QMS® Zonisamide (ZNS)

Thermo SCIENTIFIC

IVD **For In Vitro Diagnostic Use Only**

Rx Only

REF **0373571**
10017230

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 Zonisamide assay is intended for the quantitative determination of zonisamide in human serum or plasma on automated clinical chemistry analyzers.

Zonisamide concentrations can be used as an aid in management of patients treated with zonisamide.

Summary and Explanation of the Test
Zonisamide (1,2-benzisoxazole-3-methanesulfonamide) is an anticonvulsant drug approved for use as an adjunct for the treatment of partial seizures in adults over age 16 with epilepsy.[1-4] Zonisamide has proven effective in the treatment of many patients otherwise refractory to other anticonvulsant treatments.[2,3]

Principles of the Procedure
The QMS Zonisamide 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 zonisamide antibody reagent. The zonisamide-coated microparticle reagent is rapidly agglutinated in the presence of the anti-zonisamide antibody reagent and in the absence of any competing drug in the sample. The rate of absorbance change is measured photometrically, and is directly proportional to the rate of agglutination of the particles. When a sample containing zonisamide 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 zonisamide concentration and the lowest agglutination rate at the highest zonisamide concentration.

Reagents
Reagent Kit

QMS Zonisamide, **REF** 0373571, 10017230 is supplied as a liquid, ready-to-use, two-reagent kit that contains:

REF	0373571	**REF**	10017230
R1	Reagent 1 2 x 22 mL	**R1**	Reagent 1 1 x 19 mL
R2	Reagent 2 2 x 8 mL	**R2**	Reagent 2 1 x 8 mL

Reactive Ingredients

INGRED	Ingredient	Concentration
R1	Anti-zonisamide Polyclonal Antibody (Rabbit)	<5.0%
	Sodium Azide	≤0.05%
R2	Zonisamide-coated Microparticles	<0.5%
	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 Zonisamide (ZNS) 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 Zonisamide assay:

	Glass	Plastic
Serum	• No Additives • Serum Separator Tube with Clot Activators	• Not Tested
Plasma	• Lithium Heparin • Sodium Heparin • EDTA	• EDTA

Other specimen collection tubes have not been validated for use with the QMS Zonisamide assay. Follow the manufacturer's processing instructions for serum or plasma collection 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.[5]
- Specimens removed from the cells, clot, and 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) prior to being tested. Specimen frozen up to four weeks showed no performance differences from fresh samples. Care should be taken to limit number of freeze-thaw cycles.
- It is recommended that samples for the QMS Zonisamide assay be drawn just prior to a dose (trough level). The trough concentration is most indicative of the therapeutic level of zonisamide.[6,7]

Procedure
Materials Provided
- QMS Zonisamide Reagents, **REF** 0373571, 10017230

Materials Required but not Provided
- QMS Zonisamide Calibrators, **REF** 0373381
  CAL A-F: A (1 x 2.5 mL); B-F (1 × 1.0 mL each)
- QMS Zonisamide Controls, **REF** 0373373
  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 Zonisamide 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 zonisamide concentrations reported as greater than 50.0 µg/mL by making a dilution of the specimen with QMS Zonisamide 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 functional sensitivity of 3.0 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 Zonisamide assay must be calibrated using a full calibration (6-point) procedure. To perform a full calibration, test the QMS Zonisamide 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: Zonisamide 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 Zonisamide assay:

- A minimum of two levels of controls spanning the medical decision range should be included with each run.
- 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 Zonisamide assay can be reported as µg/mL or µmol/L. To convert results from µg/mL zonisamide to µmol/L zonisamide, multiply µg/mL by 4.71.[4]

As with all analyte determinations, the zonisamide value should be used in conjunction with information available from clinical evaluation 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 zonisamide has not been well established Zonisamide has an elimination half-life of 63 hours. Once a stable dose is reached a steady-state is achieved within 14 days.[1] Steady state concentrations have been reported to be within 20 to 30 µg/mL.[8-12] Some studies have reported steady-state concentrations of patients with seizure control to be 10 to 20 µg/mL[3] and 10 to 30 µg/mL.[13] Therapeutic ranges between 7 and 40 µg/mL[8,14,15] and 17 to 50 µg/mL[16] have also been reported.

