

REF	CONTENT	Analyzer(s) on which <b>cobas c</b> pack(s) can be used
03263991 190	Creatinine plus ver.2 250 tests	System-ID 07 6612 7 Roche/Hitachi <b>cobas c</b> 311, <b>cobas c</b> 501/502
10759350 190	Calibrator f.a.s. (12 x 3 mL)	Code 401
10759350 360	Calibrator f.a.s. (12 x 3 mL, for USA)	Code 401
12149435 122	Precinorm U plus (10 x 3 mL)	Code 300
12149435 160	Precinorm U plus (10 x 3 mL, for USA)	Code 300
12149443 122	Precipath U plus (10 x 3 mL)	Code 301
12149443 160	Precipath U plus (10 x 3 mL, for USA)	Code 301
10171743 122	Precinorm U (20 x 5 mL)	Code 300
10171735 122	Precinorm U (4 x 5 mL)	Code 300
10171778 122	Precipath U (20 x 5 mL)	Code 301
10171760 122	Precipath U (4 x 5 mL)	Code 301
03121313 122	Precinorm PUC (4 x 3 mL)	Code 240
03121291 122	Precipath PUC (4 x 3 mL)	Code 241
05117003 190	PreciControl ClinChem Multi 1 (20 x 5 mL)	Code 391
05947626 190	PreciControl ClinChem Multi 1 (4 x 5 mL)	Code 391
05947626 160	PreciControl ClinChem Multi 1 (4 x 5 mL, for USA)	Code 391
05117216 190	PreciControl ClinChem Multi 2 (20 x 5 mL)	Code 392
05947774 190	PreciControl ClinChem Multi 2 (4 x 5 mL)	Code 392
05947774 160	PreciControl ClinChem Multi 2 (4 x 5 mL, for USA)	Code 392
04489357 190	Diluent NaCl 9 % (50 mL)	System-ID 07 6869 3

**English****System information****cobas c** 311/501 analyzers**CREA2:** ACN 452 (serum, plasma, urine)**cobas c** 502 analyzer**CREA2:** ACN 8452 (serum, plasma)**CRE2U:** ACN 8152 (urine)**Intended use**

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

**Summary**<sup>1,2,3,4,5</sup>

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<sup>2</sup> 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.

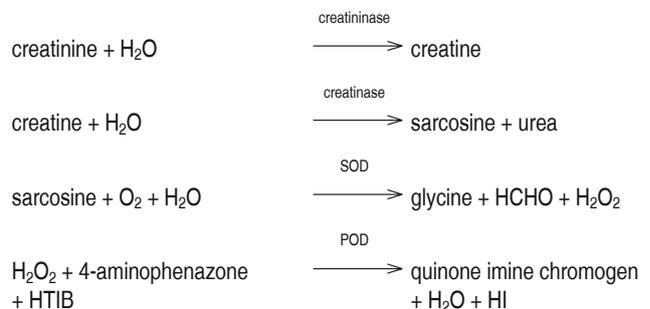
Since a rise in blood creatinine is observed only with marked damage of the nephrons, it is not suited to detect early stage kidney disease. A considerably more sensitive test and better estimation of glomerular filtration rate (GFR) is given by the creatinine clearance test based on creatinine's concentration 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 Cockcroft 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 should be used.<sup>6,7,8,9</sup>

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<sup>a</sup> 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.



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

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



**Reagents - working solutions**

- R1** TAPS buffer (N-Tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid): 30 mmol/L, pH 8.1; creatinase (microorganisms):  $\geq 332 \mu\text{kat/L}$ ; sarcosine oxidase (microorganisms):  $\geq 132 \mu\text{kat/L}$ ; ascorbate oxidase (microorganisms):  $\geq 33 \mu\text{kat/L}$ ; catalase (microorganisms):  $\geq 1.67 \mu\text{kat/L}$ ; HTIB: 1.2 g/L; detergents; preservative
- R3** TAPS buffer: 50 mmol/L, pH 8.0; creatinase (microorganisms):  $\geq 498 \mu\text{kat/L}$ ; peroxidase (horseradish):  $\geq 16.6 \mu\text{kat/L}$ ; 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.

