Elecsys CK-MB

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REF		Σ	SYSTEM
07027087190* 07027087214*	07027087500	100	**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)	Application
CKMB	10041	18 minutes
CKMBST	10058	9 minutes (STAT = Short Turn Around Time)

Intended use

Immunoassay for the in vitro quantitative determination of the MB isoenzyme of creatine kinase in human serum and plasma.

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

Summary

Measurements of CK-MB, measured with this device, in human serum and plasma, are used as an aid in diagnosis of myocardial infarction.

Creatine kinase (CK) is a dimeric enzyme which occurs in 4 different forms: a mitochondrial isoenzyme and the cytosolic isoenzymes CK-MM (muscle type), CK-BB (brain type) and CK-MB (muscle-brain type).[1,2]

CK-MB is an important biomarker of acute myocardial infarction and other causes of myocardial injury, such as heart failure and myocarditis.[3] CK-MB is detectable in the blood about 3-8 hours after the onset of cardiac symptoms and can remain detectable over a lengthy period of time, depending on the course of the condition.[1]

CK-MB may also appear in other clinical conditions, e.g. in rhabdomyolysis and stroke.[1,4] Within the scope of laboratory diagnostics, the determination of total CK, troponin T and/or myoglobin can contribute to the differentiation of these clinical pictures. Because of their higher sensitivity and specificity, cardiac troponins, measured by high-sensitivity assays, are the preferred biomarkers to define myocardial infarction,[3] and if a troponin assay is not available, the best alternative is CK-MB measured by a mass assay.[3]

The sensitivity of a CK-MB determination is dependent upon the time at which a sample was taken. Follow-up assays are therefore meaningful.[1,5]

The Elecsys CK-MB assay employs two different monoclonal antibodies directed against human CK-MB.

Test principle

Sandwich principle.

Total duration of assay: 18 minutes.

- 1st incubation: 9 µL of sample, a biotinylated monoclonal anti-CK-MB antibody, and a monoclonal CK-MB-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.

Total duration of assay: 9 minutes.

- During a 9 minute incubation, antigen in the sample (9 µL), a biotinylated monoclonal anti-CK-MB antibody, a monoclonal CK-MB-specific antibody labeled with a ruthenium complex and streptavidin-coated microparticles react to form a sandwich complex, which is bound to the solid phase.

For both assay applications:

- 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 CKMB.

M Streptavidin-coated microparticles, 1 bottle, 7.2 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-CK-MB-Ab~biotin, 1 bottle, 9.9 mL:
Biotinylated monoclonal anti-CK-MB antibody (mouse) 1.2 mg/L; phosphate buffer 100 mmol/L, pH 7.0; preservative.

R2 Anti-CK-MB-Ab~$Ru(bpy)_3^{2+}$, 1 bottle, 9.9 mL:
Monoclonal anti-CK-MB antibody (mouse) labeled with ruthenium complex 1.2 mg/L; phosphate buffer 100 mmol/L, pH 7.0; preservative.

Precautions and warnings

For in vitro diagnostic use for laboratory 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.

Disposal:

P501 Dispose of contents/container to an approved waste disposal plant.

Hazardous components:

- 2-methyl-2H-isothiazol-3-one hydrochloride

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).

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Reagent handling

The Elecsys CK-MB assay can be used for both the 9-minute application and the 18-minute application.

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 + intercept within ≤ ± 0.5x Limit of Detection + coefficient of correlation ≥ 0.95.

Stable for 5 hours at 20-25 °C, 12 hours at 2-8 °C, 3 months at -20 °C (± 5 °C). Freeze only once.

CK-MB stability is extremely temperature-dependent. A CK-MB decrease of > 10 % can occur after the sample has stood for 1 hour at 32 °C.

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 07394667190, CalSet CK-MB, for 4 x 1.0 mL
- REF 04917049190, PreciControl Cardiac II, for 4 x 2.0 mL
- REF 07299010190, Diluent MultiAssay, 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: The Elecsys CK-MB assay is traceable to the Abbott IMx CK-MB assay and linearized using human recombinant CK-MB[6] from Seradyn.

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:

- every 12 weeks when using the same reagent lot
- every 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

Use PreciControl Cardiac II or other suitable controls for routine quality control procedures.

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).

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	≤ 581 µmol/L or ≤ 34 mg/dL
Hemoglobin	≤ 0.621 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 1500 mg/dL
Albumin	≤ 20 g/dL
Biotin	≤ 123 nmol/L or ≤ 30 ng/mL
Rheumatoid factors	≤ 1500 IU/mL
IgG	≤ 7.0 g/dL
IgA	≤ 1.6 g/dL
IgM	≤ 1.0 g/dL

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Criterion: For concentrations of 0.3-5 ng/mL the deviation is ± 1 ng/mL. For concentrations > 5 ng/mL the deviation is ± 20 %.

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 CK-MB concentrations up to 5000 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 cardiac drugs were tested. No interference with the assay was found.

