QMS® Vancomycin (VANCO)

thermo scientific

IVD **For In Vitro Diagnostic Use Only**

Rx Only

REF **0373589**
10017224

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® Vancomycin assay is intended for the quantitative determination of vancomycin in human serum or plasma on automated clinical chemistry analyzers.

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

Summary and Explanation of the Test

Vancomycin hydrochloride is a tricyclic glycopeptide derived from *Amycolatopsis orientalis*.[1] It has come to be known as the last line of defense in treatment of methicillin-resistant *Staphylococcus aureus* infections.[2] This glycopeptide inhibits the growth of the bacterium by intervening in the cell wall synthesis, thereby killing the bacterium. The peak therapeutic range for vancomycin is between 20 to 40 µg/mL, the trough being at 5 to 10 µg/mL.[3] Side effects of vancomycin are deafness (ototoxicity) and renal failure (nephrotoxicity) at levels above therapeutic range. Extensive review articles have been published which fully examine vancomycin's effectiveness and pharmacokinetics.[1]

Vancomycin is absorbed minimally from the gastrointestinal tract. In the first 24 hours after intravenous dosing, the usual route of administration, about 90% of the vancomycin is excreted unchanged by the kidneys. The average half-life in patients with normal renal function is about 6 hours. Vancomycin is approximately 55% bound to plasma proteins. Therapeutic serum levels vary depending on the microorganism involved and the patient's tolerance to the drug.[4,5] Vancomycin serum or plasma concentrations are monitored to guide therapy, since individual patient differences require dose changes that are difficult to predict. Monitoring serum or plasma levels of vancomycin decreases the frequency of serious toxic effects.

Principles of the Procedure

The QMS Vancomycin 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 vancomycin antibody reagent. The vancomycin-coated microparticle reagent is rapidly agglutinated in the presence of the anti-vancomycin 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 vancomycin 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 vancomycin concentration and the lowest agglutination rate at the highest vancomycin concentration.

Reagents

QMS Vancomycin, **REF** 0373589, 10017224 is supplied as a liquid, ready-to-use, two-reagent kit that contains:

REF 0373589		**REF** 10017224	
R1	Reagent 1 1 x 22 mL	**R1**	Reagent 1 1 x 19 mL
R2	Reagent 2 1 x 22 mL	**R2**	Reagent 2 1 x 19 mL

Reactive Ingredients

INGRED	Ingredient	Concentration
R1	Anti-vancomycin Monoclonal Antibody (Mouse)	<1.0%
	Sodium Azide	≤0.05%
R2	Vancomycin-coated Microparticles	<0.3%
	Sodium Azide	≤0.05%

Reagent Handling and Storage

- **R1** and **R2** 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 **R1** or the **R2** 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, 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. **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.

DANGER: QMS Vancomycin (VANCO) assay contains ≤5.0% Drug-specific antibody and ≤2.0% Human Serum Albumin (HSA).
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 Vancomycin assay:

	Glass	Plastic
Serum	• Serum Separator Tube	• No Additive • Clot Activator
Plasma	• EDTA (K_3) • Plasma Separator Lithium Heparin Tube • Sodium Heparin Tube (Sprayed Sodium Heparin)	• EDTA (K_2)

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

- Some specimens, especially those from patients receiving anticoagulant or thrombolytic therapy may exhibit increased clotting time.
- Inadequate centrifugation of the specimen may cause an erroneous result.
- Ensure specimens are free of fibrin, red blood cells, and other particulate matter.
- Remove the plasma or serum from the cells, clot, or gel as soon as possible after collection. Some gel separator tubes may not be suitable for use with therapeutic drug monitoring assays; refer to information provided by the tube manufacturer.[6]
- Specimens removed from the cells, clot, or gel may be stored up to one week at 2 to 8°C. If testing will be delayed more than one week, specimen should be stored frozen (≤-10°C) up to 14 days prior to being tested.
- Samples for the QMS Vancomycin 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 most indicative of the therapeutic level of vancomycin.

