QMS® Lamotrigine (LTG)

thermo scientific

IVD **For In Vitro Diagnostic Use Only**

Rx Only

REF **0373795**

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

Lamotrigine concentrations can be used as an aid in management of patients treated with lamotrigine.

Summary and Explanation of the Test

Lamotrigine [3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine] is an anticonvulsant drug approved for use in the treatment of epilepsy and is often prescribed as monotherapy or as one component of a multiple anti-epileptic drug therapy.[1-3]

Principles of the Procedure

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

Reagents

Reagent Kit

QMS Lamotrigine, **REF** 0373795, is supplied as a liquid, ready-to-use, two-reagent kit that contains:

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

Reactive Ingredients

INGRED	Ingredient	Concentration
R1	Anti-lamotrigine Polyclonal Antibody (Sheep)	<5.0%
	Sodium Azide	≤0.09%
R2	Lamotrigine-coated Microparticles	<1.0%
	Sodium Azide	≤0.09%

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 Lamotrigine (LTG) 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 Lamotrigine assay:

	Glass	Plastic
Serum	• No Additive	• With Silicon • Serum Separator Tube (gel) • Clot Activator
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 Lamotrigine 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 serum or plasma tubes may not be suitable for use with therapeutic drug monitoring assays; refer to information provided by the tube manufacturer.[4]
- 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) prior to being tested. Specimens stored at 2 to 8°C for up to one week or frozen up to four weeks showed no performance differences (±10% of lamotrigine concentration at time zero) from fresh samples. Care should be taken to limit the number of freeze-thaw cycles.
- It is recommended that samples for the QMS Lamotrigine assay be drawn just prior to a dose (trough level). The trough concentration is most indicative of the therapeutic level of lamotrigine.[5,6]

Procedure

Materials Provided

- QMS Lamotrigine Reagents, **REF** 0373795

Materials Required but not Provided

- QMS Lamotrigine Calibrators, **REF** 0373787
  CAL A-F: A (1 x 2.0 mL); B-F (1 × 1.0 mL each)
- QMS Lamotrigine Controls, **REF** 0374090
  Level 1-3: 1 x 2.5 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 Procedures

Use QMS Lamotrigine 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 lamotrigine concentrations reported as greater than 40.0 µg/mL by making a dilution of the specimen with QMS Lamotrigine 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 2.0 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 Lamotrigine assay must be calibrated using a full calibration (6-point) procedure. To perform a full calibration, test the QMS Lamotrigine 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: Lamotrigine 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 Lamotrigine 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 Lamotrigine assay can be reported as µg/mL or µmol/L. To convert results from µg/mL lamotrigine to µmol/L lamotrigine, multiply µg/mL by 3.90.[7]

As with all analyte determinations, the lamotrigine 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

Serum/Plasma

A therapeutic range for lamotrigine has not been well established. Some reports in the literature suggest a target range for steady-state concentrations of 3 to 15 µg/mL.[7,8] However, there is not a clear relationship between lamotrigine serum concentrations and clinical response.[7,8] Due to individual patient differences and other co-administered medications, considerable overlap in lamotrigine concentrations has been observed between serum responders and non-responders as well as between serum levels associated with seizure control and adverse effects.[1-3, 6-8,10-15] In one study, the highest mean serum level (trough) reported was 8.8 µg/mL, and less than 15% of patients reported an adverse event at serum concentrations less than 10 µg/mL.[9] Mild to moderate adverse effects are more commonly associated with patients with lamotrigine concentrations above 15 µg/mL.[8,15] Once a stable dose is reached up to seven days may be needed to reach a steady state concentration.[1]

Lamotrigine drug concentrations should not be the only means of therapeutic drug management. The assay should be used in conjunction with information available from clinical evaluations and other diagnostic procedures. Clinicians should carefully monitor patients during therapy initiation and dosage adjustments. It may be necessary to obtain multiple samples to determine expected variations of optimal (steady-state) concentrations for individual patients.

