


REF		CONTENT		Analyzer(s) on which cobas c pack(s) can be used
04791959190	04791959500	ONLINE TDM Amikacin (75 tests)	System-ID 07 6926 6	cobas c 311 , cobas c 501/502

Materials required (but not provided):

03375781190	Preciset TDM II Calibrators CAL A-F (6 x 5 mL) Diluent (1 x 10 mL)	Codes 743-748	
04521536190	TDM Control Set Level I (2 x 5 mL) Level II (2 x 5 mL) Level III (2 x 5 mL)	Code 310 Code 311 Code 312	

English

System information

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

AMIK2: ACN 456

For **cobas c 502** analyzers:

AMIK2: ACN 8456

Intended use

In vitro test for the quantitative determination of amikacin in serum and plasma on **cobas c** systems.

Summary

Amikacin measurements performed with this assay, in human serum and plasma, are used for monitoring amikacin treatment to ensure appropriate therapy.

Amikacin is a semisynthetic aminoglycoside antibiotic used in the treatment of serious Gram-negative infections.¹ Like all aminoglycoside antibiotics, amikacin blocks the production of protein by inhibiting messenger RNA translation in the bacterial cells.^{1,2} It is excreted unchanged by glomerular filtration by the kidney.¹ For patients with impaired renal function, elderly patients and critically ill patients, serum amikacin concentrations should be monitored by appropriate assay procedures and doses should be adjusted accordingly.^{1,2,3,4,5}

Toxicity associated with aminoglycosides manifests as ototoxicity (delayed-onset vestibular or cochlear sensory cell destruction) and nephrotoxicity.² The degree and severity of cell damage are variable among the different drugs, but they all cause cell damage if the concentrations are high.²

Amikacin therapeutic drug monitoring is recommended by manufacturers and guidelines to maximize the efficacy of aminoglycosides and reduce incidences of drug toxicity.^{1,3,6,7,8}

Test principle

Kinetic interaction of microparticles in solution (KIMS) as measured by changes in light transmission.

The assay is a homogeneous immunoassay based on the principle of measuring changes in scattered light or absorbance which result when activated microparticles aggregate. The microparticles are coated with amikacin and rapidly aggregate in the presence of an amikacin antibody solution. When a sample containing amikacin is introduced, the aggregation reaction is partially inhibited, slowing the rate of the aggregation process. Antibody bound to sample drug is no longer available to promote microparticle aggregation, and subsequent particle lattice formation is inhibited. Thus, a classic inhibition curve with respect to amikacin concentration is obtained, with the maximum rate of aggregation at the lowest amikacin concentration. By monitoring the change in scattered light or absorbance, a concentration-dependent curve is obtained.

Reagents - working solutions

R1 Anti-amikacin antibody (mouse monoclonal) and human-sourced material in buffer with preservative

R2 Conjugated amikacin derivative microparticles, human-sourced material, and preservative

R1 is in position A and R2 is in position B.

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:



Danger

H318 Causes serious eye damage.

Prevention:

P280 Wear eye protection/ face protection.

Response:

P305 + P351 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do.
+ P338
+ P310 Continue rinsing. Immediately call a POISON CENTER/ doctor.

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

All human material should be considered potentially infectious. All products derived from human blood are prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV. The testing methods use assays that have been approved or cleared by the FDA or that are in compliance with the legal rules of the European Union (IVDR 2017/746/EU, IVDD 98/79/EC, Annex II, List A). However, as no testing method can rule out the potential risk of infection with absolute certainty, the material should be handled with the same level of care as a patient specimen. In the event of exposure, the directives of the responsible health authorities should be followed.^{9,10}

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: Collect serum using standard sampling tubes.

Plasma: K₂- or K₃-EDTA or Na or Li heparin plasma.

Stability:	8 hours capped at 15-25 °C
	48 hours capped at 2-8 °C
	4 weeks capped at -20 °C (± 5° C)

Freeze only once.

Do not induce foaming of specimens.

Invert thawed specimens several times prior to testing.

Centrifuge samples containing precipitates before performing the assay.

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.

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

Usual sampling time varies dependent upon desired measurement of peak or trough values.¹¹

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 / 10-26		
Wavelength (sub/main)	- /700 nm		
Reaction direction	Increase		
Unit	µg/mL		
Reagent pipetting	Diluent (H ₂ O)		
R1	167 µL	-	
R2	50 µL	-	
Sample volumes	Sample	Sample dilution	
		Sample	Diluent (NaCl)
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 / 16-38

Wavelength (sub/main)	- /700 nm		
Reaction direction	Increase		
Unit	µg/mL		
Reagent pipetting	Diluent (H ₂ O)		
R1	167 µL	-	
R2	50 µL	-	
Sample volumes	Sample	Sample dilution	
		Sample	Diluent (NaCl)
Normal	2.0 µL	-	-
Decreased	2.0 µL	-	-
Increased	2.0 µL	-	-

Calibration

Calibrator	S1-6: Preciset TDM II Calibrators
Calibration mode	RCM
Calibration frequency	6-point calibration
	• after reagent lot change
	• every 6 weeks
	• 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. The calibrators are prepared to contain known quantities of amikacin 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

cobas c systems automatically calculate the analyte concentration of each sample.

Conversion factor:¹² µg/mL x 1.71 = µmol/L

Limitations - interference

Criterion: Recovery within ± 10 % of initial value at amikacin levels of approximately 5.0 and 30 µg/mL (8.6 and 51.3 µmol/L).

Icterus:¹³ No significant interference up to an I index of 50 for conjugated bilirubin and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 50 mg/dL or 855 µmol/L).

Hemolysis:¹³ No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 1000 mg/dL or 621 µmol/L).

