Elecsys CA 125 II

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, K3-EDTA and K2-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 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 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 and can be detected in serum.3,4 It does not occur on the surface epithelium of normal ovaries (adult and fetal). Ovarian carcinoma accounts for about 29 % of gynecological tumors; the incidence is 15/100000.5 CA 125 has been found in the amniotic fluid and in the coelomic fluid; 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.6

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,6,8,9,10,11,12 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 specificity and sensitivity 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 complex6 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.

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)32−, 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

Materials provided
See "Reagents – working solutions" section for reagents.

Materials required (but not provided)
- 07030207190, CA 125 II CalSet II, for 4 x 1.0 mL
- 11776452160, PreciControl Tumor Marker, for 4 x 3.0 mL
- 07299001190, Diluent Universal, 36 mL sample diluent
- General laboratory equipment
  - cobas e analyzer
  - Additional materials for cobas e 402 and cobas e 801 analyzers:
    - 06908799190, ProCell II M, 2 x 2 L system solution
    - 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
    - 07485409001, Reservoir Cup, 8 cups to supply ProCell II M and CleanCell M
    - 0690853190, PreClean II M, 2 x 2 L wash solution
    - 05694302001, Assay Tip/Assay Cup tray, 6 magazines x 5 magazine stacks x 105 assay tips and 105 assay cups, 3 wasteliner cups
    - 07485425001, Liquid Flow Cleaning Cup, 2 adaptor cups to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning Detection Unit
    - 07485433001, PreWash Liquid Flow Cleaning Cup, 1 adaptor cup to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning PreWash Unit
    - 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.
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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

<table>
<thead>
<tr>
<th>Compound</th>
<th>Concentration tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>≤ 1130 μmol/L or ≤ 66 mg/dL</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≤ 2.0 mmol/L or ≤ 3200 mg/dL</td>
</tr>
<tr>
<td>Intralipid</td>
<td>≤ 2000 mg/dL</td>
</tr>
<tr>
<td>Biotin</td>
<td>≤ 143 nmol/L or ≤ 35 ng/mL</td>
</tr>
<tr>
<td>Rheumatoid factors</td>
<td>≤ 1200 IU/mL</td>
</tr>
</tbody>
</table>

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

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

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.

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

### Table: Results

<table>
<thead>
<tr>
<th>Subject</th>
<th>N</th>
<th>Mean U/mL</th>
<th>Median U/mL</th>
<th>Range U/mL</th>
<th>Reference range (5th, 95th Percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign conditions - gynecological</td>
<td>219</td>
<td>53.5</td>
<td>23.5</td>
<td>5.00-995</td>
<td>8.90, 151</td>
</tr>
<tr>
<td>Benign conditions - other</td>
<td>2</td>
<td>11.2</td>
<td>11.2</td>
<td>9.50-12.9</td>
<td>9.50, 12.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4</td>
<td>33.9</td>
<td>19.5</td>
<td>7.70-89.1</td>
<td>7.70, 89.1</td>
</tr>
<tr>
<td>Pregnant</td>
<td>40</td>
<td>20.7</td>
<td>18.0</td>
<td>11.5-64.9</td>
<td>12.2, 41.5</td>
</tr>
<tr>
<td>Benign conditions - gynecological</td>
<td>152</td>
<td>31.2</td>
<td>17.5</td>
<td>4.20-849</td>
<td>7.10, 81.8</td>
</tr>
<tr>
<td>Benign conditions - other</td>
<td>38</td>
<td>40.0</td>
<td>16.4</td>
<td>3.60-541</td>
<td>6.40, 183</td>
</tr>
<tr>
<td>Bladder</td>
<td>2</td>
<td>23.0</td>
<td>23.0</td>
<td>6.40-39.6</td>
<td>6.40, 39.6</td>
</tr>
<tr>
<td>Breast</td>
<td>12</td>
<td>116</td>
<td>13.6</td>
<td>9.80-811</td>
<td>9.80, 811</td>
</tr>
<tr>
<td>Endometrial</td>
<td>12</td>
<td>84.5</td>
<td>22.4</td>
<td>9.50-658</td>
<td>9.50, 656</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>9</td>
<td>25.8</td>
<td>24.0</td>
<td>13.3-46.3</td>
<td>13.3, 46.3</td>
</tr>
<tr>
<td>Lung</td>
<td>3</td>
<td>35.9</td>
<td>46.2</td>
<td>10.9-50.7</td>
<td>10.9, 50.7</td>
</tr>
<tr>
<td>Bladder</td>
<td>37</td>
<td>29.5</td>
<td>18.5</td>
<td>4.40-215</td>
<td>5.80, 101</td>
</tr>
<tr>
<td>Breast</td>
<td>28</td>
<td>51.4</td>
<td>18.9</td>
<td>4.50-348</td>
<td>4.80, 206</td>
</tr>
<tr>
<td>Endometrial</td>
<td>28</td>
<td>88.4</td>
<td>19.7</td>
<td>6.90-1117</td>
<td>8.60, 273</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>31</td>
<td>36.7</td>
<td>15.4</td>
<td>7.10-306</td>
<td>7.20, 231</td>
</tr>
<tr>
<td>Lung</td>
<td>37</td>
<td>32.4</td>
<td>29.5</td>
<td>9.30-64.3</td>
<td>10.6, 62.3</td>
</tr>
</tbody>
</table>

### Analytical specificity

The Elecsys CA 125 II 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.

### References

Elecsys CA 125 II


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).

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
- **STIN**
  - Volume for reconstitution
- **GTIN**
  - Global Trade Item Number

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