Procedure

Materials Provided

- QMS Vancomycin Reagents, **REF** 0373589, 10017224

Materials Required but not Provided

- Vancomycin Controls
- QMS Vancomycin Calibrators, **REF** 0373597
  CAL A-F: 1 x 1.0 mL each

Assay Procedure

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

Specimen Dilution Procedure
Use QMS Vancomycin 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 vancomycin concentrations reported as greater than 100.0 µg/mL by making a dilution of the specimen with QMS Vancomycin 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 0.55 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 Vancomycin assay must be calibrated using a full calibration (6-point) procedure. To perform a full calibration, test the QMS Vancomycin 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: Vancomycin 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 regulations or accreditation requirements.

Recommended control requirements for the QMS Vancomycin 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 Vancomycin assay can be reported as µg/mL or µmol/L. To convert results from µg/mL vancomycin to µmol/L vancomycin, multiply µg/mL by 0.69 or divide by 1.44925.

As with all analyte determinations, the vancomycin 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
In very rare cases, patient samples may contain heterophile antibodies, which may produce low results with the QMS Vancomycin assay. Interfering heterophile antibodies occur at a low frequency in the general population. These antibodies can cause autoagglutination of the microparticle reagent leading to undetected erroneously low results.

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.

Expected Values
Therapeutic vancomycin peak serum levels of 20 to 40 µg/mL and trough levels of 5 to 10 µg/mL have been reported for most strains of staphylococci and streptococci.[7] However, therapeutic levels of vancomycin must be individually established based on patient differences and bacterial susceptibility. The risk of toxicity is appreciably increased by high concentration or prolonged therapy in patients with renal insufficiency. Toxic effects, such as ototoxicity and nephrotoxicity, have resulted when serum concentrations of vancomycin reach 80 to 100 µg/mL and are rarely seen when serum levels are maintained below 30 µg/mL.[8,9] If an glycopeptide is being used concurrently, the potential for toxicity is additive.[4]

Specific Performance Characteristics
Typical performance results obtained on a Hitachi 717 analyzer are shown below. The results obtained in your laboratory may differ from these data.

Sensitivity
Limit of Quantitation (LOQ) / Clinical Sensitivity
The LOQ of the QMS Vancomycin assay is defined as the lowest concentration for which acceptable inter-assay precision and recovery is observed (often considered ≤±20% CV with ≤±15% recovery). The LOQ was determined to be 2.0 µg/mL.

Assay Range
The range of the assay is 2.5 µg/mL to 100 µg/mL.

Accuracy
Accuracy by recovery was determined by spiking vancomycin into human serum to achieve concentrations across the assay range and analyzing in triplicate for vancomycin. 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
100.0	95.02	95.02
75.0	73.24	97.65
50.0	52.25	104.50
37.5	39.70	105.88
25.0	27.65	110.61
17.5	17.45	99.70
10.0	9.27	92.70
7.5	6.83	91.11
5.0	4.97	99.33

Mean percent recovery: 99.61

Linearity
Linearity was determined by dilution using a procedure described in National Committee for Clinical Laboratory Standards (NCCLS) Protocol EP6-A.[10] QMS Vancomycin Calibrator F (100.0 µg/mL) was diluted with QMS Vancomycin Calibrator A (0.0 µg/mL) to achieve samples at 75.0, 37.5, 17.5, 7.5, and 2.5 µg/mL. The samples were analyzed in triplicate using the QMS Vancomycin 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
75.0	75.77	101.02
37.5	37.20	99.21
17.5	16.75	95.71
7.5	7.33	97.69
2.5	2.68	107.20

Mean percent recovery: 100.17

Method Comparison
Correlation studies were performed using NCCLS Protocol EP9-A.[11] Results from the QMS Vancomycin assay were compared with results from a commercially available FPIA immunoassay as a reference method. The patient samples consisted of serum. The vancomycin concentrations ranged from 0.04 µg/mL to 100 µg/mL. Results of the Passing-Bablok regression analysis for the study are shown below.

