initial value (concentration range > 1-15.0 ng/mL), recovery within ± 15 % of initial value (concentration range > 0.5-1 ng/mL) and recovery of ± 0.075 ng/mL (concentration range of 0.025-0.500 ng/mL).

Pharmaceutical substances

In vitro tests were performed on 17 commonly used pharmaceuticals and 2 special pharmaceuticals. Of these, only phenylbutazone at therapeutic dosage levels showed interference with the assay (testosterone values increased).

A strong interaction with Nandrolone (INN international nonproprietary name, WHO) was found. Do not use samples from patients under Nandrolone treatment.

Testosterone esters, e.g. used in testosterone substitution therapies, are metabolized to testosterone after administration. The Elecsys Testosterone II assay does not differentiate between endogenous testosterone and exogenous testosterone resulting from metabolized testosterone under testosterone supplementation therapy. In general, steroid drugs may interfere with Elecsys Testosterone II assay.

In isolated cases, elevated testosterone levels can be seen in samples from female patients with end stage renal disease (ESRD).

Implausible elevated testosterone values in women should be verified by an extraction method or a validated LC-MS/MS tandem method.[8]

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

0.025-15.0 ng/mL or 0.087-52.0 nmol/L (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 0.025 ng/mL or < 0.087 nmol/L. Values above the measuring range are reported as > 15.0 ng/mL or > 52.0 nmol/L.

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 0.015 ng/mL or 0.052 nmol/L

Limit of Detection = 0.025 ng/mL or 0.087 nmol/L

Limit of Quantitation = 0.120 ng/mL or 0.416 nmol/L

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

The Limit of Quantitation was determined using the result of functional sensitivity testing.

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 measured with a total allowable error of ≤ 20 %.

Dilution

Not necessary due to the broad measuring range.

Expected values

The following tables show the results obtained using the Elecsys Testosterone II assay in a reference population of 95 males (7-18 years) and 100 females (8-18 years), who were in good endocrinological health. Subjects were clinically characterized according to their Tanner Stage. Tanner Stage was characterized according to the method of Marshall and Tanner.[14,15]

Reference values for males (7-18 years) characterized by Tanner Stage

Tanner Stage	N	Median	5-95th percentiles (ng/mL)
1	26	< 0.025	< 0.025
2	18	0.597	< 0.025-4.32
3	15	2.45	0.649-7.78
4	16	3.44	1.80-7.63
5	20	4.46	1.88-8.82

Reference values for females (8-18 years) characterized by Tanner Stage

Tanner Stage	N	Median	5-95th percentiles (ng/mL)
1	37	< 0.025	< 0.025-0.061
2	12	< 0.025	< 0.025-0.104
3	12	0.079	< 0.025-0.237
4	12	0.122	< 0.025-0.268
5	27	0.197	0.046-0.383

The following table shows the results obtained with the Elecsys Testosterone II assay in an apparently healthy group of 214 males and 160 females without intake of contraceptives and prescription drugs (study number CIM 000669). Blood samples were taken between 6.30 am and 1.00 pm. This clinical study with focus on the Elecsys Testosterone II assay included measurements in parallel with the Elecsys SHBG assay. The results were evaluated for the Elecsys Testosterone II and Elecsys SHBG assays and commonly used parameters derived from different calculation procedures, including albumin as an important parameter involved.[16]

- Free testosterone index (% FTI) or free androgen index (% FAI) as calculated on a molar/molar basis:

  FTI (%) = (testosterone in nmol/L divided by SHBG in nmol/L) x 100
- Free testosterone calculated (FTc) in nmol/L and %
- Bioavailable testosterone calculated (BATc) in nmol/L and %

FTc and BATc were calculated by means of individual concentrations for total testosterone, SHBG, and albumin and via the association constant of albumin to testosterone. A detailed description of the calculation procedure is available on request. Refer also to the homepage of www.issam.ch/freetesto.html.