Special cardiac drugs

Drug	Concentration tested mg/L
Carvedilol	37.5
Clopidogrel	75
Digoxin	0.25
Epinephrine (Adrenaline)	0.50
Insulin	1.60
Lidocaine	80.0
Lisinopril	10.0
Methylprednisolone	7.50
Metoprolol	150
Nifedipine	30.0
Phenprocoumon	3.00
Propafenone	300
Reteplase	33.3
Simvastatin	30.0
Spironolactone	75.0
Tolbutamide	1500
Torasemide	15.0
Verapamil	240

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

0.3-300 ng/mL (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 0.3 ng/mL. Values above the measuring range are reported as > 300 ng/mL (or up to 600 ng/mL for 2-fold diluted samples).

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 0.1 ng/mL

Limit of Detection = 0.3 ng/mL

Limit of Quantitation = 1 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 %.

Dilution

Samples with CK-MB concentrations above the measuring range can be diluted with Diluent MultiAssay. The recommended dilution is 1:2 (either automatically by the analyzers or manually). The concentration of the diluted sample must be ≥ 50 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

The values below were obtained in two studies (Kiel I and Kiel II) using the Elecsys CK-MB assay (4th generation). The calculation is based on samples from 879 apparently healthy volunteers (463 women, 416 men).

	N	Median ng/mL	97.5th percentile ng/mL	99th percentile ng/mL
Women	463	1.39	3.61	4.88
Men	416	1.72	4.87	6.22

When myocardial infarction is suspected the diagnostic strategy proposals in the consensus documents of European and American cardiologists should in general be followed.[3,7,8]

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 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 (18-minute application)					
		Repeatability		Intermediate precision	
Sample	Mean ng/mL	SD ng/mL	CV %	SD ng/mL	CV %
Human serum 1	1.62	0.048	3.0	0.058	3.6
Human serum 2	5.04	0.101	2.0	0.154	3.1
Human serum 3	9.54	0.179	1.9	0.272	2.9
Human serum 4	166	3.55	2.1	4.55	2.7
Human serum 5	291	5.91	2.0	8.71	3.0
PC[b)] Cardiac II 1	5.40	0.100	1.9	0.168	3.1
PC Cardiac II 2	56.8	1.03	1.8	1.49	2.6

b) PC = PreciControl

cobas e 402 and **cobas e** 801 analyzers (9-minute application)					
		Repeatability		Intermediate precision	
Sample	Mean ng/mL	SD ng/mL	CV %	SD ng/mL	CV %
Human serum 1	1.57	0.033	2.1	0.048	3.0
Human serum 2	4.98	0.093	1.9	0.141	2.8
Human serum 3	9.43	0.167	1.8	0.273	2.9

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cobas e 402 and **cobas e** 801 analyzers (9-minute application)					
		Repeatability		**Intermediate precision**	
Sample	Mean ng/mL	SD ng/mL	CV %	SD ng/mL	CV %
Human serum 4	170	2.80	1.6	4.07	2.4
Human serum 5	294	4.69	1.6	8.72	3.0
PC Cardiac II 1	5.26	0.117	2.2	0.213	4.0
PC Cardiac II 2	56.6	1.27	2.2	2.77	4.9

Method comparison

a) A comparison of the Elecsys CK-MB assay, REF 07027087190 (9-minute application; y) with the Elecsys CK-MB assay, REF 07027087190 (18-minute application; x) on the **cobas e** 801 analyzer gave the following correlations (ng/mL):

Number of samples measured: 149

Passing/Bablok[9]	Linear regression
y = 1.009x - 0.015	y = 1.017x + 0.002
τ = 0.990	r = 0.999

The sample concentrations were between 0.341 and 296 ng/mL.

b) A comparison of the Elecsys CK-MB assay, REF 07027087190 (9-minute application, **cobas e** 801 analyzer; y) with the Elecsys CK-MB STAT assay, REF 05957648190 (**cobas e** 601 analyzer; x) gave the following correlations (ng/mL):

Number of samples measured: 151

Passing/Bablok[9]	Linear regression
y = 1.035x - 0.144	y = 1.078x - 1.24
τ = 0.989	r = 0.999

The sample concentrations were between 0.381 and 274 ng/mL.

c) A comparison of the Elecsys CK-MB assay, REF 07027087190 (**cobas e** 402 analyzer; y) with the Elecsys CK-MB assay, REF 07027087190 (**cobas e** 801 analyzer; x) gave the following correlations (ng/mL):

Number of samples measured: 150

Passing/Bablok[9]	Linear regression
y = 0.988x + 0.015	y = 0.951x + 0.963
τ = 0.988	r = 0.999

The sample concentrations were between 0.892 and 298 ng/mL.

Analytical specificity

For the monoclonal antibodies used the following cross-reactivities were found: CK-MM n. d.*, CK-BB n. d.*

*n. d. = not detectable

References

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4 Ay H, Arsava EM, Saribas O. Creatine Kinase-MB Elevation After Stroke is not cardiac in origin. Stroke 2002;(33)286-289.

5 Apple FS. Diagnostic markers for detection of acute myocardial infarction and reperfusion. Laboratory Medicine 1992;23(5):297-322.

6 Christenson RH, Vaidya H, Landt Y, et al. Standardization of Creatine Kinase-MB (CK-MB) Mass Assays: The Use of Recombinant CK-MB as a Reference Material. Clin Chem 1999;45(9):1414-1423.

7 Collet JP, Thiele H, Barbato E, et al.; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021 Apr 7;42(14):1289-1367.

8 Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021 Nov 30;144(22):e368-e454

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 user guide or 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:

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
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

CE 0123

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