510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K201089

B Applicant

ARK Diagnostics, Inc.

C Proprietary and Established Names

ARK Lacosamide Assay

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
NWM	Class II	21 CFR 862.3350 - Diphenylhydantoin Test System	TX - Clinical Toxicology

II Submission/Device Overview:

A Purpose for Submission:

New device

B Measurand:

Lacosamide

C Type of Test:

Quantitative homogeneous enzyme immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:
The ARK Lacosamide Assay is a homogeneous enzyme immunoassay intended for the quantitative determination of lacosamide in human serum on automated clinical chemistry analyzers. The measurements obtained are used in monitoring levels of lacosamide to help ensure appropriate therapy.

C Special Conditions for Use Statement(s):
Rx - For Prescription Use Only

D Special Instrument Requirements:

Performance characteristics studies were conducted on the Beckman AU680 clinical chemistry analyzer.

IV Device/System Characteristics:

A Device Description:

The ARK Lacosamide Assay consists of:

- Reagent R1: anti-lacosamide polyclonal antibody, glucose-6-phosphate, nicotinamide adenine dinucleotide, bovine serum albumin, sodium azide, and stabilizers
- Reagent R2: lacosamide labeled with bacterial G6PDH enzyme, buffer, bovine serum albumin, sodium azide, and stabilizers

B Principle of Operation:

The device is a homogenous enzyme immunoassay based on competition of free drug in the sample and drug labeled with enzyme for antibody binding sites. In the absence of free drug in the sample, the antibody binds the enzyme-labeled drug, resulting in inhibition of enzyme activity. In the presence of drug in the sample, enzyme activity increases and is directly related to the drug concentration. The enzyme activity is measured spectrophotometrically on an automated clinical chemistry analyzer.

V Substantial Equivalence Information:

A Predicate Device Name(s):
Topiramate Assay, Ark Topiramate Calibrator And Ark Topiramate Control

B Predicate 510(k) Number(s):
K083799

C Comparison with Predicate(s):

Device & Predicate Device(s):	K201089	K083799
Device Trade Name	ARK Lacosamide Assay	ARK Topiramate Assay
General Device		

Characteristic Similarities		
Intended Use/Indications For Use	Same	Homogeneous quantitative enzyme immunoassay intended for the quantitative determination of antiepileptic drug in human samples. Results are used to help ensure appropriate therapy.
Method	Same	Homogeneous Enzyme Immunoassay (EIA)
General Device Characteristic Differences		
Sample Matrix	Human serum	Human serum or plasma
Analyte	Lacosamide	Topiramate

VI Standards/Guidance Documents Referenced:

CLSI EP05-A3: Evaluation of Precision of Quantitative Measurement Procedures

CLSI EP06-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach

CLSI EP07-A3: Interference Testing in Clinical Chemistry

CLSI EP14-A3: Evaluation of Commutability of Processed Samples

CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures

CLSI EP25-A: Evaluation of Stability of In Vitro Diagnostic Reagents

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Precision studies were performed in accordance with CLSI guideline EP05-A3 at one site with one analyzer and one lot of reagents. The study was performed for 20 days with two runs per day, at least two hours apart and four replicates per run, giving a total of 160 determinations per sample (n = 160). Human serum was spiked with lacosamide stock solution to final concentrations of 1.49, 7.10, and 15.18 µg/mL. Mean lacosamide concentration, standard deviation (SD), and coefficients of variation (%CVs) were calculated for within-run, between-day, and total precision.

Sample	N	Mean (µg/mL)	Within Run		Between Day		Total	
			SD	CV(%)	SD	CV(%)	SD	CV(%)
ARK Lacosamide Control								
LOW	160	1.55	0.049	3.1	0.049	3.1	0.070	4.5
MID	160	7.13	0.202	2.8	0.204	2.9	0.287	4.0
HIGH	160	14.94	0.450	3.0	0.445	3.0	0.664	4.4
Human Serum								
LOW	160	1.49	0.045	3.0	0.037	2.5	0.058	3.9
MID	160	7.10	0.175	2.5	0.217	3.1	0.283	4.0
HIGH	160	15.18	0.456	3.0	0.432	2.8	0.657	4.3

An additional precision study was performed in accordance with CLSI guideline EP05-A3 at one site with one analyzer and three lots of reagents. The study was performed for five days with two runs per day, four replicates per run, giving a total of 40 determinations per sample (n = 40). Human serum was spiked with lacosamide stock solution to final concentrations of 1.49, 7.00, 14.68, and 21.72 µg/mL (mean measurements for three lots). Mean lacosamide concentration, standard deviation (SD), and coefficients of variation (%CVs) were calculated for within-run, between-day, and total precision. Results below are from a single representative lot.

