

REF



SYSTEM

07027028190

07027028500

300

cobas e 801

## English

### System information

Short name	ACN (application code number)
CA 19-9	10019

### Please note

The measured CA 19-9 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 19-9 assay method used. CA 19-9 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 19-9 assay procedure used while monitoring therapy, then the CA 19-9 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 CA 19-9 in human serum and plasma.

The electrochemiluminescence immunoassay "ECLIA" is intended for use on the **cobas e 801** immunoassay analyzer.

### Summary

CA 19-9 (carbohydrate antigen 19-9 or sialylated Lewis (a) antigen) is a biomarker which is primarily used in the management of pancreatic cancer patients in addition to other diagnostic methods.<sup>1</sup> The CA 19-9 antibody binds to the Lewis (a) antigen on a mucin.<sup>2,3</sup> Elevated concentrations are frequently present in the blood of patients with various gastrointestinal conditions, such as pancreatic-, colorectal-, gastric-, hepatocellular- and cholangiocellular carcinomas.<sup>4</sup>

No data exist today which support the use of CA 19-9 in screening for malignancies<sup>5</sup> also concerning the fact that approximately 6 % of the population belong to the Lewis (a-/b-) blood group, lacking the antigenic determinant CA 19-9 and will therefore not release CA 19-9 even when a malignancy is present. This must be taken into account when interpreting the findings.<sup>6</sup>

Among non-malignant conditions, obstructive jaundice is frequently associated with increases in CA 19-9<sup>7</sup> and unspecific elevation of CA 19-9 in serum reflects both inflammatory hypersecretion and leakage of biliary mucins into serum.<sup>8</sup> CA 19-9 levels have also been reported in benign diseases like cystic fibrosis, hydronephrosis, and Hashimoto's thyroiditis.<sup>9</sup>

In addition, there is a strong correlation between the serum CA 19-9 concentration and the degree of cholestasis as well as the levels of alkaline phosphatase and bilirubin during acute liver failure, acute hepatitis or chronic liver diseases.<sup>10,11</sup> The common underlying mechanism for elevations in non-malignant conditions is probably inflammatory hypersecretion of CA 19-9 by epithelial cells.

In pancreatic cancer, levels > 100 U/mL are highly suggestive of unresectability or metastatic disease and levels < 100 U/mL imply a likely resectable disease.<sup>12</sup>

The European Group of Tumor Markers (EGTM) advise that CA 19-9 may be used as a diagnostic aid and for monitoring therapy in patients with pancreatic adenocarcinoma.<sup>13</sup> CA 19-9 has been found to be prognostic for survival following resection of pancreatic ductal adenocarcinoma.<sup>14</sup>

In hepatobiliary carcinoma, CA 19-9 independently predicted a 2.6-fold increased mortality in a prospectively collected group of HCC patients in a multivariable analysis.<sup>15</sup> In colorectal cancer, CA 19-9 is described as an additional marker for disease monitoring in patients without an increase in CEA.<sup>16</sup>

### Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 6 µL of sample, a biotinylated monoclonal CA 19-9-specific antibody, and a monoclonal CA 19-9-specific antibody labeled with a ruthenium complex<sup>a)</sup> 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)<sub>3</sub><sup>2+</sup>)

### Reagents - working solutions

The **cobas e** pack is labeled as CA19-9.

- M Streptavidin-coated microparticles, 1 bottle, 14.1 mL:  
Streptavidin-coated microparticles 0.72 mg/mL; preservative.
- R1 Anti-CA 19-9-Ab~biotin, 1 bottle, 18.8 mL:  
Biotinylated monoclonal anti-CA 19-9 antibody (mouse) 3 mg/L,  
phosphate buffer 100 mmol/L, pH 6.5; preservative.
- R2 Anti-CA 19-9-Ab~Ru(bpy)<sub>3</sub><sup>2+</sup>, 1 bottle, 21.0 mL:  
Monoclonal anti-CA 19-9 antibody (mouse) labeled with ruthenium  
complex 4 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 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: 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 <b>cobas e</b> 801 analyzer	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<sub>2</sub>-EDTA and K<sub>3</sub>-EDTA plasma.

Do not use sodium citrate plasma.

Criterion: Slope 0.9-1.1 + coefficient of correlation  $\geq$  0.95.

Stable for 14 days at 2-8 °C, 5 days at 20-25 °C, 3 months at -20 °C ( $\pm$  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.

## Materials provided

See "Reagents – working solutions" section for reagents.

