Elecsys HCG+β

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REF		Σ	SYSTEM
07251025190	07251025500	300	**cobas e** 402 **cobas e** 801

English

System information

Short name	ACN (application code number)
HCG-BETA	10072

Please note

The measured hCG value of a patient's sample can vary depending on the testing procedure used. The laboratory finding must therefore always contain a statement on the hCG assay method used. hCG values determined on patient samples by different testing procedures cannot be directly compared with one another and could be the cause of erroneous medical interpretations.

If there is a change in the hCG assay procedure used while monitoring therapy, then the hCG values obtained upon changing over to the new procedure must be confirmed by parallel measurements with both methods.

Intended use

Immunoassay for the in vitro quantitative determination of the sum of human chorionic gonadotropin (hCG) plus the hCG β-subunit in human serum and plasma.

This assay is intended for use as an aid in:

- Early detection and monitoring of pregnancy. The test is also intended for the use as one component in combination with other parameters to evaluate the risk of trisomy 21 (Down syndrome). Further testing is required for diagnosis of chromosomal aberrations.
- Oncology, to serve the management of patients with trophoblastic diseases. This assay is useful in the detection and monitoring of hCG-producing tumor cells of either ovarian, placental or testicular origin.

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

Summary

Similarly to LH (Luteinizing hormone), FSH (Follicle-stimulating hormone) and TSH (Thyroid-stimulating hormone), human chorionic gonadotropin (hCG) is a member of the glycoprotein family and consists of 2 subunits (α- and β-chains) which are associated to form the intact hormone.[1] The α-chains in all four of these glycoprotein hormones are virtually identical, whereas the β-chains have greatly differing structures and are responsible for the respective specific hormonal functions.[2]

hCG is produced in the placenta during pregnancy. In non-pregnant women, it can also be produced by tumors of the trophoblast, germ cell tumors with trophoblastic components and some non-trophoblastic tumors.[3]

Human chorionic gonadotropin consists of a number of isohormones[4] with differing molecular size. The biological action of hCG serves to maintain the corpus luteum during pregnancy. It also influences steroid production. The serum of pregnant women contains mainly intact hCG.[5]

Elevated values here serve as an indication of chorionic carcinoma, hydatidiform mole or multiple pregnancy.

Depressed values indicate threatening or missed abortion,[6] ectopic pregnancy, gestosis or intra-uterine death.

Measurement of hCG+β makes also a contribution to the risk assessment for trisomy 21 (Down syndrome) in the second trimester of pregnancy together with AFP (Alpha-fetoprotein) and other parameters, such as exact gestational age and maternal weight. In a trisomy 21 affected pregnancy the maternal serum concentration of AFP is decreased whereas the maternal serum hCG+β concentration is approximately twice the normal median.[7] The risk for a trisomy 21 affected pregnancy in the second trimester can be calculated by a suitable software (see "Materials required, but not provided" section) using the algorithm as described by Wald[8] and the respective assay-specific parameters.[7,8,9,10,11,12,13,14]

Elevated hCG concentrations not associated with pregnancy are found in patients with diseases such as tumors of the germ cells, ovaries, bladder, pancreas, stomach, lungs, and liver.[2,15]

In the following the prevalence (%) of elevated serum hCG + hCG+β values in various malignancies is listed: Testicular or placental choriocarcinoma (100), hydatidiform mole (97), nonseminomatous testicular germ cell tumor (48-86), seminoma (10-22), pancreatic cancer adenocarcinoma (11-80) and islet-cell carcinoma (22-50), gastric cancer (0-52), ovarian cancer, epithelial (18-41), colon cancer (0-37), lung cancer (0-36), breast cancer (7-25), hepatoma, liver cancer (17-21), tumors of small intestine (13), and renal carcinoma (10).[14,16]

hCG assays detecting the intact hCG plus the free β-subunit are well established markers as an aid in the management of patients with trophoblastic tumors[16] and together with AFP in patients with testicular and other germ cell tumors. [17]

The combination of the specific monoclonal antibodies used in the Elecsys HCG+β assay recognize the holo-hormone, "nicked" forms of hCG, the β-core fragment and the free β-subunit. The ruthenium-labeled and biotinylated antibodies used are directed against different epitopes of the hCG molecule.

