CK

Creatine Kinase

Order information

REF		CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
08057460190*	08057460500	Creatine Kinase (500 tests)	System-ID 2042 001	**cobas c** 303, **cobas c** 503, **cobas c** 703
08057460214*	08057460500	Creatine Kinase (500 tests)	System-ID 2042 001	**cobas c** 303, **cobas c** 503, **cobas c** 703

Materials required (but not provided):

10759350190	Calibrator f.a.s. (12 x 3 mL)	Code 20401	
05117003190	PreciControl ClinChem Multi 1 (20 x 5 mL)	Code 20391	
05947626190	PreciControl ClinChem Multi 1 (4 x 5 mL)	Code 20391	
05117216190	PreciControl ClinChem Multi 2 (20 x 5 mL)	Code 20392	
05947774190	PreciControl ClinChem Multi 2 (4 x 5 mL)	Code 20392	
08063494190	Diluent NaCl 9 % (123 mL)	System-ID 2906 001	

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

English

System information

CK2: ACN 20420

Intended use

In vitro test for the quantitative determination of creatine kinase (CK) in human serum and plasma on **cobas c** systems.

Summary

Measurements of creatine kinase (CK), performed with this assay in human serum and plasma, are used as an aid in diagnosis of muscular injuries and diseases.

CK is a dimeric enzyme occurring in 4 different forms: a mitochondrial isoenzyme and the cytosolic isoenzymes CK MM (skeletal muscle type), CK BB (brain type) and CK MB (myocardial type).[1] Elevated total CK is observed in patients with skeletal and heart muscle injuries and diseases.[2]

The determination of CK and CK isoenzyme activities is utilized in the diagnosis and monitoring of muscular injuries and diseases in the acute (e.g. rhabdomyolysis or acute myocardial injury) and chronic settings (e.g. myopathies such as the progressive Duchenne muscular dystrophy). In acute rhabdomyolysis, for example, serum CK activities above 200 times the upper reference limit may be found. Serum CK activity is elevated in all types of muscular dystrophy.[3] In progressive muscular dystrophy, enzyme activity in serum may be increased long before the disease is clinically apparent.[3]

Following injury to the myocardium, such as occurs with acute myocardial infarction,[1] CK is released from the damaged myocardial cells. In early cases, a rise in the CK activity can be found just 4 hours after an infarction.[1,4] The CK activity reaches a maximum after 12-24 hours and then falls back to the normal range after 3-4 days.[1,4] According to the 4th Universal Definition of Myocardial Infarction, cardiac troponins are the preferred biomarkers for the evaluation of myocardial injury, since other biomarkers are less specific and less sensitive.[5]

The determination of CK levels can also be used for evaluation of drug toxicity. The European Society of Cardiology and the European Atherosclerosis Society recommend measuring CK in patients before initiation of lipid-lowering drug therapy, and in patients on lipid-lowering drugs, presenting with muscle pain and weakness, in order to identify the limited number of patients where treatment is contraindicated.[6]

The assay method using creatine phosphate and ADP was first described by Oliver,[7] modified by Rosalki[8] and further improved for optimal test conditions by Szasz et al.[9] CK is rapidly inactivated by oxidation of the sulfhydryl groups in the active center. The enzyme can be reactivated by the addition of acetylcysteine (NAC).[9] Interference by adenylate kinase is prevented by the addition of diadenosine pentaphosphate[10] and AMP.[9,10]

Standardized methods for the determination of CK with activation by NAC were recommended by the German Society for Clinical Chemistry (DGKC)[10] in 1977 and the International Federation of Clinical Chemistry (IFCC)[11] in 1991. In 2002 the IFCC confirmed their recommendation and extended it to 37 °C.[12,13] The method described here is derived from the formulation recommended by the IFCC and was optimized for performance and stability.

Test principle

UV-test

$$\text{Creatine phosphate} + \text{ADP} \xrightarrow{\text{CK}} \text{creatine} + \text{ATP}$$

$$\text{ATP} + \text{D-glucose} \xrightarrow{\text{HK}} \text{ADP} + \text{G6P}$$

$$\text{G6P} + \text{NADP}^+ \xrightarrow{\text{G6PDH}} \text{D-6-phosphogluconate} + \text{NADPH} + \text{H}^+$$

Equimolar quantities of NADPH and ATP are formed at the same rate. The photometrically measured rate of formation of NADPH is directly proportional to the CK activity.

Reagents - working solutions

R1 Imidazole buffer: 123 mmol/L, pH 6.5 (37 °C); EDTA: 2.46 mmol/L; Mg^{2+}: 12.3 mmol/L; ADP: 2.46 mmol/L; AMP: 6.14 mmol/L; diadenosine pentaphosphate: 19 µmol/L; $NADP^+$ (yeast): 2.46 mmol/L; N-acetylcysteine: 24.6 mmol/L; HK (yeast): ≥ 36.7 µkat/L; G6PDH (E. coli): ≥ 23.4 µkat/L; preservative; stabilizers; additives.

R3 CAPSO* buffer: 20 mmol/L, pH 8.8 (37 °C); glucose: 120 mmol/L; EDTA: 2.46 mmol/L; creatine phosphate: 184 mmol/L; preservative; stabilizers.

