

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE**

A. 510(k) Number:

k070645

B. Purpose for Submission:

New device

C. Measurand:

Topiramate (2,3:4,5-Di-*O*-isopropylidene- β -D-fructopyranose)

D. Type of Test:

Quantitative

E. Applicant:

Seradyn, Inc.

F. Proprietary and Established Names:

Seradyn QMS[®] Topiramate (TPM)

G. Regulatory Information:

1. Regulation section:

21 CFR 862.3660, Phenobarbital test system

2. Classification:

Class II

3. Product codes:

NWM

4. Panel:

91 (Toxicology)

H. Intended Use:

1. Intended use(s):

Refer to Indications for Use

2. Indication(s) for use:

The QMS® Topiramate assay is intended for the quantitative determination of Topiramate in human serum or plasma on automated clinical chemistry analyzers. The results obtained are used in the diagnosis and treatment of Topiramate overdose and in monitoring levels of Topiramate to help ensure appropriate therapy.

3. Special conditions for use statement(s):

Topiramate 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. It may be necessary to obtain multiple samples to determine the expected variation of optimal (steady-state) concentrations for individual patients.

4. Special instrument requirements:

Automated clinical chemistry analyzers

I. Device Description:

The QMS® Topiramate assay consists of separately packaged reagents (R1 and R2), calibrators (A through F), and controls (Levels 1, 2, 3).

The calibrators and controls were previously cleared under k970509 and k970517, respectively.

The R1 Antibody Reagent includes

Topiramate Antibody Reagent: sheep antisera (polyclonal Ab) in a buffer as stabilizer and <0.1% sodium azide as preservative.

The R2 Microparticles include

Topiramate Microparticle Reagent: topiramate-coated microparticles and <0.1% sodium azide as preservative.

This product contains human sourced and/or potentially infectious components. Components sourced from human blood have been tested by FDA approved methods and confirmed to be nonreactive for Hepatitis B surface Ag (HBsAg), HIV Type 1 and 2 Antibodies (anti-HIV1/HIV-2), and Hepatitis C antibodies (anti-HCV).

J. Substantial Equivalence Information:1. Predicate device name(s):

Seradyn Innofluor[®] Topiramate assay

2. Predicate 510(k) number(s):

k970510

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use / Indications for Use	Same	The QMS Topiramate assay is intended for the quantitative determination of topiramate in human serum or plasma. The measurements obtained are used in monitoring levels of topiramate to ensure appropriate therapy.
Methodology	Same	Immunoassay
Matrices	Same	Serum, plasma

Differences		
Item	Device	Predicate
Reagent Components	Two (2) reagent system: Anti-topiramate Antibody Reagent (R1) in buffers containing protein stabilizers with sodium azide Topiramate-coated Microparticle Reagent (R2) in buffer containing surfactant as stabilizers with sodium azide	Three (3) reagent system: • Topiramate Antiserum (A) (Sheep) in buffer with protein stabilizer and <0.1% sodium azide • Topiramate-fluorescein Tracer (T) in buffer with surfactant, protein stabilizer, and <0.1% sodium azide • Pretreatment Buffer (B) with surfactant
Reportable Range	1.5 – 32.0 µg/mL	0.3 – 32.0 µg/mL

Differences		
Item	Device	Predicate
Methodology	Homogeneous particle-enhanced turbidimetric immunoassay (particle agglutination) (PETIA)	Fluorescence Polarization Immunoassay (FPIA)

K. Standard/Guidance Document Referenced (if applicable):

CLSI (formerly NCCLS) guideline *EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods*.

CLSI (formerly NCCLS) guideline *EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach*.

CLSI (formerly NCCLS) Guideline *EP7-A2: Interference Testing in Clinical Chemistry*.

CLSI (formerly NCCLS) Guideline *EP9-A2: Method Comparison and Bias Estimation Using Patient Samples*

L. Test Principle:

The assay is a homogeneous particle-enhanced turbidimetric assay, based on antibody binding competition between topiramate in the sample and microparticle-bound topiramate.

Antibody binding causes microparticle agglutination. The rate of absorbance change, measured spectrophotometrically, is proportional to the rate of agglutination, and is converted to concentration in µg/mL.

M. Performance Characteristics (if/when applicable):

Performance was validated on a Hitachi 917 chemistry analyzer.