Specific Performance Characteristics

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

Sensitivity

Limit of Quantitation (LOQ)

The LOQ of the QMS Lamotrigine assay is defined as the lowest concentration for which acceptable inter-assay precision and recovery is observed (often considered <20% CV with ±15% recovery). A pooled patient serum containing lamotrigine and lamotrigine-spiked plasma samples were diluted and assayed in duplicate twice a day for five days. The following theoretical lamotrigine concentrations were analyzed:

Pooled patient serum samples containing lamotrigine				
Tested Target (µg/mL)	**1.74**	**2.75**	**3.78**	**4.88**
AVG	1.82	2.68	3.64	4.88
SD	0.09	0.15	0.16	0.30
Percent CV	4.74	5.69	4.30	6.25
Percent Recovery	104.48	97.27	96.24	100.00

Lamotrigine-spiked plasma samples			
Tested Target (µg/mL)	**2.00**	**2.74**	**3.54**
AVG	2.21	2.38	3.54
SD	0.07	0.10	0.10
Percent CV	3.21	3.38	2.89
Percent Recovery	110.69	103.27	100.00

The LOQ was determined to be 2.0 µg/mL.

Assay Range

The range of the assay is 2.0 to 40.0 µg/mL. Report results below this range as <2.0 µg/mL.

Accuracy

An accuracy-by-recovery test was performed by adding pharmaceutical grade lamotrigine drug into human serum negative for lamotrigine. Initially, a serum stock of approximately 40 µg/mL lamotrigine was prepared gravimetrically by adding lamotrigine to human serum. The stock concentrate was then gravimetrically added to human serum negative for lamotrigine, representing drug concentrations across the assay range. Each sample was assayed in triplicate on two separate calibration curves on an automated clinical chemistry analyzer. The results were averaged and compared to the target concentration and percent recovery calculated. 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
40.02	38.61	96
30.02	32.74	109
20.03	19.07	95
15.00	16.05	107
9.00	9.37	104
5.02	5.33	106
3.75	3.94	105
2.50	2.49	100
1.52	1.75	115

Mean percent recovery: 104

Linearity

Linearity studies were performed by diluting a high patient pool to concentrations across the assay range. The patient pool was adjusted in order to obtain a 20 to 30% value above the desired reportable range as suggested in NCCLS Protocol EP-6A.[16] The dilutions were made with QMS Lamotrigine Calibrator A (blank calibrator). Linearity at specific dilutions was considered acceptable if the percent deviation was ±10% between the predicted 1st and 2nd order regressed values. Results are shown below.

Theoretical Concentration (µg/mL)	Mean Recovered Concentration (µg/mL)	% Recovery
51.20	51.20	100
42.50	43.25	102
37.38	37.67	101
32.26	31.82	99
26.62	27.34	103
21.50	22.26	104
15.87	16.15	102
10.75	10.78	100
5.12	5.19	101
2.56	2.56	100
1.02	1.23	121

Mean percent recovery: 103

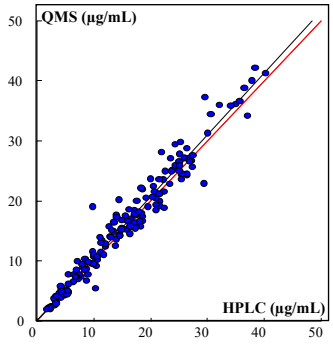
Method Comparison

Correlation studies were performed using NCCLS Protocol EP9-A2.[17] The QMS Lamotrigine method was conducted internally (Study 1) and at two different external sites (Study 2 and Study 3). Results from the QMS Lamotrigine assay were compared with results from a validated high performance liquid chromatography (HPLC) reference method.[18]

Study 1

In the first study the range of lamotrigine concentration by the QMS Lamotrigine assay was 2.02 to 43.13 µg/mL with a mean of 15.98 µg/mL. The lamotrigine concentration range for the HPLC method was 1.6 to 40.3 µg/mL with a mean concentration of 15.3 µg/mL. Results of the Passing-Bablok[19] regression analysis for the study are shown below.

