VANC3

cobas®

ONLINE TDM Vancomycin Gen.3

Order information

REF	CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
06779336190	ONLINE TDM Vancomycin Gen.3 (100 tests)	System-ID 07 7571 1	Roche/Hitachi **cobas c** 311, **cobas c** 501/502
06779344190	ONLINE TDM Vancomycin Gen.3 (200 tests)	System-ID 07 7571 1	Roche/Hitachi **cobas c** 311, **cobas c** 501/502

Materials required (but not provided):

03375790190	Preciset TDM I calibrators CAL A-F (1 × 5 mL) Diluent (1 × 10 mL)	Codes 691-696	
04521536190	TDM Control Set Level I (2 × 5 mL) Level II (2 × 5 mL) Level III (2 × 5 mL)	 Code 310 Code 311 Code 312	

English

System information

For **cobas c** 311/501 analyzers:

VANC3: ACN 159

For **cobas c** 502 analyzer:

VANC3: ACN 8159

Intended use

In vitro test for the quantitative determination of vancomycin in serum and plasma on Roche/Hitachi **cobas c** systems.

Summary[1,2,3,4]

Vancomycin is a complex glycopeptide antibiotic, which is used for the treatment of infections caused by Gram-positive organisms, primarily methicillin resistant *Staphylococcus aureus* (MRSA), coagulase-negative *Staphylococci*, *Streptococci* or *Enterococci*, particularly in patients allergic to β-lactams.

Common side effects include, amongst others, the following: (a) red man syndrome, a histamine-mediated flushing during or immediately following infusion, (b) nephrotoxicity, and (c) ototoxicity; the latter two adverse events are dose/level dependent.

In former years the monitoring of peak and trough levels has been recommended. Meanwhile the relevance of monitoring peak concentrations is questioned by some clinicians due to limited clinical data. Monitoring of trough serum or plasma levels is necessary to ascertain clinical efficacy and to limit potentially dose-dependent serious side effects, e.g. ototoxicity and nephrotoxicity. The potential for the latter two serious adverse events has established therapeutic drug monitoring (TDM) of vancomycin as the standard of care. Trough levels are typically obtained before or after the 4th dose of the drug and then monitored at least once weekly.

Test principle

The assay is based on the kinetic interaction of microparticles in a solution (KIMS). Vancomycin antibody is covalently coupled to microparticles and the drug derivative is linked to a macromolecule. The kinetic interaction of microparticles in solutions, photometrically detected by turbidity measurements is induced by binding of drug-conjugate to the antibody on the microparticles and is inhibited by the presence of vancomycin in the sample. A competitive reaction takes place between the drug conjugate and vancomycin in the serum sample for binding to the vancomycin antibody on the microparticles. The resulting turbidity is indirectly proportional to the amount of drug present in the sample.

Reagents - working solutions

R1 Vancomycin conjugate; piperazine-N,N'-bis(2-ethanesulfonic acid) (PIPES) buffer, pH 7.2; preservative; stabilizer

R2 Anti-vancomycin antibody (mouse monoclonal); latex microparticle; 3-(N-morpholino)propane sulfonic acid (MOPS) buffer, pH 7.2; stabilizer

100 Tests/Cassette: R1 is in position A and R2 is in position C.

200 Tests/Cassette: R1 is in position B and R2 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.

For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

Reagent handling

Ready for use

Carefully invert reagent container several times prior to use to ensure that the reagent components are mixed.

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:	12 weeks

Do not freeze.

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: K_2- or K_3-EDTA, lithium heparin.
Sample collection tubes containing separating gel have not been verified for use.

Stability:	48 hours capped at 15-25 °C
	14 days capped at 2-8 °C
	12 months capped at -20 °C

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.

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.

Do not induce foaming of specimens. Specimens can be repeatedly frozen and thawed up to 5 times.

Invert thawed specimens several times prior to testing.

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Usual sampling time varies dependent upon desired measurement of peak or trough values.[5]

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

Deselect Automatic Rerun for these applications in the Utility menu, Application screen, Range tab.

cobas c 311 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10 / 8-51		
Wavelength (sub/main)	800/600 nm		
Reaction direction	Increase		
Unit	µg/mL		
Reagent pipetting		Diluent (H_2O)	
R1	100 µL	–	
R2	70 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	Diluent (H_2O)
Normal	2.0 µL	–	–
Decreased	2.0 µL	–	–
Increased	2.0 µL	–	–

cobas c 501/502 **test definition**

Assay type	2-Point End		
Reaction time / Assay points	10 / 13-61		
Wavelength (sub/main)	800/600 nm		
Reaction direction	Increase		
Unit	µg/mL		
Reagent pipetting		Diluent (H_2O)	
R1	100 µL	–	
R2	70 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	Diluent (H_2O)
Normal	2.0 µL	–	–
Decreased	2.0 µL	–	–
Increased	2.0 µL	–	–

Calibration

Calibrators	S1-6: Preciset TDM I calibrators
Calibration mode	Spline
Calibration frequency	6-point calibration Calibration must be performed once per reagent lot using fresh reagent (i.e. not more than 24 hours since the reagent kit was registered on the analyzer). Renewed calibration is recommended as follows: • after 2 weeks on-board the analyzer • 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 USP reference standards.[6] The calibrators are prepared to contain known quantities of vancomycin in normal human serum.