1. Analytical performance:

a. Precision/Reproducibility:

A precision study was performed using the CLSI guideline EP5-A2. The previously cleared topiramate controls (tri-level, human serum based) were assayed on the Hitachi 917. Measurements were taken in duplicate, twice a day, with a minimum of two hours difference for 20 non-consecutive days, giving 80 measurements per control level. Data was collected on two Hitachi 917's using nine calibrations. Within run, between day, and total imprecision was calculated:

			Within Run		Between Day		Total	
Control	n	Mean (µg/mL)	SD	%CV	SD	%CV	SD	%CV
1	80	2.94	0.0813	2.77	0.0617	2.10	0.1238	4.22
2	80	10.14	0.1858	1.83	0.2371	2.34	0.3418	3.37
3	80	25.69	0.8295	3.23	0.7374	2.87	1.1405	4.44

b. Linearity/assay reportable range:

Linearity by dilution was evaluated based on the CLSI guideline EP6-A. A high topiramate patient pool was made by combining three patient samples of high therapeutic levels. Because the patient pool topiramate concentration was not sufficiently high, it was supplemented (<10% total volume) with a topiramate stock solution in order to attain a concentration 20-30% above the desired reportable range (~40 µg/mL). The pool was then diluted with Calibrator A to achieve the desired concentrations which were analyzed in triplicate. Results are summarized below:

Calculated Concentration (µg/mL)	Observed Concentration (µg/mL)
36.57	36.57
31.34	31.87
20.90	20.86
15.67	15.89
10.45	10.54
5.22	5.28
3.13	3.11
2.09	2.22
1.57	1.68

The difference between the calculated and observed concentrations for all levels was 7% or less.

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

The calibrators and controls were previously cleared under k970509 and k970517, respectively.

d. Detection limit:

The sponsor defined the Limit of Quantitation (LOQ) as the lowest concentration at which the inter-assay precision is $\leq 20\%$ CV, with a recovery of $\pm 15\%$.

Test samples were prepared using a patient specimen at the low end of the therapeutic concentration range. This sample was diluted with Cal A to produce concentrations from 0.11 to 1.69 µg/mL. The samples were run on each of two Hitachi 917's every day for five days, for a total of n = 20 for each level. The grand mean, standard deviation, and coefficient of variation were calculated for each test sample.

Based upon this study, the sponsor claims an LOQ of 1.50 µg/mL in the package insert.

e. Analytical specificity:

Topiramate metabolites. The sponsor provided two studies from the medical literature which detected low concentrations of topiramate metabolites in plasma from a total of 23 subjects.

The sponsor also performed a study using 9-Hydroxytopiramate, which is one of the major metabolites of topiramate. This compound was tested at concentrations of 4, 8 and 32 µg/mL in serum containing both low and high topiramate concentrations. The concentrations of 9-Hydroxytopiramate tested were significantly higher than those measured in the studies from the medical literature. The following results were observed:

n	Conc. of 9-Hydroxytopiramate (µg/mL)	Mean concentration of parent drug (µg/mL)	Mean concentration of parent drug plus spike (µg/mL)
3	4.00	4.31	5.10
3	8.00	4.11	5.92
3	32.00	3.63	8.61

3	4.00	22.79	23.37
3	8.00	22.25	23.25
3	32.00	19.07	24.91

Endogenous substances. Nine endogenous substances were tested for possible interference with the assay in accordance with CLSI guideline EP7-A2. Results were as follows:

Low Topiramate					
Potential Interferent	Interferent Concentration	N	Mean Control (No Interferent) (µg/mL)	Mean Sample (µg/mL)	% Recovery
Albumin	12 g/dL	3	4.76	4.83	100.63
Gamma – Globulin	12 g/dL	3	4.73	4.65	98.31
Bilirubin	70 mg/mL	3	4.67	4.84	103.64
Uric Acid	30 mg/dL	3	4.58	4.62	100.87
Hemoglobin	1000 mg/dL	3	4.73	4.65	98.31
RF	500 IU/mL	3	4.88	4.99	102.25
Heparin	185.5 USP/mL	3	4.72	4.92	104.24
Cholesterol	250 mg/dL	3	4.56	4.13	90.57
Triglycerides	825 mg/dL	3	4.36	4.04	107.75

High Topiramate					
Potential Interferent	Interferent Concentration	N	Mean Control (No Interferent) (µg/mL)	Mean Sample (µg/mL)	% Recovery
Albumin	12 g/dL	3	18.64	19.16	102.79
Gamma – Globulin	12 g/dL	3	18.87	19.79	104.88
Bilirubin	70 mg/mL	3	19.30	19.95	103.37
Uric Acid	30 mg/dL	3	19.04	19.00	97.94
Hemoglobin	1000 mg/dL	3	19.53	19.26	98.62
Rheumatoid Factor	500 IU/mL	3	19.93	19.72	98.95
Heparin	185.5 USP/mL	3	19.95	21.72	108.87
Cholesterol	250 mg/dL	3	21.16	20.43	96.50
Triglycerides	825 mg/dL	3	19.06	18.00	105.89

HAMA. For this study, a normal human serum pool (control), and HAMA type 1 and HAMA type 2 samples were spiked with the same amounts of topiramate (Low=5µg/mL; High=20µg/mL). Each of the samples was assayed in triplicate on the Hitachi 917 using the QMS Topiramate assay. The means of each duplicate HAMA sample were compared to the mean of the control normal human serum.

