

Elecsys CA 125 II

REF			SYSTEM
11776223161	11776223501	100	cobas e 411 cobas e 601 cobas e 602

English

For use in the USA only

System information

For **cobas e 411** analyzer: test number 341
 For **cobas e 601** and **cobas e 602** analyzers: Application Code Number 053

Please note

The measured CA 125 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 CA 125 assay method used. CA 125 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 CA 125 assay procedure used while monitoring therapy, then the CA 125 values obtained upon changing over to the new procedure must be confirmed by parallel measurements with both methods.

Caution: US Federal law restricts this device to sale and distribution by or on the order of a physician, or to a clinical laboratory; and its use is restricted to, by or on the order of a physician.

Intended use

Immunoassay for the in vitro quantitative determination of OC 125 reactive determinants in human serum, Li-heparin, K₂-EDTA and K₃-EDTA, as well as Li-heparin plasma tubes containing separating gel on the **cobas e** analyzers.

These determinants are associated with a high molecular weight glycoprotein in serum and plasma of women with primary epithelial invasive ovarian cancer (excluding those with cancer of low malignant potential).

This immunoassay is indicated for use as an aid in the detection of residual or recurrent ovarian carcinoma. This immunoassay is further indicated for use in monitoring patients for disease progress or response to therapy.

The electrochemiluminescence immunoassay "ECLIA" is intended for use on **cobas e** immunoassay analyzers.

Summary

CA 125 belongs to the family of hybridoma-defined tumor markers. The values measured are defined by the use of the monoclonal antibody (MAb) OC 125. The antigenic determinant CA 125 is located on a high-molecular weight glycoprotein (200-1000 kD) isolated from cell culture or serum. The antigenic determinant CA 125 has a protein structure with associated carbohydrate side-chains.¹

MAb OC 125 was obtained from lymphocytes from mice that had been immunized with OVCA (ovarian carcinoma cell line) 433, an adenocarcinoma cell line from the ovary.² In the Elecsys CA 125 II test, OC 125 is used as a detection antibody. MAb M11 is used as the capture antibody (solid-phase antibody); this has been employed in second-generation CA 125 assays since 1992. CA 125 is found in a high percentage of non-mucinous ovarian tumors of epithelial origin³ and can be detected in serum.^{4,5} It does not occur on the surface epithelium of normal ovaries (adult and fetal). Ovarian carcinoma accounts for about 20 % of gynecological tumors; the incidence is 15/100000.⁶ CA 125 has been found in the amniotic fluid and in the coelomic epithelium; both of these tissues are of fetal origin. In tissues of adult origin, the presence of CA 125 has been demonstrated in the epithelium of the oviduct, in the endometrium and in the endocervix.⁷

Elevated values are sometimes found in various benign gynecological diseases such as ovarian cysts, ovarian metaplasia, endometriosis, uterus myomatosus or cervicitis.

Slight elevations of this marker may also occur in early pregnancy and in various benign diseases (e.g. acute and chronic pancreatitis, benign

gastrointestinal diseases, renal insufficiency, autoimmune diseases and others). Markedly elevated levels have been found in benign liver diseases such as cirrhosis and hepatitis. Extreme elevations can occur in any kind of ascites due to malignant and benign diseases. Although the highest CA 125 values occur in patients suffering from ovarian carcinoma, clearly elevated values are also observed in malignancies of the endometrium, breast, gastrointestinal tract and various other malignancies.

Although CA 125 is a relatively unspecific marker,^{8,9,10,11,12} it is today the most important tumor marker for monitoring the therapy and progress of patients with serous ovarian carcinoma. At primary diagnosis the sensitivity of CA 125 depends on the FIGO stage (FIGO = Federation of Gynecology and Obstetrics); higher tumor stages are associated with higher CA 125 levels.¹³ The diagnostic sensitivity and specificity of the Elecsys CA 125 II test was calculated by comparing ovarian carcinoma patients at primary diagnosis (FIGO stage I to IV) with patients suffering from benign gynecological diseases. At a cutoff value of 65 U/mL, the sensitivity is 79 % (at a low specificity of 82 %). The cutoff level has to be raised if higher specificity is desired. The optimal clinical value is reached at 150 U/mL (sensitivity 69 %, specificity 93 %). If the specificity is 95 %, in accordance with the recommendations of van Dalen, et al.,¹⁴ a sensitivity of 63 % is obtained (cutoff 190 U/mL).

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 20 µL of sample, a biotinylated monoclonal CA 125-specific antibody, and a monoclonal CA 125-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/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.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex (Ru(bpy)₃²⁺)

Reagents - working solutions

The reagent rackpack is labeled as CA 125 II.

- M Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative.
- R1 Anti-CA 125-Ab-biotin (gray cap), 1 bottle, 9 mL: Biotinylated monoclonal anti-CA 125 antibody (M11; mouse) 1 mg/L; phosphate buffer 100 mmol/L, pH 7.4; preservative.
- R2 Anti-CA 125-Ab-Ru(bpy)₃²⁺ (black cap), 1 bottle, 9 mL: Monoclonal anti-CA 125 antibody (OC 125; mouse) labeled with ruthenium complex 1 mg/L; phosphate buffer 100 mmol/L, pH 7.4; preservative.