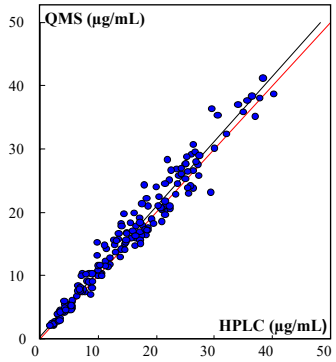
Slope (95% confidence interval)	1.03
y-intercept (95% confidence interval)	0.11
Correlation Coefficient (R^2)	0.96
Standard Error of Estimate	1.98
Number of Samples	166



Study 2

In the second study the range of lamotrigine concentration by the QMS Lamotrigine assay was 2.11 to 41.19 µg/mL with a mean of 16.11 µg/mL. The lamotrigine concentration range for the HPLC method was 1.6 to 40.3 µg/mL with a mean concentration of 15.3 µg/mL. Results of the Passing-Bablok[19] regression analysis for the study are shown below.

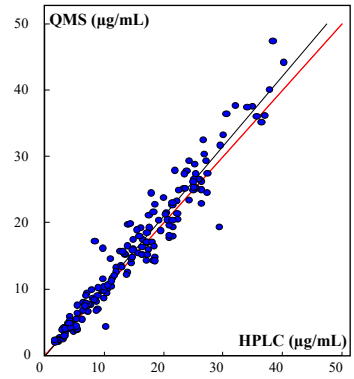
Slope (95% confidence interval)	1.03
y-intercept (95% confidence interval)	0.36
Correlation Coefficient (R^2)	0.96
Standard Error of Estimate	1.92
Number of Samples	166



Study 3

In the third study, the range of lamotrigine concentration of the QMS Lamotrigine assay was 2.01 to 47.31 µg/mL with a mean of 15.95 µg/mL. The lamotrigine concentration range for the HPLC method was 1.6 to 40.3 µg/mL with a mean concentration of 15.3 µg/mL. Results of the Passing-Bablok[19] regression analysis for the study are shown below.

Slope (95% confidence interval)	1.06
y-intercept (95% confidence interval)	-0.14
Correlation Coefficient (R^2)	0.94
Standard Error of Estimate	2.44
Number of Samples	167



Precision

Precision was determined as described in NCCLS Protocol EP5-A2.[20]

A tri-level human serum based commercial control containing lamotrigine and patient sample pools representing low, medium, and high therapeutic values were used in each study. Each level of control and patient pool was assayed in duplicate twice a day for 20 non-consecutive days. Each of the runs per day was separated by at least two hours. The means, between day, within run, total SD and percent CV's were calculated. Results are shown below.

			Within Run		Between Day		Total	
Sample	N	Mean (µg/mL)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Low Control	80	2.17	0.04	1.6	0.04	1.2	0.06	2.9
Mid Control	80	15.51	0.18	1.1	0.18	0.9	0.29	1.9
High Control	80	25.57	0.39	1.5	0.26	0.9	0.52	2.0
Low Patient Pool	80	2.81	0.05	1.6	0.02	0.7	0.08	2.8
Mid Patient Pool	80	10.79	0.10	0.9	0.12	1.1	0.21	2.0
High Patient Pool	80	23.93	0.40	1.7	0.16	0.7	0.58	2.4

Acceptance criteria: <10% total CV

Interfering Substances

Clinically high concentrations of the following potential interferents were added to serum with known levels of lamotrigine (approximately 3 and 16 µg/mL). Each sample was assayed using the QMS Lamotrigine assay, along with a serum control of lamotrigine. All substances resulted in <10% error in detecting lamotrigine.

Interfering Substance	Interferent Concentration
Albumin	12 g/dL
Bilirubin	60 mg/dL
Cholesterol	500 mg/dL
Hemoglobin	1500 mg/dL
Gamma Globulin	10 g/dL
Rheumatoid Factor*	500 IU/mL
Triglycerides*	1500 mg/dL
Uric Acid*	20 mg/dL

*Prepared by diluting a natural patient sample with lamotrigine-spiked human serum pools

Specificity

Interference studies were conducted using NCCLS Protocol EP7-A2[21] as a guideline. Cross-reactivity was tested for the known metabolites of lamotrigine. Other medications routinely administered with lamotrigine were also tested to determine whether these compounds affect the quantitation of lamotrigine concentrations using the QMS Lamotrigine assay. High levels of these compounds were spiked into serum pools containing low and high therapeutic levels of lamotrigine. The samples were assayed and the lamotrigine concentrations of samples containing interferent were compared to the control serum.

