Cancer Antigen 125 (CLIA) PACKAGE INSERT

IVD

INTENDED USE

Cancer Antigen 125 (CLIA) is a chemiluminescence immunoassay test for the quantitative measurement of circulating Cancer Antigen 125 (CA 125) in human serum or plasma (Heparin lithium, EDTA), which is intended as an aid to assess the observation of the curative effect, the judgement of prognosis and the monitoring of recurrence of ovarian cancer.
The test must be performed on the ACCRE series analyzers (including ACCRE 6, ACCRE 8, ACCRE 90, ACCRE 100, ACCRE 120 and all other ACCRE series analyzers).

For *in vitro* diagnostic use only. For professional use only.

SUMMARY

Cancer Antigen 125 (CA 125) is a high molecular mass (200-1000 kDa) cell membrane glycoprotein present in normal endometrial tissue and serous and mucous fluids.[1] CA 125 is expressed by a high percentage of epithelial ovarian tumors and can be found in the serum of patients with such tumors.[2-3] Slightly elevated serum CA 125 levels may be seen in 1-2% of healthy individuals. In addition, minor elevations in serum CA 125 can also occur during menstruation, in the first trimester of pregnancy and in patients with certain benign conditions such as peritoneal or pleural inflammation, ovarian cysts and endometriosis. Patients with pancreatic, lung, breast, endometrial, colorectal and other gastrointestinal cancers may also have elevated CA 125 values.[4]
CA 125 is also recommended as an important and independent prognostic marker, a rapid fall in CA 125 during chemotherapy may indicate a favorable prognosis while rising serum levels correlate with disease progression.[4-6] Elevated, rising or doubling levels of CA 125 post-therapy may indicate relapse, although levels below the cut-off concentration do not necessarily exclude disease presence. [7] Due to the lack of sensitivity and specificity for a single determination, serum CA 125 is not recommended for use in screening asymptomatic women.[8-9] To monitor CA 125 levels in patients with previously treated epithelial ovarian cancer patients, multiple measurements of CA 125 are required. Normal is defined as patients with no evidence of disease or those not previously diagnosed with epithelial ovarian cancer. The upper limit of CA 125 concentrations in normal patients is approximately 35 U/mL. In patients diagnosed with previously treated epithelial ovarian cancer patients, values above 35 U/mL suggest the presence of disease and values below 35 U/mL suggest no evidence of disease. These results must be interpreted in conjunction with all other clinical and laboratory data before a medical decision is determined.

ASSAY PRINCIPLES

The Cancer Antigen 125(CLIA) hereinafter also referred to as the "CA125" is a two-sites immunoassay sandwich method with enzyme catalytic chemiluminescence detection (CLIA). The principle is described as following:
The sample was manually pipette into the sample well of reagent cartridge, then sample, CA 125 antibody labeled with alkaline phosphatase and CA 125 antibody labeled magnetic particles are mixed thoroughly together, incubating at 37°C. The analyte in the sample, labelled antibody and magnetic particles were bonded together as sandwich immuno-complex. The immuno-complex was then washed to eliminate the unbound components in the sample. The substrate was added to trigger the chemiluminescent reaction, the resulting chemiluminescent reaction was measured by photomultiplier tube (PMT) as relative light units (RLUs). At the end the results were automatically calculated by the instrument in relation to the calibration curve stored.

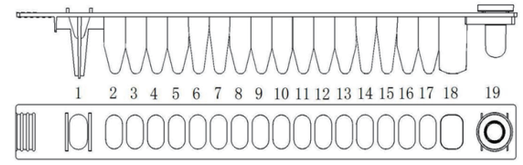
CONTENT OF THE KIT

Package: 60 tests/kit with quality controls, 36 tests/kit with quality controls,60 tests/kit without quality controls,36 tests/kit without quality controls

