Elecsys CEA

cobas®

REF		Σ	SYSTEM
07027079190* 07027079214*	07027079500	300	**cobas e** 402 **cobas e** 801

* Some kits shown may not be available in all countries.

English

System information

Short name	ACN (application code number)
CEA	10003

Please note

The measured CEA 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 CEA assay method used. CEA 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 CEA assay procedure used while monitoring therapy, then the CEA 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 carcinoembryonic antigen in human serum and plasma. This assay is further indicated for serial measurement of CEA to aid in the management of cancer patients.

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

Summary

Carcinoembryonic antigen (CEA) is a highly glycosylated molecule with a molecular weight of approximately 180 kDa.[1] CEA, like AFP, belongs to the group of carcinofetal antigens that are produced during the embryonic and fetal period. CEA has been postulated to play a role in a number of biological processes including cell adhesion, immunity and apoptosis.[2] The formation of CEA is suppressed after birth, and shows a low expression in normal adult tissues.[2] Therefore only very low CEA levels in the blood of healthy adults can be observed.[2] The CEA gene family consists of about 17 active genes in two subgroups. The first group contains CEA and the non-specific cross-reacting antigens (NCA); the second group contains the pregnancy-specific glycoproteins (PSG).[3] High CEA concentrations are frequently found in cases of colorectal adenocarcinoma.[4] Slight to moderate CEA elevations can also occur in non-malignant diseases of the intestine, the pancreas, the liver, and the lungs (i.e. liver cirrhosis, chronic hepatitis, pancreatitis, ulcerative colitis, Crohn's Disease).[5] Smoking can also lead to elevated CEA values and needs to be taken into account when interpreting CEA levels.[6] CEA determinations are not recommended for cancer-screening in the general population and CEA concentrations within the normal range do not exclude the possible presence of a malignant disease. The main indication for CEA determinations is to monitor colorectal carcinoma treatment, to identify recurrences after treatment or surgical resection and to aid in staging and assessing metastasis.[7]

Preoperative measurement of CEA is desirable as this may give independent prognostic information, help with surgical management and provide a baseline level for subsequent determinations. For patients with stage II and III, CEA levels should be measured every 2-3 months for at least 3 years after diagnosis. For monitoring treatment of advanced disease, CEA should also be tested every 2-3 months.[8,9] The antibodies inside the Elecsys CEA assay react with CEA and with the meconium antigen NCA-2[10,11] and especially the cross-reaction with NCA-2 was found to be useful in early detection of colorectal cancer metastasis and relapse.[12]

The antigenic determinants of CEA have been characterized, and the available monoclonal antibodies were classified into 5 epitope groups.[2,11] The antibodies used in the Elecsys CEA assay react with epitopes 2 and 5.

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 6 µL of sample, a biotinylated monoclonal CEA-specific antibody, and a monoclonal CEA-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 CEA.

M Streptavidin-coated microparticles, 1 bottle, 16.0 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-CEA-Ab~biotin, 1 bottle, 21.0 mL:
Biotinylated monoclonal anti-CEA antibody (mouse/human) 3.0 mg/L; phosphate buffer 100 mmol/L, pH 6.0; preservative.

R2 Anti-CEA-Ab~$Ru(bpy)_3^{2+}$, 1 bottle, 15.8 mL:
Monoclonal anti-CEA antibody (mouse) labeled with ruthenium complex 4.0 mg/L; phosphate buffer 100 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:

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.

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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 7 days at 20-25 °C, 14 days at 2-8 °C, 6 months at -20 °C (± 5 °C). The samples may be frozen 3 times.

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 11731645322, CEA CalSet, 4 x 1.0 mL
- REF 11776452122, PreciControl Tumor Marker, for 4 x 3.0 mL or REF 11731416190, PreciControl Universal, 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 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 1st IRP WHO Reference Standard 73/601.

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 or PreciControl Universal.

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 ng/mL or µg/L).

1 ng/mL CEA corresponds to 16.9 mIU/mL.

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	≤ 0.621 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 2000 mg/dL
Biotin	≤ 286 nmol/L or ≤ 70 ng/mL
Rheumatoid factors	≤ 1200 IU/mL

Criterion: Recovery ± 1 ng/mL of initial value ≤ 10 ng/mL and ± 10 % of initial value > 10 ng/mL.

