Elecsys SHBG

cobas®

REF		Σ	SYSTEM
07258496190	07258496500	300	**cobas e** 402 **cobas e** 801

English

System information

Short name	ACN (application code number)
SHBG	10071

Intended use

Immunoassay for the in vitro quantitative determination of sex hormone-binding globulin 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

Sex hormone-binding globulin (SHBG) measurements, performed with this assay, in human serum and plasma are used as an aid in diagnosis of conditions associated with altered androgen levels, such as hyperandrogenism and hypogonadism.

SHBG is the blood transport protein for testosterone, estradiol (E2) and other steroids. It is produced mainly, but not exclusively, by the liver and its synthesis is regulated by metabolic as well as endocrine factors. In healthy individuals, body composition and in particular the ratio of fat to lean mass, is one of the main factors determining circulating levels of SHBG.[1] Body weight, body-mass-index (BMI) and waist-to-hip ratio (WHR) correlate inversely with SHBG levels.[2] Metabolic and hormonal changes throughout life are reflected in fluctuations in SHBG levels.[1,2]

SHBG exists as a homodimeric glycoprotein composed of two identical subunits. Dimerization is required for the integrity of a single steroid binding site per dimer.[3] SHBG has low binding capacity but a very high binding affinity for steroids, showing highest affinities for dihydrotestosterone, testosterone, androstenediol, and estradiol (E2).[4,5] Besides transportation, SHBG regulates the bioavailability of sex-steroids via control of their respective metabolic clearance rates and their access to target tissues.[5,6] The SHBG-binding sites are mainly occupied by testosterone, thus SHBG serum concentrations are major determinant of the total testosterone concentrations. Only a small percentage (2 to 3 %) of testosterone circulates in the bloodstream freely, the majority is either strongly bound to SHBG, or weakly bound to non-specific proteins like albumin. In men, 44 % to 65 % of testosterone is bound to SHBG while in women, the percentages range from 66 % to 78 %. In addition, SHBG levels are about two times lower in men than women.[1,5] In women, circulating estradiol is mainly present in a form bound to SHBG but the affinity of SHBG for estradiol is about five times lower than its affinity for testosterone.[4,5,6]

The free and non-specifically bound plasma hormone levels generally reflect the clinical situation more accurately than total plasma hormone levels. Serum SHBG and testosterone measurements have been used in algorithms to calculate free testosterone levels in patients with suspected hyperandrogenism or hypoandrogenism.[6] The estimated amount of free testosterone can be calculated by performing the ratio of total testosterone (T) to SHBG which provides the so-called free androgen index or free testosterone index [% FAI or FTI = (100 T/SHBG)]. By additionally taking into account the non-specifically albumin-bound testosterone, it is possible to calculate the bioavailable testosterone, which is the sum of free testosterone (non-SHBG bound testosterone) and the albumin-bound testosterone fraction, calculated via the association constant to albumin.[7] Free and bioavailable testosterone are also referred to as non-SHBG-bound testosterone.[8] Similar calculations can be performed for E2, to explain how serum SHBG levels contribute to abnormal estrogen exposures, especially in postmenopausal women.[6,9]

Clinical conditions of androgen excess (hyperandrogenemia) or conditions where the effect of androgen on its target organs is excessive, are associated with decreased SHBG serum levels. In clinical conditions where androgen levels are normal, but clinical symptoms indicate androgen in excess, low SHBG titer can be an important indicator of an excessive/chronic androgenic action.[10] Low SHBG is one of the typical features of polycystic ovary syndrome (PCOS).[1,2] Diagnosis of PCOS can involve assessment of SHBG levels to define biochemical hyperandrogenism upon calculation of the free androgen index.[11]

Decreased SHBG levels may be associated with: inflammation processes (indicator of response to anti-inflammatory treatment), cardiovascular disease (risk factor), type 2 diabetes and breast cancer.[11,12,13,14,15,16,17] Decreased SHBG concentrations are often seen in patients with hypothyroidism, obesity, and acromegaly.[10,12,18]

