CREJ2

Creatinine Jaffé Gen.2

cobas®

• Indicates **cobas c** systems on which reagents can be used

Order information

			Roche/Hitachi **cobas c** systems	
Creatinine Jaffé Gen.2			**cobas c** 311	**cobas c** 501
700 tests	Cat. No. **04810716** 190	System-ID 07 6928 2	•	•
Calibrator f.a.s. (12 x 3 mL)	Cat. No. **10759350** 190	Code 401		
Calibrator f.a.s. (12 x 3 mL, for USA)	Cat. No. **10759350** 360	Code 401		
Precinorm U plus (10 x 3 mL)	Cat. No. **12149435** 122	Code 300		
Precinorm U plus (10 x 3 mL, for USA)	Cat. No. **12149435** 160	Code 300		
Precipath U plus (10 x 3 mL)	Cat. No. **12149443** 122	Code 301		
Precipath U plus (10 x 3 mL, for USA)	Cat. No. **12149443** 160	Code 301		
Precinorm U (20 x 5 mL)	Cat. No. **10171743** 122	Code 300		
Precipath U (20 x 5 mL)	Cat. No. **10171778** 122	Code 301		
Precinorm PUC (4 x 3 mL)	Cat. No. **03121313** 122	Code 240		
Precipath PUC (4 x 3 mL)	Cat. No. **03121291** 122	Code 241		
Diluent NaCl 9 % (50 mL)	Cat. No. **04489357** 190	System-ID 07 6869 3		

English

System information

CREJ2: ACN 690 (Rate blanked, compensated, serum and plasma)
CRJ2U: ACN 691 (Rate blanked, urine)
SCRE2: ACN 773 (STAT, compensated, serum and plasma, reaction time: 4)
SCR2U: ACN 774 (STAT, urine, reaction time: 4)

Intended use

In vitro test 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 Schwartz formula is used.

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[6,7,8]

This kinetic colorimetric assay is based on the Jaffé method. In alkaline solution, creatinine forms a yellow-orange complex with picrate. The rate of dye formation is proportional to the creatinine concentration in the specimen. The assay uses "rate-blanking" to minimize interference by bilirubin. To correct for non-specific reaction caused by serum/plasma pseudo-creatinine chromogens, including proteins and ketones, the results for serum or plasma are corrected by -26 µmol/L (-0.3 mg/dL).

Creatinine + picric acid $\xrightarrow{\text{Alkaline pH}}$ yellow-orange complex

Reagents - working solutions

R1	Potassium hydroxide: 900 mmol/L; phosphate: 135 mmol/L; pH ≥ 13.5; preservative; stabilizer
R2/R3	Picric acid: 38 mmol/L; pH 6.5; non reactive buffer

Precautions and warnings

For in vitro diagnostic use.
Exercise the normal precautions required for handling all laboratory reagents.
Safety data sheet available for professional user on request.
Disposal of all waste material should be in accordance with local guidelines.
This kit contains components classified as follows according to the European directive 1999/45/EC.


C – Corrosive. R1 contains potassium hydroxide.
R 1: Explosive when dry. R 4: Forms very sensitive, explosive metallic compounds. R 34: Causes burns.
S 24-25: Avoid contact with skin and eyes. S 26: In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. S 35: This material and its container must be disposed of in a safe way.
S 36/37/39: Wear suitable protective clothing, gloves and eye/face protection.
S 45: In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).
Contact phone: all countries: +49-621-7590, USA: +1-800-428-2336

Reagent handling

Ready for use.

Storage and stability

CREJ2

Shelf life at 15-25 °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[9]

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.

