UA2

cobas®

Uric Acid ver.2

Order information

REF		CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
08058750190*	08058750500	Uric Acid ver.2 (1300 tests)	System-ID 2117 001	**cobas c** 303, **cobas c** 503, **cobas c** 703
08058750214*	08058750500	Uric Acid ver.2 (1300 tests)	System-ID 2117 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

UA2: ACN 21170 (Serum/plasma)

UA2U: ACN 21171 (Urine)

Intended use

In vitro test for the quantitative determination of uric acid in human serum, plasma and urine on **cobas c** systems.

Summary

Uric acid measurements, performed with this assay, in human serum, plasma and urine are used as aid in diagnosis and treatment of numerous renal and metabolic disorders associated with hyper- or hypo-uricemia.

Uric acid is the major final product of purine metabolism in the human organism. Purines from dietary nucleic acids are converted in the liver and small intestine to uric acid.[1] Uric acid is present as a normal intracellular component and in biological fluids. Chemically, it is a reducing agent and accounts for nearly half of the antioxidant activity in blood. Uric acid production is balanced between purine ingestion, de novo synthesis, reabsorption, and degradation. Two-thirds of uric acid is excreted renally, while one-third is eliminated through the gastrointestinal system. Serum uric acid levels increase physiologically and gradually over the course of human life and are strongly influenced by the diet.[1,2]

High serum levels of uric acid can adversely affect organ systems. Overproduction of uric acid, insufficient excretion of uric acid, or often a combination of both can lead to hyperuricemia.[3] Primary causes of hyperuricemia include idiopathic and hereditary metabolic disorders. Secondary causes of increased uric acid formation include excessive dietary intake of purines and increased nucleic acid turnover (e.g. in myeloproliferative disorders, lymphoproliferative disorders, psoriasis, sarcoidosis, hemolytic anemia, cytotoxic drug treatments). Major causes of decreased uric acid excretion are: acute or chronic kidney disease, increased renal tubular reabsorption, reduced tubular secretion, lead poisoning, preeclampsia, low doses of salicylate, thiazide diuretics, Down syndrome.[1]

Hyperuricemia is mostly asymptomatic, but persistent hyperuricemia and uric acid precipitation may lead to the accumulation of urate crystals in many tissues, resulting in either acute painful conditions, such as gout/tophaceous gout/gouty arthritis, urolithiasis, or, in severe cases, in uric acid kidney diseases.[4]

Hypouricemia is much less common than hyperuricemia. Hypouricemia is often defined as serum uric acid levels ≤ 2.0 mg/dL (0.12 mmol/L). It may be secondary to any one of a number of underlying conditions, such as severe hepatocellular disease with reduced purine synthesis or xanthine oxidase activity, defective renal tubular reabsorption of uric acid (congenital or acquired), overtreatment of hyperuricemia, treatment with uricosuric drugs and cancer chemotherapy with 6-mercaptopurine or azathioprine.[1,5]

Phosphotungstic acid (PTA), uricase, and HPLC-based methods have been described for measuring uric acid. PTA methods are now rarely used.[1,6] The uricase-based method utilizes the enzyme uricase to oxidize uric acid.[7] Uricase can be employed in methods that involve the UV measurement of the consumption of uric acid or in combination with other enzymes to provide a colorimetric assay.[1]

The colorimetric method developed by Town, et al. involves initial sample incubation with a reagent mixture containing ascorbate oxidase and a clearing system. In this test system it is important that any ascorbic acid present in the sample is eliminated in the preliminary reaction; this precludes any ascorbic acid interference with the subsequent peroxidase (POD) indicator reaction. Upon addition of the starter reagent, oxidation of uric acid by uricase begins.[8]

The Roche assay described here is a slight modification of the colorimetric method described above. In this reaction, the peroxide reacts in the presence of peroxidase (POD), N-ethyl-N-(2-hydroxy-3-sulfopropyl)-3-methylaniline (TOOS), and 4-aminophenazone to form a quinone-diimine dye. The intensity of the red color formed is proportional to the uric acid concentration and is determined photometrically.

Test principle

Enzymatic colorimetric test.

Uricase cleaves uric acid to form allantoin and hydrogen peroxide.

$$\text{Uric acid} + 2\ H_2O + O_2 \xrightarrow{\text{Uricase}} \text{allantoin} + CO_2 + H_2O_2$$

In the presence of peroxidase, 4-aminophenazone is oxidized by hydrogen peroxide to a quinone-diimine dye.

$$2\ H_2O_2 + H^+ + \text{TOOS}^{a)} + \text{4-aminophenazone} \xrightarrow{\text{Peroxidase}} \text{quinone-diimine dye} + 4\ H_2O$$

a) N-ethyl-N-(2-hydroxy-3-sulfopropyl)-3-methylaniline

The color intensity of the quinone-diimine formed is directly proportional to the uric acid concentration and is determined by measuring the increase in absorbance.