Clinical conditions of androgen deficiency, such as male hypogonadism, are usually associated with low total testosterone or low testosterone action. Evaluation of SHBG levels is particularly recommended in the presence of conditions that alter SHBG levels, or when total testosterone is in the borderline range.[19,20,21]

High serum SHBG concentrations have been proposed to be associated with change of diet resulting in loss of weight.[22,23] Elderly men, late postmenopausal women, patients with hyperthyroidism and patients with cirrhosis also often show an increase in SHBG levels.[2,24] Pregnant women have markedly higher SHBG serum concentrations due to their increased estrogen production. Specific medications, such as oral contraceptives or antiepileptic drugs can increase SHBG levels.[2] Hormone therapy in postmenopausal women modulates SHBG levels, depending on regimens and routes of administration.[25,26,27]

The Elecsys SHBG assay employs two monoclonal antibodies specifically directed against human SHBG. Cross-reactivity with α_1-fetoprotein (AFP), corticosteroid binding globulin (CBG), dihydrotestosterone (DHT), E2, fibrinogen, human immunoglobulin A (IgA), human immunoglobulin G (IgG), plasminogen, thyroxine binding globulin (TBG), testosterone, thyroglobulin (Tg), transferrin, and thyrotropin (TSH) is negligible.

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 6 µL of sample, a biotinylated monoclonal SHBG-specific antibody, and a monoclonal SHBG-specific antibody labeled with a ruthenium complex[a)] 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 SHBG.

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

R1 Anti-SHBG-Ab~biotin, 1 bottle, 21 mL:
Biotinylated monoclonal anti-SHBG antibody (mouse) 1.25 mg/L; phosphate buffer 100 mmol/L, pH 7.2; preservative.

R2 Anti-SHBG-Ab~$Ru(bpy)_3^{2+}$, 1 bottle, 21 mL:
Monoclonal anti-SHBG antibody (mouse) labeled with ruthenium complex 1.25 mg/L; phosphate buffer 100 mmol/L, pH 7.2; 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.

Elecsys SHBG

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Warning

H317	May cause an allergic skin reaction.

Prevention:

P261	Avoid breathing mist or vapours.
P272	Contaminated work clothing should not be allowed out of the workplace.
P280	Wear protective gloves.

Response:

P333 + P313	If skin irritation or rash occurs: Get medical advice/attention.
P362 + P364	Take off contaminated clothing and wash it before reuse.

Disposal:

P501	Dispose of contents/container to an approved waste disposal plant.

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

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

Reagent handling

The 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, or lithium heparin plasma.

Li-heparin plasma tubes containing separating gel can be used.

Do not use EDTA plasma.

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

Stable for 5 days at 20-25 °C, 7 days at 2-8 °C, 12 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 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 03052028190, SHBG CalSet, for 4 x 1.0 mL
- REF 11731416190, PreciControl Universal, for 4 x 3.0 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 1st International Standard for SHBG from the National Institute for Biological Standards and Control (NIBSC) code 95/560.

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

Calibration frequency: Calibration must be performed once per reagent lot using fresh reagent (i.e. not more than 24 hours since the **cobas e** pack was registered on the analyzer).

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Renewed calibration is recommended as follows:

- after 12 weeks when using the same reagent lot
- after 28 days when using the same **cobas e** pack on the analyzer
- as required: e.g. quality control findings outside the defined limits

Quality control

Use PreciControl 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 **cobas e** pack, and following each calibration.

Elecsys SHBG

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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/mL or mg/L.

Conversion factors: nmol/L x 0.095 = µg/mL (mg/L)

µg/mL (mg/L) x 10.53 = nmol/L

Limitations - interference

The effect of the following endogenous substances and pharmaceutical compounds on assay performance was tested. Interferences were tested up to the listed concentrations and no impact on results was observed.

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 1129 µmol/L or ≤ 66 mg/dL
Hemoglobin	≤ 0.62 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 2700 mg/dL
Biotin	≤ 287 nmol/L or ≤ 70 ng/mL
Rheumatoid factors	≤ 1200 IU/mL
Human serum albumin	≤ 7 g/dL

Criterion: For concentrations of 0.8-20 nmol/L the deviation is ≤ 2 nmol/L. For concentrations > 20 nmol/L the deviation is ≤ 10 %.

