QMS® Quinidine (QUIN)

Thermo SCIENTIFIC

IVD **For In Vitro Diagnostic Use Only**

Rx Only

REF **0373936**

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

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

Summary and Explanation of the Test

Quinidine is used for the prevention and treatment of ventricular arrhythmias, junctional (nodal) arrhythmias, and supraventricular (atrial) arrhythmias.[1] The quinidine dosage required to achieve therapeutic serum levels is dependent on the drug formulation, patient age, and individual variability in absorption and metabolism.

Principles of the Procedure

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

Reagents

Reagent Kit

QMS Quinidine, **REF** 0373936, is supplied as a liquid, ready-to-use, two-reagent kit that contains:

R1 Reagent 1 2 x 19 mL
R2 Reagent 2 2 x 7 mL

Reactive Ingredients

INGRED	Ingredient	Concentration
R1	Anti-quinidine Monoclonal Antibody (Mouse)	<1.0%
	Sodium Azide	<0.1%
R2	Quinidine-coated Microparticles	≤0.5%
	Sodium Azide	<0.1%

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.

⚠ **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.
- Contains nonsterile mouse monoclonal antibodies.

DANGER: QMS Quinidine (QUIN) assay contains <5.0% Drug-specific antibody, ≤3.5% IgM Antisera 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. Specific treatment (see First Aid information on product label and/or Section 4 of the SDS). 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 Quinidine assay:

	Glass	Plastic
Serum	• No Additives • Serum Separator Tube (gel) • Clot Activator	• Serum Separator Tube (gel)
Plasma	• EDTA (K_3)	• EDTA (K_2) • Lithium Heparin • Sodium Heparin • Plasma Separator Tube with Lithium Heparin (gel)

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

- 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.[2]
- 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, specimens should be stored frozen (≤-10°C). Specimens frozen up to two weeks showed no performance differences from fresh samples. Care should be taken to limit the number of freeze-thaw cycles.

Procedure

Materials Provided

- QMS Quinidine Reagents, **REF** 0373936

Materials Required but not Provided

- QMS Quinidine Calibrators, **REF** 0374165
  CAL A-F: 1 x 1.0 mL each
- Quinidine Controls

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 Quinidine CAL A (0.0 µg/mL) to manually dilute samples outside the reportable range of the assay.

Manual Dilution Protocol

A manual dilution can be performed on patient samples with quinidine concentrations reported as greater than 8.0 µg/mL by making a dilution of the specimen with QMS Quinidine 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 0.2 µg/mL. The concentration reported must be multiplied by the manual dilution factor to obtain the final sample concentration.

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

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

Calibration
The QMS Quinidine assay must be calibrated using a full calibration (6-point) procedure. To perform a full calibration, test the QMS Quinidine 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: Quinidine 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 Quinidine 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 Quinidine assay can be reported as µg/mL or µmol/L. To convert results from µg/mL quinidine to µmol/L quinidine, multiply µg/mL by 3.08.

As with all analyte determinations, the quinidine 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
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
Quinidine is approximately 75% bound to serum protein.[3] The elimination half-life of quinidine ranges from 4 to 10 hours in healthy individuals and may be prolonged in the elderly. About 70 to 80% of the dose is metabolized by the liver, with renal excretion of the unchanged drug accounting for much of the remainder.[1,3] Serum quinidine levels of 1.5 to 5 µg/mL have been reported as therapeutic, based on nonspecific methodologies that measure quinidine metabolites as well as quinidine.[3,4] The therapeutic range using newer, more specific assays has not been established. However, effective reduction of premature ventricular contraction has been reported with blood levels less than 1.0 µg/mL.[3] Toxicity has been reported at a level of 6 µg/mL.[5] Toxic side effects include ventricular tachycardia, heart block, thrombocytopenia and "cinchonism", a group of symptoms including headache, dizziness, tinnitus, nervousness, blurred vision, nausea, and vomiting. Measured quinidine levels are lower using specific methods (HPLC and immunoassays). Clinicians requesting serum quinidine determinations should ask that the method of analysis be specified.[3]

