QMS™ Tobramycin (TOBRA)

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IVD

Read Highlighted Changes: Revised November 2023

For In Vitro Diagnostic Use Only

REF **10017109**

Rx Only

This Quantitative Microsphere System (QMS) package insert must be read carefully prior to use. Package insert instructions must be followed accordingly. Reliability of assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.

Intended Use

The QMS™ Tobramycin assay is intended for the quantitative determination of tobramycin in human serum or plasma on automated clinical chemistry analyzers.

The results obtained are used in the diagnosis and treatment of tobramycin overdose and in monitoring levels of tobramycin to help ensure appropriate therapy.

Summary and Explanation of the Test

Tobramycin Sulfate is an aminoglycoside derived from Streptomyces tenebrarius.[1] This aminoglycoside antibiotic is used to treat serious bacterial infections by inhibiting the growth of the bacterium by intervening in the cell wall synthesis thereby killing the bacterium.[2] The therapeutic range for tobramycin is between 2.0 and 8.0 µg/mL, the trough being at 1.0 to 2.0 µg/mL.[2] Side effects of tobramycin include deafness (ototoxicity) and renal failure (nephrotoxicity) at levels above the therapeutic range.

Tobramycin is absorbed minimally from the gastrointestinal tract. In the first 24 hours after intravenous dosing, the usual route of administration, about 99% of the tobramycin is excreted unchanged by the kidneys. The average half-life in patients with normal renal function is about 2-3 hours.[3] Therapeutic serum levels vary depending on the microorganism involved and the patient's tolerance to the drug. Tobramycin serum or plasma concentrations are monitored to help guide therapy, since individual patient differences require dose changes that are difficult to predict.[4,5] Monitoring serum or plasma levels of tobramycin decreases the frequency of serious toxic effects.

Principles of the Procedure

The QMS Tobramycin assay is a homogeneous particle-enhanced turbidimetric immunoassay. The assay is based on competition between drug in the sample and drug coated onto a microparticle for antibody binding sites of the tobramycin antibody reagent. The tobramycin-coated microparticle reagent is rapidly agglutinated in the presence of the anti-tobramycin antibody reagent and in the absence of any competing drug in the sample. The rate of absorbance change is measured photometrically. When a sample containing tobramycin is added, the agglutination reaction is partially inhibited, slowing down the rate of absorbance change. A concentration-dependent classic agglutination inhibition curve can be obtained with maximum rate of agglutination at the lowest tobramycin concentration and the lowest agglutination rate at the highest tobramycin concentration.

Reagents

Reagent Kit

QMS Tobramycin, REF 10017109 is supplied as a liquid, ready-to-use, two-reagent kit that contains:

REF 10017109
Reagent 1 1 x 14 mL
Reagent 2 1 x 12 mL

Reactive Ingredients

INGRED	Ingredient	Concentration
Reagent 1	Anti-tobramycin Monoclonal Antibody (Mouse)	≤0.1%
	Sodium Azide	≤0.09%
Reagent 2	Tobramycin-coated Microparticles	<0.3%
	Sodium Azide	≤0.09%

Reagent Handling and Storage

- Reagent 1 and Reagent 2 Ready for Use.
- Before use, invert several times, avoiding the formation of bubbles.
- Remove air bubbles, if present in the reagent cartridge, with a new applicator stick. Alternatively, allow the reagent to sit at the appropriate storage temperature to allow the bubbles to dissipate. To minimize volume depletion, do not use a transfer pipette to remove the bubbles.
- When either the Reagent 1 or the Reagent 2 reagent cartridge becomes empty, replace both cartridges and verify calibration with at least two levels of controls according to the established Quality Control requirements for your laboratory. If control results fall outside acceptable ranges, recalibration may be necessary.
- In the case of accidental spill, clean and dispose of material according to your laboratory's SOP, and local, state and country regulations, with consideration that the material contains potentially infectious materials.
- In the case of damaged packaging on arrival, contact your technical support representative (contact details listed at the end of this package insert).

⚠ **CAUTION:** Reagent bubbles may interfere with proper detection of reagent level in the cartridge, causing insufficient reagent aspiration that could impact results.