Precautions and warnings

For in vitro diagnostic use for healthcare 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.

Contact phone: 1-800-428-2336

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	6 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, K₂-EDTA and K₃-EDTA plasma, as well as Li-heparin plasma tubes containing separating gel.

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

Stable for 5 days at 2-8 °C, 6 months at -20 °C.¹⁵

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.

Sample stability claims were established by experimental data by the manufacturer or based on reference literature and only for the temperatures/time frames as stated in the method sheet. It is the responsibility of the individual laboratory to use all available references and/or its own studies to determine specific stability criteria for its laboratory.

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

- [REF] 11776452160, PreciControl Tumor Marker, for 4 x 3.0 mL
- [REF] 07030207190, CA 125 II CalSet II, for 4 x 1.0 mL
- [REF] 03183971122, Diluent Universal, 2 x 36 mL sample diluent
- General laboratory equipment

cobas e analyzer

Additional materials for **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] 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] 11298500160, 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.

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 has been standardized against the Enzymun-Test CA 125 II method. This in turn has been standardized against the CA 125 II RIA from Fujirebio Diagnostics.

Elecsys CA 125 II

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 8 weeks 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 Tumor Marker 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 U/mL, U/L or kU/L.

Limitations - interference

The assay is unaffected by icterus (bilirubin < 1129 µmol/L or < 66 mg/dL), hemolysis (Hb < 2.0 mmol/L or < 3.2 g/dL), lipemia (Intralipid < 2000 mg/dL), and biotin (< 143 nmol/L or < 35 ng/mL).

Criterion: Recovery within ± 10 % of initial value.

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

No interference was observed from rheumatoid factors up to a concentration of 1200 IU/mL.

There is no high-dose hook effect at CA 125 concentrations up to 50000 U/mL.

In vitro tests were performed on 16 commonly used pharmaceuticals and 23 special drugs. No interference with the assay was found.

Testing was performed in 3-fold determination with 1 reagent lot in 1 run on 1 **cobas e 411** analyzer. The mean value was used to calculate the absolute deviation (U/mL, for samples ≤ 15 U/mL) and percent deviation (% , for samples > 15 U/mL) of the drug sample to the reference.

Criterion:

Limit of Quantitation to 15 U/mL: SD ≤ 1.5 U/mL recovery to reference

> 15-3000 U/mL: ≤ 10 % recovery to reference

Drug	Concentration
Carboplatin	1000 mg/L
Cisplatin	225 mg/L
Cyclophosphamide	1000 mg/L
Dexamethasone	20 mg/L
Doxorubicin	75 mg/L
Pegylated Liposomal Doxorubicin (CAELYX)	75 mg/L
Leucovorin	750 mg/L
Melphalan	15 mg/L

Drug	Concentration
Methotrexate	1000 mg/L
Paclitaxel	265 mg/L
5-FU	500 mg/L
Avastin	750 mg/L
Tarceva	150 mg/L
MabThera	750 mg/L
Herceptin	600 mg/L
Tamoxifen	50 mg/L
Mitomycin	25 mg/L
Etoposide	400 mg/L
Flutamide	1000 mg/L
Taxol	5.5 mg/L
Gemcitabine	1500 mg/L
Docetaxel (Taxotere)	112 mg/L
Lynparza (Olaparib)	800 mg/L

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

2.0-3000 U/mL (defined by the Limit of Quantitation and the maximum of the master curve). Values below the Limit of Quantitation are reported as < 2.0 U/mL. Values above the measuring range are reported as > 3000 U/mL (or up to 15000 U/mL for 5-fold diluted samples).

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 0.6 U/mL

Limit of Detection = 1.2 U/mL

Limit of Quantitation = 2.0 U/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 $n \geq 60$ 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 relative error of ≤ 20 %.

For Limit of Quantitation, 3 human serum samples were diluted and measured in 6 runs over ≥ 3 days on 2 analyzers with a total allowable relative error of ≤ 20 %.

Dilution

Samples with CA 125 concentrations above the measuring range can be diluted with Elecsys Diluent Universal. The recommended dilution is 1:5 (either automatically by the analyzers or manually). The concentration of the diluted sample must be > 600 U/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.

Note: In rare cases, sample-dependent non-linearity upon dilution is seen with samples having analyte levels beyond the measuring range.

Elecsys CA 125 II

Expected values

Studies were performed using the Elecsys CA 125 II assay. Of the 975 samples tested 240 were from healthy females (pre- and postmenopausal), and yielded a value of 38.1 U/mL (95th percentile). Elevated CA 125 concentrations can be found in samples from patients with serositis or other tumors besides ovarian carcinoma, endometrial carcinoma and carcinoma of the fallopian tube.