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 6 µL of sample, biotinylated monoclonal hCG-specific antibodies, and a monoclonal hCG-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 HCG-BETA.

M Streptavidin-coated microparticles, 1 bottle, 13.2 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-hCG-Ab~biotin, 1 bottle, 19.7 mL:
Biotinylated monoclonal anti-hCG antibodies (mouse) 2.6 mg/L; phosphate buffer 40 mmol/L, pH 7.5; preservative.

R2 Anti-hCG-Ab~$Ru(bpy)_3^{2+}$, 1 bottle, 21.0 mL:
Monoclonal anti-hCG antibody (mouse) labeled with ruthenium complex 4.6 mg/L; phosphate buffer 40 mmol/L, pH 6.5; 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:

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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.

Li-heparin, K_2-EDTA and K_3-EDTA plasma.

Plasma tubes containing separating gel can be used.

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

Stable for 5 days at 20-25 °C, 14 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 03302652190, HCG+β CalSet, for 4 x 1.0 mL
- REF 11731416190, PreciControl Universal, for 4 x 3.0 mL or
  REF 11776452122, PreciControl Tumor Marker, for 4 x 3.0 mL
- REF 07299001190, Diluent Universal, 36 mL sample diluent
- General laboratory equipment
- **cobas e** analyzer

For risk calculation of trisomy 21:

- A suitable software, e.g.
  REF 05126193, SsdwLab (V5.0 or later), single user licence
  REF 05195047, SsdwLab (V5.0 or later), multi user licence
- REF 04481798190, AFP, 100 tests
- REF 04491742190, AFP, 200 tests
- REF 07026706190, Elecsys AFP, 300 tests
- REF 04487761190, AFP CalSet II, for 4 x 1 mL

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 4th International Standard for Chorionic Gonadotropin from the National Institute for Biological Standards and Control (NIBSC) code 75/589.

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 Universal or PreciControl Tumor Marker.

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 mIU/mL or IU/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.

Women with renal insufficiency can have elevated hCG levels in the absence of a tumor.[18]

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 1129 µmol/L or ≤ 66 mg/dL
Hemoglobin	≤ 0.621 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 2000 mg/dL
Biotin	≤ 287 nmol/L or ≤ 70 ng/mL
Rheumatoid factors	≤ 1200 IU/mL

Criterion: For concentrations from 0.2-5 mIU/mL the deviation is ± 0.500 mIU/mL. For concentrations from 5-10000 mIU/mL 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 hCG concentrations up to 750000 mIU/mL.

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

0.200-10000 mIU/mL (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 0.200 mIU/mL. Values above the measuring range are reported as > 10000 mIU/mL (or up to 1000000 mIU/mL for 100-fold diluted samples).

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 0.100 mIU/mL

Limit of Detection = 0.200 mIU/mL

Limit of Quantitation = 0.6 mIU/mL

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

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

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

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

Dilution

Samples with hCG concentrations above the measuring range can be diluted with Diluent Universal. The recommended dilution is 1:100 (either automatically by the analyzer or manually). The concentration of the diluted sample must be > 100 mIU/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.

Expected values

Results from a multicenter study in clinical centers in Belgium, France, and Germany using the HCG+β assay (REF 03271749190) are listed below (Study No. B01P019).

Serum samples from healthy individuals:

- ≤ 1 mIU/mL hCG for 97.5 % of the values obtained from 181 healthy, non-pregnant premenopausal women. The corresponding upper 95 % confidence limit ranges up to 5.3 mIU/mL.
- ≤ 7 mIU/mL hCG for 97.5 % of the values obtained from 143 healthy, postmenopausal women. The corresponding upper 95 % confidence limit ranges up to 8.3 mIU/mL.
- < 2 mIU/mL hCG for 97.5 % of the values obtained from 290 men. The corresponding upper 95 % confidence limit ranges up to 2.6 mIU/mL.
- During pregnancy (weeks of pregnancy - defined as completed weeks of pregnancy beginning with the start of the last menstruation phase), the following values have been determined.

Data are given only for the weeks of gestation for which the case numbers (n) were greater than 10.