Slope	1.031
Y-Intercept	1.115
Correlation Coefficient (R^2)	0.970
Number of Samples	146

Precision

Precision was determined as described in NCCLS Protocol EP5-A.[12]

A tri-level human serum based commercial control containing vancomycin 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 between day, within run, 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	7.57	0.27	3.59	0.43	5.72	0.70	8.84
2	80	20.79	0.51	2.44	0.97	4.66	1.29	6.21
3	80	33.65	0.80	2.37	0.95	2.83	1.72	5.12

Acceptance criteria: <10% total CV

Interfering Substances

The following compounds, when tested with the QMS Vancomycin assay at the concentrations indicated, resulted in less than 10% error in detecting vancomycin. Interference studies were conducted using NCCLS Protocol EP7-A.[13] Representative results are shown below.

Interfering Substance	Interferent Concentration	N	Vancomycin (µg/mL)	% Recovery
Albumin	10 g/dL	3	24.92	93.64
Bilirubin	70 mg/dL	3	27.00	100.07
Cholesterol	500 mg/dL	3	25.97	97.58
IgG	6 g/dL	3	25.90	97.34
Hemoglobin	1150 mg/dL	3	21.18	91.64
HAMA type 1*	Normal human level	3	28.27	105.31
HAMA type 2*	Normal human level	3	28.55	103.91
Heparin	500 USP units/mL	3	26.46	99.44
Triglyceride	1000 mg/dL	3	9.41	92.62
Rheumatoid Factor	1100 IU/mL	3	6.70	93.23

*HAMA = human anti-mouse antibodies

Specificity

Cross-Reactivity

The cross-reactivity of the vancomycin antibody to teicoplanin, a structurally similar compound, was examined. Teicoplanin at the following concentrations was added to serum containing 25 µg/mL vancomycin and tested in the QMS Vancomycin assay. Representative results are shown below.

Teicoplanin Concentration (µg/mL)	% Cross-Reactivity
100	0.99
50	0.29
25	0.16
10	0.04

Metabolite Cross-Reactivity

Vancomycin slowly degrades to its metabolite CDP-I (Crystalline Degradation Product-I).[14] The metabolite is structurally similar to vancomycin. CDP-I was tested at 100 µg/mL in serum containing 25 µg/mL vancomycin. Results show that the metabolite exhibits <5% cross-reactivity.

Drug Interference

Cross-reactivity was tested with drugs that are routinely administered with vancomycin. Testing also determined whether these compounds affect the quantitation of vancomycin concentrations using the QMS Vancomycin assay. Cross-reactants were analyzed at 500 µg/mL in a vancomycin spiked serum pool at 25 µg/mL. The samples were assayed and the vancomycin concentrations of the spiked samples were compared to a control serum. All of the following cross-reactants showed <0.3% cross-reactivity.

Cross-Reactants		
Acetaminophen	Cephalosporin C	Fusidic Acid
Amikacin	Cephalothin	Gentamicin
Amphotericin B	Chloramphenicol	Hydrochlorothiazde
Ampicillin	Chlorothiazide	Ibuprofen

Table continued

Cross-Reactants		
Bendroflumethiazide	Clindamycin	Isoniazid
Caffeine	Erythromycin	Kanamycin A
Carbenicillin	Ethacrynic Acid	Kanamycin B
Cefamandole Nafate	Ethambutol	Lincomycin
Cefazolin	5-Fluorocytosine	Methotrexate
Cephalexin	Furosemide	Methylprednisolone
Nalidixic Acid	Penicillin V	Spectinomycin
Naproxen	Phenacetin	Sulfadiazine
Neomycin Sulfate	Prednisolone	Sulfamethoxazole
Niacin	Prednisone	Sulfisoxazole
Nitrofurantoin	Rifampicin	Tetracycline
Oxytetracycline	Salicyclic Acid	Tobramycin
Penicillin G	Sisomicin	Trimethoprim

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Glossary:

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