**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: 8 weeks

**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: 12 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.

Plasma: Li-heparin and K<sub>2</sub>-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.

Stability in *serum/plasma*:<sup>10</sup> 7 days at 15-25 °C  
7 days at 2-8 °C  
3 months at (-15)-(-25) °C

Stability in *urine* (without preservative):<sup>10</sup> 2 days at 15-25 °C  
6 days at 2-8 °C  
6 months at (-15)-(-25) °C

Stability in *urine* (with preservative):<sup>11</sup> 3 days at 15-25 °C  
8 days at 2-8 °C  
3 weeks at (-15)-(-25) °C

Centrifuge samples containing precipitates before performing the assay.

**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 311 test definition**

Assay type	2-Point End		
Reaction time / Assay points	10 / 25-57		
Wavelength (sub/main)	700/546 nm		
Reaction direction	Increase		
Units	$\mu\text{mol/L}$ (mg/dL, mmol/L)		
Reagent pipetting	Diluent (H <sub>2</sub> O)		
R1	77 $\mu\text{L}$	–	
R3	38 $\mu\text{L}$	–	
Sample volumes	Sample	Sample dilution	
		Sample	Diluent (NaCl)
Normal	2 $\mu\text{L}$	–	–
Decreased	5 $\mu\text{L}$	15 $\mu\text{L}$	135 $\mu\text{L}$
Increased	2 $\mu\text{L}$	–	–

**cobas c 501 test definition**

Assay type	2-Point End		
Reaction time / Assay points	10 / 37-70		
Wavelength (sub/main)	700/546 nm		
Reaction direction	Increase		
Units	$\mu\text{mol/L}$ (mg/dL, mmol/L)		
Reagent pipetting	Diluent (H <sub>2</sub> O)		
R1	77 $\mu\text{L}$	–	
R3	38 $\mu\text{L}$	–	
Sample volumes	Sample	Sample dilution	
		Sample	Diluent (NaCl)
Normal	2 $\mu\text{L}$	–	–
Decreased	5 $\mu\text{L}$	15 $\mu\text{L}$	135 $\mu\text{L}$
Increased	2 $\mu\text{L}$	–	–

**cobas c 502 test definition**

Assay type	2-Point End		
Reaction time / Assay points	10 / 37-70		
Wavelength (sub/main)	700/546 nm		



Reaction direction	Increase		
Units	μmol/L (mg/dL, mmol/L)		
Reagent pipetting		Diluent (H <sub>2</sub> O)	
R1	77 μL	–	
R3	38 μL	–	
<i>Sample volumes</i>	<i>Sample</i>	<i>Sample dilution</i>	
		<i>Sample</i>	<i>Diluent (NaCl)</i>
Normal	2 μL	–	–
Decreased	5 μL	15 μL	135 μL
Increased	4 μL	–	–

**Application for urine****cobas c 311 test definition**

Assay type	2-Point End		
Reaction time / Assay points	10/25-57		
Wavelength (sub/main)	700/546 nm		
Reaction direction	Increase		
Units	μmol/L (mg/dL, mmol/L)		
Reagent pipetting		Diluent (H <sub>2</sub> O)	
R1	77 μL	–	
R3	38 μL	–	
<i>Sample volumes</i>	<i>Sample</i>	<i>Sample dilution</i>	
		<i>Sample</i>	<i>Diluent (NaCl)</i>
Normal	5 μL	3 μL	147 μL
Decreased	2 μL	3 μL	147 μL
Increased	5 μL	3 μL	147 μL

**cobas c 501 test definition**

Assay type	2-Point End		
Reaction time / Assay points	10 / 37-70		
Wavelength (sub/main)	700/546 nm		
Reaction direction	Increase		
Units	μmol/L (mg/dL, mmol/L)		
Reagent pipetting		Diluent (H <sub>2</sub> O)	
R1	77 μL	–	
R3	38 μL	–	
<i>Sample volumes</i>	<i>Sample</i>	<i>Sample dilution</i>	
		<i>Sample</i>	<i>Diluent (NaCl)</i>
Normal	5 μL	3 μL	147 μL
Decreased	2 μL	3 μL	147 μL
Increased	5 μL	3 μL	147 μL

