CREP2

cobas®

Creatinine plus ver.2

Order information

REF	CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
05168589 190	Creatinine plus ver.2 (600 tests)	System-ID 05 6612 7	Roche/Hitachi **cobas c** 701/702
10759350 360	Calibrator f.a.s. (12 x 3 mL)	Code 401	
12149435 160	Precinorm U plus (10 x 3 mL)	Code 300	
12149443 160	Precipath U plus (10 x 3 mL)	Code 301	
03121313 122	Precinorm PUC (4 x 3 mL)	Code 240	
03121291 122	Precipath PUC (4 x 3 mL)	Code 241	
05947626 160	PreciControl ClinChem Multi 1 (4 x 5 mL)	Code 391	
05947774 160	PreciControl ClinChem Multi 2 (4 x 5 mL)	Code 392	
05172152 190	Diluent NaCl 9 % (119 mL)	System-ID 08 6869 3	

English

For use in the USA only

System information

CREA2: ACN 8452 (serum and plasma)

CRE2U: ACN 8152 (urine)

Intended use

In vitro assay for the quantitative determination of creatinine in human serum, plasma and urine on Roche/Hitachi **cobas c** systems.

Summary[1,2,3,4,5]

Chronic kidney disease is a worldwide problem that carries a substantial risk for cardiovascular morbidity and death. Current guidelines define chronic kidney disease as kidney damage or glomerular filtration rate (GFR) less than 60 mL/min per 1.73 m^2 for three months or more, regardless of cause.

The assay of creatinine in serum or plasma is the most commonly used test to assess renal function. Creatinine is a break-down product of creatine phosphate in muscle, and is usually produced at a fairly constant rate by the body (depending on muscle mass). It is freely filtered by the glomeruli and, under normal conditions, is not re-absorbed by the tubules to any appreciable extent. A small but significant amount is also actively secreted.

Since a rise in blood creatinine is observed only with marked damage of the nephrons, it is not suited to detect early stage kidney disease. A considerably more sensitive test and better estimation of glomerular filtration rate (GFR) is given by the creatinine clearance test based on creatinine's concentration in urine and serum or plasma, and urine flow rate. For this test a precisely timed urine collection (usually 24 hours) and a blood sample are needed. However, since this test is prone to error due to the inconvenient collection of timed urine, mathematical attempts to estimate GFR based only on the creatinine concentration in serum or plasma have been made. Among the various approaches suggested, two have found wide recognition: that of Cockroft and Gault and that based on the results of the MDRD trial. While the first equation was derived from data obtained with the conventional Jaffé method, a newer version of the second is usable for IDMS-traceable creatinine methods. Both are applicable for adults. In children, the Bedside Schwartz formula is used.[6,7,8,9]

In addition to the diagnosis and treatment of renal disease, the monitoring of renal dialysis, creatinine measurements are used for the calculation of the fractional excretion of other urine analytes (e. g., albumin, α-amylase). Numerous methods were described for determining creatinine. Automated assays established in the routine laboratory include the Jaffé alkaline picrate method in various modifications, as well as enzymatic tests.

Test principle

This enzymatic method is based on the conversion of creatinine with the aid of creatininase, creatinase, and sarcosine oxidase to glycine, formaldehyde and hydrogen peroxide. Catalyzed by peroxidase the liberated hydrogen peroxide reacts with 4-aminophenazone and HTIB[a] to form a quinone imine chromogen. The color intensity of the quinone imine chromogen formed is directly proportional to the creatinine concentration in the reaction mixture.

a) 2,4,6-triiodo-3-hydroxybenzoic acid

$$\text{creatinine} + H_2O \xrightarrow{\text{creatininase}} \text{creatine}$$

$$\text{creatine} + H_2O \xrightarrow{\text{creatinase}} \text{sarcosine} + \text{urea}$$

$$\text{sarcosine} + O_2 + H_2O \xrightarrow{\text{SOD}} \text{glycine} + HCHO + H_2O_2$$

$$H_2O_2 + \text{4-aminophenazone} + \text{HTIB}^{b} \xrightarrow{\text{POD}} \text{quinone imine chromogen} + H_2O + HI$$

b) 2,4,6-triiodo-3-hydroxybenzoic acid

Creatine of the sample is destroyed by creatinase, SOD and catalase during incubation in R1.

