

REF	CONTENT	Analyzer(s) on which cobas c pack(s) can be used
03263991 190	Creatinine plus ver.2 (250 tests)	System-ID 07 6612 7 COBAS INTEGRA 400 plus COBAS INTEGRA 800
10759350 190	Calibrator f.a.s. (12 × 3 mL)	System-ID 07 3718 6
10759350 360	Calibrator f.a.s. (12 × 3 mL, for USA)	System-ID 07 3718 6
12149435 122	Precinorm U plus (10 × 3 mL)	System-ID 07 7999 7
12149435 160	Precinorm U plus (10 × 3 mL, for USA)	System-ID 07 7999 7
12149443 122	Precipath U plus (10 × 3 mL)	System-ID 07 8000 6
12149443 160	Precipath U plus (10 × 3 mL, for USA)	System-ID 07 8000 6
10171743 122	Precinorm U (20 × 5 mL)	System-ID 07 7997 0
10171735 122	Precinorm U (4 × 5 mL)	System-ID 07 7997 0
10171778 122	Precipath U (20 × 5 mL)	System-ID 07 7998 9
10171760 122	Precipath U (4 × 5 mL)	System-ID 07 7998 9
05117003 190	PreciControl ClinChem Multi 1 (20 × 5 mL)	System-ID 07 7469 3
05947626 190	PreciControl ClinChem Multi 1 (4 × 5 mL)	System-ID 07 7469 3
05947626 160	PreciControl ClinChem Multi 1 (4 × 5 mL, for USA)	System-ID 07 7469 3
05117216 190	PreciControl ClinChem Multi 2 (20 × 5 mL)	System-ID 07 7470 7
05947774 190	PreciControl ClinChem Multi 2 (4 × 5 mL)	System-ID 07 7470 7
05947774 160	PreciControl ClinChem Multi 2 (4 × 5 mL, for USA)	System-ID 07 7470 7
03121313 122	Precinorm PUC (4 × 3 mL)	System-ID 07 6756 5
03121291 122	Precipath PUC (4 × 3 mL)	System-ID 07 6757 3

English

System information

Test CRE2, test ID 0-612 (serum, plasma)

Test CRE2U, test ID 0-512 (urine)

Intended use

In vitro test for the quantitative determination of the creatinine concentration in human serum, plasma, and urine on COBAS INTEGRA 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 m² 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.

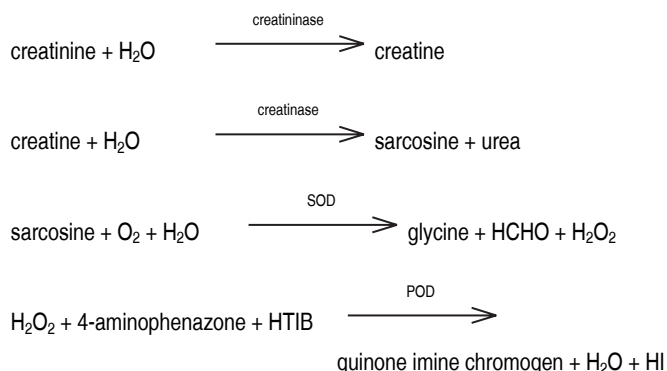
Since a rise in blood creatinine is observed only with marked damage of the nephrons, it is not suited to detect early stage kidney disease. A considerably more sensitive test and better estimation of glomerular filtration rate (GFR) is given by the creatinine clearance test based on creatinine's concentration 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.^{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

Enzymatic colorimetric method

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.



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^{b)} buffer: 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

SR TAPS^{b)} 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

b) N-Tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid

CREP2

Creatinine plus ver.2

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

Precautions and warnings

Pay attention to all precautions and warnings listed in Section 1 / Introduction of this Method Manual.

For USA: For prescription use only.