Quality control

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

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

Conversion factor:[7] µg/mL x 0.690 = µmol/L

Limitations - interference

Criterion: Recovery within ± 10 % of initial value at vancomycin levels of approximately 7.5 and 30 µg/mL (5.18 and 20.7 µmol/L).

Serum/Plasma

Icterus:[8] No significant interference up to an I index of 60 for conjugated bilirubin and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 60 mg/dL or 1026 µmol/L).

Hemolysis:[8] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 1000 mg/dL or 622 µmol/L).

Lipemia (Intralipid):[8] No significant interference up to an L index of 1000. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Triglycerides: No significant interference from triglycerides up to a concentration of 1000 mg/dL (11.4 mmol/L).

Rheumatoid factors: No significant interference from rheumatoid factors up to a concentration of 1200 IU/mL.

Total protein: No significant interference from total protein up to a concentration of 2 to 12 g/dL.

As with any assay employing mouse antibodies, the possibility exists for interference by human anti-mouse antibodies (HAMA) in the sample, which could cause falsely lowered results.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[9] In very rare cases (less than 1 reported case per 1000000 tests) certain immunoglobulins can unspecifically interfere with the agglutination reaction leading to unreliable results.

Note: A test result flagged with ">Kin" indicates unusual reaction kinetics. There is a high possibility that the sample contains an interfering substance which accelerates the reaction kinetics. For such samples it is not possible to report a reliable analyte concentration with this assay.

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. The latest version of the carry-over evasion list can be found with 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 required in certain cases.

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

Limits and ranges

Measuring range

4.0-80.0 µg/mL (2.76-55.2 µmol/L)

Manually dilute samples above the measuring range 1 + 1 with the Preciset TDM I diluent (0 µg/mL) and reassay. Multiply the result by 2 to obtain the specimen value.

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 1.0 µg/mL (0.69 µmol/L)

Limit of Detection = 1.5 µg/mL (1.04 µmol/L)

Limit of Quantitation = 4.0 µg/mL (2.76 µmol/L)

The Limit of Blank and Limit of Detection 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 from n ≥ 60 measurements of low concentration samples over several independent series. 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 for vancomycin is 4.0 µg/mL (2.76 µmol/L) determined in accordance with the guidelines in CLSI document EP17-A2, based on a minimum of 48 determinations; and a total error goal of 20 % calculated using the RMS error model.

Expected values

The practice of routine monitoring and adjustment of serum vancomycin concentrations has been the subject of intense debate for many years.[3] Historically trough concentrations between 5 to 10 µg/mL and peak concentrations between 20 to 40 µg/mL were generally accepted for therapeutic effectiveness.[3,4,7] The increased prevalence of resistant organisms, increasing vancomycin minimum inhibitory concentrations in target pathogens (particularly MRSA) and vancomycin failures have prompted more aggressive vancomycin dosing practices and recommendations.[3,10] Therefore, current guidelines recommend higher trough concentrations in the range of 10-15 µg/mL for uncomplicated MRSA bacteremia and even 15-20 µg/mL in cases of sustained MRSA bacteremia or endocarditis and other severe invasive MRSA infections (i.e. prosthetic joint infections, hospital-acquired pneumonia or central nervous system infections).[2,3] However, higher doses of vancomycin used have been associated with significantly higher vancomycin trough levels, acute renal failure and ototoxicity.[10,11,12,13] The decision to target increased vancomycin trough concentrations should be based on an assessment of the severity of the infection and must consider the risk associated with increased vancomycin levels.

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 accordance with the CLSI (Clinical and Laboratory Standards Institute) EP5-A2 requirements with repeatability (n = 84) and intermediate precision (2 aliquots per run, 2 runs per day, 21 days). The following results were obtained on a Roche/Hitachi **cobas c** 501 analyzer:

Serum/Plasma

Repeatability	*Mean*		*SD*		*CV*
	µg/mL	*µmol/L*	*µg/mL*	*µmol/L*	*%*
Control 1	7.45	5.14	0.39	0.27	5.2
Control 2	21.5	14.8	0.5	0.3	2.3
Control 3	36.2	25.0	0.9	0.6	2.4
HS 1[a)]	4.82	3.33	0.40	0.28	8.2
HS 2	7.95	5.49	0.41	0.28	5.2
HS 3	32.1	22.1	0.8	0.6	2.5
HS 4	40.0	27.6	1.0	0.7	2.5
HS 5	71.4	49.3	2.0	1.4	2.8

a) HS = human serum

Intermediate precision	*Mean*		*SD*		*CV*
	µg/mL	*µmol/L*	*µg/mL*	*µmol/L*	*%*
Control 1	7.45	5.14	0.46	0.32	6.2
Control 2	21.5	14.8	0.8	0.6	3.7
Control 3	35.5	24.5	1.1	0.8	3.2
HS 1	4.93	3.40	0.52	0.36	10.5
HS 2	7.95	5.49	0.47	0.32	5.9
HS 3	32.1	22.1	1.1	0.8	3.4
HS 4	39.5	27.3	1.1	0.8	2.9
HS 5	71.4	49.3	2.2	1.5	3.1

The data obtained on **cobas c** 501 analyzer(s) are representative for **cobas c** 311 analyzer(s).