Metabolites of quinidine which may be found in serum are 3(S)-hydroxyquinidine, 2-oxoquinidinone, quinidine-N-oxide, o-desmethylquinidine, and quinidine 10, 11-dihydrodiol. Most of these have been shown to have pharmacological activity in human or animal studies, and some quinidine metabolites may be as potent as the parent drug.[1,4,5,6,7] Because of variability seen in patient metabolism, relative proportions of these metabolites are reported in the literature in differing amounts.[1,8-10] Quinidine serum specimens may also contain dihydroquinidine, an analog contained in quinidine formulations at levels of 5 to 10% of the dosage. Dihydroquinidine has anti-arrhythmic activity comparable to quinidine.[4,11] Recent reports indicate that plasma concentrations of digoxin increase when quinidine is given concurrently. Patients on concomitant therapy should be carefully monitored.[3]

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

Least Detectable Dose (LDD)/Analytical Sensitivity
The LDD, or analytical sensitivity, of the QMS Quinidine assay is defined as the lowest measurable concentration that can be distinguished from zero with 95% confidence. The LDD was determined to be 0.2 µg/mL.

Assay Range
The range of the assay is 0.2 to 8.0 µg/mL.

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

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

Theoretical Concentration (µg/mL)	Mean Recovered Concentration (µg/mL)	% Recovery
2.0	1.94	97.0
4.0	3.95	98.8
8.0	7.79	97.4

Mean percent recovery: 97.7

Linearity
Each level of QMS Quinidine calibrator was diluted with equal volume of the next higher level calibrator to achieve samples at 0.25, 0.75, 1.50, 3.00, and 6.00 µg/mL. The samples were analyzed in duplicate using the QMS Quinidine assay. A mean of the replicates for each sample was determined and a percent recovery calculated. Results are shown below.

Theoretical Concentration (µg/mL)	Mean Recovered Concentration (µg/mL)	% Recovery
0.25	0.22	88.0
0.75	0.72	96.0
1.50	1.42	94.7
3.00	2.98	99.3
6.00	6.20	103.3

Mean percent recovery: 96.3

Method Comparison
Correlation studies were performed using NCCLS Protocol EP9-A.[12] Results from the QMS Quinidine assay were compared with results from a commercially available fluorescence polarization immunoassay. The patient samples consisted of serum. The quinidine concentrations ranged from 0.71 µg/mL to 7.92 µg/mL. Results of the Passing-Bablok regression analysis for the study are shown below.

Slope	1.06
y-intercept	-0.21
Correlation Coefficient (R^2)	0.978
Number of Samples	50

Precision
Precision was determined as described in NCCLS protocol EP5-A.[13]

A tri-level human serum based commercial control containing quinidine 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	1.02	0.06	5.83	0.01	1.53	0.09	9.09
2	80	3.17	0.08	2.45	0.00	0.00	0.20	6.37
3	80	5.18	0.08	1.62	0.00	0.00	0.30	5.83

Acceptance criteria: <10% total CV

Interfering Substances

The following compounds, when tested with the QMS Quinidine assay at the concentrations indicated, resulted in less than 10% error in detecting quinidine. Interference studies were conducted using NCCLS protocol EP7-P.[14] The results are shown below.

Interfering Substance	Interferent Concentration	n	Quinidine (µg/mL)	% Recovery
Total protein	12 g/dL	3	6.32	99.7
Bilirubin	15 mg/dL	3	5.82	103.0
Hemoglobin	10 g/dL	2	5.82	100.0
HAMA type 1*	Normal human level	2	6.42	91.1
HAMA type 2*	Normal human level	2	6.42	90.6
Intralipid	1,127 mg/dL	3	6.05	92.2

*HAMA = human anti-mouse antibodies

Specificity

Metabolite Cross-Reactivity

Metabolites of quinidine were spiked into human serum and tested using the QMS Quinidine assay for cross-reactivity. A mean of the replicates for each sample was determined and percent recovery calculated. The results are shown below.

Metabolite	Metabolite Concentration (µg/mL)	Quinidine (µg/mL)	% Cross-Reactivity
3-Hydroxyquinidine	5.0	5.71	1.3
Quinidine-N-oxide	5.0	5.72	65.6
O-Desmethylquinidine	5.0	5.72	16.8
2-Oxoquinidinone	5.0	5.71	7.6
10, 11-Dihydroquinidinediol	5.0	5.37	12.5