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 CEA concentrations up to 200000 ng/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	225
Cyclophosphamide	1000
Doxorubicin	75
Etoposide	400
Fluorouracil	500
Flutamide	1000
Methotrexate	1000
Mitomycin	25
Tamoxifen	50
Taxol	5.5

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

0.3-1000 ng/mL (defined by the Limit of Blank and the maximum of the master curve). Values below the Limit of Blank are reported as < 0.3 ng/mL. Values above the measuring range are reported as > 1000 ng/mL (or up to 50000 ng/mL for 50-fold diluted samples).

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 0.3 ng/mL

Limit of Detection = 0.6 ng/mL

Limit of Quantitation = 1.8 ng/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 %.

An internal study was performed based on guidance from the CLSI protocol EP17-A2 . Limit of Blank and Limit of Detection were determined to be the following:

Limit of Blank = 0.134 ng/mL

Limit of Detection = 0.269 ng/mL

For Limit of Quantitation ≥ 4 human serum samples were measured over 5 days with 5 replicates per day on one analyzer. With an intermediate precision CV of ≤ 20 % the Limit of Quantitation was 0.403 ng/mL.

Dilution

Samples with CEA concentrations above the measuring range can be diluted with Diluent Universal. The recommended dilution is 1:50 (either automatically by the analyzer or manually). The concentration of the diluted sample must be ≥ 20 ng/mL).

After manual dilution, multiply the result by the dilution factor.

After dilution by the analyzer, the software automatically takes the dilution into account when calculating the sample concentration.

Expected values

Studies with the Elecsys CEA assay were performed on 352 healthy subjects. The following results were obtained:

	All subjects		Non-smokers (past/never smokers)		Smokers (current)	
Age (years)	20-69	40-69	20-69	40-69	20-69	40-69
95th percentile (ng/mL)	4.7	5.2	3.8	5.0	5.5	6.5
N	352	203	242	154	110	49

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 ng/mL	SD ng/mL	CV %	SD ng/mL	CV %
Human serum 1	0.863	0.0209	2.4	0.0227	2.6
Human serum 2	1.77	0.0486	2.8	0.0581	3.3
Human serum 3	3.77	0.0659	1.7	0.0823	2.2
Human serum 4	522	10.8	2.1	12.1	2.3
Human serum 5	930	20.5	2.2	21.3	2.3
PreciControl TM[b)]1	4.96	0.0797	1.6	0.103	2.1
PreciControl TM2	47.6	0.710	1.5	0.979	2.1
PreciControl U[c)]1	4.63	0.0758	1.6	0.104	2.2
PreciControl U2	47.6	0.744	1.6	0.851	1.8

b) TM = Tumor Marker

c) U = Universal

Method comparison

A comparison of the Elecsys CEA assay, REF 07027079190 (**cobas e** 801 analyzer; y) with the Elecsys CEA assay, REF 11731629322 (**cobas e** 601 analyzer; x) gave the following correlations (ng/mL):

Number of serum samples measured: 141

Passing/Bablok[13]	Linear regression
y = 1.02x + 0.021	y = 1.01x + 1.09
τ = 0.993	r = 1.00

The sample concentrations were between 0.641 and 965 ng/mL.

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A comparison of the Elecsys CEA assay, REF 07027079190 (**cobas e** 402 analyzer; y) with the Elecsys CEA assay, REF 07027079190 (**cobas e** 801 analyzer; x) gave the following correlations ng/mL):

Number of samples measured: 139

Passing/Bablok[13]	Linear regression
y = 0.979x + 0.183	y = 0.975x + 0.818
τ = 0.984	r = 1.00

The sample concentrations were between 0.488 and 986 ng/mL.

Analytical specificity

No investigations into possible cross-reactivity with glycoproteins from the lungs and liver have been performed.

References

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3 Thompson JA. Molecular cloning and expression of carcinoembryonic antigen gene family members. Tumor Biol 1995;16:10-16.

4 Ballesta AM, Molina R, Filella X, et al. Carcinoembryonic Antigen in Staging and Follow-up of Patients with Solid Tumors. Tumor Biol 1995;16:32-41.

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12 Hanada H, Muggi S, Takeoka K, et al. Early detection of colorectal cancer metastasis and relapse by recognizing non-specific cross-reacting antigen 2 in commercial carcinoembryonic antigen assays. Clin Chem 2009;55(9):1747-1748.

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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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