There is no clear relationship between zonisamide serum concentrations and clinical response.[1-4] Due to individual patient differences, considerable overlap in zonisamide concentrations has been observed between serum responders and non-responders as well as between serum levels associated with seizure control and adverse effects.[8,9,12,17,18] Mild to moderate adverse effects are more commonly associated with patients with zonisamide concentrations above 30 µg/mL.[3,9,10,17]

Zonisamide drug concentrations should not be the only means of therapeutic drug management. Clinicians should carefully monitor patients during therapy initiation and dosage adjustments. It may be necessary to obtain multiple samples to determine expected variation 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 Zonisamide assay is defined as the lowest drug concentration for which acceptable inter-assay precision and recovery is observed (often considered <20% CV with ±15% recovery). A zonisamide-spiked serum sample was diluted and assayed in replicates of ten. The following theoretical zonisamide concentrations were analyzed.

Data are summarized below.

Tested Target (µg/mL)	1.0	2.0	3.0	4.0
AVG	1.01	2.00	3.20	4.25
n	60	60	59	60
SD	0.22	0.42	0.54	0.37
Percent CV	22	21	17	9
Percent Recovery	101	100	107	106

The LOQ was determined to be 3.0 µg/mL.

Assay Range
The range of the assay is 3.0 to 50.0 µg/mL. Report results below this range as <3.0 µg/mL.

Accuracy and Linearity
Accuracy and linearity were determined by dilution using a guidance from National Committee for Clinical Laboratory Standards (NCCLS) approved guideline EP6-A.[19] A serum pool with an approximate concentration of 80.0 µg/mL of zonisamide was diluted with human serum negative for zonisamide at several concentrations. The diluted sera were analyzed in replicates of five using the QMS Zonisamide assay. A mean of the replicates for each sample was determined. Percent recoveries for each level were calculated using the following formula.

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

Theoretical Concentration (µg/mL)	Mean Recovered Concentration (µg/mL)	% Recovery
2.5	2.87	115
4	4.41	110
8	7.86	98
16	15.30	96
32	30.25	95
48	45.49	95

Mean percent recovery: 102

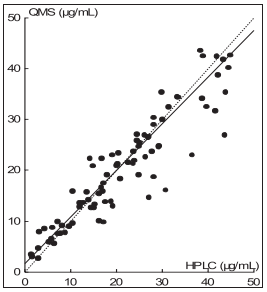
The data was plotted with the calculated target on the x-axis and the observed recovery on the y-axis. Regression equations of the 1st and 2nd order polynomial were determined and predicted values for the data set were generated by substituting the recovered concentration for y in each equation. Linearity at specific dilutions was considered acceptable if the percent deviation was ±10% between the predicted 1st and 2nd order values.

Method Comparison
Correlation studies were performed using NCCLS protocol EP9-A as a guideline.[20] Results from the QMS Zonisamide assay were compared to validated high performance liquid chromatography (HPLC) reference methods in three separate studies. In each study, serum or plasma samples from patients on zonisamide therapy were assayed by the QMS Zonisamide and HPLC method. Study 1 was conducted externally. Studies 2 and 3 had HPLC conducted externally and QMS assays performed internally.

Study 1
In the first study the range of zonisamide concentrations for the QMS Zonisamide assay was 2.71 to 43.60 µg/mL with a mean concentration of 20.50 µg/mL. The zonisamide concentration range for the HPLC method was 2.30 to 44.70 µg/mL with a mean concentration of 21.42 µg/mL.

Results of the Passing-Bablok regression analysis for the study are shown below.