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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:*[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 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	Rate A		
Reaction time / Assay points	10/27-37 - 15-23 (STAT 4/12-19)		
Wavelength (sub/main)	570/505 nm		
Reaction direction	Increase		
Units	µmol/L (mg/dL, mmol/L)		
Reagent pipetting		Diluent (H_2O)	
R1	13 µL	77 µL	
R3	17 µL	30 µL	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	10 µL	–	–
Decreased	10 µL	20 µL	80 µL
Increased	10 µL	–	–

Enter the correction value for the non-specific protein reaction as the instrument factor **y = ax + b** for mg/dL or for µmol/L, where **a = 1.0** and **b = -0.3** (mg/dL) or **a = 1.0** and **b = -26** (µmol/L).

cobas c 501 **test definition**

Assay type	Rate A		
Reaction time / Assay points	10/42-52 - 24-34 (STAT 4/17-27)		
Wavelength (sub/main)	570/505 nm		
Reaction direction	Increase		
Units	µmol/L (mg/dL, mmol/L)		
Reagent pipetting		Diluent (H_2O)	
R1	13 µL	77 µL	
R3	17 µL	30 µL	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	10 µL	–	–
Decreased	10 µL	20 µL	80 µL
Increased	10 µL	–	–

Enter the correction value for the non-specific protein reaction as the instrument factor **y = ax + b** for mg/dL or for µmol/L, where **a = 1.0** and **b = -0.3** (mg/dL) or **a = 1.0** and **b = -26** (µmol/L).

Application for urine

cobas c 311 **test definition**

Assay type	Rate A		
Reaction time / Assay points	10/27-37 - 15-23 (STAT 4/12-19)		
Wavelength (sub/main)	570/505 nm		
Reaction direction	Increase		
Units	µmol/L (mg/dL, mmol/L)		
Reagent pipetting		Diluent (H_2O)	
R1	13 µL	77 µL	
R3	17 µL	30 µL	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	10 µL	6 µL	144 µL
Decreased	10 µL	2 µL	180 µL
Increased	10 µL	10 µL	115 µL

cobas c 501 **test definition**

Assay type	Rate A		
Reaction time / Assay points	10/42-52 - 24-34 (STAT 4/17-27)		
Wavelength (sub/main)	570/505 nm		
Reaction direction	Increase		
Units	µmol/L (mg/dL, mmol/L)		
Reagent pipetting		Diluent (H_2O)	
R1	13 µL	77 µL	
R3	17 µL	30 µL	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	10 µL	6 µL	144 µL
Decreased	10 µL	2 µL	180 µL
Increased	10 µL	10 µL	115 µL

Calibration

Calibrators	S1: H_2O S2: C.f.a.s.
Calibration mode	Linear
Calibration frequency	2-point calibration - after reagent lot change - and as required following quality control procedures

Traceability: This method has been standardized against ID/MS. For the USA, this method has been standardized against a primary reference material (SRM 914).

Quality control

For quality control, use control materials as listed in the "Order information" section.
Other suitable control material can be used in addition.

Serum/plasma

For quality control use undiluted serum control material as listed above.
Other suitable control material can be used in addition.

Urine

For quality control use Precinorm PUC and Precipath PUC as listed above.
Other suitable control material can be used in addition.

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 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[12]

Criterion: Recovery within ± 10 % of initial value at a creatinine concentration of 80 µmol/L (0.90 mg/dL) in serum/plasma and 2500 µmol/L (28.3 mg/dL) in urine.

Serum/plasma

Icterus (*CREJ2*): No significant interference up to an I index of 5 for conjugated bilirubin and 10 for unconjugated bilirubin (approximate conjugated bilirubin concentration: 86 µmol/L (5 mg/dL) and approximate unconjugated bilirubin concentration: 171 µmol/L (10 mg/dL)).

Icterus (*SCRE2*): No significant interference up to an I index of 2 for conjugated bilirubin and 3 for unconjugated bilirubin (approximate conjugated bilirubin concentration: 34 µmol/L (2 mg/dL) and approximate unconjugated bilirubin concentration: 51 µmol/L (3 mg/dL)).

Hemolysis: No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 621 µmol/L (1000 mg/dL)).

Lipemia (Intralipid): No significant interference up to an L index of 800. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Drugs: No interference was found at therapeutic levels using common drug panels.[13,14]

Exception: Cefoxitin causes artificially high creatinine results.

Exception: Cyanokit (Hydroxocobalamin) may cause interference with results.

Values < 15 µmol/L (< 0.17 mg/dL) or negative results are reported in rare cases in children < 3 years and in elderly patients. In such cases use the Creatinine plus test to assay the sample.