The following results were obtained:

Testosterone

Test subjects	Percentiles				
	N	Median	5-95th	Median	5-95th
		ng/mL		nmol/L	
Males 20-49 years	136	5.36	2.49-8.36	18.6	8.64-29.0

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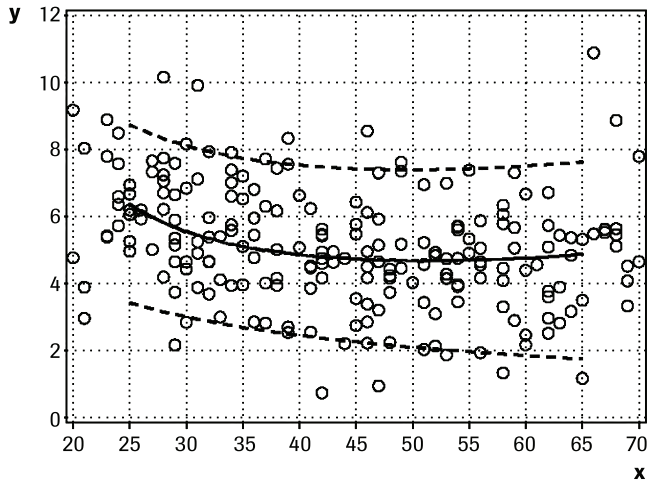
Test subjects	Percentiles				
	N	Median	5-95th	Median	5-95th
		ng/mL		nmol/L	
Males ≥ 50 years	78	4.76	1.93-7.40	16.5	6.68-25.7
Females 20-49 years	89	0.271	0.084-0.481	0.941	0.290-1.67
Females ≥ 50 years	71	0.162	0.029-0.408	0.563	0.101-1.42

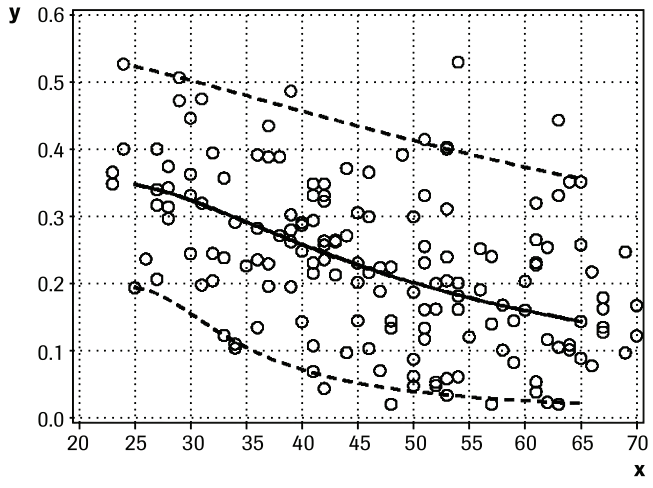
Distribution of testosterone values in the apparently healthy male group based on age (n = 214). Solid line: 50 % percentile, upper line: 95 % percentile, lower line: 5 % percentile.



x: Age (years)

y: Testosterone (ng/mL) - male group

Distribution of testosterone values in the apparently healthy female group based on age (n = 160). Solid line: 50 % percentile, upper line: 95 % percentile, lower line: 5 % percentile.



x: Age (years)

y: Testosterone (ng/mL) - female group

SHBG

Test subjects	N	Median	5-95th percentiles
		nmol/L	
Males 20-49 years	136	33.5	16.5-55.9
Males ≥ 50 years	78	40.8	19.3-76.4
Females 20-49 years	89	64.3	24.6-122
Females ≥ 50 years	71	57.4	17.3-125

Free testosterone index or free androgen index

Test subjects	N	Median	5-95th percentiles
		FTI or FAI (%)	
Males 20-49 years	136	57.2	35.0-92.6
Males ≥ 50 years	78	38.2	24.3-72.1
Females 20-49 years	89	1.53	0.297-5.62
Females ≥ 50 years	71	1.15	0.187-3.63

Free testosterone, calculated

Test subjects	N	Percentiles			
		Median	5-95th percentiles	Median	5-95th percentiles
		FTc (nmol/L)		FTc (%)	
Males 20-49 years	136	0.379	0.198-0.619	2.10	1.53-2.88
Males ≥ 50 years	78	0.304	0.163-0.473	1.91	1.23-2.59
Females 20-49 years	89	0.011	0.003-0.033	1.19	0.701-2.19
Females ≥ 50 years	71	0.008	0.001-0.020	1.26	0.685-2.64

Bioavailable testosterone, calculated

Test subjects	N	Percentiles			
		Median	5-95th percentiles	Median	5-95th percentiles
		BATc (nmol/L)		BATc (%)	
Males 20-49 years	136	9.10	4.36-14.3	49.8	35.0-66.3
Males ≥ 50 years	78	6.63	3.59-11.0	42.1	27.5-60.7
Females 20-49 years	89	0.246	0.059-0.756	25.7	15.3-47.7
Females ≥ 50 years	71	0.168	0.030-0.430	28.0	15.1-55.2