## Materials required (but not provided)

- [REF] 11776215122, CA 19-9 CalSet, for 4 x 1.0 mL
- [REF] 11776452122, PreciControl Tumor Marker, for 4 x 3.0 mL
- [REF] 07299001190, Diluent Universal, 45.2 mL sample diluent
- General laboratory equipment

- **cobas e** 801 analyzer

Accessories for the **cobas e** 801 analyzer:

- [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 Cups, 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 Enzymun-Test CA 19-9 method.

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.

## Calculation

The analyzer automatically calculates the analyte concentration of each sample (either in U/mL 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	$\leq$ 1130 $\mu$ mol/L or $\leq$ 66 mg/dL
Hemoglobin	$\leq$ 0.621 mmol/L or $\leq$ 1000 mg/dL
Intralipid	$\leq$ 1500 mg/dL
Biotin	$\leq$ 409 nmol/L or $\leq$ 100 ng/mL
Rheumatoid factors	$\leq$ 1200 IU/mL

Criterion: Recovery  $\pm$  4.5 U/mL of initial value for samples  $\leq$  30 U/mL and within  $\pm$  15 % of initial value for samples  $>$  30 U/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 CA 19-9 concentrations up to 500000 U/mL.

### Pharmaceutical substances

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



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- 5 Duffy MJ, van Dalen A, Haglund C. et al. Clinical Utility of Biochemical Markers in Colorectal Cancer: European Group on Tumour Markers (EGTM) Guidelines. *Eur J Cancer* 2003;39(6):718-727.
- 6 Orntoft TF, Holmes EH, Johnson P, et al. Differential Tissue Expression of the Lewis Blood Group Antigens: Enzymatic, Immunohistologic, and Immunochemical Evidence for Lewis a and b Antigen Expression in Le(a-b-) Individuals. *Blood* 1991;77(6):1389-1396.
- 7 Mann DV, Edwards R, Ho S, et al. Elevated tumor marker CA19.9: clinical interpretation and influence of obstructive jaundice. *Eur J Surg Oncol* 2000;26(5):474-479.
- 8 von Ritter C, Eder MI, Stieber P, et al. Biliary mucin secreted by cultured human gallbladder epithelial cells carries the epitope of CA 19-9. *Anticancer Res* 1997;17(4B):2931-2934.
- 9 Parra JL, Kaplan S, Barkin JS, et al. Elevated CA 19-9 Caused by Hashimoto's Thyroiditis: Review of the Benign Causes of Increased CA 19-9 Level. *Dig Dis Sci* 2005;50(4):694-695.
- 10 Maestranzi S, Przemioslo R, Mitchell H, et al. The effect of benign and malignant liver disease on the tumour markers CA19.9 and CEA. *Ann Clin Biochem* 1998;35(1):99-103.
- 11 Halme L, Karkkainen P, Isoniemi H, et al. Carbohydrate 19-9 antigen as a marker of non-malignant hepatocytic ductular transformation in patients with acute liver failure. A comparison with alpha-fetoprotein and carcinoembryonic antigen. *Scand J Gastroenterol* 1999;34(4):426-431.
- 12 Ballehaninna UK, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence based appraisal. *Journal of Gastrointestinal Oncology* 2012;3(2):105-119.
- 13 Duffy MJ, Sturgeon C, Lamerz R, et al. Tumor markers in pancreatic cancer: a European Group on Tumor Markers (EGTM) status report. *Annals of Oncol* 2010;21: 441-447.
- 14 NCCN Guidelines 2.2015 Pancreatic Adenocarcinoma; [http://www.nccn.org/professionals/physician\\_gls/pdf/pancreatic.pdf](http://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf)
- 15 Hsu CC, Goyal A, Iuga A, et al. Elevated CA19-9 Is Associated With Increased Mortality In A Prospective Cohort Of Hepatocellular Carcinoma Patients. *Clin Transl Gastroenterol* 2015; 6: e74.
- 16 Stikma J, Grootendorst DC, van den Linden PW. CA19-9 As a Marker in Addition to CEA to Monitor Colorectal Cancer. *Clin Colorectal Cancer* 2014;13(4): 239-244.
- 17 Suresh MR. Immunoassays for cancer-associated carbohydrate antigens. *Semin Cancer Biol* 1991 Dec;2(6):367-377.
- 18 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).

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.



CA 19-9 is a registered trademark of Fujirebio Diagnostics, Inc.

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](http://dialog.roche.com) for definition of symbols used):

	Contents of kit
	Analyzers/Instruments on which reagents can be used
	Reagent
	Calibrator
	Volume after reconstitution or mixing
	Global Trade Item Number

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