Do not use Creatinine Jaffé for the testing of creatinine in hemolyzed samples from neonates, infants or adults with HbF levels ≥ 60 mg/dL for *CREJ2* applications (≥ 30 mg/dL for *SCRE2* applications).[15] In such cases, use the Creatinine plus test (≤ 600 mg/dL HbF) to assay the sample.

Estimation of the Glomerular Filtration Rate (GFR) on the basis of the Schwartz Formula can lead to an overestimation.[16]

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

Urine

Icterus: No significant interference up to a conjugated bilirubin concentration of 855 µmol/L (50 mg/dL).

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

Glucose < 120 mmol/L (< 2162 mg/dL) and urobilinogen < 676 µmol/L (< 40 mg/dL) do not interfere.

Drugs: No interference was found at therapeutic levels using common drug panels.[14]

Exception: Cyanokit (Hydroxocobalamin) may cause interference with results.

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

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. Refer to the latest version of the Carry over evasion list found with the NaOHD/SMS/Multiclean/SCCS Method Sheet and the operator manual for further instructions.

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

15-2200 µmol/L (0.17-24.9 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 by the rerun function are automatically multiplied by a factor of 5.

Urine

375-55000 µmol/L (4.2-622 mg/dL)

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:3.6 dilution. Results from samples diluted by the rerun function are automatically multiplied by a factor of 3.6.

Lower limits of measurement

Lower detection limit of the test

Serum/plasma

15 µmol/L (0.17 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

375 µmol/L (4.2 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[17]

Females	44-80 µmol/L	(0.50-0.90 mg/dL)
Males	62-106 µmol/L	(0.70-1.20 mg/dL)

Children[18]

Neonates (premature)	25-91 µmol/L	(0.29-1.04 mg/dL)
Neonates (full term)	21-75 µmol/L	(0.24-0.85 mg/dL)
2-12 m	15-37 µmol/L	(0.17-0.42 mg/dL)
1-< 3 y	21-36 µmol/L	(0.24-0.41 mg/dL)
3-< 5 y	27-42 µmol/L	(0.31-0.47 mg/dL)
5-< 7 y	28-52 µmol/L	(0.32-0.59 mg/dL)
7-< 9 y	35-53 µmol/L	(0.40-0.60 mg/dL)
9-< 11 y	34-65 µmol/L	(0.39-0.73 mg/dL)
11-< 13 y	46-70 µmol/L	(0.53-0.79 mg/dL)
13-< 15 y	50-77 µmol/L	(0.57-0.87 mg/dL)

Urine

1st morning urine[17]

Females	2470-19200 µmol/L	(28-217 mg/dL)
Males	3450-22900 µmol/L	(39-259 mg/dL)

24-hour urine[19]

Females	7000-14000 µmol/24 h	(740-1570 mg/24 h)
Males	9000-21000 µmol/24 h	(1040-2350 mg/24 h)

Creatinine clearance[19,20] 71-151 mL/min

Refer to reference 16 for a prospective study on creatinine clearance in children.[21]

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 human samples and controls in an internal protocol. *Serum/plasma:* repeatability* (n = 21), intermediate precision** (3 aliquots per run, 1 run per day, 21 days);
Urine: repeatability* (n = 21), intermediate precision** (3 aliquots per run, 1 run per day, 10 days). The following results were obtained:

Serum/plasma (CREJ2)

*Repeatability**	*Mean µmol/L (mg/dL)*	*SD µmol/L (mg/dL)*	*CV %*
Precinorm U	105 (1.19)	2 (0.03)	2.1
Precipath U	360 (4.07)	4 (0.05)	1.1
Human serum 1	206 (2.33)	3 (0.03)	1.2
Human serum 2	422 (4.77)	5 (0.06)	1.3

*Intermediate precision***	*Mean µmol/L (mg/dL)*	*SD µmol/L (mg/dL)*	*CV %*
Precinorm U	101 (1.14)	4 (0.05)	3.5
Precipath U	351 (3.97)	8 (0.09)	2.2
Human serum 3	201 (2.27)	5 (0.06)	2.5
Human serum 4	411 (4.64)	9 (0.10)	2.2

