# CEA

cobas®

| REF | Σ | SYSTEM |
|---|---|---|
| **11731629** 160 | 100 | MODULAR ANALYTICS E170<br>**cobas e** 411<br>**cobas e** 601<br>**cobas e** 602 |

For USA: Elecsys CEA Assay

**English**

**For use in the USA only**

## System Information

For **cobas e** 411 analyzer: test number 301
For MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number 049

**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.
Caution: US Federal law restricts this device to sale and distribution by or on the order of a physician, or to a 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 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 Elecsys and **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 the follow-up and therapy-management of colorectal carcinoma.

The antigenic determinants of CEA have been characterized, and the available monoclonal antibodies were classified into 5 epitope groups.[2,7] 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: 10 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/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 ($Ru(bpy)_3^{2+}$)

## Reagents - working solutions

The reagent rackpack is labeled as CEA.

M Streptavidin-coated microparticles (transparent cap), 1 bottle, 8 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-CEA-Ab~biotin (gray cap), 1 bottle, 10 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~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 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.
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.

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 MODULAR ANALYTICS E170, **cobas e** 411 and **cobas e** 601 analyzers | 6 weeks |
| on **cobas e** 602 analyzer | 4 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 2-8 °C, 6 months at -20 °C (± 5 °C).[8]

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.

The claims, including those pertaining to sample stability made in the labeling of the cleared/approved reagents of Roche Diagnostics are part of the clearance/approval of the overall IVD test system (assay). Sample stability was tested only for the temperatures/time frame as claimed by the manufacturer under the conditions claimed 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 11731645322, CEA CalSet, for 4 x 1 mL
- REF 11776452160, PreciControl Tumor Marker, for 4 x 3 mL
  REF 11731416160, PreciControl Universal, for 4 x 3 mL
- REF 03183971122, Diluent Universal, 2 x 36 mL sample diluent
- General laboratory equipment
- MODULAR ANALYTICS E170 or **cobas e** analyzer

Accessories 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

Accessories for MODULAR ANALYTICS E170, **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

Accessories 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 (except for the **cobas e** 602 analyzer).

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 1st IRP WHO Reference Standard 73/601.

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 1 month (28 days) 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**

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 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 ng/mL or µg/L).

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

**Limitations - interference**

The assay is unaffected by icterus (bilirubin < 1129 µmol/L or < 66 mg/dL), hemolysis (Hb < 1.4 mmol/L or < 2.2 g/dL), lipemia (Intralipid < 1500 mg/dL) and biotin (< 491 nmol/L or < 120 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 1500 IU/mL.

There is no high-dose hook effect at CEA concentrations up to 200000 ng/mL.

In vitro tests were performed on 26 commonly used pharmaceuticals. No interference with the assay was found.

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

0.200-1000 ng/mL (defined by the lower detection limit and the maximum of the master curve). Values below the lower detection limit are reported as < 0.200 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 detection limit of the test

Lower detection limit: 0.200 ng/mL

The Lower Detection Limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying two standard deviations above that of the lowest standard (master calibrator, standard 1 + 2 SD, repeatability study, n = 21).

#### 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 analyzers 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 analyzers, 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, pooled human sera and controls in a modified protocol (EP5-A) of the CLSI (Clinical and Laboratory Standards Institute): 6 times daily for 10 days (n = 60); repeatability on MODULAR ANALYTICS E170 analyzer, n = 21. The following results were obtained:

| **cobas e** 411 analyzer | | | | | |
|---|---|---|---|---|---|
| | | Repeatability | | Intermediate precision | |
| Sample | Mean ng/mL | SD ng/mL | CV % | SD ng/mL | CV % |
| Human serum 1 | 2.2 | 0.11 | 5.0 | 0.12 | 5.4 |
| Human serum 2 | 19.6 | 0.32 | 1.6 | 0.44 | 2.3 |
| Human serum 3 | 528 | 6.82 | 1.3 | 10.6 | 2.0 |
| PreciControl TM[b)]1 | 4.9 | 0.12 | 2.5 | 0.18 | 3.6 |
| PreciControl TM2 | 34.1 | 0.58 | 1.7 | 1.02 | 3.0 |

b) TM = Tumor Marker

| MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers | | | | | | |
|---|---|---|---|---|---|---|
| | Repeatability | | | Intermediate precision | | |
| Sample | Mean ng/mL | SD ng/mL | CV % | Mean ng/mL | SD ng/mL | CV % |
| Human serum 1 | 3.32 | 0.05 | 1.3 | 3.90 | 0.18 | 4.7 |
| Human serum 2 | 225 | 2.53 | 1.0 | 252 | 11.6 | 4.6 |
| Human serum 3 | 626 | 11.8 | 1.9 | 699 | 34.8 | 5.0 |
| PreciControl TM1 | 4.38 | 0.10 | 2.5 | 4.74 | 0.24 | 5.1 |
| PreciControl TM2 | 33.8 | 0.73 | 2.0 | 34.9 | 1.71 | 4.9 |

#### Method comparison

A comparison of the Elecsys CEA assay (y) with the Enzymun-Test CEA method (x) using clinical samples gave the following correlations:

Number of samples measured: 108

| Passing/Bablok[9] | Linear regression |
|---|---|
| y = 0.91x + 0.06 | y = 0.90x + 0.04 |
| τ = 0.913 | r = 0.992 |

The sample concentrations were between 0.7 and 52 ng/mL.

#### Analytical specificity

For the monoclonal antibodies used, the following cross-reactivities were found:

NCA1 < 0.7 %, NCA2 72 %.

No cross-reactivity with AFP and $\alpha_1$-acid glycoprotein.

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

#### References

1 Thompson J, Zimmermann W. The carcinoembryonic antigen gene family: structure, expression and evolution. Tumour Biol 1988;9(2-3):63-83.

2 Hammarström S. The carcinoembryonic antigen (CEA) family: structures, suggested functions and expression in normal and malignant tissues. Semin Cancer Biol 1999;9(2):67-81.

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.

5 Ruibal Morell A. CEA serum levels in nonneoplastic disease. Int J Biol Markers 1992;7(3):160-166.

6 Fukuda I, Yamakado M, Kiyose H. Influence of Smoking on Serum Carcinoembryonic Antigen Levels in Subjects Who Underwent Multiphasic Health Testing and Services. J Med Syst 1998;22(2):89-93.

7 Bormer OP, Thrane-Steen K. Epitope group specificity of six immunoassays for carcino-embryonic antigen. Tumor Biol 1991;12:9-15.

8 Guder WG, Narayanan S, Wisser H, et al. List of Analytes; Pre-analytical Variables. Brochure in: Samples: From the Patient to the Laboratory. GIT-Verlag, Darmstadt 1996:10. ISBN 3-928865-22-6.

9 Bablok W, Passing H, Bender R, et al. A general regression procedure for method transformation. Application of linear regression procedures for method comparison studies in clinical chemistry, Part III. J Clin Chem Clin Biochem 1988 Nov;26(11):783-790.

For further information, please refer to the appropriate operator's manual for the analyzer concerned, the respective application sheets, the product information and the Method Sheets of all necessary components (if available in your country).

#### Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see https://usdiagnostics.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 after reconstitution or mixing |
| GTIN | Global Trade Item Number |

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