Reagents - working solutions

R1 Phosphate buffer: 0.05 mol/L, pH 7.8; TOOS: 7 mmol/L; fatty alcohol polyglycol ether: 4.8 %; ascorbate oxidase (EC 1.10.3.3; zucchini) ≥ 83.5 µkat/L (25 °C); stabilizers; preservative

R3 Phosphate buffer: 0.1 mol/L, pH 7.8; potassium hexacyanoferrate (II): 0.3 mmol/L; 4-aminophenazone ≥ 3 mmol/L; uricase (EC 1.7.3.3; Arthrobacter protophormiae) ≥ 83.4 µkat/L (25 °C); peroxidase (POD) (EC 1.11.1.7; horseradish) ≥ 50 µkat/L (25 °C); stabilizers; preservative

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:

Warning

H319	Causes serious eye irritation.

Prevention:

P264	Wash skin thoroughly after handling.
P280	Wear eye protection/ face protection.

Response:

P305 + P351 + P338	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P337 + P313	If eye irritation persists: Get medical advice/attention.

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:	26 weeks
	6 months at -20 °C (± 5 °C)

Freeze only once.

Stability in urine[9] (upon NaOH addition):	4 days at 20-25 °C

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.

EDTA plasma values are approximately 7 % lower than serum values.

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: Assay urinary uric acid as soon as possible. Do not refrigerate.

To prevent ureate precipitation in urine samples, add sodium hydroxide to keep urine alkaline (pH > 8.0). To achieve stated uric acid stability, add NaOH prior to sample collection. Urine samples are diluted 1 + 10 with distilled/deionized water or 0.9 % NaCl. This dilution is taken into account in the calculation of the results. If stabilizers are added to the sample, the sample index feature must not be used.

Centrifuge samples containing precipitates before performing the assay.

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

Stability in serum/plasma:[9]	7 days at 4-8 °C
	3 days at 20-25 °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

Test definition

Reporting time	10 min	
Wavelength (sub/main)	700/546 nm	
Reagent pipetting		Diluent (H_2O)
R1	55 µL	19 µL
R3	11 µL	15 µL

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	2.3 µL	–	–
Decreased	3.6 µL	21 µL	61 µL
Increased	2.3 µL	–	–

Application for urine

Test definition

Reporting time	10 min	
Wavelength (sub/main)	700/546 nm	
Reagent pipetting		Diluent (H_2O)
R1	55 µL	19 µL
R3	11 µL	15 µL

Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	2.3 µL	10 µL	100 µL
Decreased	2.3 µL	4 µL	106 µL
Increased	2.3 µL	10 µL	100 µL

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

Calibration

Application for serum/plasma (ACN 21170)

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

Calibration frequency	Automatic full calibration - after reagent lot change Full calibration - every 12 weeks on-board - as required following quality control procedures

Application for urine (ACN 21171)

Transfer of calibration from serum/plasma application (ACN 21170)

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

Traceability: This method has been standardized against ID/MS.[10]

Quality control

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

Serum/plasma:	PreciControl ClinChem Multi 1, PreciControl ClinChem Multi 2
Urine:	Quantitative urine controls are recommended for routine quality control.

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 26 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.

Calculation

cobas c systems automatically calculate the analyte concentration of each sample in the unit mg/dL (µmol/L, mg/L, mmol/L).

Conversion factors:	mg/dL x 59.5 = µmol/L
	mg/dL x 10.0 = mg/L
	mg/dL x 0.0595 = mmol/L

Limitations - interference

Criterion: Recovery within ± 10 % of initial value at a uric acid concentration of 7 mg/dL (417 µmol/L) in serum/plasma and at a uric acid concentration of 92 mg/dL (5474 µmol/L) in urine. Recovery within ± 10 % for drug interference.

Serum/plasma

Icterus:[11] No significant interference up to an I index of 40 for conjugated and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 684 µmol/L or 40 mg/dL).

Hemolysis:[11] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 621 µmol/L or 1000 mg/dL).

Lipemia (Intralipid):[11] No significant interference up to an L index of 1500. 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.[12,13] Exceptions: Calcium dobesilate causes artificially low uric acid results.

Dicynone (Etamsylate) at therapeutic concentrations may lead to false-low results.[14]

Ascorbic acid: No significant interference from ascorbic acid up to a concentration of 0.17 mmol/L (3 mg/dL).

Uricase reacts specifically with uric acid. Other purine derivatives can inhibit the uric acid reaction.

Acetaminophen intoxications are frequently treated with N-Acetylcysteine. N-Acetylcysteine at the therapeutic concentration when used as an antidote 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.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[15]

Urine

Drugs: No interference was found at therapeutic concentrations using common drug panels.[13] Exceptions: Calcium dobesilate, Levodopa and methyldopa can all cause artificially low uric acid results.

Dicynone (Etamsylate) at therapeutic concentrations may lead to false-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.

Hemolysis: No significant interference up to an H index of 750 (approximate hemoglobin concentration: 466 µmol/L or 750 mg/dL).

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

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

Serum/plasma

0.2-25 mg/dL (11.9-1487 µmol/L)

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.