**cobas c 502 test definition**

Assay type	2-Point End		
Reaction time / Assay points	10 / 37-70		
Wavelength (sub/main)	700/546 nm		
Reaction direction	Increase		
Units	μmol/L (mg/dL, mmol/L)		
Reagent pipetting		Diluent (H <sub>2</sub> O)	

R1	77 μL	–	
R3	38 μL	–	
<i>Sample volumes</i>	<i>Sample</i>	<i>Sample dilution</i>	
		<i>Sample</i>	<i>Diluent (NaCl)</i>
Normal	5 μL	3 μL	147 μL
Decreased	2 μL	3 μL	147 μL
Increased	10 μL	3 μL	147 μL

**Calibration**

Calibrators	S1: H <sub>2</sub> O 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

Traceability: This method has been standardized against ID/MS.

**Quality control***Serum/plasma*

For quality control use undiluted Precinorm U, Precipath U, PreciControl ClinChem Multi 1 and PreciControl ClinChem Multi 2 as listed above.

In addition, other suitable control material can be used.

*Urine*

For quality control use Precinorm PUC and Precipath PUC as listed above.

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:<sup>12</sup> 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:<sup>12</sup> No significant interference up to an H index of 800 (approximate hemoglobin concentration: 497 μmol/L or 800 mg/dL).

Lipemia (Intralipid):<sup>12</sup> 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: < 1.70 mmol/L or < 300 mg/L does not interfere.

Drugs: No interference was found at therapeutic concentrations using common drug panels.<sup>13,14</sup>



Exceptions: Rifampicin, Levodopa and Calcium dobesilate (e.g. Dexium) cause artificially low creatinine results. Dicynone (Etamsylate) at therapeutic concentrations may lead to false-low results.

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

No significant interference up to a creatine level of 4 mmol/L (524 mg/L).

Hemolyzed samples from neonates, infants or adults with HbF values  $\geq 600$  mg/dL interfere with the test.<sup>15</sup>

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

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.<sup>16</sup>

Estimation of the glomerular filtration rate (GFR) on the basis of the Schwartz formula can lead to an overestimation.<sup>17</sup>

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

#### Urine

Icterus: No significant interference up to an approximate conjugated bilirubin concentration of 1197  $\mu\text{mol/L}$  (70 mg/dL).

Hemolysis: No significant interference up to an approximate hemoglobin concentration of 621  $\mu\text{mol/L}$  (1000 mg/dL).

Ascorbic acid  $< 22.7$  mmol/L ( $< 4000$  mg/L), glucose  $< 120$  mmol/L ( $< 2162$  mg/dL) and urobilinogen  $< 676$   $\mu\text{mol/L}$  ( $< 40$  mg/dL) do not interfere.

Drugs: No interference was found at therapeutic concentrations using common drug panels.<sup>14</sup>

Exceptions: Calcium dobesilate (e.g. Dexium), Levodopa and  $\alpha$ -methyl dopa cause artificially low creatinine results. Dicynone (Etamsylate) at therapeutic concentrations may lead to false-low results.

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

#### 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. The latest version of the carry-over evasion list can be found with the NaOHD/SMS/Multiclean/SCCS or the NaOHD/SMS/SmpCln1+2/SCCS Method Sheets. For further instructions refer to the operator's manual. **cobas c** 502 analyzer: All special wash programming necessary for avoiding carry-over is available via the **cobas** link, manual input is not required.

**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  $\mu\text{mol/L}$  (0.06-30.5 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  $\mu\text{mol/L}$  (1.1-610 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  $\mu\text{mol/L}$  (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 three standard deviations above that of the lowest standard (standard 1 + 3 SD, repeatability, n = 21).

###### Urine

100  $\mu\text{mol/L}$  (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 three standard deviations above that of the lowest standard (standard 1 + 3 SD, repeatability, n = 21).