Reagents - working solutions

R1 TAPS buffer (N-Tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid): 30 mmol/L, pH 8.1; creatinase (microorganisms): ≥ 332 µkat/L; sarcosine oxidase (microorganisms): ≥ 132 µkat/L; ascorbate oxidase (microorganisms): ≥ 33 µkat/L; catalase (microorganisms): ≥ 1.67 µkat/L; HTIB: 1.2 g/L; detergents; preservative

R3 TAPS buffer: 50 mmol/L, pH 8.0; creatininase (microorganisms): ≥ 498 µkat/L; peroxidase (horseradish): ≥ 16.6 µkat/L; 4-aminophenazone: 0.5 g/L; potassium hexacyanoferrate (II): 60 mg/L; detergent; preservative

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

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.

Reagent handling

Ready for use

Storage and stability

CREP2

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label.
On-board in use and refrigerated on the analyzer:	4 weeks
On-board on the Reagent Manager:	24 hours

CREP2

Creatinine plus ver.2

Diluent NaCl 9 %

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label.
On-board in use and refrigerated on the analyzer:	4 weeks
On-board on the Reagent Manager:	24 hours

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.
Plasma: Li-heparin and K_2-EDTA 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.

Urine.

Collect urine without using additives. If urine must be collected with a preservative for other analytes, only hydrochloric acid (14 to 47 mmol/L urine, e.g. 5 mL 10 % HCl or 5 mL 30 % HCl per liter urine) or boric acid (81 mmol/L, e.g. 5 g per liter urine) may be used.

Centrifuge samples containing precipitates before performing the assay.

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

Sample stability claims were established by experimental data by the manufacturer or based on reference literature and only for the temperatures/time frames as stated 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.

Stability in *serum/plasma:* [10]	7 days at 15-25 °C
	7 days at 2-8 °C
	3 months at (-15)-(-25) °C
Stability in *urine* (without preservative):[10]	2 days at 15-25 °C
	6 days at 2-8 °C
	6 months at (-15)-(-25) °C
Stability in *urine* (with preservative):	3 days at 15-25 °C
	8 days at 2-8 °C
	3 weeks at (-15)-(-25) °C

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

cobas c 701/702 **test definition**

Assay type	2-Point End	
Reaction time / Assay points	10/22-38	
Wavelength (sub/main)	700/546 nm	
Reaction direction	Increase	
Units	µmol/L (mg/dL, mmol/L)	
Reagent pipetting		Diluent (H_2O)
R1	77 µL	–
R3	38 µL	–

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	2 µL	–	–
Decreased	5 µL	15 µL	135 µL
Increased	2 µL	–	–

A correction value of -4 µmol/L (-0.045 mg/dL) is required for this creatinine procedure.

Enter the correction value as the instrument factor **y = ax + b** for µmol/L or mg/dL, where **a = 1.0** and **b = -4** (µmol/L) or **a = 1.0** and **b = -0.045** (mg/dL).

Application for urine

cobas c 701/702 **test definition**

Assay type	2-Point End	
Reaction time / Assay points	10/22-38	
Wavelength (sub/main)	700/546 nm	
Reaction direction	Increase	
Units	µmol/L (mg/dL, mmol/L)	
Reagent pipetting		Diluent (H_2O)
R1	77 µL	–
R3	38 µL	–

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	5 µL	3 µL	147 µL
Decreased	2 µL	3 µL	147 µL
Increased	5 µL	3 µL	147 µL

A correction value of -120 µmol/L (-1.36 mg/dL) is required for this creatinine procedure.

Enter the correction value as the instrument factor **y = ax + b** for µmol/L or mg/dL, where **a = 1.0** and **b = -120** (µmol/L) or **a = 1.0** and **b = -1.36** (mg/dL).

Calibration

Calibrators	S1: H_2O
	S2: C.f.a.s.
Calibration mode	Linear

Calibration frequency	Blank calibration - after 4 weeks during shelf life 2-point calibration - after reagent lot change - 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 ID/MS.

Quality control

Serum/plasma

For quality control, use control materials as listed in the "Order information" section.

In addition, other suitable control material can be used.

Urine

For quality control, use Precinorm PUC and Precipath PUC 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. 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.

Calculation

Roche/Hitachi **cobas c** systems automatically calculate the analyte concentration of each sample.

Conversion factors:	µmol/L x 0.0113 = mg/dL
	µmol/L x 0.001 = mmol/L

Limitations - interference

Criterion: Recovery within ± 10 % of initial values at creatinine concentrations of 80 µmol/L (0.9 mg/dL) in serum and 2500 µmol/L (28.3 mg/dL) in urine.

Serum/plasma

Icterus:[11] No significant interference up to an I index of 15 for conjugated bilirubin and 20 for unconjugated bilirubin (approximate conjugated bilirubin concentration: 257 µmol/L or 15 mg/dL; approximate unconjugated bilirubin concentration: 342 µmol/L or 20 mg/dL).