Contents	Quantities				Notice
	REF W104A	REF W104C	REF W137A	REF W137C	
CA 125 Reagents Cartridge	60 strips	36 strips	60 strips	36 strips	Ready to use
CA 125 Calibrator 1 (CAL1)	1.0 mL x 1 vial	1.0 mL x 1 vial	1.0 mL x 1 vial	1.0 mL x 1 vial	Mops buffer, 50mM; ProClin300, 0.5g/L; BND, 0.2g/L; BSA, 10g/L; Human Cancer Antigen 125, 10 U/mL
CA 125 Calibrator 2 (CAL2)	1.0 mL x 1 vial	1.0 mL x 1 vial	1.0 mL x 1 vial	1.0 mL x 1 vial	Mops buffer, 50mM; ProClin300, 0.5g/L; BND, 0.2g/L; BSA, 10g/L; Human Cancer Antigen 125, 500 U/mL
CA 125 Quality Control Level 1 (QC1)	1.0 mL x 1 vial	1.0 mL x 1 vial	/	/	Mops buffer, 50mM; ProClin300, 0.5g/L; BND, 0.2g/L; BSA, 10g/L; Human Cancer Antigen 125, 30 U/mL
CA 125 Quality Control Level 2 (QC2)	1.0 mL x 1 vial	1.0 mL x 1 vial	/	/	Mops buffer, 50mM; ProClin300, 0.5g/L; BND, 0.2g/L; BSA, 10g/L; Human Cancer Antigen 125, 150 U/mL
Instruction for Use	1	1	1	1	N/A
Reagent Registration Card	1	1	1	1	N/A
Calibrator Barcode Sheet	1	1	1	1	N/A
Quality Control Sheet	1	1	/	/	Only for the configurations with Quality Controls

Traceability: This method has been standardized against the Elecsys CA 125 II by cobas e 411 analyzer.

The Reagents Cartridge
The strip consists of 19 wells. The 1st well is the sample well and the last well 19th is the reading well for chemiluminescent signal. From the 2nd to the 18th well are all covered with a label, aluminum foil seal. The label comprises a barcode which mainly indicates the reagent assay information, reagent lot number and expiration date. All reagent components needed for the assay are ready-to-use and pre-dispensed in the cartridges. And please do not interchange integral component from different reagents or lots.



Description of The Reagent Cartridge

Well	Component	Content	Volume
5	Sample Diluent	Tris Buffer, 50mmol/L; ProClin300, 0.5g/L; BND, 0.2g/L; BSA, 5g/L	160ul
7	Magnetic Particles	Mouse anti-CA 125 antibody coated magnetic particles, 0.2g/L; Tris Buffer, 50mmol/L; ProClin300, 0.5g/L; BND, 0.2g/L	50μL
9	Enzyme Label	ALP (alkaline phosphatase) labeled mouse anti-CA 125 antibody , 2 μg/mL; MES Buffer, 50mmol/L; ProClin300, 0.5g/L; BND, 0.2g/L	50μL
10, 11, 12	Wash Solutions	Tris Buffer,50mmol/L; ProClin300,0.5g/L; BND,0.2g/L	350μL
16	Substrate	Disodium [(4-chlorophenyl)sulfanyl] (10-methyl-9(10H)-acridinylidene) methyl phosphate	200μL

Note: Well 1, 2, 3, 4, 6, 8,13,14,15,17,18 are empty.

MATERIALS AND DISPOSABLES REQUIRED BUT NOT PROVIDED

- Sample diluent (manufactured by Tisenc).
- Pipette with disposable tip to dispense 200 μL.
- Powderless, disposable gloves.
- For other specific materials and disposables, please refer to the Instrument User Manual.
- Instruments of the ACCRE series analyzers.

WARNINGS AND PRECAUTIONS

- For *in vitro* diagnostic use only.
- For professional use only by qualified laboratory personnel.
- The kit contains products of human origin. No known analysis method can totally guarantee the absence of transmissible pathogenic agents. It is therefore recommended that these products be treated as potentially infectious and handled observing the usual safety precautions (see Laboratory Biosafety Manual - WHO - Geneva - latest edition).
- This kit contains products of animal origin. Certified knowledge of the origin and/or sanitary state of the animals does not totally guarantee the absence of transmissible pathogenic agents. It is therefore recommended that these products be treated as potentially infectious, and handled observing the usual safety precautions (do not ingest; do not inhale).
- Do not use reagents after the expiration date indicated on the box label.
- Do not use if the packaging of reagent cartridge is damaged or leaked.
- Do not use the reagents if the quantity is obviously insufficient.
- If any component adhere to inside wall of wells or aluminum film of the reagent cartridge, please gently switch the reagent cartridge to let the component back the wells.
- Do not reverse the reagent cartridge. Otherwise, the result will be unreliable.
- Do not mix reagents (or disposables) from different lots.
- Package insert instructions must be carefully followed. Reliability of assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.
- Use powderless gloves, as powder has been reported to cause false results for certain enzyme immunoassay tests.