#### Expected values

##### Serum/plasma

###### Adults<sup>18</sup>

Females	45-84 $\mu\text{mol/L}$	(0.51-0.95 mg/dL)
Males	59-104 $\mu\text{mol/L}$	(0.67-1.17 mg/dL)

###### Children<sup>19</sup>

Neonates (premature)	29-87 $\mu\text{mol/L}$	(0.33-0.98 mg/dL)
Neonates (full term)	27-77 $\mu\text{mol/L}$	(0.31-0.88 mg/dL)
2-12 m	14-34 $\mu\text{mol/L}$	(0.16-0.39 mg/dL)
1-< 3 y	15-31 $\mu\text{mol/L}$	(0.18-0.35 mg/dL)
3-< 5 y	23-37 $\mu\text{mol/L}$	(0.26-0.42 mg/dL)
5-< 7 y	25-42 $\mu\text{mol/L}$	(0.29-0.47 mg/dL)
7-< 9 y	30-47 $\mu\text{mol/L}$	(0.34-0.53 mg/dL)
9-< 11 y	29-56 $\mu\text{mol/L}$	(0.33-0.64 mg/dL)
11-< 13 y	39-60 $\mu\text{mol/L}$	(0.44-0.68 mg/dL)
13-< 15 y	40-68 $\mu\text{mol/L}$	(0.46-0.77 mg/dL)

###### Urine

###### 1 st morning urine<sup>18</sup>

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<sup>20</sup>

Females	6-13 mmol/24 h	(720-1510 mg/24 h)
Males	9-19 mmol/24 h	(980-2200 mg/24 h)

###### Creatinine clearance<sup>20</sup>

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. *Serum/plasma*: repeatability (n = 21) and intermediate precision (3 aliquots per run, 1 run per day, 21 days). *Urine*: repeatability (n = 21) and intermediate precision (3 aliquots per run, 1 run per day, 10 days). The following results were obtained:

###### Serum/plasma

Repeatability	Mean	SD	CV
	$\mu\text{mol/L}$ (mg/dL)	$\mu\text{mol/L}$ (mg/dL)	%
Precinorm U	96.1 (1.08)	0.9 (0.01)	0.9



Precipath U	341 (3.85)	2 (0.02)	0.6
Human serum 1	191 (2.16)	2 (0.02)	1.1
Human serum 2	398 (4.50)	4 (0.05)	1.0

<i>Intermediate precision</i>	<i>Mean</i>	<i>SD</i>	<i>CV</i>
	$\mu\text{mol/L (mg/dL)}$	$\mu\text{mol/L (mg/dL)}$	%
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**

<i>Repeatability</i>	<i>Mean</i>	<i>SD</i>	<i>CV</i>
	$\mu\text{mol/L (mg/dL)}$	$\mu\text{mol/L (mg/dL)}$	%
Control Level 1	7280 (82.3)	92 (1.0)	1.3
Control Level 2	14031 (159)	179 (2)	1.3
Human urine 1	17289 (195)	237 (3)	1.4
Human urine 2	7035 (79.5)	68 (0.8)	1.0

<i>Intermediate precision</i>	<i>Mean</i>	<i>SD</i>	<i>CV</i>
	$\mu\text{mol/L (mg/dL)}$	$\mu\text{mol/L (mg/dL)}$	%
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

**Method comparison**

Creatinine values for human serum, plasma and urine samples obtained on a Roche/Hitachi **cobas c** 501 analyzer (y) were compared with those determined using the corresponding reagent on a Roche/Hitachi 917 analyzer (x).

**Serum/plasma**

Sample size (n) = 63

Passing/Bablok <sup>21</sup>	Linear regression
$y = 1.002x - 0.434 \mu\text{mol/L}$	$y = 0.991x + 2.94 \mu\text{mol/L}$
$r = 0.978$	$r = 1.000$

The sample concentrations were between 49 and 1891  $\mu\text{mol/L}$  (0.55 and 21.4 mg/dL).

**Urine**

Sample size (n) = 75

Passing/Bablok <sup>21</sup>	Linear regression
$y = 0.985x + 21.3 \mu\text{mol/L}$	$y = 0.977x + 80.0 \mu\text{mol/L}$
$r = 0.990$	$r = 1.000$

The sample concentrations were between 438 and 52577  $\mu\text{mol/L}$  (4.95 and 594 mg/dL).

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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.

**Symbols**

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard.

**CONTENT**



Contents of kit

Volume after reconstitution or mixing



# CREP2

Creatinine plus ver.2



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