Hemolysis:[11] No significant interference up to an H index of 800 (approximate hemoglobin concentration: 497 µmol/L or 800 mg/dL).

Lipemia (Intralipid):[11] No significant interference up to an L index of 2000. There is a poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Ascorbic acid: No significant interference from ascorbic acid up to a concentration of 1.70 mmol/L (300 mg/L).

Drugs: No interference was found at therapeutic concentrations using common drug panels.[12,13] Exceptions: Rifampicin, Levodopa and Calcium dobesilate (e.g. Dexium) cause artificially low creatinine results. As tested according to CLSI recommendation Methyldopa causes artificially low creatinine results.[14]

N-ethylglycine at therapeutic concentrations and DL-proline at concentrations ≥ 1 mmol/L (≥ 115 mg/L) give falsely high results.

Creatine: No significant interference from creatine up to a concentration of 4 mmol/L (524 mg/L).

Hemolyzed samples from neonates, infants or adults with HbF values ≥ 600 mg/dL interfere with the test.[15]

2-Phenyl-1,3-indandion (phenindion) at therapeutic concentrations interferes with the assay.

Dicynone (Etamsylate) at therapeutic concentrations may lead to falsely low results.[16]

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[17]

Estimation of the glomerular filtration rate (GFR) on the basis of the Schwartz formula can lead to an overestimation.[18]

Acetaminophen intoxications are frequently treated with N-Acetylcysteine. N-Acetylcysteine at a plasma concentration above 333 mg/L and the Acetaminophen metabolite N-acetyl-p-benzoquinone imine (NAPQI) independently may cause falsely low results.

Venipuncture should be performed prior to the administration of Metamizole. Venipuncture immediately after or during the administration of Metamizole may lead to falsely low results. A significant interference may occur at any plasma Metamizole concentration.

Urine

Icterus: No significant interference up to a conjugated bilirubin concentration of 1197 µmol/L or 70 mg/dL.

Hemolysis: No significant interference up to a hemoglobin concentration of 621 µmol/L or 1000 mg/dL.

Ascorbic acid: No significant interference from ascorbic acid up to a concentration of 22.7 mmol/L (4000 mg/L).

Glucose: No significant interference from glucose up to a concentration of 120 mmol/L (2162 mg/dL).

Urobilinogen: No significant interference from urobilinogen up to a concentration of 676 µmol/L (40 mg/dL).

Urea: No significant interference from urea up to a concentration of 2100 mmol/L (12612 mg/dL).

Drugs: No interference was found at therapeutic concentrations using common drug panels.[13] As tested according to CLSI recommendation α-methyldopa, Levodopa and Calcium dobesilate (e.g. Dexium) cause artificially low creatinine results.

Dicynone (Etamsylate) at therapeutic concentrations may lead to falsely low results.

High homogentisic acid concentrations in urine samples lead to false results.

Acetaminophen, Acetylcysteine and Metamizole are metabolized quickly. Therefore, interference from these substances is unlikely but cannot be excluded.

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 Roche/Hitachi **cobas c** systems. All special wash programming necessary for avoiding carry-over is available via the **cobas** link, manual input is required in certain cases. The latest version of the carry-over evasion list can be found with the NaOHD/SMS/SmpCln1+2/SCCS Method Sheet and for further instructions refer to the operator's manual.

Where required, special wash/carry-over evasion programming must be implemented prior to reporting results with this test.

Limits and ranges

Measuring range

Serum/plasma

5-2700 µmol/L (0.06-30.5 mg/dL)

The technical limit in the instrument setting is defined as 9-2704 µmol/L (0.105-30.6 mg/dL) due to the instrument factor of -4 µmol/L (-0.045 mg/dL). Manually edit the lower technical limit to 9 µmol/L (0.105 mg/dL).

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:4 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 4.

Urine

100-54000 µmol/L (1.1-610 mg/dL)

The technical limit in the instrument setting is defined as 220-54120 µmol/L (2.46-612 mg/dL) due to the instrument factor of -120 µmol/L (-1.36 mg/dL). Manually edit the lower technical limit to 220 µmol/L (2.46 mg/dL).

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:2.5 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 2.5.

Lower limits of measurement

Lower detection limit of the test

Serum/plasma

5 µmol/L (0.06 mg/dL)

The lower detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying 3 standard deviations above that of the lowest standard (standard 1 + 3 SD, repeatability, n = 21).

Urine

100 µmol/L (1.1 mg/dL)

The lower detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying 3 standard deviations above that of the lowest standard (standard 1 + 3 SD, repeatability, n = 21).