Reagent handling

Ready for use

Storage and stabilityShelf life at 2-8 °C See expiration date on
cobas c pack label

COBAS INTEGRA 400 plus system

On-board in use at 10-15 °C 8 weeks

COBAS INTEGRA 800 system

On-board in use at 8 °C 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

Plasma: Li-heparin, Na-heparin, K₃-EDTA, or Na₂-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 (14-47 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. Urine samples are automatically prediluted 1:20 (1+19) with water by the instrument.

Centrifuge samples containing precipitates before performing the assay.

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):¹¹ 3 days at 15-25 °C
6 days at 2-8 °C
3 weeks at (-15)-(-25) °C

Materials provided

See "Reagents – working solutions" section for reagents.

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.

Applications for serum, plasma, and urine**COBAS INTEGRA 400 plus test definition**

Measuring mode	Absorbance
Abs. calculation mode	Endpoint
Reaction direction	Increase
Wavelength A/B	552/659 nm

Calc. first/last	35/65
<i>Serum, plasma</i>	
Reaction mode	R1-S-SR
Unit	µmol/L
<i>Urine</i>	
Reaction mode	D-R1-S-SR
Predilution factor	20
Unit	mmol/L

Pipetting parameters

<i>Serum, plasma</i>		Diluent (H ₂ O)
R1	77 µL	
Sample	2 µL	5 µL
SR	38 µL	
Total volume	122 µL	
<i>Urine</i>		Diluent (H ₂ O)
R1	77 µL	
Sample	2 µL	5 µL
SR	38 µL	
Total volume	122 µL	

COBAS INTEGRA 800 test definition

Measuring mode	Absorbance
Abs. calculation mode	Endpoint
Reaction direction	Increase
Wavelength A/B	552/659 nm
Calc. first/last	46/98
<i>Serum, plasma</i>	
Reaction mode	R1-S-SR
Unit	µmol/L
<i>Urine</i>	
Reaction mode	D-R1-S-SR
Predilution factor	20
Unit	mmol/L

Pipetting parameters

<i>Serum, plasma</i>		Diluent (H ₂ O)
R1	77 µL	
Sample	2 µL	5 µL
SR	38 µL	
Total volume	122 µL	
<i>Urine</i>		Diluent (H ₂ O)
R1	77 µL	
Sample	2 µL	5 µL
SR	38 µL	
Total volume	122 µL	

Calibration

Calibrator	Calibrator f.a.s.
	Use deionized water as zero calibrator.
Calibration mode	Linear regression
Calibration replicate	Duplicate recommended

Calibration interval Each lot and as required following quality control procedures

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

Quality control

Quality control serum/plasma	Precinorm U, Precinorm U plus or PreciControl ClinChem Multi 1 Precipath U, Precipath U plus or PreciControl ClinChem Multi 2
Quality control urine	Precinorm PUC or Precipath PUC
Control interval	24 hours recommended
Control sequence	User defined
Control after calibration	Recommended

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. 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

COBAS INTEGRA analyzers automatically calculate the analyte concentration of each sample. For more details, please refer to Data Analysis in the Online Help (COBAS INTEGRA 400 plus/800 analyzers).

Conversion factor: $\mu\text{mol/L} \times 0.0113 = \text{mg/dL}$

Limitations - interference

Criterion: Recovery within $\pm 10\%$ of initial value.

Serum, plasma

Icterus:¹² No significant interference up to an I index of 20 for conjugated and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 340 $\mu\text{mol/L}$ or 20 mg/dL).

Hemolysis:¹² No significant interference up to an H index of 800 (approximate hemoglobin concentration: 497 $\mu\text{mol/L}$ or 800 mg/dL).

Lipemia (Intralipid):¹² No significant interference up to an L index of 1000. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Drugs: No interference was found at therapeutic concentrations using common drug panels.^{13,14}

Exceptions: Levodopa and calcium dobesilate cause artificially low creatinine levels at the tested drug level while DL-proline at a concentration of $> 1 \text{ mmol/L}$ causes falsely high results.