Lipemia (Intralipid):¹³ No significant interference up to an L index of 2000. 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 800 mg/dL (9.0 mmol/L).

Rheumatoid factors: No significant interference from rheumatoid factors up to a concentration of 100 IU/mL.

Total protein: No significant interference from total protein in the concentration range of 2-12 g/dL.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.¹⁴

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. 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

0.8-40 µg/mL (1.4-68.4 µmol/L)

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

Lower limits of measurement

Lower detection limit of the test

0.8 µg/mL (1.4 µmol/L)

The lower detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying 2 standard deviations above that of the 0 µg/mL calibrator (standard 1 + 2 SD, repeatability, n = 21).

Expected values

Although optimum values may vary, peak serum values of amikacin in the range of 20 to 25 µg/mL (34.2 to 42.8 µmol/L) and trough values in the range of 5 to 10 µg/mL (8.6 to 17.1 µmol/L) are generally accepted for therapeutic effectiveness. Toxicity is associated with peak levels greater than 35 µg/mL (59.9 µmol/L) and trough values greater than 10 µg/mL (17.1 µmol/L).¹⁵ The most serious toxic effect is permanent damage to the vestibular division of the eighth cranial nerve, which has been reported to occur most frequently in patients with renal failure. Since amikacin is inherently stable, is not metabolized, and is excreted primarily by glomerular filtration, the presence of renal impairment drastically alters its pharmacokinetics. If dosage regimens are not adjusted, excess accumulation leading to ototoxicity and further renal impairment could be encountered.^{16,17,18,19} While serum levels can be toxic, indiscriminately low dosages of amikacin will result in ineffective treatment for many strains of gram-negative bacteria. Organisms which are resistant to amikacin will often show increased resistance to all other available aminoglycosides. This observation²⁰ points out the possibility that the indiscriminate use of low dosages of amikacin could engender the emergence of drug-resistant organisms and possibly render the drug ineffective in treating infectious disease.^{21,22}

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

Expected values reflect the data and information provided in the reference and do not necessarily represent therapeutic recommendations and/or dosage instructions. For therapeutic recommendations and dosage instructions refer to applicable guidelines and the full prescription information of the drug.

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 a modified NCCLS EP5-A protocol (repeatability n = 63, intermediate precision n = 63). The following results were obtained on a **cobas c** 501 analyzer.

Repeatability	Mean		SD		CV
	µg/mL	µmol/L	µg/mL	µmol/L	%
Control 1	5.07	8.67	0.14	0.24	2.7
Control 2	14.4	24.6	0.16	0.27	1.1
Control 3	28.2	48.2	0.27	0.46	1.0
HS 1	4.98	8.52	0.13	0.22	2.6

HS 2	32.6	55.7	0.31	0.53	0.9
Intermediate precision	Mean		SD		CV
	µg/mL	µmol/L	µg/mL	µmol/L	%
Control 1	5.07	8.67	0.19	0.32	3.8
Control 2	14.4	24.6	0.19	0.32	1.3
Control 3	28.2	48.2	0.36	0.62	1.3
HS 1	4.98	8.52	0.17	0.29	3.5
HS 2	32.6	55.7	0.41	0.70	1.3

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

Method comparison

Amikacin values for human serum and plasma samples obtained on a **cobas c** 501 analyzer (y) were compared with those determined using the corresponding reagent on a Roche/Hitachi 917 analyzer (x) and on a COBAS INTEGRA 700 analyzer (x).

<i>Roche/Hitachi 917 analyzer</i>	Sample size (n) = 57
Passing/Bablok ²³	Linear regression
y = 0.988x - 0.078 µg/mL	y = 0.986x - 0.033 µg/mL
τ = 0.981	r = 1.000

The sample concentrations were between 1.1 and 37.4 µg/mL (1.88 and 64.0 µmol/L).

<i>COBAS INTEGRA 700 analyzer</i>	Sample size (n) = 53
Passing/Bablok ²³	Linear regression
y = 0.950x - 0.195 µg/mL	y = 0.949x - 0.327 µg/mL
τ = 0.934	r = 0.993

The sample concentrations were between 1.4 and 39.8 µg/mL (2.39 and 68.1 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
Amphotericin	20	ND
Ampicillin	90	ND
Carbenicillin	500	ND
Cephalexin	500	ND
Cephalosporin C	500	ND
Cephalothin	60	ND
Chloramphenicol	300	ND
Clindamycin	5	ND
Erythromycin	200	ND
Ethacrynic acid	500	ND
5-Fluorocytosine	700	ND
Furosemide	100	ND
Fusidic acid	500	ND
Gentamicin	100	ND
Kanamycin A	25	ND
Kanamycin B	25	ND
Lincomycin	30	ND

Methotrexate	23	ND
Methylprednisolone	500	ND
Neomycin	100	ND
Netilmycin	80	ND
Oxytetracycline	40	ND
Penicillin V	50	ND
Prednisolone	500	ND
Rifampin	320	ND
Spectinomycin	200	ND
Streptomycin	200	ND
Sulfadiazine	1500	ND
Sulfamethoxazole	2000	ND
Tetracycline	40	ND
Tobramycin	100	ND
Trimethoprim	120	ND
Vancomycin	400	ND

ND = not detectable

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

Acetaminophen	Doxycycline
Acetyl cysteine	Ibuprofen
Acetylsalicylic acid	Levodopa
Ampicillin-Na	Methyldopa + 1.5 H ₂ O
Ascorbic acid	Metronidazole
Ca-Dobesilate	Phenylbutazone
Cefoxitin	Rifampicin
Cyclosporine	Theophylline

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.

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:

	Contents of kit
	Volume for reconstitution
	Global Trade Item Number

Rx only

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

04791959500V12.0



AMIK2

ONLINE TDM Amikacin

cobas®

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