*CAPSO: 3-(cyclohexylamine)-2-hydroxy-1-propanesulfonic acid

R1 is in position B and R3 is in position C.

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:

CK

Creatine Kinase

Danger

H360D	May damage the unborn child.

Prevention:

P201	Obtain special instructions before use.
P202	Do not handle until all safety precautions have been read and understood.
P280	Wear protective gloves/ protective clothing/ eye protection/ face protection/ hearing protection.

Response:

P308 + P313	IF exposed or concerned: Get medical advice/attention.

Storage:

P405	Store locked up.

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

Reagent handling

Ready for use

Storage and stability

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label.
On-board in use and refrigerated on the analyzer:	8 weeks

Specimen collection and preparation

For specimen collection and preparation only use suitable tubes or collection containers.

Only the specimens listed below were tested and found acceptable.
Serum: Nonhemolyzed serum is the specimen of choice and also recommended by IFCC.
Plasma: Li-heparin, K_2-, K_3-EDTA plasma.

Please note: Differences in the degree of hemolysis resulting from the blood sampling procedure used can lead to deviating results in serum and plasma.

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.

See the limitations and interferences section for details about possible sample interferences.

Stability in serum:[14]	2 days at 20-25 °C
	7 days at 4-8 °C
	4 weeks at -20 °C (± 5 °C)

Freeze only once.

Stability in EDTA/heparin plasma:	2 days at 15-25 °C
	7 days at 2-8 °C
	4 weeks at -20 °C (± 5 °C)

Freeze only once.

Materials provided

See “Reagents – working solutions” section for reagents.

Materials required (but not provided)

See “Order information” section

General laboratory equipment

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.

The performance of applications not validated by Roche is not warranted and must be defined by the user.

Application for serum and plasma

Test definition

Reporting time	10 min		
Wavelength (sub/main)	546/340 nm		
Reagent pipetting		Diluent (H_2O)	
R1	79 µL	–	
R3	16 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	2.2 µL	–	–
Decreased	2.2 µL	10 µL	100 µL
Increased	2.2 µL	–	–

For further information about the assay test definitions refer to the application parameters setting screen of the corresponding analyzer and assay.

Calibration

Calibrators	S1: H_2O
	S2: C.f.a.s.
Calibration mode	Linear
Calibration frequency	Automatic full calibration - after reagent lot change
	Full calibration - as required following quality control procedures

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Traceability: This method has been standardized against the IFCC Method for Creatine Kinase.[12]

Quality control

For quality control, use control materials as listed in the “Order information” section. In addition, other suitable control material can be used.

The control intervals and limits should be adapted to each laboratory’s individual requirements. It is recommended to perform quality control always after lot calibration and subsequently at least every 8 weeks. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

Follow the applicable government regulations and local guidelines for quality control.

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Calculation

cobas c systems automatically calculate the analyte activity of each sample in the unit U/L (µkat/L).

Conversion factor: U/L x 0.0167 = µkat/L

Limitations - interference

Criterion: Recovery within ± 10 % of initial value at a creatine kinase activity of 140 U/L.

Icterus:[15] No significant interference up to an I index of 60 for conjugated and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 1026 µmol/L or 60 mg/dL).

Hemolysis:[15] No significant interference up to an H index of 100 (approximate hemoglobin concentration: 62.1 µmol/L or 100 mg/dL). The level of interference may be variable depending on the exact content of erythrocytes.

Lipemia (Intralipid):[15] No significant interference up to an L index of 1000. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration. Highly lipemic specimens (L index > 1000) may cause high absorbance flagging.

Drugs: No interference was found at therapeutic concentrations using common drug panels.[16,17] Cyanokit (hydroxocobalamin) at therapeutic concentrations interferes with the test.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[18]

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

ACTION REQUIRED

Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on **cobas c** systems. All special wash programming necessary for avoiding carry-over is available via the **cobas** link. The latest version of the carry-over evasion list can be found with the NaOHD/SMS/SCCS Method Sheet. For further instructions refer to the operator's manual.

Limits and ranges

Measuring range

7-2000 U/L (0.12-33.4 µkat/L)

Determine samples having higher activities via the rerun function. Dilution of samples via the rerun function is a 1:11 dilution. Results from samples diluted by the rerun function are automatically multiplied by a factor of 11.

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank	= 7 U/L (0.12 µkat/L)
Limit of Detection	= 7 U/L (0.12 µkat/L)
Limit of Quantitation	= 7 U/L (0.12 µkat/L)

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 activity 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 activity samples.

The Limit of Detection corresponds to the lowest analyte activity which can be detected (value above the Limit of Blank with a probability of 95 %).

The Limit of Quantitation is the lowest analyte activity that can be reproducibly measured with a total error of 20 %. It has been determined using low activity creatine kinase samples.

Expected values

Reference intervals strongly depend on the patient group and the specific clinical situation.