Weeks of gestation	N	hCG mIU/mL	
		Median	5-95th percentile
3	25	17.5	5.8-71.2
4	43	141	9.5-750
5	23	1398	217-7138
6	19	3339	158-31795
7	13	39759	3697-163563
8	23	90084	32065-149571
9	23	106257	63803-151410
10	20	85172	46509-186977
12	17	66676	27832-210612
14*	67	34440	13950-62530
15*	666	28962	12039-70971
16*	766	23930	9040-56451
17*	190	20860	8175-55868
18*	64	19817	8099-58176

* For the gestational weeks 14 to 18, which are the relevant weeks for the trisomy 21 risk assessment, the values from serum samples of 1753 pregnant women in total were evaluated from measurements with the Elecsys HCG+β assay and the Elecsys AFP assay in the 5 clinical centers.

The individual results were analyzed for normal distribution of the log MoM (Multiple of Median) values. The standard deviations of the MoM values are comparable to published data.

Distribution of Elecsys HCG+β results from healthy subjects and patients with benign and malignant diseases:

The results from patients with benign and malignant diseases are summarized data from measurements with the HCG+β assay (REF 03271749190) and the HCG+β assay (REF 11973193122).

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Concentration mIU/mL	N	Percent (%)				
		≤ 2	> 2 - ≤ 7	> 7 - ≤ 100	> 100	> 1000
Healthy subjects	614					
Males	290	97.9	2.1	0	0	0
Females premenopause	181	98.9	1.1	0	0	0
Females postmenopause	143	53.1	46.2	0.7	0	0
Malignant diseases	839					
Choriocarcinoma	64	10.9	10.9	21.9	10.9	45.3
Seminoma	29	89.7	3.4	6.9	0	0
Germ cell tumor	109	78.0	3.7	0.9	5.5	11.9
Yolk sac tumor	45	20.0	6.7	22.2	8.9	42.2
Ovarian cancer	38	76.3	18.4	5.3	0	0
Gestational trophoblastic diseases	169	19.5	10.7	29.6	20.1	20.1
Mole	72	1.4	4.2	26.4	27.8	40.3
Others	313	52.7	13.1	8.6	11.8	13.7

Note: For prenatal testing it is recommended that the median values be re-evaluated periodically (1 to 3 years) and whenever methodology changes.

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 mIU/mL	SD mIU/mL	CV %	SD mIU/mL	CV %
Human serum 1	1.12	0.047	4.2	0.071	6.3
Human serum 2	5.82	0.162	2.8	0.248	4.3
Human serum 3	2592	62.6	2.4	98.5	3.8
Human serum 4	5934	125	2.1	233	3.9
Human serum 5	9672	287	3.0	427	4.4
PreciControl U[b)]1	5.90	0.147	2.5	0.239	4.0
PreciControl U2	46.7	0.989	2.1	1.62	3.5
PreciControl TM[c)]1	9.94	0.291	2.9	0.483	4.9
PreciControl TM2	1128	28.4	2.5	56.6	5.0

b) U = Universal

c) TM = Tumor Marker

Method comparison

a) A comparison of the Elecsys HCG + β assay, REF 07251025190 (**cobas e** 801 analyzer; y) with the Elecsys HCG + β assay, REF 03271749190 (**cobas e** 601 analyzer; x) gave the following correlations (mIU/mL):

Number of serum samples measured: 127

Passing/Bablok[19]	Linear regression
y = 0.945x + 0.205	y = 0.945x +0.482
τ = 0.991	r = 1.00

The sample concentrations were between 0.290 and 9986 mIU/mL.

b) A comparison of the Elecsys HCG + β assay, REF 07251025190 (**cobas e** 402 analyzer; y) with the Elecsys HCG + β assay, REF 07251025190 (**cobas e** 801 analyzer; x) gave the following correlations (mIU/mL):

Number of samples measured: 136

Passing/Bablok[19]	Linear regression
y = 1.00x - 1.00	y = 1.00x + 5.81
τ = 0.980	r = 0.999

The sample concentrations were between 0.598 and 9614 mIU/mL.

Analytical specificity

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

Substance	**Additive concentration mIU/mL**	**Cross-reactivity %**
LH	4000	n. d.[d)]
FSH	4000	0.1
TSH	2000	n. d.

d) n. d. = not detectable

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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.

The Summary of Safety & Performance Report can be found here: https://ec.europa.eu/tools/eudamed

Symbols

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

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume for reconstitution
GTIN	Global Trade Item Number

CE 0123

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