Low Topiramate (µg/mL)

	Rep 1	Rep 2	Rep 3	mean	SD	CV	% Recovery
Control	4.71	4.85	4.60	4.72	0.1253	2.65%	n/a
HAMA Type -1	4.86	4.66	4.90	4.81	0.1286	2.68%	101.84
HAMA Type -2	4.70	4.72	4.61	4.68	0.0586	1.25%	99.08

High Topiramate (µg/mL)

	Rep 1	Rep 2	Rep 3	mean	SD	CV	% Recovery
Control	21.51	21.18	20.00	20.90	0.7939	3.80%	n/a
HAMA Type -1	19.9	20.34	20.04	20.09	0.2248	1.12%	96.16
HAMA Type -2	21.44	21.14	20.66	21.08	0.3934	1.87%	100.88

Common Co-Administered Drugs. Commonly prescribed and OTC drugs were tested for interference with low (5 µg/mL) and high (20 µg/mL) concentration samples of topiramate. The package insert will indicate drugs tested that resulted in <10% difference in recovery of topiramate, as well as the following drugs that may cross react with >10% difference in recovery: Ibuprofen, Phenytoin, and Tiagabine.

f. Assay cut-off:

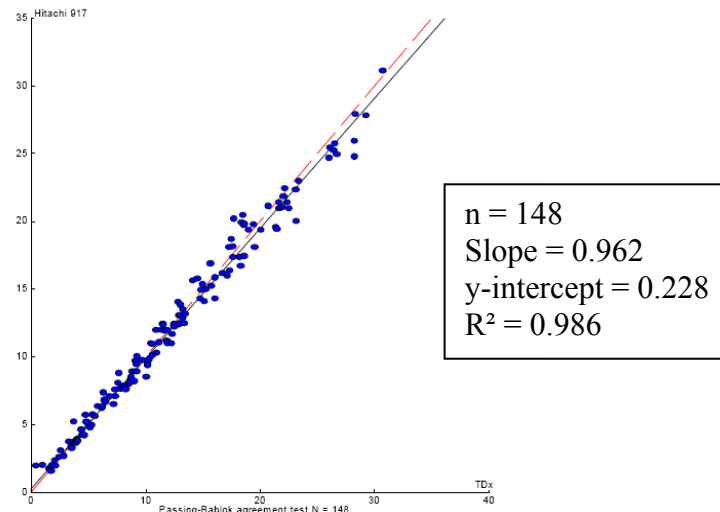
Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

A study was conducted according to CLSI Guideline *EP9-A2* comparing results obtained by the QMS® Topiramate assay to that of the predicate Innofluor® Topiramate assay. Samples tested were from patients whose topiramate level are being monitored and routinely sent to a well established laboratory for analysis. Samples ranging from 1.56 to 30.72 µg/mL topiramate were tested using both the Innofluor Topiramate assay on TDx and the QMS Topiramate assay on Hitachi 917. The analysis for each method was separated by no more than 2 hours. The data collected contained no outliers and was analyzed in singlet. Results for the Innofluor TDx reference method were plotted against those for the QMS Hitachi 917 method. Results below the LOQ of the QMS Hitachi 917 assay were not plotted or used in the statistical

analysis. The linear regression statistics and graphical presentation are as follows:



b. Matrix comparison:

This assay can be run using either serum or plasma samples. Anticoagulant evaluations were conducted to determine sample recovery by the assay, as well as stability at 2 to 8°C and -20°C. Blood from eight donors was collected into each tube type listed below:

- Plastic K2 EDTA tube
- Glass plasma K3 EDTA tube
- Plastic Sodium Heparin tube
- Plastic Lithium Heparin Tube, Plasma separator gel
- Glass serum tube, no additives (**Control Tube**)
- Plastic serum tube, no additive
- Plastic serum separator tube
- Plastic Lithium heparin tube

All tubes were processed per the manufacturer's instructions.. Serum or plasma from each tube type was then analyzed on a Hitachi 917 analyzer in triplicate.

Baseline results were obtained on day zero for each type of tube. Percent recoveries were calculated by the equation below:

$$(\text{Mean Sample Tube} - \text{Mean of Control Tube}) / \text{Mean of Control Tube}$$

(the control tube is plain glass with no additives.)

The sponsor's acceptance criterion was a mean recovery of $\pm 15\%$ for each tube type as compared to the control tube. The data collected satisfied this criterion for the anticoagulant tubes tested.

The sponsor also performed a study using aliquots from each anticoagulant tube in the matrix comparison study above to demonstrate topiramate sample stability in serum and plasma. The samples were tested for 7 days at 2-8° C, 14 days at -10° C or lower, and 30 days at -10° C or lower. The sponsor's acceptance criterion was a recovery of $\pm 10\%$ of the day 0 concentration. Based on this the sponsor elected to limit sample stability claims in frozen samples to 14 days.

3. Clinical studies:

a. *Clinical Sensitivity:*

Not applicable.

b. *Clinical specificity:*

Not applicable.

c. Other clinical supportive data (when a. and b. are not applicable):

4. Clinical cut-off:

Not applicable.

5. Expected values/Reference range:

A therapeutic range for topiramate has not been well established. Some reports in the literature suggest a target range for steady-state concentrations of 2 to 25 µg/mL. Inconsistent correlation exists between levels of circulating topiramate to toxicity, adverse effects, or clinical efficacy.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.