STORAGE

- Store the Cancer Antigen 125 (CLIA) kits **upright** at 2-8°C, kits can be stored for 18 months from manufactured date. After the reagent cartridge is on-board in the ACCRE analyzer, the testing should be finished within 2 hours.
- Store the calibrators and quality controls at 2-8°C till expiry date. When opened, the calibrators and/or controls will be stable for 30 days at 2-8°C and longer time at -20°C or below -20°C for 90 days. The calibrators and quality controls can only be frozen and thawed once.
- Keep away from sunlight.
- Do not freeze reagent cartridge.

SAMPLES

The sample volume for Cancer Antigen 125 (CLIA) assay is 40μL, please note that at least 65μL of sample has to be pipetted manually into the reagent cartridge.

Sample type and collection
Human serum or plasma (Heparin lithium or EDTA-K_2 or EDTA-K_3) are recommended.
Types of tubes:
- Plastic tube with clot activator,
- Plastic tube with clot activator and separation gel,
- Plastic tube with Heparin lithium,
- Plastic tube with EDTA-K_2,
- Plastic tube with EDTA-K_3.

It is recommended to validate collection tubes before using them as some may contain substances which interfere with test results.
Note: Blood sampling tube results may vary from one manufacturer to another depending on the materials and additives used.
It is the responsibility of each laboratory to validate the type of sample tube used and to follow the manufacturer's recommendations for use.

Sample preparation
The current revision of the WHO/DIL/LAB/99.1 document provides recommendations for the preparation of samples.
For use of the sample tubes, follow the tube manufacturer's instructions for use.
The pre-analytical step, including the preparation of blood samples, is an essential part of medical analyses. In accordance with Good Laboratory Practice, this step is performed under the responsibility of the laboratory manager.
Insufficient clot time can result in the formation of fibrin with micro-clots that are invisible to the naked eye. The presence of fibrin, red blood cells, or suspended particles can lead to erroneous results.
Samples containing suspended fibrin particles or erythrocyte stroma should be centrifuged before testing.
If there is a lipid layer over the sample after centrifuging, please transfer the clear sample into a new sample tube without transferring the lipid layer.
Severe hemolysis samples (hemoglobin >2000mg/dL) or heat-inactivated samples are not recommended for applying on the reagents.
Preparation of frozen-stored samples: after thawing, these samples must be thoroughly mixed before testing.
Mix using a vortex-type mixer. If necessary, clarify samples by centrifuging before testing.

Sample stability
Samples (serum and plasma) can be stored at room temperature (15-30° C) for up to 8 hours or at 2~8°C for up to 5 days; if longer storage is required, freeze the serum or

plasma at -20°C or below -20°C for up to 12 months, without exceeding 2 freeze/thaw cycles.

INSTRUCTIONS FOR USE

For complete instructions, see the Instrument User Manual.
When using the assay for the first time:
Register the assay using the registration code in the reagent kit before any assay is used in the ACCRE analyzer for the first time. Calibration, QC and sample test are only available after assay was registered successfully.

When opening a new lot of reagents:
Each new lot of reagent must be registered by using the registration code in Reagent Registration Card within the reagent kit.

Calibration
Calibration must be performed with the reagents and calibrators from Manufacturer.
Calibration is necessary under the following conditions:
(1) New reagent lot number applied;
(2) Same lot of reagents used more than 4 weeks;
(3) Quality control out of control;
(4) When necessary, for example: system maintenance or repair that may affect the analytic performance.

Test Procedure
1. Remove the kit from storage at 2-8°C and take out the required number of reagent cartridges. Allow the reagent cartridges, specimens, calibrators, and/or controls to equilibrate to room temperature (15-30°C) prior to testing.
2. Use each assay strips for each sample, calibrator or control respectively.
3. Place the reagent cartridges into the reagent rack.
4. Manually pipette the Samples, Calibrators or Controls into the sample well of each reagent cartridge.

Please note that at least 65μL of sample has to be pipetted manually into the reagent cartridge and 40μL sample is needed for each test.
(Before pipetting: Mix the samples using a vortex-type mixer if necessary, and ensure that the samples and sample diluent（if applicable) DO NOT have any bubbles. The same for calibrators and controls.)