U/L

For healthy people, according to Klein et al.:[19]

CK	Men	39-308 U/L
	Women	26-192 U/L

Consensus values:[20]

CK	Men	< 190 U/L
	Women	< 170 U/L
CK-MB	Men/women	< 25 U/L

Myocardial infarction: There is a high probability of myocardial damage when the following 3 conditions are fulfilled:[21]

1	CK_{men}	> 190 U/L
	CK_{women}	> 167 U/L
2	CK-MB	> 24 U/L
3	The CK-MB activity accounts for 6-25 % of the total CK-activity.	

According to Tietz:[22]

CK	Adult males > 19 years	20-200 U/L
	Adult females > 19 years	20-180 U/L

µkat/L

For healthy people, according to Klein et al.:[19]*

CK	Men	0.65-5.14 µkat/L
	Women	0.43-3.21 µkat/L

*calculated by unit conversion factor

Consensus values:[20]

CK	Men	< 3.20 µkat/L
	Women	< 2.85 µkat/L
CK-MB	Men/women	< 0.42 µkat/L

Myocardial infarction: There is a high probability of myocardial damage when the following 3 conditions are fulfilled:[21]

1	CK_{men}	> 3.17 µkat/L
	CK_{women}	> 2.79 µkat/L
2	CK-MB	> 0.40 µkat/L
3	The CK-MB activity accounts for 6-25 % of the total CK-activity.	

According to Tietz:[22]*

CK	Adult males > 19 years	0.33-3.34 µkat/L
	Adult females > 19 years	0.33-3.01 µkat/L

*calculated by unit conversion factor

The reference values according to Klein et al. are based on the 95th percentile of a group of healthy persons (202 men and 217 women) not involved in high-intensity athletic activities.

In order to ensure high sensitivity in the diagnosis of heart diseases the values given by Tietz are recommended. The loss of diagnostic specificity thereby incurred can be compensated for by additionally determining CK-MB and/or troponin T. When myocardial infarction is suspected the diagnostic strategy proposals in the consensus document of European and American cardiologists should in general be followed.[23]

If despite the suspicion of myocardial infarction the values found remain below the stated limits, a fresh infarction may be involved. In such cases, the determinations should be repeated after 4 hours.

CK varies with physical activity level and race in healthy individuals.[22,24]

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

CK

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Specific performance data

Representative performance data on the analyzers are given below. These data represent the performance of the analytical procedure itself.

Results obtained in individual laboratories may differ due to heterogenous sample materials, aging of analyzer components and mixture of reagents running on the analyzer.

Precision

Precision was determined using human samples and controls in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP05-A3 requirements with repeatability (n = 84) and intermediate precision (2 aliquots per run, 2 runs per day, 21 days). Results for repeatability and intermediate precision were obtained on the **cobas c** 503 analyzer.

Repeatability	*Mean* *U/L*	*SD* *U/L*	*CV* *%*
PCCC1[a)]	155	0.764	0.5
PCCC2[b)]	287	0.988	0.3
Human serum 1	19.5	0.524	2.7
Human serum 2	85.7	0.510	0.6
Human serum 3	176	1.12	0.6
Human serum 4	900	3.28	0.4
Human serum 5	1588	4.52	0.3

Intermediate precision	*Mean* *U/L*	*SD* *U/L*	*CV* *%*
PCCC1[a)]	155	1.04	0.7
PCCC2[b)]	287	2.02	0.7
Human serum 1	19.4	0.582	3.0
Human serum 2	85.7	1.01	1.2
Human serum 3	176	1.96	1.1
Human serum 4	895	10.7	1.2
Human serum 5	1588	18.7	1.2

a) PreciControl ClinChem Multi 1

b) PreciControl ClinChem Multi 2

The data obtained on **cobas c** 503 analyzer(s) are representative for **cobas c** 303 analyzer(s) and **cobas c** 703 analyzer(s).

Method comparison

Creatine kinase values for human serum and plasma samples obtained on a **cobas c** 503 analyzer (y) were compared with those determined using the corresponding reagent on a **cobas c** 501 analyzer (x).

Sample size (n) = 80

Passing/Bablok[25]	Linear regression
y = 0.988x + 1.20 U/L	y = 0.993x - 0.788 U/L
τ = 0.996	r = 1.000

The sample activities were between 8.20 and 1938 U/L.

Creatine kinase values for human serum and plasma samples obtained on a **cobas c** 303 analyzer (y) were compared with those determined using the corresponding reagent on a **cobas c** 501 analyzer (x).

Sample size (n) = 110

Passing/Bablok[25]	Linear regression
y = 1.006x + 0.553 U/L	y = 1.013x - 1.03 U/L
τ = 0.990	r = 1.000

The sample activities were between 11.0 and 1959 U/L.

Creatine kinase values for human serum and plasma samples obtained on a **cobas c** 703 analyzer (y) were compared with those determined using the corresponding reagent on a **cobas c** 503 analyzer (x).

Sample size (n) = 75

Passing/Bablok[25]	Linear regression
y = 1.004x + 0.512 U/L	y = 1.006x - 0.256 U/L
τ = 0.995	r = 1.000

The sample concentrations were between 51.2 and 1939 U/L.

References

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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 navifyportal.roche.com for definition of symbols used):

CONTENT	Contents of kit
→	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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