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 SHBG concentrations up to 1000 nmol/L.

Pharmaceutical substances

In vitro tests were performed on 16 commonly used pharmaceuticals. 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

0.8-200 nmol/L (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 0.8 nmol/L. Values above the measuring range are reported as > 200 nmol/L (or up to 2000 nmol/L for 10-fold diluted samples).

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 0.5 nmol/L

Limit of Detection = 0.8 nmol/L

Limit of Quantitation = 2 nmol/L

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

The Limit of Blank is the 95th percentile value from n ≥ 60 measurements of analyte-free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low concentration samples. The Limit of Detection corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95 %).

The Limit of Quantitation is the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of ≤ 20 %.

Dilution

Samples with SHBG 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 > 20 nmol/L.

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

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

Expected values

The following table shows the results obtained from a group of 415 males and 343 females using the Elecsys SHBG assay. All subjects were apparently healthy, non-obese (BMI, body mass index ≤ 30), non-pregnant adults without intake of any contraceptive or relevant prescription drugs (study number CIM 000669). Blood samples were taken from fasting donors between 6.30 am and 2.00 pm. This clinical study focusing on the Elecsys Testosterone II assay included measurements in parallel using the Elecsys SHBG assay. Please refer to the Elecsys Testosterone II package insert for SHBG values in combination with testosterone.

SHBG

		SHBG (nmol/L)	
	N	Median	5-95th percentiles
Males (20-49 years)	241	33.2	18.3-54.1
Males (≥ 50 years)	174	40.6	20.6-76.7
Females (20-49 years)	166	67.8	32.4-128
Females (≥ 50 years)	177	62.4	27.1-128

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 402 and **cobas e** 801 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean nmol/L	SD nmol/L	CV %	SD nmol/L	CV %
Human serum 1	3.03	0.0732	2.4	0.105	3.5
Human serum 2	10.7	0.160	1.5	0.236	2.2
Human serum 3	20.9	0.351	1.7	0.495	2.4
Human serum 4	96.3	2.13	2.2	2.75	2.9
Human serum 5	171	5.23	3.1	6.44	3.8
PC[b)] Universal1	53.5	1.03	1.9	1.41	2.6
PC Universal2	28.0	0.544	1.9	0.681	2.4

b) PC = PreciControl

Method comparison

A comparison of the Elecsys SHBG assay, REF 07258496190 (**cobas e** 801 analyzer; y) with the Elecsys SHBG assay, REF 03052001190 (**cobas e** 601 analyzer; x) gave the following correlations (nmol/L):

Number of samples measured: 133

Passing/Bablok[28]	Linear regression
y = 0.996x + 0.165	y = 0.996x + 0.0209
τ = 0.977	r = 0.999

The sample concentrations were between 1.14 and 191 nmol/L.

A comparison of the Elecsys SHBG assay, REF 07258496190 (**cobas e** 402 analyzer; y) with the Elecsys SHBG assay, REF 07258496190 (**cobas e** 801analyzer; x) gave the following correlations (nmol/L):

Number of samples measured: 209

Passing/Bablok[28]	Linear regression
y = 1.047x - 0.464	y = 1.048x - 0.527
τ = 0.985	r = 0.999

The sample concentrations were between 1.15 and 192 nmol/L.

Analytical specificity

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

Substance	Maximum concentration tested mg/L	Cross-reactivity %
Transferrin	20000	n. d.[c)]
Fibrinogen	50000	n. d.
CBG	100	n. d.
TBG	200	n. d.
TG	1000	n. d.
TSH	0.0125[d)]	n. d.
AFP	10	n. d.
Testosterone	0.05	n. d.
E2	0.005	n. d.
DHT	0.05	n. d.
Plasminogen	3000	n. d.
human IgG	100000	n. d.
human IgA	20000	n. d.

c) n. d. = not detectable

d) 0.0125 mg/L = 100 µIU/mL

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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.

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