Subject	N	Mean U/mL	Median U/mL	Range U/mL	Reference range (5 th , 95 th Percentiles)
Apparently healthy subjects					
Postmenopause	120	14.8	12.5	4.10-47.9	6.20, 31.5
Premenopause	120	19.6	16.1	5.40-127	6.90, 45.9
Pre- and Postmenopausal subjects combined	240	17.2	14.1	4.10-127	6.40, 38.1

Subject	N	Mean U/mL	Median U/mL	Range U/mL	Reference range (5 th , 95 th Percentiles)
Premenopausal benign subjects					
Benign conditions - gynecological	219	53.5	23.5	5.00-995	8.90, 151
Benign conditions - other	2	11.2	11.2	9.50-12.9	9.50, 12.9
Hypertension	4	33.9	19.5	7.70-89.1	7.70, 89.1
Pregnant	40	20.7	18.0	11.5-64.9	12.2, 41.5
Postmenopausal benign subjects					
Benign conditions - gynecological	152	31.2	17.5	4.20-849	7.10, 81.8
Benign conditions - other	38	40.0	16.4	3.60-541	6.40, 183
Hypertension	36	19.4	15.9	6.00-61.8	6.20, 46.7

Subject	N	Mean U/mL	Median U/mL	Range U/mL	Reference range (5 th , 95 th Percentiles)
Premenopausal cancer subjects					
Bladder	2	23.0	23.0	6.40-39.6	6.40, 39.6
Breast	12	116	13.6	9.80-811	9.80, 811
Endometrial	12	84.5	22.4	9.50-656	9.50, 656
Gastrointestinal	9	25.8	24.0	13.3-46.3	13.3, 46.3
Lung	3	35.9	46.2	10.9-50.7	10.9, 50.7
Postmenopausal cancer subjects					
Bladder	37	29.5	18.5	4.40-215	5.80, 101
Breast	28	51.4	18.9	4.50-348	4.80, 206
Endometrial	28	88.4	19.7	6.90-1117	8.60, 273
Gastrointestinal	31	36.7	15.4	7.10-306	7.20, 231
Lung	37	32.4	29.5	9.30-64.3	10.6, 62.3
Epithelial ovarian cancer					
Cancer stages I-II Postmenopausal	9	85.2	57.4	13.5-284	13.5, 284

Subject	N	Mean U/mL	Median U/mL	Range U/mL	Reference range (5 th , 95 th Percentiles)
Cancer stages I-II Premenopausal	3	488	571	101-791	101, 791
Cancer stages III-IV Postmenopausal	28	1416	648	32.2-12500	59.1, 4116
Cancer stages III-IV Premenopausal	5	1247	880	105-2522	105, 2522

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 for human serum samples 1, 2, 3 and 4 at 1 site using 1 Elecsys reagent lot and controls in a protocol (EP5-A2) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplicate each for 20 days (n = 80). Precision was determined at another site for serum samples 5 and 6 using the same protocol. The following results were obtained:

cobas e 411 analyzer					
Sample	Mean U/mL	Repeatability		Intermediate precision	
		SD U/mL	CV %	SD U/mL	CV %
Human serum 1	14.7	0.460	3.1	0.609	4.1
Human serum 2	3.07	0.093	3.0	0.129	4.2
Human serum 3	2399	62.0	2.6	82.0	3.4
Human serum 4	35.0	0.681	1.9	1.04	3.0
Human serum 5	121	1.13	0.9	1.52	1.3
Human serum 6	330	3.61	1.1	4.45	1.3

Precision was determined using Elecsys reagents, samples and controls in a protocol (EP5-A2) 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 601 and cobas e 602 analyzers					
Sample	Mean U/mL	Repeatability		Intermediate precision	
		SD U/mL	CV %	SD U/mL	CV %
Human serum 1	15.1	0.121	0.8	0.326	2.2
Human serum 2	3.21	0.099	3.1	0.208	6.5
Human serum 3	2480	16.2	0.7	44.1	1.8
Human serum 4	35.5	0.301	0.8	0.710	2.0

Method comparison

A comparison of the Elecsys CA 125 II assay (y) with Fujirebio Diagnostics CA 125 RIA (x) using clinical samples gave the following correlations. Number of samples measured: 139

Passing/Bablok¹⁶

$$y = 0.93x + 5.57$$

$$r = 0.81$$

The sample concentrations were between 4 and 500 U/mL.

Elecsys CA 125 II

A comparison of the Elecsys CA 125 II assay with modified sample/reagent ratios (y) with the CA 125 II (x) using clinical samples gave the following correlations.

Number of samples measured: 80

Passing/Bablok¹⁶

$$y = 0.981x + 1.20$$

$$r = 0.966$$

The sample concentrations were between 4.7 and 2680 U/mL.

Analytical specificity

The Elecsys CA 125 II tumor marker assay is based on the monoclonal M11 and OC 125 antibodies which are only available from Fujirebio Diagnostics, its licensees and its representatives. The performance characteristics of test procedures using these antibodies cannot be assumed for test methods using other antibodies.

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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).

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.



CA 125 is a registered trademark of Fujirebio Diagnostics, Inc.

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):

	Contents of kit
	Analyzers/Instruments on which reagents can be used
	Reagent
	Calibrator
	Volume for reconstitution
	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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