Elecsys CA 125 II

cobas®

REF		Σ	SYSTEM
07026986190	07026986501	300	**cobas e** 402 **cobas e** 801

English

For use in the USA only

System information

Short name	ACN (application code number)
CA125 2	10018

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, K_2-EDTA and K_3-EDTA, as well as Li-heparin plasma tubes containing separating gel on **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 **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "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 kDa) 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 origin[3] 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: 12 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 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 CA125 2.

M Streptavidin-coated microparticles, 1 bottle, 14.1 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-CA 125-Ab~biotin, 1 bottle, 18.8 mL:
Biotinylated monoclonal anti-CA 125 antibody (M 11; mouse) 1 mg/L; phosphate buffer 100 mmol/L, pH 7.4; preservative.

R2 Anti-CA 125-Ab~$Ru(bpy)_3^{2+}$, 1 bottle, 18.8 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.

Exercise the normal precautions required for handling all laboratory reagents.

Disposal of all waste material should be in accordance with local guidelines.

Safety data sheet available for professional user on request.

For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

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

Warning

Elecsys CA 125 II

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H317	May cause an allergic skin reaction.

Prevention:

P261	Avoid breathing dust/fume/gas/mist/vapours/spray.
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 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.

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

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

Stable for 8 hours at 20-25 °C, 5 days at 2-8 °C, 24 weeks 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.

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 07030207190, CA 125 II CalSet II, for 4 x 1.0 mL
- REF 11776452160, PreciControl Tumor Marker, for 4 x 3.0 mL
- REF 07299001190, Diluent Universal, 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 11298500160, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution (for USA)

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

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 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.

Elecsys CA 125 II

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Calculation

The analyzer automatically calculates the analyte concentration of each sample (either in U/mL, U/L or kU/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	≤ 1130 µmol/L or ≤ 66 mg/dL
Hemoglobin	≤ 2.0 mmol/L or ≤ 3200 mg/dL
Intralipid	≤ 2000 mg/dL
Biotin	≤ 143 nmol/L or ≤ 35 ng/mL
Rheumatoid factors	≤ 1200 IU/mL

Criterion: For concentrations of 2.0-12 U/mL the deviation is ± 1.2 U/mL. For concentrations > 12 U/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 CA 125 concentrations up to 50000 U/mL.

Pharmaceutical substances
In vitro tests were performed on 16 commonly used pharmaceuticals. No interference with the assay was found.

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

Special cancer drugs

Drug	Concentration tested mg/L
Carboplatin	1000
Cisplatin L	225
Cyclophosphamide	1000
Dexamethasone	20
Doxorubicin	75
Leucovorin	750
Melphalan	15
Methotrexate	1000
Paclitaxel	265
5-FU	500
Avastin	750
Tarceva	150
MabThera	750
Herceptin	600
Tamoxifen	50
Mitomycin	25
Etoposide	400
Flutamide	1000
Taxol	5.5
Gemcitabine	1500
Docetaxel (Taxotere)	112
PEG lip.Doxorubicin (CAELYX)	75
Lynparza (Olaparib)	80

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 ≥ 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 CA 125 concentrations above the measuring range can be diluted with Diluent Universal. The recommended dilution is 1:5 (automatically by the analyzer 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.

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 (5th, 95th 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

Elecsys CA 125 II

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Subject	N	Mean U/mL	Median U/mL	Range U/mL	Reference range (5th, 95th 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
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
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 using Elecsys reagents, samples 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 U/mL	SD U/mL	CV %	SD U/mL	CV %
Human serum 1	2.38	0.0457	1.9	0.0541	3.4
Human serum 2	34.3	0.384	1.1	0.650	1.9
Human serum 3	1205	13.5	1.1	26.0	2.2
Human serum 4	2911	32.7	1.1	48.3	1.7
PreciControl TM[b)]1	29.1	0.452	1.6	0.619	2.1
PreciControl TM2	90.4	1.29	1.4	1.70	1.9

b) TM = Tumor Marker

Method comparison

A comparison of the Elecsys CA 125 II assay on the **cobas e** 801 analyzer (y) with the Elecsys CA 125 II assay on the **cobas e** 601 analyzer (x) gave the following correlations U/mL:

Number of samples measured: 150

Passing/Bablok[15]	Linear regression
y = 0.959x - 0.539	y = 0.996x - 6.62
τ = 0.993	r = 1.00

The sample concentrations were between approximately 2.70 and 2988 U/mL.

Analytical specificity

The Elecsys CA 125 II tumor marker assay is based on the monoclonal M 11 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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Elecsys CA 125 II

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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).

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FUJIREBIO Diagnostics, Inc.

CA 125 is a 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 dialog.roche.com for definition of symbols used):

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

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