Method comparison

Serum/plasma

Vancomycin values for human serum samples obtained on a Roche/Hitachi **cobas c** 501 analyzer (y) were compared with those determined using the commercially available EMIT assay on a Roche/Hitachi **cobas c** 501 analyzer (x).

Sample size (n) = 125

Passing/Bablok[14]	Deming regression weighted[15]
y = 0.993x + 0.641 µg/mL	y = 0.994x + 0.679 µg/mL
τ = 0.949	r = 0.994

The sample concentrations were between 4.10 and 77.5 µg/mL (2.83 and 53.5 µmol/L).

Vancomycin values for human serum samples obtained on a Roche/Hitachi **cobas c** 501 analyzer (y) were compared with those determined using LC-MS/MS[16] (x).

Sample size (n) = 134

Passing/Bablok[14]	Deming regression weighted[15]
y = 0.982x + 1.08 µg/mL	y = 0.992x + 0.841 µg/mL
τ = 0.935	r = 0.991

The sample concentrations were between 3.50 and 77.2 µg/mL (2.42 and 53.3 µmol/L).

The data obtained on **cobas c** 501 analyzer(s) are representative for **cobas c** 311 analyzer(s).

Analytical specificity

The following compounds were tested for cross-reactivity.

Compound	**Concentration Tested (µg/mL)**	**% Cross-reactivity**
Acyclovir	50	ND

Amikacin	100	ND
Amphotericin B	10	ND
Aztreonam	450	ND
Caffeine	60	ND
CDP-1	20	ND
Cefazoline	500	ND
Cefotaxine	300	ND
Chloramphenicol	60	ND
Ciprofloxicin	12	ND
Cisplatin	15	ND
Clindamycin	50	ND
Cyclosporine	3	ND
Digoxin	0.009	ND
Epinephrine	1	ND
Erythromycin	60	ND
Ethacrynic acid	1.5	ND
Flucytosine	300	ND
Furosemide	60	ND
Fusidic acid	600	ND
Gentamicin	30	ND
Imipenem	250	ND
Methicillin	250	ND
Methotrexate	455	ND
Metronidazole	150	ND
Netilmicin	30	ND
Nitroprusside	90	ND
Penicillin G	36	ND
Pentamidine	1.5	ND
Phenobarbital	150	ND
Rifampin	60	ND
Salicylate	750	ND
Sulphamethoxazole	400	ND
Theophylline	60	ND
Tobramycin	30	ND
Trimethoprim	40	ND

ND = Not Detected

Tests were performed on 16 drugs. No significant interference with the assay was found.

Acetaminophen	Heparin
Acetyl cysteine	Ibuprofen
Acetylsalicylic acid	Levodopa
Ampicillin-Na	Methyldopa + 1.5 H_2O
Ascorbic acid	Metronidazole
Cefoxitin	Phenylbutazone
Cyclosporine	Rifampicin
Doxycycline (Tetracycline)	Theophylline

References

1 Sorrell TC, Packham S, Shanker M, et al. Vancomycin therapy for methicillin-resistant Staphylococcus aureus. Ann Intern Med 1982;97:344-350.

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3 Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2009;66(1):82-98.

4 Hammett-Stabler CA, Johns T. Laboratory guidelines for monitoring of antimicrobial drugs. Clin Chem 1998;44(5):1129-1140.

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11 Hidayat LK, Hsu DI, Quist R, et al. High-dose vancomycin therapy for methicillin-resistant Staphylococcus aureus infections: efficacy and toxicity. Arch Intern Med 2006;166(19):2138-2144.

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15 Linnet, K. Evaluation of regression procedures for method comparison studies. Clinical Chemistry 1993 Mar;39(3):424-432.

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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.

The Summary of Safety & Performance Report can be found here: https://ec.europa.eu/tools/eudamed

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see dialog.roche.com for definition of symbols used):

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

VANC3

ONLINE TDM Vancomycin Gen.3

FOR US CUSTOMERS ONLY: LIMITED WARRANTY

Roche Diagnostics warrants that this product will meet the specifications stated in the labeling when used in accordance with such labeling and will be free from defects in material and workmanship until the expiration date printed on the label. THIS LIMITED WARRANTY IS IN LIEU OF ANY OTHER WARRANTY, EXPRESS OR IMPLIED, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR PARTICULAR PURPOSE. IN NO EVENT SHALL ROCHE DIAGNOSTICS BE LIABLE FOR INCIDENTAL, INDIRECT, SPECIAL OR CONSEQUENTIAL DAMAGES.

CE 0123

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