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, samples and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards

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Institute): 2 runs per day in duplicate each for 21 days (n = 84). The following results were obtained:

cobas e 411 analyzer					
			Repeatability		
Sample	Mean		SD		CV
	ng/mL	nmol/L	ng/mL	nmol/L	%
Human serum 1	0.117	0.406	0.008	0.028	6.7
Human serum 2	0.341	1.18	0.009	0.031	2.7
Human serum 3	0.773	2.68	0.014	0.049	1.8
Human serum 4	2.15	7.46	0.034	0.118	1.6
Human serum 5	14.6	50.7	0.242	0.840	1.7
PreciControl U[b)]1	5.70	19.8	0.075	0.260	1.3
PreciControl U2	2.53	8.78	0.042	0.146	1.6

b) U = Universal

cobas e 411 analyzer					
			Intermediate precision		
Sample	Mean		SD		CV
	ng/mL	nmol/L	ng/mL	nmol/L	%
Human serum 1	0.117	0.406	0.010	0.035	8.2
Human serum 2	0.341	1.18	0.012	0.042	3.4
Human serum 3	0.773	2.68	0.018	0.062	2.3
Human serum 4	2.15	7.46	0.049	0.170	2.3
Human serum 5	14.6	50.7	0.267	0.926	1.8
PreciControl U1	5.70	19.8	0.093	0.323	1.6
PreciControl U2	2.53	8.78	0.056	0.194	2.2

cobas e 601 and **cobas e** 602 analyzers					
			Repeatability		
Sample	Mean		SD		CV
	ng/mL	nmol/L	ng/mL	nmol/L	%
Human serum 1	0.093	0.323	0.008	0.028	8.9
Human serum 2	0.303	1.05	0.013	0.045	4.4
Human serum 3	0.717	2.49	0.013	0.045	1.8
Human serum 4	2.00	6.94	0.025	0.087	1.2
Human serum 5	13.5	46.8	0.259	0.899	1.9
PreciControl U1	5.34	18.5	0.097	0.337	1.8
PreciControl U2	2.41	8.36	0.047	0.163	2.0

cobas e 601 and **cobas e** 602 analyzers					
			Intermediate precision		
Sample	Mean		SD		CV
	ng/mL	nmol/L	ng/mL	nmol/L	%
Human serum 1	0.093	0.323	0.014	0.049	14.5
Human serum 2	0.303	1.05	0.018	0.062	5.9
Human serum 3	0.717	2.49	0.023	0.080	3.2
Human serum 4	2.00	6.94	0.041	0.142	2.1
Human serum 5	13.5	46.8	0.407	1.41	3.0
PreciControl U1	5.34	18.5	0.157	0.545	2.9
PreciControl U2	2.41	8.36	0.074	0.257	3.1

Method comparison

A comparison of the Elecsys Testosterone II assay, REF 08946353190 (**cobas e** 601 analyzer; y) with the Elecsys Testosterone II assay, REF 05200067190 (**cobas e** 601 analyzer; x) gave the following correlations (ng/mL):

Number of samples measured: 168

Passing/Bablok[17]	Linear regression
y = 0.948x + 0.0002	y = 0.950x - 0.009
τ = 0.976	r = 0.998

The sample concentrations were between 0.031 and 15.0 ng/mL.

Analytical specificity

For the antibody derivative used, the following cross-reactivities were found (in %):

	Concentration (ng/mL)	Cross-reactivity (%)
Androstendione	100	2.66
Cortisol	1000	0.016
Cortisone	2000	0.002
Danazol	1000	0.442
Dexamethasone	2000	0.0004
DHEA	1000	0.007
DHEA-S	50000	0.001
D-5-Androstene-3β,17β-diol	1000	0.186
Estradiol	1000	0.148
Estrone	1000	n.d.[c)]
Ethisterone	1000	2.78
Norgestrel	1000	0.461
Testosterone propionate	100	3.73
5-α-Androstane-3β,17β-diol	1000	3.65
5-α-Dihydro-testosterone	500	1.84
11-β-Hydroxy-testosterone	100	20.4
11-Keto-testosterone	1000	3.79
19-Norethisterone	40	3.44
Prednisone	1000	0.004
Prednisolone	1000	0.016
Progesterone	1000	0.023

c) n.d. = not detectable

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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.

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.

CE 0123

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