Expected values

Serum/plasma

Adults[19]		
Females	45-84 µmol/L	(0.51-0.95 mg/dL)
Males	59-104 µmol/L	(0.67-1.17 mg/dL)
Children[20]		
Neonates (premature)	29-87 µmol/L	(0.33-0.98 mg/dL)
Neonates (full term)	27-77 µmol/L	(0.31-0.88 mg/dL)
2-12 m	14-34 µmol/L	(0.16-0.39 mg/dL)
1-< 3 y	15-31 µmol/L	(0.18-0.35 mg/dL)
3-< 5 y	23-37 µmol/L	(0.26-0.42 mg/dL)
5-< 7 y	25-42 µmol/L	(0.29-0.47 mg/dL)
7-< 9 y	30-47 µmol/L	(0.34-0.53 mg/dL)
9-< 11 y	29-56 µmol/L	(0.33-0.64 mg/dL)
11-< 13 y	39-60 µmol/L	(0.44-0.68 mg/dL)
13-< 15 y	40-68 µmol/L	(0.46-0.77 mg/dL)

Urine

1st morning urine[19]		
Females	2.55-20.0 mmol/L	(29-226 mg/dL)
Males	3.54-24.6 mmol/L	(40-278 mg/dL)
24-hour urine[21]		
Females	6-13 mmol/24 h	(720-1510 mg/24 h)
Males	9-19 mmol/24 h	(980-2200 mg/24 h)
Creatinine clearance[21]	66-143 mL/min	

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

Roche has not evaluated reference ranges in a pediatric population.

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using human samples and controls in an internal protocol with repeatability (n = 21) and intermediate precision (3 aliquots per run, 1 run per day, 21 days). The following results were obtained:

Serum/plasma

Repeatability	*Mean*	*SD*	*CV*
	µmol/L (mg/dL)	*µmol/L (mg/dL)*	*%*
Precinorm U	86.2 (0.974)	0.7 (0.008)	0.8
Precipath U	353 (3.99)	2 (0.023)	0.6
Human serum A	68.3 (0.772)	0.7 (0.008)	1.1
Human serum B	202 (2.28)	1 (0.011)	0.6
Human serum C	2286 (25.8)	12 (0.136)	0.5
Intermediate precision	*Mean*	*SD*	*CV*
	µmol/L (mg/dL)	*µmol/L (mg/dL)*	*%*
Precinorm U	94.9 (1.07)	1.4 (0.02)	1.4
Precipath U	338 (3.82)	4 (0.05)	1.1
Human serum 3	190 (2.15)	2 (0.02)	1.1
Human serum 4	395 (4.46)	5 (0.06)	1.2

Urine

Precision was determined using human samples and controls in an internal protocol with repeatability (n = 21) and intermediate precision (3 aliquots per run, 1 run per day, 10 days). The following results were obtained:

Repeatability	*Mean*	*SD*	*CV*
	µmol/L (mg/dL)	*µmol/L (mg/dL)*	*%*
Control Level 1	8445 (95.4)	44 (0.5)	0.5
Control Level 2	4406 (49.8)	38 (0.4)	0.9
Human urine A	2339 (26.4)	21 (0.2)	0.9
Human urine B	19793 (224)	120 (1)	0.6
Human urine C	47582 (538)	366 (4)	0.8
Intermediate precision	*Mean*	*SD*	*CV*
	µmol/L (mg/dL)	*µmol/L (mg/dL)*	*%*
Control Level 1	7219 (81.6)	112 (1.3)	1.5
Control Level 2	14018 (158)	212 (2)	1.5
Human urine 3	17326 (196)	244 (3)	1.4
Human urine 4	7008 (79.2)	104 (1.2)	1.5

Results for intermediate precision were obtained on the master system **cobas c** 501 analyzer.

Method comparison

Creatinine values for human serum, plasma and urine samples obtained on a Roche/Hitachi **cobas c** 701 analyzer (y) were compared with those determined using the corresponding reagent on a Roche/Hitachi **cobas c** 501 analyzer (x).

Serum/plasma

Sample size (n) = 145

Passing/Bablok[22]	Linear regression
y = 0.996x - 0.759 µmol/L	y = 0.992x - 0.407 µmol/L
τ = 0.992	r = 1.00

The sample concentrations were between 48 and 2674 µmol/L (0.542 and 30.2 mg/dL).

Urine

Sample size (n) = 118

Passing/Bablok[22]	Linear regression
y = 1.03x + 34.3 µmol/L	y = 1.02x + 82.2 µmol/L
τ = 0.992	r = 1.00

The sample concentrations were between 427 and 49327 µmol/L (4.83 and 557 mg/dL).

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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
→	Volume after reconstitution or mixing
GTIN	Global Trade Item Number

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