2°C – 8°C The unopened reagents are stable until the expiration date when stored at 2 to 8°C. Once opened and stored tightly capped at 2-8°C, the reagents are stable for up to 62 days or until expiration, whichever occurs first.

Do not freeze reagents or expose them to temperatures above 32°C.

Warnings and Precautions

Precautions for Users

- For in vitro diagnostic use.
- Do not mix materials from different kit lot numbers.
- Contains nonsterile mouse monoclonal antibodies.
- The reagents contain ≤0.2% bovine serum albumin (BSA). Avoid contact with skin and mucous membranes. Avoid inhalation. May cause topical or respiratory allergic reaction. Flush affected areas with copious amounts of water. In case of accident by inhalation, remove to fresh air and keep at rest.

DANGER: QMS Tobramycin (TOBRA) contains ≤5.0% Drug-specific antibody, ≤3.5% IgM, and ≤0.2% Bovine serum albumin (BSA).
H317 - May cause allergic skin reaction.
H334 - May cause allergy or asthma symptoms or breathing difficulties if inhaled.

Avoid breathing mist or vapor. Contaminated work clothing should not be allowed out of the workplace. Wear protective gloves/eye protection/face protection. In case of inadequate ventilation wear respiratory protection. If on skin: Wash with plenty of soap and water. IF INHALED: If breathing is difficult, remove victim to fresh air and keep at rest in a position comfortable for breathing. If skin irritation or rash occurs: Get medical advice/attention. If experiencing respiratory symptoms: Call a POISON CENTER or doctor/physician. Wash contaminated clothing before reuse. Dispose of contents/container to location in accordance with local/regional/national/international regulations.

⚠ **CAUTION:** This product contains human sourced and/or potentially infectious components. Components sourced from human blood have been tested and found to be nonreactive for HBsAg, anti-HIV 1/2, and anti-HCV. No known test method can offer complete assurance that products derived from human sources or inactivated microorganisms will not transmit infection. Therefore, it is recommended that all human sourced materials be considered potentially infectious and handled with appropriate biosafety practices.

Specimen Collection and Handling

The following specimen collection tubes may be used for the QMS Tobramycin assay:

	Glass	Plastic
Serum	• No Additives • Serum Separator	• With Silicon coating • Serum Separator with clot activators
Plasma	• Lithium Heparin • Sodium Heparin • K_3-EDTA	• K_2-EDTA

Other specimen collection tubes have not been validated for use with the QMS Tobramycin assay. Follow the manufacturer's processing instructions for serum or plasma tubes.

- Specimens containing particulate matter of red blood cells may give inconsistent results and should be centrifuged before testing (recommended 8,000 to 10,000 RCF* x 10 minutes).
- *Relative Centrifugal Force
- Samples for the QMS Tobramycin assay should be drawn just prior to a dose (trough level), usually early in the morning, to confirm that an adequate dose has been prescribed. The trough concentration is the most indicative of the therapeutic level of tobramycin.
- Separated samples may be stored for up to seven days at 2 to 8°C prior to being tested.
- If testing will be delayed more than seven days, separated samples may be stored frozen at <-10°C for up to 14 days.

Procedure

Materials Provided

- QMS Tobramycin Reagents, REF 10017109

Materials Required but not Provided

- QMS Tobramycin Calibrators, REF 0374116
  CAL A-F: 1 × 1.0 mL each
- QMS Tobramycin Controls

Recommended quality control material:

- Liquichek Immunoassay Plus (Bio-Rad Laboratories, Catalog Number 360)
- Other commercially available quality control set containing tri-level tobramycin concentrations in human serum/plasma or compatible synthetic matrix
- Alternatively, call Thermo Fisher Scientific Technical Support for recommendations on suitable control material.

Assay Procedure

For a detailed description of how to run and calibrate an assay, refer to the instrument specific operations manual.

Specimen Dilution Procedures
Use QMS Tobramycin CAL A (0.0 µg/mL) to manually dilute samples outside the linearity of the assay.