5. Put the sample rack into the reagent chamber of the ACCRE analyzer.
6. Place the assay tips into the reagent chamber of the ACCRE analyzer.
7. Input Sample ID, sample type, dilution etc. into the software as directed by USER MANUAL.
8. **Cancer Antigen 125 (CLIA) assay will be completed within approximately 15 minutes.** Assays will be performed automatically by the ACCRE analyzer.
9. After the assay is completed, remove the reagent rack from the ACCRE analyzer. Dispose the used reagent cartridge into an appropriate recipient.

Dilution
Samples with concentrations above 5000 U/mL can be diluted with negative serum or plasma or sample diluent manually. The recommended dilution is 1:5. After manual dilution, multiply the result by the dilution factor. ACCRE analyzer cannot perform automatic dilution for samples.

Quality Control
Quality control should be performed in accordance with local regulations or requirements related to accreditation, as well as requirements defined in the laboratory's quality control procedure.

RESULTS AND INTERPRETATION

Calculation of Results
The results are automatically calculated by the ACCRE analyzer using stored calibration curve which generated by 2-point calibration, and calculated according to a predefined mathematical model, the results expressed in **U/mL.**

Interpretation of Results
Results of CA 125 assays are determined by testing specimens from a study in clinical centers with a group of totally 289 healthy adult individuals in China. The 95th percentile value is 35 U/mL.
** Please note that results may differ between laboratories due to variations in population and test method. If necessary, each laboratory should establish its own reference range.*

LIMITATIONS

1. For diagnostic purposes, results should be used in conjunction with other data; e.g., symptoms, results of other tests, clinical impressions, etc.
2. Please note that heterophile antibody in human serum or plasma can interfere the test result.
3. High concentration of HAMA can also cause a false positive or false negative result.
4. If the test results are inconsistent with clinical evidence, additional testing is suggested to confirm the result.
5. The detection range of the kit is 0.6 U/mL~5000 U/mL. Samples with Cancer Antigen 125 concentration below the upper detection limit can be quantified, if the concentration is above the upper detection limit, the results are reported as＞5000 U/mL. The product supports manual sample dilution of 1:5 and can be diluted with negative serum or plasma or sample diluent.

PERFORMANCE CHARACTERISTICS

Lower limit of measurement
LoB (Limit of Blank) =0.6 U/mL.
LoD (Limit of Detection) =1.2 U/mL.
LoB and LoD were determined in accordance with the CLSI® (Clinical and Laboratory Standards Institute) EP17-A2 requirements.

Measurement range
The measurement range is the range of values corresponding to the acceptable performance limits (precision and linearity).
The measurement range of the Cancer Antigen 125 (CLIA) assay is: 0.6 U/mL to 5000 U/mL.

Linearity
Linearity was evaluated according to CLSI® EP06-A recommendations. The Cancer Antigen 125 (CLIA) assay is linear between 0.6U/mL and 5000 U/mL. The absolute linear correlation coefficient(r) should be bigger than 0.9900.

Precision
A precision study was performed according to CLSI® EP05-A3 recommendations.
The Within-lot precision CV% is less than 10%.
The between-lot precision CV% is less than 10%.

Interfering Substances
Potential interference substances were studied according to CLSI® EP07-A3 recommendations. No significant interference was detected up to the maximum concentrations tested.

Substance	Concentration	Substance	Concentration
Hemoglobin	≤2000mg/dL	Total Protein	≤10g/dL
Bilirubin	≤66mg/dL	Rheumatoid factor	≤1200IU/mL
Triglyceride	≤2000mg/dL	/	/

Accuracy
A known concentration of high value CA125 samples was added to a low value serum sample, with recoveries ranging from 85% to 115%.

WASTE DISPOSAL

Dispose used or unused reagents as well as any other contaminated disposable materials following procedures for infectious or potentially infectious products.
It is the responsibility of each laboratory to handle waste and effluents produced according to their nature and degree of hazardousness and to treat and dispose of them (or have them treated and disposed of) in accordance with any applicable regulations.

INDEX OF SYMBOLS

Symbol	Meaning	Symbol	Meaning	Symbol	Meaning
	Consult instructions for use		Contains sufficient for <n> tests		Date of manufacture
IVD	*In vitro* diagnostic medical device		Use-by date		Do not re-use
	Temperature limit	LOT	Batch code	REF	Catalogue number
	Keep away from sunlight		Keep dry		Manufacturer
EU REP	Authorized representative in the European Community/ European Union		Do not use if package is damaged and consult instructions for use	BIO	Contains biological material of animal origin
	Biological risks		Caution	CE	CE marking
	Upright		Fragile, handle with care		Do not roll
CONTROL	Control				

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