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

Dicynone (Ethamsylate) at therapeutic concentrations may lead to false-low results.¹⁵

Ascorbic acid: No significant interference up to an ascorbic acid concentration of 1.70 mmol/L (30 mg/dL)

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 plasma Metamizole concentrations above 0.05 mg/mL.

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

No significant interference up to a creatine concentration of 0.38 mmol/L (50 mg/L).

Urine

Drugs: No interference was found at therapeutic concentrations using common drug panels.¹⁴

Exceptions: Levodopa causes artificially low results.

Dicynone (Ethamsylate) at therapeutic concentrations may lead to false-low results.

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

No significant interference up to a creatine concentration of 3.05 mmol/L (40 mg/dL).

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

Estimation of the Glomerular Filtration Rate (GFR) on the basis of the Schwartz Formula can lead to an overestimation.¹⁷

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 INTEGRA analyzers. Refer to the CLEAN Method Sheet for further instructions and for the latest version of the Extra wash cycle list.

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 $\mu\text{mol/L}$ (0.057-30.5 mg/dL)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:10 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 10.

Urine

0.1-40 mmol/L (1.13-452 mg/dL)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:5 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 5.

Lower limits of measurement

Serum/plasma

Lower detection limit of the test:

5 $\mu\text{mol/L}$ (0.057 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 a zero sample (zero sample + 3 SD, repeatability, $n = 30$).

Urine

Lower detection limit of the test:

0.1 mmol/L (1.13 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 a zero sample (zero sample + 3 SD, repeatability, $n = 30$).

Expected values

Serum, plasma

Adults¹⁸

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)

Children¹⁹

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 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)

Roche has not evaluated reference ranges in a pediatric population.

Urine

1st morning urine¹⁸

Females	2.55-20.0 mmol/L	(29-226 mg/dL)
Males	3.54-24.6 mmol/L	(40-278 mg/dL)

24h urine²⁰

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

Creatinine clearance²⁰ 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.

Specific performance data

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

Precision

Serum/plasma

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

Repeatability	Level 1	Level 2
Mean	89.7 µmol/L (1.02 mg/dL)	329 µmol/L (3.72 mg/dL)
CV	1.6 %	0.7 %

Intermediate precision	Level 1	Level 2
Mean	92.0 µmol/L (1.04 mg/dL)	335 µmol/L (3.79 mg/dL)
CV	1.3 %	0.9 %

Urine

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

Repeatability	Level 1	Level 2
Mean	9.35 mmol/L (106 mg/dL)	20.5 mmol/L (232 mg/dL)
CV	0.8 %	1.8 %

Intermediate precision	Level 1	Level 2
Mean	9.55 mmol/L (108 mg/dL)	21.1 mmol/L (238 mg/dL)
CV	2.0 %	3.9 %

Method comparison

Creatinine values for human serum, plasma and urine samples obtained on a COBAS INTEGRA 400 analyzer using the COBAS INTEGRA Creatinine plus ver.2 reagent (y) were compared with those determined using the commercially available Creatinine plus reagent on a Roche/Hitachi 917 analyzer (x).

Serum/plasma

Roche/Hitachi 917 analyzer	Sample size (n) = 53
Corr. coefficient (r)	0.999

Lin. regression $y = 1.010x + 1.13 \mu\text{mol/L}$

Passing/Bablok²¹ $y = 1.013x - 1.50 \mu\text{mol/L}$

The sample concentrations were between 53 and 2300 µmol/L (0.60 and 26.1 mg/dL).

Urine

Roche/Hitachi 917 analyzer Sample size (n) = 54

Corr. coefficient (r) 0.998

Lin. regression $y = 0.935x + 0.625 \text{ mmol/L}$

Passing/Bablok²¹ $y = 0.960x + 0.308 \text{ mmol/L}$

The sample concentrations were between 1.3 and 36 mmol/L (14.7 and 406 mg/dL).

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CREP2

Creatinine plus ver.2




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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.

	Contents of kit
	Volume after reconstitution or mixing
	Global Trade Item Number

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