Urine (CRJ2U)

*Repeatability**	*Mean µmol/L (mg/dL)*	*SD µmol/L (mg/dL)*	*CV %*
Control Level 1	8083 (91.3)	115 (1.3)	1.4
Control Level 2	15618 (177)	213 (2)	1.4
Human urine 1	19318 (218)	234 (3)	1.2
Human urine 2	7958 (89.9)	130 (1.5)	1.6

*Intermediate precision***	*Mean µmol/L (mg/dL)*	*SD µmol/L (mg/dL)*	*CV %*
Control Level 1	8130 (91.9)	164 (1.9)	2.0
Control Level 2	15533 (176)	251 (3)	1.6
Human urine 3	19353 (219)	385 (4)	2.0
Human urine 4	7932 (89.6)	166 (1.9)	2.1

Serum/plasma (SCRE2)

*Repeatability**	*Mean µmol/L (mg/dL)*	*SD µmol/L (mg/dL)*	*CV %*
Precinorm U	106 (1.20)	2 (0.02)	2.2
Precipath U	346 (3.91)	5 (0.06)	1.5
Human serum 1	543 (6.14)	6 (0.07)	1.1
Human serum 2	69 (0.78)	2 (0.02)	3.1

*Intermediate precision***	*Mean µmol/L (mg/dL)*	*SD µmol/L (mg/dL)*	*CV %*
Precinorm U	100 (1.13)	4 (0.05)	4.0
Precipath U	334 (3.77)	10 (0.11)	3.0
Human serum 3	522 (5.90)	12 (0.14)	2.4
Human serum 4	64 (0.72)	3 (0.03)	5.0

Urine (SCR2U)

*Repeatability**	*Mean µmol/L (mg/dL)*	*SD µmol/L (mg/dL)*	*CV %*
Control Level 1	6287 (71.0)	82 (0.9)	1.2
Control Level 2	15252 (172)	182 (2)	1.2
Human urine 1	24174 (273)	212 (2)	0.9
Human urine 2	2146 (24.2)	48 (0.5)	2.2

*Intermediate precision***	*Mean µmol/L (mg/dL)*	*SD µmol/L (mg/dL)*	*CV %*
Control Level 1	6943 (78.5)	114 (1.3)	1.6
Control Level 2	15394 (174)	229 (3)	1.5
Human urine 3	24230 (274)	354 (4)	1.5
Human urine 4	2184 (24.7)	54 (0.6)	2.5

* repeatability = within-run precision
** intermediate precision = total precision / between run precision / between day precision

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 on Roche/Hitachi 917/MODULAR P analyzers (x), using the corresponding Roche/Hitachi reagent.

Serum/plasma (CREJ2)
Sample size (n) = 273

Passing/Bablok[22]	Linear regression
y = 1.000x - 0.65 µmol/L	y = 1.002x - 0.98 µmol/L
τ = 0.973	r = 0.999

The sample concentrations were between 38 and 2178 µmol/L (0.43 and 24.6 mg/dL).

Urine (CRJ2U)
Sample size (n) = 223

Passing/Bablok[22]	Linear regression
y = 0.999x + 20.66 µmol/L	y = 0.999x + 41.55 µmol/L
τ = 0.969	r = 0.999

The sample concentrations were between 934 and 50228 µmol/L (10.6 and 568 mg/dL).

Serum/plasma (SCRE2)
Sample size (n) = 224

Passing/Bablok[22]	Linear regression
y = 1.000x - 14.36 µmol/L	y = 0.996x - 12.17 µmol/L
τ = 0.964	r = 0.999

The sample concentrations were between 66 and 1775 µmol/L (0.75 and 20.1 mg/dL).

Urine (SCR2U)
Sample size (n) = 223

Passing/Bablok[22]	Linear regression
y = 0.999x + 67.83 µmol/L	y = 0.998x + 112.72 µmol/L
τ = 0.973	r = 0.999

The sample concentrations were between 931 and 48729 µmol/L (10.5 and 551 mg/dL).

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