Metabolites

Lamotrigine is metabolized primarily via UDP-glucuronyltransferase to form a pharmacologically inactive metabolite, N-2 glucuronide.[22,23] Three other minor metabolites, N-5 glucuronide, N-2 oxide, and N-2 methyl, have been proposed in literature.[22,24] Of the excreted dose (predominately found in urine), lamotrigine parent drug was found unchanged at approximately 10%. The metabolites were found at the following approximate concentrations: N-2 glucuronide (71%), N-5 glucuronide* (9%), N-2 methyl (0 to 5%), and N-2 oxide (0 to 5%).[24,25] These metabolites were spiked into two separate samples each containing low and high lamotrigine concentrations of 3 and 16 µg/mL, respectively. The following metabolites were tested for cross-reactivity.

*Proposed lamotrigine metabolite N-5 glucuronide, was unavailable for testing.

Metabolite	Metabolite Concentration (µg/mL)	Percent Cross-Reactivity	
		Low Concentration Lamotrigine	High Concentration Lamotrigine
N-2 Glucuronide	400	0.06	0.30
	80	0.08	1.60
	40	0.23	1.30
	20	ND	6.40
	10	0.40	11.90
	5	-7.90	ND
N-2 Methyl	400	0.10	0.20
	80	ND	0.50
	40	-0.10	2.10
	20	-0.40	1.30
	10	-2.00	2.60
	5	-4.70	ND
N-2 Oxide	400	2.20	4.20
	80	4.60	10.70
	40	6.00	15.10
	20	9.60	25.10
	10	13.00	36.50
	5	19.70	92.50

ND=None detected

Drug Interference

Studies using the QMS Lamotrigine assay were conducted to examine if any of the commonly administered compounds have any effect on the recovery of lamotrigine concentration.

A high concentration of each compound was spiked into normal human serum with known levels of lamotrigine (approximately 3 and 16 µg/mL) and assayed along with a serum control of lamotrigine. All compounds resulted in <10% error in detecting lamotrigine. The compounds and the concentrations tested are listed below.

Compound	Compound Concentration*	Compound	Compound Concentration*
Acetaminophen	200	Lidocaine	100
Acetazolamide	100	Lincomycin	2000
Acetyl Salicylic Acid	500	Mephenytoin	100
Amikacin	20	Mesoridazine	5
Amitriptyline	1	Methicillin	200
Amoxapine	1	Methylprednisolone	200
Amphotericin B	100	N-Acetyl procainamide	120
Ampicillin	50	Nefazodone	3
Ascorbic Acid	30	Neomycin	1000
Buproprion	3	Niacin	12,000
Caffeine	100	Nirvanol	100
Carbamazepine	120	Nitrazepam	1.8
Carbamazepine-10,11-Epoxide	120	Nordoxepin	1
Carbenicillin	2500	Nortriptyline	1
Chloramphenicol	250	Olanzapine	0.3
Chlorpromazine	2	Oxcarbazepine	500
Citalopram	0.8	Paroxetine	1
Clobazam	100	Penicillin V	100
Clonazepam	0.7	Perphenazine	90
Cyclosporin A	1	Phenytoin	100
Desipramine	1	Phenobarbital	15
Diazepam	20	Primidone	100
Digitoxin	0.25	Procainamide	25
Digoxin	0.02	Prochlorperazine	1
Doxepin	1	Ranitidine	200
Epedrine Sulfate	1000	Rifampin	50
Erythromycin	200	Risperidone	0.6
Ethanol	3500	Sertraline	0.6
Ethosuximide	1000	Spectinomycin	100
Felbamate	1000	Sulfamethoxazole	400
Fluoxetine	3.75	Theophylline	250
Furosemide	100	Thioridazine	5
Gabapentin	200	Tobramycin	20
Gentamicin	1000	Topiramate	250
Haloperidol	1	Trazodone	5
Heparin	8000 IU/L	Trimethoprim	20
Ibuprofen	400	Valproic Acid	1000
Imipramine	0.72	Vancomycin	630
Kanamycin A	400	Vigabatrin	100
Kanamycin B	400	Zonisamide	400
Levetiracetam	400		

*µg/mL unless otherwise noted

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Glossary:
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