Drug Cross-Reactivity

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

Compound	Compound Concentration (µg/mL)	Quinidine Concentration (µg/mL)	% Cross-Reactivity*
Acetaminophen	200	5.57	ND
Acetyl cysteine	1000	5.68	ND
Acetylsalycilic acid	3000	5.77	ND
Ampicillin	50	5.30	ND
Ascorbic Acid	30	5.12	-0.51
Cefoxitin	1000	5.73	ND
Cyclosporine	600	5.61	ND
Digitoxin	0.25	5.57	ND
Digoxin	0.02	4.93	ND
Disopyramide	50	6.00	0.76
Ephedrine	1000	5.71	ND
Furosemide	100	5.96	ND
Hydrochlorothiazide	40	5.44	ND
Ibuprofen	7000	5.66	ND
Isoproterenol	0.06	5.54	ND
Levodopa	1000	5.64	ND
Lidocaine	50	5.52	ND
Metronidazole	1000	5.66	ND
N-Acetylprocainamide	400	5.63	ND
Phenylbutazone	1000	5.55	ND
Phenytoin (DPH)	200	5.40	ND
Procainamide	100	5.56	ND
Propranolol	1	5.57	4.33
Quinine	5	6.45	14.8
Reserpine	1000	5.41	ND
Rifampicin	50	5.42	ND
Tetracycline	2000	5.57	ND
Theophylline	200	5.52	ND

*ND = not detected

Bibliography

1. Hoyer GL, Clawson DC, Brookshier LA. High-performance liquid chromatographic method for the quantitation of quinidine and selected quinidine metabolites. J Chromatogr 1991;572:159-69.
2. Dasgupta A, Dean R, Saldana S, Kinnaman G, McLawhon RW. Absorption of therapeutic drugs by barrier gels in serum separator blood collection tubes. Volume-and time-dependent reduction in total and free drug concentrations. Am J Clin Pathol 1994;101:456-61.
3. Physicians' Desk Reference. 47th ed. Montvale, NJ: Medical Economics Data; 1993:688-9.
4. Gerson B. Essentials of Therapeutic Drug Monitoring. 1st ed. Tokyo, Japan: Igaku-Shoin Ltd.; 1983:133-40.
5. Goodman LS, Gillman A, eds. The Pharmacological Basis of Therapeutics 8th ed. New York: Pergamon Press, 1990:1704-5.
6. Drayer DE, Lowenthal DT, Restivo KM, Schwartz A, Cook CE, Reidenberg MM. Steady-state serum levels of quinidine and active metabolites in cardiac patients with varying degrees of renal function. Clin Pharmacol Ther 1978;24:31-9.
7. Drayer DE, Restivo K, Reidenberg MM. Specific determination of quinidine and (3S)-3-hydroxyquinidine in human serum by high-pressure liquid chromatography. J Lab Clin Med 1977;90:816-22.
8. Bonora MR, Guentert TW, Upton RA, Riegelman S. Determination of quinidine and metabolites in urine by reverse-phase high-pressure liquid chromatography. Clin Chim Acta 1979;91:277-84.
9. Leroyer R, Jarreau C, Pays M. Specific determination of quinidine and metabolites in biological fluids by reversed-phase high-performance liquid chromatography. J Chromatogr 1982;228:366-71.
10. Leroyer R, Varoquaux O, Advenier C, Pays M. Quinidine oxidative metabolism. Identification and biosynthesis of quinidine 10, 11-dihydrodiol stereoisomers. Biomed Chromatogr 1990;4:61-4.
11. Drayer DE, Hughes M, Lorenzo B, Reidenberg MM. Prevalence of high (3S)-3-hydroxyquinidine/quinidine ratios in serum, and clearance of quinidine in cardiac patients with age. Clin Pharmacol Ther 980;27:72-5.
12. NCCLS Approved Guideline EP9-A. Method comparison and bias estimation using patient samples. Wayne, PA: National Committee for Clinical Laboratory Standards, December 1995.
13. NCCLS Approved Guideline EP5-A. Evaluation of precision performances of clinical chemistry devices. Wayne, PA: National Committee for Clinical Laboratory Standards, February 1999.
14. NCCLS Proposed Guideline EP7-P. Interference testing in clinical chemistry. Wayne, PA: National Committee for Clinical Laboratory Standards, August 1986.

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

Microgenics Corporation
46500 Kato Road
Fremont, CA 94538 USA
US Customer and
Technical Support:
1-800-232-3342

EC REP
B·R·A·H·M·S GmbH
Neuendorfstrasse 25
16761 Hennigsdorf, Germany

For insert updates go to:
www.thermoscientific.com/diagnostics

Other countries:
Please contact your local Thermo Fisher Scientific representative.

0155248-K-EN
2018 01

Thermo SCIENTIFIC