Urine

2.2-275 mg/dL (131-16362 µmol/L)

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

Limit of Blank, Limit of Detection and Limit of Quantitation

Serum/plasma

Limit of Blank	= 0.2 mg/dL
Limit of Detection	= 0.2 mg/dL
Limit of Quantitation	= 0.2 mg/dL

Urine

Limit of Blank	= 2.2 mg/dL
Limit of Detection	= 2.2 mg/dL
Limit of Quantitation	= 2.2 mg/dL

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 concentration 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 concentration samples.

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

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

Expected values
mg/dL

Serum/plasma[16]

Males: 3.4-7.0 mg/dL

Females: 2.4-5.7 mg/dL

Urine (reference range according to Krieg and Colombo)

1st morning urine[17] 37-92 mg/dL*

24-hour urine[18] 200-1000 mg/day*

corresponding to 13-67 mg/dL

(calculated from a urine volume of 1.5 L/24 h)

µmol/L

Serum/plasma[16]

Males: 202.3-416.5 µmol/L*

Females: 142.8-339.2 µmol/L*

* calculated by unit conversion factor

Urine (reference range according to Krieg and Colombo)

1st morning urine[17] 2200-5475 µmol/L

24-hour urine[18] 1200-5900 µmol/day

corresponding to 773-3986 µmol/L

(calculated from a urine volume of 1.5 L/24 h)

Urine (reference range according to Tietz)[19]

Average diet		250-750 mg/24 hours
Low purine diet		
	Females	< 400 mg/24 hours
	Males	< 480 mg/24 hours
High purine diet		< 1000 mg/24 hours

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. 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.

Serum/plasma

Repeatability	*Mean mg/dL*	*SD mg/dL*	*CV %*
PCCC1[b)]	4.60	0.0193	0.4
PCCC2[c)]	10.6	0.0655	0.6
Human serum 1	0.430	0.00713	1.7
Human serum 2	2.32	0.0147	0.6
Human serum 3	6.66	0.0347	0.5
Human serum 4	12.0	0.0756	0.6
Human serum 5	21.4	0.129	0.6

Intermediate precision	*Mean mg/dL*	*SD mg/dL*	*CV %*
PCCC1[b)]	4.60	0.0467	1.0
PCCC2[c)]	10.6	0.0983	0.9
Human serum 1	0.430	0.00880	2.0
Human serum 2	2.32	0.0185	0.8
Human serum 3	6.66	0.0400	0.6
Human serum 4	12.0	0.0940	0.8
Human serum 5	21.4	0.143	0.7

b) PreciControl ClinChem Multi 1
c) PreciControl ClinChem Multi 2

Urine

Repeatability	*Mean mg/dL*	*SD mg/dL*	*CV %*
Control 1[d)]	9.05	0.0780	0.9
Control 2[d)]	16.1	0.0957	0.6
Human urine 1	2.91	0.0584	2.0
Human urine 2	37.1	0.171	0.5
Human urine 3	74.7	0.279	0.4
Human urine 4	115	0.556	0.5
Human urine 5	224	0.866	0.4

Intermediate precision	*Mean mg/dL*	*SD mg/dL*	*CV %*
Control 1[d)]	9.18	0.144	1.6
Control 2[d)]	16.1	0.159	1.0
Human urine 1	3.06	0.576	18.8
Human urine 2	37.1	0.615	1.7
Human urine 3	74.9	1.93	2.6
Human urine 4	115	4.34	3.8
Human urine 5	224	1.39	0.6

d) commercially available control material

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

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

Serum/plasma

Sample size (n) = 88

Passing/Bablok[20]	Linear regression
y = 1.004x - 0.0207 mg/dL	y = 1.008x - 0.0265 mg/dL
τ = 0.985	r = 1.000

The sample concentrations were between 0.290 and 24.6 mg/dL.

Urine

Sample size (n) = 81

Passing/Bablok[20]	Linear regression
y = 1.002x - 0.168 mg/dL	y = 1.004x - 0.162 mg/dL
τ = 0.987	r = 1.000

The sample concentrations were between 3.27 and 270 mg/dL.

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

Serum/plasma

Sample size (n) = 83

Passing/Bablok[20]	Linear regression
y = 1.000x + 0.003 mg/dL	y = 1.023x - 0.141 mg/dL
τ = 0.979	r = 0.998

The sample concentrations were between 0.200 and 23.7 mg/dL.

Urine

Sample size (n) = 102

Passing/Bablok[20]	Linear regression
y = 1.038x - 0.0408 mg/dL	y = 1.057x - 0.990 mg/dL
τ = 0.991	r = 1.000

The sample concentrations were between 2.45 and 243 mg/dL.

Uric acid values for human serum, plasma and urine 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).

Serum/plasma

Sample size (n) = 76

Passing/Bablok[20]	Linear regression
y = 1.009x - 0.0125 mg/dL	y = 0.999x + 0.0327 mg/dL
τ = 0.963	r = 1.000

The sample concentrations were between 0.294 and 23.3 mg/dL.

Urine

Sample size (n) = 66

Passing/Bablok[20]	Linear regression
y = 0.990x - 0.0957 mg/dL	y = 0.994x - 0.220 mg/dL
τ = 0.997	r = 1.000

The sample concentrations were between 4.41 and 254 mg/dL.

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.

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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