Slope (95% confidence interval)	0.92 (0.81 to 0.99)
y-intercept (95% confidence interval)	1.67 (0.33 to 2.72)
Correlation Coefficient (r)	0.91
Standard Error of Estimate	4.17
Number of Samples	83



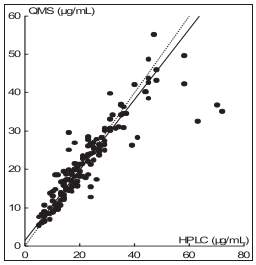
Study 2

In the second study the range of zonisamide concentrations for the QMS Zonisamide assay was 5.39 to 49.63 µg/mL with a mean concentration of 21.53 µg/mL. The zonisamide concentration range for the HPLC method was 5 to 58 µg/mL with a mean concentration of 22.29 µg/mL. The patients ranged in age from 2 to 80 years old with a mean age of 41 years old. The male to female ratio was 43 to 53%.

Results of the Passing-Bablok regression analysis for the study are shown below.

Slope (95% confidence interval)	0.93 (0.88 to 0.98)
y-intercept (95% confidence interval)	1.29 (0.43 to 2.24)
Correlation Coefficient (r)	0.93 (0.91*)
Standard Error of Estimate	3.49 (4.70*)
Number of Samples	145 (148*)

*Outliers included in analysis

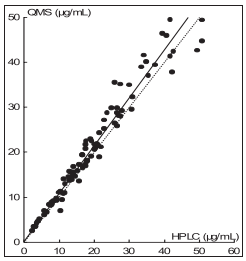


Study 3

In the third study, the range of zonisamide concentrations for the QMS Zonisamide assay was 2.59 to 49.49 µg/mL with a mean concentration of 20.69 µg/mL. The zonisamide concentration range for the HPLC method was 2.30 to 50.70 µg/mL with a mean concentration of 19.27 µg/mL.

Results of the Passing-Bablok regression analysis for the study are shown below.

Slope (95% confidence interval)	1.06 (1.02 to 1.12)
y-intercept (95% confidence interval)	0.18 (-0.37 to 0.74)
Correlation Coefficient (r)	0.98
Standard Error of Estimate	2.67
Number of Samples	97



Precision

Precision was determined as described in NCCLS protocol EP5-A.[21] Two separate precision studies were conducted. A tri-level human serum based commercial control containing zonisamide and patient sample pools representing low, medium and high therapeutic values were used in each study. In the first study, each level of control and patient samples were assayed in duplicate twice a day for twenty non-consecutive days. In the second study, controls were run in duplicate and patient sample pools were run in singlet. Each of the runs per day was separated by at least two hours. The means were determined and within run, total SD and percent CVs were calculated.

The following are representative results from pooled data.

Study 1

			Within Run		Total	
Sample	N	Mean (µg/mL)	SD	CV (%)	SD	CV (%)
Low Patient Pool	80	10.42	0.59	5.7	0.86	8.3
Mid Patient Pool	80	27.74	1.38	5.0	2.19	7.9
High Patient Pool	80	40.74	2.45	6.0	3.06	7.5
Level 1 Control	80	8.90	0.37	4.2	0.61	6.8
Level 2 Control	80	27.39	1.50	5.5	1.80	6.6
Level 3 Control	80	52.30	2.17	4.1	3.00	5.7

Study 2

			Within Run		Total	
Sample	N	Mean (µg/mL)	SD	CV (%)	SD	CV (%)
Low Patient Pool	*24	7.30	n/a	n/a	0.84	11.5
Mid Patient Pool	*24	26.22	n/a	n/a	2.09	8.0
High Patient Pool	*24	48.92	n/a	n/a	5.56	11.4
Level 1 Control	80	8.07	0.65	8.0	0.73	9.0
Level 2 Control	80	26.14	1.48	5.7	1.88	7.2
Level 3 Control	80	50.52	3.05	6.0	4.45	8.8

*Patient sample pools were run on 12 non-consecutive days during the study.