Manual Dilution Protocol
A manual dilution can be performed on patient samples with tobramycin concentrations reported as greater than 10.0 µg/mL by making a dilution of the specimen with QMS Tobramycin CAL A (0.0 µg/mL) before pipetting the sample into the sample cup. The dilution must be performed so the diluted test results read greater than the assay sensitivity of 0.4 µg/mL. The concentration reported must be multiplied by the manual dilution factor to obtain the final sample concentration.

$$\text{Final Sample Concentration} = \text{Reported Concentration} \times \text{Manual Dilution Factor}$$

$$\text{Manual Dilution Factor} = \frac{\text{Volume of Sample + Volume of CAL A)}}{\text{Volume of Sample}}$$

Calibration
The QMS Tobramycin assay must be calibrated using a full calibration (6-point) procedure. To perform a full calibration, test the QMS Tobramycin Calibrators A, B, C, D, E, and F in duplicate.

Calibration is required with each new lot number. Verify the calibration curve with at least two levels of controls according to the established Quality Control requirements for your laboratory. If control results fall outside acceptable ranges, recalibration may be necessary.

Note: Tobramycin CAL A is the calibration blank for this assay.

Quality Control
As appropriate, refer to your laboratory Standard Operating Procedure(s) and/or Quality Assurance Plan for additional quality control requirements and potential corrective actions. All quality control requirements should be performed in conformance with local, state, and/or federal guidelines or accreditation requirements.

Recommended control requirements for the QMS Tobramycin assay:
- A minimum of two levels of controls spanning the medical decision range should be run every 24 hours.
- If more frequent control monitoring is required, follow the established Quality Control procedures for your laboratory.
- If quality control results do not fall within an acceptable range defined by your laboratory, patient values may be suspect and corrective action should be taken.

Results
The result unit for the QMS Tobramycin assay can be reported as µg/mL or µmol/L. To convert results from µg/mL tobramycin to µmol/L tobramycin, multiply µg/mL by 2.12.

As with all analyte determinations, the tobramycin value should be used in conjunction with information available from clinical evaluations and other diagnostic procedures.

Result Error Codes
Some results may contain Result Error Codes. Refer to the instrument-specific operations manual for a description of the error codes.

Limitations of the Procedure
For diagnostic purposes, interfering heterophile antibodies occur at low frequency in the general population. These antibodies can cause auto-agglutination of the microparticle reagent leading to erroneous results that may be unexpectedly low or unexpectedly high. An erroneous result could lead to incorrect patient management; incorrect patient management could potentially cause serious injury or death. Test results should not be used in isolation to make patient management decisions. Results should always be assessed in conjunction with the patient's medical history, clinical examinations, and other clinicopathological findings. An alternative test method should be used to confirm results when results are inconsistent with clinical expectations.

See the SPECIMEN COLLECTION AND HANDLING and SPECIFIC PERFORMANCE CHARACTERISTICS sections of this package insert.

The assay is intended for use in clinical laboratories.

Expected Values
Therapeutic tobramycin peak serum levels of 5 to 8 µg/mL and trough levels of 1 to 2 µg/mL have been reported for serious bacterial infections. A therapeutic range of 2 to 8 µg/mL has been suggested for tobramycin.[2-4] Due to great individual differences in dosage requirements to achieve efficacious therapy as well as reported adverse effects at concentrations of 5 to 8 µg/mL, determination of tobramycin serum concentrations is required to optimize therapeutic drug management.[2]

Specific Performance Characteristics
Representative performance results obtained on a commercially available automated clinical chemistry analyzer that employs turbidimetric quantitative analysis are shown below.

Limit of Quantitation (LOQ)
The LOQ of the QMS Tobramycin assay is defined as the lowest concentration of an analyte that can be reliably detected and at which the total error meets accuracy requirements. The LOQ was determined to be 0.4 µg/mL.

Assay Range
The range of the assay is 0.4 to 10.0 µg/mL.

