

## Order information

REF	CONTENT	Analyzer(s) on which <b>cobas c</b> pack(s) can be used
04791959 190	ONLINE TDM Amikacin (75 tests)	System-ID 07 6926 6 Roche/Hitachi <b>cobas c</b> 311, <b>cobas c</b> 501/502
Materials required (but not provided):		
03375781 190	Preciset TDM II Calibrators CAL A-F (6 x 5 mL) Diluent (1 x 10 mL)	Codes 743-748
04521536 190	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 Roche/Hitachi **cobas c** systems.

## Summary

Amikacin is a semi-synthetic aminoglycoside that exhibits bactericidal activity against a wide range of pathogens, including many organisms resistant to other aminoglycosides.<sup>1,2,3,4</sup> Amikacin is active in vitro against gram-negative organisms, penicillinase and non-penicillinase producing staphylococci. The strength of this drug is due primarily to its high degree of resistance to aminoglycoside-inactivating enzymes.<sup>5</sup> Determination of serum or plasma drug levels is required to achieve optimum therapeutic efficacy and minimize toxicity.<sup>6</sup>

## 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.

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

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 Continue rinsing. Immediately call a POISON CENTER/ doctor.  
+ P310

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590, USA: 1-800-428-2336

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 by the FDA or that are in compliance with the legal rules applicable to placing in vitro diagnostic medical devices for human use on the market in the European Union.

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.<sup>7,8</sup>

## 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: K<sub>2</sub>- or K<sub>3</sub>-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

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 should not be repeatedly frozen and thawed.

Invert thawed specimens several times prior to testing.

Usual sampling time varies dependent upon desired measurement of peak or trough values.<sup>9</sup>

**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 <sub>2</sub> 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 <sub>2</sub> 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 <ul style="list-style-type: none"> <li>• after reagent lot change</li> <li>• every 6 weeks</li> <li>• as required following quality control procedures</li> </ul>

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**

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

Conversion factor:<sup>10</sup> 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).

**Serum/Plasma**

Icterus:<sup>11</sup> 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:<sup>11</sup> No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 1000 mg/dL or 621 µmol/L).

Lipemia (Intralipid):<sup>11</sup> 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.<sup>12</sup>

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-SmpCin1+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 Preciset 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).<sup>6</sup> 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.<sup>13,14,15,16</sup> 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 observation<sup>17</sup> 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.<sup>5,18</sup>

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

**Serum/Plasma**

<i>Repeatability</i>	<i>Mean</i>		<i>SD</i>		<i>CV</i>
	<i>µg/mL</i>	<i>µmol/L</i>	<i>µg/mL</i>	<i>µmol/L</i>	<i>%</i>
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

<i>Intermediate precision</i>	<i>Mean</i>		<i>SD</i>		<i>CV</i>
	<i>µg/mL</i>	<i>µmol/L</i>	<i>µg/mL</i>	<i>µmol/L</i>	<i>%</i>
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****Serum/plasma**

Amikacin values for human serum and plasma samples obtained on a Roche/Hitachi **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>	<i>Sample size (n) = 57</i>
Passing/Bablok <sup>19</sup>	Linear regression
$y = 0.988x - 0.078 \mu\text{g/mL}$	$y = 0.986x - 0.033 \mu\text{g/mL}$
$\tau = 0.981$	$r = 1.000$

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>	<i>Sample size (n) = 53</i>
Passing/Bablok <sup>19</sup>	Linear regression
$y = 0.950x - 0.195 \mu\text{g/mL}$	$y = 0.949x - 0.327 \mu\text{g/mL}$
$\tau = 0.934$	$r = 0.993$

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.

<b>Compound</b>	<b>Concentration Tested (µg/mL)</b>	<b>% Cross-reactivity</b>
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 <sub>2</sub> O
Ascorbic acid	Metronidazole
Ca-Dobesilate	Phenylbutazone
Cefoxitin	Rifampicin
Cyclosporine	Theophylline

**References**

- Price KE, Chisholm DR, Misiek M et al. Microbiological evaluation of BB-K8, a new semi-synthetic aminoglycoside. *J Antibiot* 1972;25:709.
- Bodey GP, Steward D. In vitro studies of BB-K8, a new aminoglycoside antibiotic. *Antimicrob Ag Chemother* 1973;4:186.
- Young LS, Hewitt WL. Activity of five aminoglycoside antibiotics in vitro against gram-negative bacilli and staphylococcus aureus. *Antimicrob Ag Chemother* 1973;4:617-625.
- Yourassowsky E, Schoutens E, Vanderlinden MD et al. Comparison of the in vitro activity of BB-K8 and three other aminoglycosides against 215 strains of pseudomonas and enterobacteriaceae with variable sensitivity tokanamycin and gentamicin. *Chemother* 1975;21:45.
- Price KE, Pursiano TA, DeFuria MD et al. Activity of BB-K8 (amikacin) against clinical isolates resistant to one or more aminoglycoside antibiotics. *Antimicrob Ag Chemother* 1974;5:143-152.
- Jacobs DS, Kaster BL Jr, Demott WR, et al. *Laboratory Test Handbook*. Stowe, 2nd ed. OH. Lexi-Compl. Mosby 1990;771.
- Occupational Safety and Health Standards: Bloodborne pathogens. (29 CFR Part 1910.1030). Fed. Register.
- Directive 2000/54/EC of the European Parliament and Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work.
- Riff LJ, Jackson GG. Pharmacology of gentamicin in man. *J Infect Dis* 1971;124(Suppl):98-105.
- Ashwood ER, Burtis CA. *Tietz Textbook of CLinical Chemistry*. 2nd ed. Philadelphia, PA: WB Saunders Co 1994:2214.
- Glick MR, Ryder KW, Jackson SA. Graphical Comparisons of Interferences in Clinical Chemistry Instrumentation. *Clin Chem* 1986;32:470-475.

- Bakker AJ, Mücke M. Gammopathy interference in clinical chemistry assays: mechanisms, detection and prevention. *Clin Chem Lab Med* 2007;45(9):1240-1243.
- Levy J, Klastersky J. Correlation of serum creatinine concentration and amikacin half-life. *J Clin Pharmac* 1975;705-707.
- Cabana BE, Taggart BE, Taggart JG. Comparative pharmacokinetics of BB-K8 and kanamycin in dogs and humans. *Antimicrob Ag Chemother* 1973; 3:478.
- Clarke JT, Libke, RD, Regamey C, et al. Comparative pharmacokinetics of amikacin and kanamycin. *Clin Pharm Ther* 1974;15:610.
- Marik PE, Havlik I, Monteagudo FSE, et al. The pharmacokinetic of amikacin in critically ill adult and pediatric patients: comparison of amikacin in critically ill adult and pediatric patients: comparison of once-versus twice-daily dosing regimens. *J Antimicrob Chemother* 1991;27(No. C Suppl):81-89."
- Overturf G, Zawacki BE, Wilkins J et al. Emergence of resistance to amikacin during treatment of burn wounds: the role of antimicrobial susceptibility testing. *Surgery* 1976;79:224-228.
- Beniviste R, Davies J. Mechanisms of antibiotic resistance in bacteria. *J Ann Rev Biochem* 1973;42:471.
- Bablok W, Passing H, Bender R, et al. A general regression procedure for method transformation. Application of linear regression procedures for method comparison studies in clinical chemistry, Part III. *J Clin Chem Clin Biochem* 1988 Nov;26(11):783-790.




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](http://dialog.roche.com) for definition of symbols used):

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

**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.

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