Specificity

Interference studies were conducted using NCCLS protocol EP7-A as a guideline.[22] Cross-reactivity was tested for the major metabolites of zonisamide. Other medications routinely administered with zonisamide and endogenous substances were also tested to determine whether these compounds affect the quantitation of zonisamide concentrations using the QMS Zonisamide assay. High levels of these compounds and endogenous substances were spiked into serum pools (control) containing low and high therapeutic levels of zonisamide. The samples were assayed and the zonisamide concentrations of samples containing interferent were compared to the control serum.

Metabolites

Zonisamide undergoes acetylation to form N-acetyl zonisamide (NAZ) and reduction to form the open ring metabolite, 2-sulfamoylacetyl phenol (SMAP). Of the excreted dose, 35% was recovered as zonisamide, 15% as NAZ and 50% as the glucuronide of SMAP Reduction of zonisamide to SMAP is mediated by cytochrome P450 isozyme 3A4 (CYP3A4).[1,23]

Studies were conducted to examine the cross-reactivity of the QMS Zonisamide antiserum to the 2 major metabolites. Various concentrations of NAZ and SMAP were added to normal human serum with known levels of zonisamide (approximately 12 and 36 µg/mL) and tested with the QMS Zonisamide assay.

Metabolite	Metabolite Concentration (µg/mL)	Percent Cross-Reactivity		
		No Zonisamide	Low Concentration Zonisamide	High Concentration Zonisamide
NAZ	500	0.20	0.20	0.20
	100	ND	ND	ND
	50	ND	ND	ND
	25	ND	ND	ND
	5	ND	ND	ND
SMAP	500	2.60	2.30	ND
	100	11.30	1.30	ND
	50	2.90	ND	4.40
	25	3.70	ND	5.70
	5	9.30	ND	4.20

ND = None detected

Drug Interference

Studies using the QMS Zonisamide assay were conducted to examine if any of the commonly administered or structurally similar compounds to zonisamide have any affect on the recovery of zonisamide concentration.

A high concentration of each compound was spiked into normal human serum with known levels of zonisamide (approximately 12 and 36 µg/mL) and assayed along with a serum control of zonisamide. All compounds resulted in <5% error in detecting zonisamide. The compounds and the concentrations tested are listed below.

Interfering Substance	Interferent Concentration*	Interfering Substance	Interferent Concentration*
10-hydroxy-carbamazapine	100	Ibuprofen	400
2-Ethyl-2-phenylmalondiamide	1000	Lamotrigine	300
Acetaminophen	200	Leviteracetam	100

Table continued

Interfering Substance	Interferent Concentration*	Interfering Substance	Interferent Concentration*
Caffeine	100	Phenobarbital	400
Carbamazepine	120	Phenytoin	200
Carbamazepine-10,11-epoxide	120	Primidone	100
Clonazapam	0.5	Salicylic Acid	500
Cyclosporine A	40	Sulfamethoxazole	400
Diazapam	10	Sulfisoxazole	1000
Erythromycin	200	Theophylline	250
Ethosuximide	1000	Topiramate	250
Felbamate	1000	Trimethoprim	20
Heparin	8500/U/L	Valproic Acid	1000

*µg/mL unless otherwise noted

Endogenous Substances

Clinically high concentrations of potential endogenous interferents were added to serum with known levels of zonisamide (approximately 12 and 36 µg/mL). Each sample was assayed using the QMS Zonisamide assay, along with a serum control of zonisamide. All substances resulted in <10% error in detecting zonisamide. The endogenous substances and the concentrations tested are listed below.

Interfering Substance	Interferent Concentration
Albumin	12 g/dL
Bilirubin	20 mg/dL
Cholesterol	500 mg/dL
Hemoglobin	1150 mg/dL
Gamma Globulin	12 g/dL
Rheumatoid Factor*	500 IU/mL
Triglycerides*	1500 mg/dL
Uric Acid*	20 mg/dL

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

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Glossary:

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