Accuracy
Accuracy by recovery was determined by spiking tobramycin into human serum to achieve concentrations across the assay range and analyzing in triplicate for tobramycin. A mean of the replicates for each sample was determined and percent recovery calculated. Representative results are shown below.

$$\text{Percent Recovery} = \frac{\text{Mean recovered concentration}}{\text{Theoretical concentration}} \times 100$$

Theoretical Concentration (µg/mL)	Mean Recovered Concentration (µg/mL)	% Recovery
1.5	1.36	90.7
3.0	2.78	92.7
4.5	4.30	95.6
6.0	5.86	97.7

Mean percent recovery: 94.2

Linearity
Tobramycin in a human serum pool was diluted with human serum negative for tobramycin to achieve concentrations across the range of the assay. The samples were analyzed in triplicate with the QMS Tobramycin assay. A mean of the replicates for each sample was determined and percent recovery calculated. Representative results are shown below.

Theoretical Concentration (µg/mL)	Mean Recovered Concentration (µg/mL)	% Recovery
0.47	0.48	104.0
0.93	0.91	97.6
1.86	1.82	98.0
3.72	3.53	95.1
5.57	5.47	98.2
7.43	7.33	98.6
9.29	9.29	100.0

Mean percent recovery: 98.8

Method Comparison
Correlation studies were performed using NCCLS Protocol EP9-A2.[7] Results from the QMS Tobramycin assay were compared with results from a commercially available fluorescence polarization immunoassay. The patient samples consisted of serum and plasma. The tobramycin concentrations ranged from 0.08 to 9.73 µg/mL. Results of the Passing-Bablok regression analysis[8-10] for the study are shown below.

Slope	0.979
y-intercept	-0.086
Correlation Coefficient (R^2)	0.984
Number of Samples	67

Precision
Precision is a combination of repeatability (within-assay) and reproducibility (between instruments).

Repeatability
Precision was determined as described in NCCLS protocol EP5-A2.[11]
A tri-level human serum based commercial control containing tobramycin was used in the study. Each level of control was assayed in duplicate twice a day for 20 days. Each of the runs per day was separated by at least two hours. The means were calculated, and the Within Run, Between Day, and Total SD and percent CVs were calculated. Representative results are shown below.

			Within Run		Between Day		Total	
Sample	N	Mean (µg/mL)	SD	CV (%)	SD	CV (%)	SD	CV (%)
1	80	1.11	0.02	1.99	0.05	4.91	0.08	7.54
2	80	3.83	0.05	1.30	0.12	3.13	0.16	4.22
3	80	8.06	0.13	1.62	0.06	0.71	0.34	4.26

Acceptance criteria: <10% total CV

Reproducibility

The reproducibility study was performed based on guidance from the CLSI EP05-A3[13]. A tri-level human serum based commercial control containing tobramycin was used in the study. Each level of control was assayed on each of three Hitachi 917 instruments for five days, one run per day, five replicates per run. Two reagent lots were used in this study. For each lot of reagents, this resulted in a total of 75 replicates for each control level. The means, repeatability (within-run), between-day, and between- instrument SD and %CV were calculated. Representative results are shown below.

			Total Repeatability (Within-Run)		Total Between-Day		Total Between-Instrument		Reproducibility	
Sample	Total N	Grand Mean (µg/mL)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
1	75	0.89	0.04	4.83	0.05	5.22	0.02	2.12	0.07	7.42
2	75	3.07	0.06	2.03	0.11	3.53	0.03	0.98	0.13	4.19
3	75	5.31	0.10	1.85	0.21	3.94	0.10	1.80	0.25	4.71

Acceptance Criteria: Reproducibility ≤ 10% CV for all control levels

Interfering Substances

The following compounds, when tested with the QMS Tobramycin assay at the concentrations indicated, resulted in less than 10% error in detecting tobramycin. Interference studies were conducted using NCCLS protocol EP7-A2.[12] The results are shown below.

Interfering Substance	Interferent Concentration	N	Tobramycin (µg/mL)	% Recovery
Albumin	12 g/dL	3	8.53	97.7
Bilirubin	40 mg/dL	3	8.41	92.3
Cholesterol	500 mg/dL	3	7.02	105.8
IgG	12 g/dL	3	7.02	97.4
Hemoglobin	20 mg/dL	3	8.09	97.2
Hemoglobin	500 mg/dL	3	8.09	108.7
HAMA type 1*	Normal human level	3	8.09	92.6
HAMA type 2*	Normal human level	3	8.09	93.8
Uric Acid	20 mg/dL	3	7.02	90.3
Rheumaoid Factor**	705 IU/mL	3	6.99	103.3
Triglyceride	1200 mg/dL	3	7.58	91.0

*HAMA = human anti-mouse antibodies

** Patient samples containing Reumatoid Factor levels above 1,240 IU may produce erroneous results with this assay.

Specificity

Cross-Reactivity

Amikacin, kanamycin, A, and kanamycin B cross-react with the Tobramycin Assay due to their structural similarity. These compounds were added to serum containing tobramycin and tested with the QMS Tobramycin Assay. The results of this assay cannot be used to accurately quantitate tobramycin serum or plasma levels in patients receiving any of these drugs in combination with tobramycin.

Representative results are shown below.

Compound	Cross-Reactant Concentration (µg/mL)	N	Mean Measured Tobramycin Concentration of Control Sample (µg/mL)	Mean Measured Tobramycin Concentration of Cross-Reactant Sample (µg/mL)	% Cross-Reactivity
Amikacin	200	5	6.4	7.4	0.52
Kanamycin A	0.5	5	6.3	8.7	484
Kanamycin B	1	5	6.3	8.1	186

Drug Cross-Reactivity

Cross-reactivity was tested with drugs that are routinely administered with Tobramycin. The following compounds were tested.

Compound	Cross-Reactant Concentration (µg/mL)	N	Mean Measured Tobramycin Concentration of Control Sample (µg/mL)	Mean Measured Tobramycin Concentration of Cross-Reactant Sample (µg/mL)	% Cross-Reactivity
5-Fluorocytosine	30	5	6.5	6.5	0.00
Acetaminophen	200	5	6.3	6.3	0.00
Amphotericin B	100	5	6.4	6.6	0.22
Ampicillin	50	5	6.4	6.6	0.52
Carbenicillin	2500	5	6.4	6.0	-0.02
Cefamandole nafate	250	5	6.6	7.1	0.19
Cephalexin	320	5	6.4	6.6	0.07
Cephalosporin C	1000	5	6.4	6.5	0.01
Cephalothin	1000	5	6.4	7.1	0.06
Chloramphenicol	250	5	6.5	6.5	-0.03
Clindamycin	2000	5	6.3	6.2	0.00
Ephedrine	1000	5	6.3	6.4	0.01
Erythromycin	500	5	6.5	6.4	-0.02
Ethacrynic Acid	400	5	6.5	6.3	-0.04
Furosemide	100	5	6.7	6.5	-0.18
Fusidic Acid	1000	5	6.3	6.3	0.00
Gentamicin	100	5	6.3	6.3	0.06
Ibuprofen	7000	5	6.5	5.9	-0.01
Lincomycin	2000	5	6.4	6.3	0.00
Methicillin	200	5	6.6	6.3	-0.15
Methotrexate	50	5	6.6	6.6	-0.04
Methylprednisolone	200	5	6.3	6.2	-0.03
Neomycin	1000	5	6.3	6.6	0.03
Netilmicin	125	5	6.3	6.3	0.02
Oxytetracycline	2000	5	5.6	5.4	-0.01
Penicillin V	100	5	6.5	6.7	0.12
Prednisolone	12	5	6.6	6.4	-1.17
Rifampin	50	5	6.4	6.4	-0.08
Sisomicin	100	5	6.3	6.3	0.00
Spectinomycin	100	5	6.5	6.6	0.12
Streptomycin	400	5	6.4	6.4	0.01
Sulfadiazine	1000	5	6.4	6.2	-0.02
Sulfamethoxazole	400	5	6.5	6.6	0.01
Tetracycline	2000	5	6.3	6.2	-0.01
Trimethoprim	20	5	6.6	6.5	-0.30
Vancomycin	400	5	6.4	6.3	-0.02

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Glossary:
http://www.thermofisher.com/symbols-glossary

The summary of safety and performance is on EUDAMED and available upon request.

Important Notice
Any serious incident that has occurred in relation to the device shall be reported to Microgenics Corporation and to the National Competent Authority in which the user and/or the patient is established unless differently instructed by such National Competent Authorities.

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