Sample	N	Mean (µg/mL)	Within Run		Between Day		Total	
			SD	CV(%)	SD	CV(%)	SD	CV(%)
ARK Lacosamide Control								
LOW	40	1.53	0.054	3.5	0.045	2.9	0.068	4.4
MID	40	6.85	0.153	2.2	0.159	2.3	0.244	3.6
HIGH	40	14.59	0.550	3.8	0.425	2.9	0.752	5.2
Human Serum								
LOW	40	1.46	0.040	2.7	0.073	5.0	0.084	5.8
MID	40	6.73	0.151	2.2	0.135	2.0	0.231	3.4
HIGH	40	14.09	0.416	3.0	0.243	1.7	0.510	3.6
21	40	21.65	1.363	6.3	0.678	3.1	1.495	6.9

2. Analytical Recovery and Dilution Linearity:

To evaluate linearity, a lacosamide-negative human serum pool spiked with lacosamide at 25.00 µg/mL was serially diluted with lacosamide-negative human serum to generate ten intermediate levels (0.00, 0.40, 1.50, 3.00, 6.00, 9.00, 12.00, 15.00, 18.00, 21.00, and 25.00 µg/mL). Each sample was run in replicates of six, and the average was used to determine percent recovery compared to the expected target value. The observed result (y) and the target expected result (x) were compared using the first-order polynomial regression method. The regression equation and correlation obtained were:

$y = 0.9998x - 0.0170$; $r^2 = 0.9994$

This evaluation supports linearity within the claimed measuring range of 0.40 to 24.00 µg/mL.

Recovery

An analytical recovery study was conducted on the Beckman Coulter AU680 to determine the effect of differing concentrations of lacosamide on recovery by spiking lacosamide into human serum negative for lacosamide. Two analytical runs of three replicates of each sample were assayed; the results of all six replicates of each sample were averaged and compared to the target concentration. The results are as follows:

Theoretical Concentration (µg/mL)	Mean Recovered Concentration (µg/mL)	Percent Recovery (%)
0.40	0.36	90.4
0.50	0.47	93.3
1.00	1.04	104.2
3.00	3.07	102.3
6.00	6.15	102.6
9.00	8.92	99.1
15.00	14.42	96.1
20.00	21.15	105.8

3. Analytical Specificity/Interference:

Interference from Endogenous Substances:

Interference from elevated lipid levels or endogenous substances was evaluated by spiking compounds into lacosamide-negative human serum spiked with lacosamide stock solution to a final concentration of 2.00 µg/mL and 15.00 µg/mL. The samples were tested in two analytical runs of three replicates (n = 6) for each sample, and mean measurements were calculated. Percentage recovery of lacosamide in the presence of elevated endogenous interfering compound was calculated versus the respective mean control lacosamide measurement. A substance was considered to not interfere if the mean measurement of lacosamide in its presence was equivalent to its corresponding mean control measurement ±10%. Concentrations tested and results are shown below. No significant interference was observed.

Interfering Substance	Highest interferent concentration tested that showed no significant interference
Human Albumin	12 g/dL
Bilirubin (conjugated)	70 mg/dL
Bilirubin (unconjugated)	70 mg/dL
Cholesterol	620 mg/dL
Human IgG	12 g/dL
Hemoglobin	1000 mg/dL
Rheumatoid Factor	1000 IU/mL
Triglycerides	1000 mg/dL
Uric Acid	30 mg/dL

Interference from Exogenous Substances:

Cross-reactivity or potential interference from the lacosamide metabolite O-desmethyl-lacosamide or potentially coadministered compounds was assessed by supplementing pooled human serum with the potential interferent, then spiking the serum with a lacosamide stock solution to a final concentration of 2.00 µg/mL and 15.00 µg/mL. The samples were tested in two analytical runs of three replicates (n = 6) for each sample, and mean measurements were calculated. Percentage recovery of lacosamide in the presence of elevated endogenous interfering compound was calculated versus the respective mean control lacosamide measurement. No significant interference was observed.

O-Desmethyl Lacosamide:

O-Desmethyl Lacosamide (µg/mL)	**Measured Lacosamide in Absence/Presence of Metabolite (µg/mL)**			
	Lacosamide (2.00 µg/mL)		**Lacosamide (15.00 µg/mL)**	
	Metabolite Absent	**Metabolite Present**	**Metabolite Absent**	**Metabolite Present**
5.0	2.18	2.23	Not Tested	
30.0	Not Tested		15.51	16.40

Co-administered Drugs and Common OTC Drugs:

#	**Compound**	**Highest concentration tested that showed no significant interference (µg/mL)**
1	Acetaminophen	200
2	Acetazolamide	100
3	Acetylsalicylic acid	1000
4	Amikacin	100
5	Amitriptyline	20
6	Amoxapine	10
7	Amphotericin B	100
8	Ampicillin	100
9	Ascorbic acid	100
10	Baclofen	100
11	Buproprion	10
12	Caffeine	100
13	Carbamazepine	100
14	Chloramphenicol	250
15	Chlorpromazine	10
16	Citalopram	10
17	Clobazam	100
18	Clonazepam	10
19	Cyclosporin A	40
20	Diazepam	20
21	Digoxin	10
22	Doxepin	10

#	Compound	Highest concentration tested that showed no significant interference (µg/mL)
23	Erythromycin	200
24	Ethanol	4000 (0.4%)
25	Ethotoin	100
26	Ethosuximide	250
27	Felbamate	250
28	Fluoxetine	10
29	Furosemide	100
30	Gabapentin	200
31	Gentamicin	100
32	Haloperidol	10
33	Heparin	200 U/mL
34	Ibuprofen	500
35	Imipramine	10
36	Kanamycin A	200
37	Lamotrigine	400
38	Levetiracetam	400
39	Lidocaine	100
40	Lincomycin	1000
41	Mephenytoin	100
42	Mesoridazine	10
43	Methicillin	250
44	Naproxen	600
45	Neomycin	1000
46	Niacin	100
47	Nitrazepam	20
48	Nortriptyline	20
49	Olanzapine	10
50	Oxcarbazepine	100
51	Paroxetine	10
52	2-phenyl-2-ethyl-malonamide (PEMA)	1000
53	Penicillin V	100
54	Perphenazine	100
55	Phenobarbital	200
56	Phenytoin	200
57	Pregabalin	200
58	Primidone	100
59	Procainamide	100
60	Prochloroperazine	10
61	Ranitidine	100
62	Rifampin	100
63	Risperidone	100
64	Sertraline	100
65	Spectinomycin	100

#	Compound	Highest concentration tested that showed no significant interference (µg/mL)
66	Stiripentol	100
67	Sulfamethoxazole	400
68	Theophylline	200
69	Thioridazine	10
70	Tobramycin	100
71	Tiagabine	200
72	Topiramate	250
73	Trimethoprim	40
74	Valproic Acid	600
75	Vancomycin	250
76	Vigabatrin	150
77	Zonisamide	400

4. Assay Reportable Range:

   Human serum containing 0.40 to 24.00 µg/mL lacosamide

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

   Traceability:

   The ARK Lacosamide Calibrator is traceable to a certified reference standard (Cerilliant), and the uncertainty in the lacosamide concentration is 5% relative to the concentration in the certified reference standard.

   Specimen Stability:

   Real-time stability study protocols and acceptance criteria were reviewed and found to be adequate. Simulated serum specimens were shown to be stable for at least 48 hours at room temperature (22°C), 28 days when refrigerated (2-8°C), and after three successive freeze/thaw cycles; clinical specimens were shown to be stable when frozen (-20°C) for at least 34 months.

   Product Stability/Shelf Life:

   Protocols for real-time and accelerated stability and shelf life studies were reviewed and found to be acceptable. Results supported a shelf-life stability claim of up to 18 months for the ARK Lacosamide Reagents when stored unopened at 2-8°C. Reagents were stable up to 60 days when stored on-board the instrument.

6. Detection Limit:

   Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ) were determined according to CLSI Guideline EP17-A2. Samples were prepared by spiking lacosamide-negative human serum with a stock solution of lacosamide.

LoB and LoD were evaluated by testing 60 replicates of pooled human serum and 60 replicates of the first positive level, 0.10 µg/mL lacosamide. The analyzer was then calibrated and three analytical runs were performed; in each, 20 blank replicates and 20 replicates of 0.10 µg/mL lacosamide were analyzed, for each of four device lots. The grand mean and root mean square standard deviation (RMSD) were calculated. The LoB was calculated to be 0.00 µg/mL lacosamide, and the LoD was calculated to be 0.02 µg/mL lacosamide.

LoQ was defined as the lowest concentration for which acceptable inter-assay precision (≤20% CV) and recovery (±15%) were observed. To determine LoQ, three levels were tested below the lowest positive calibrator concentration (0.75 µg/mL). Pooled human serum representative of the patient specimen matrix was supplemented with lacosamide to give concentrations of 0.30, 0.40, and 0.50 µg/mL lacosamide. Eight replicates of each sample were tested in each of five runs to give a minimum of 40 replicates of each LoQ sample tested for each of four device lots. The grand mean, RMSD, and coefficient of variance for each test sample were calculated. The LoQ was determined to be 0.40 µg/mL lacosamide.

7. Assay Cut-Off:

Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

A method comparison study was conducted with one lot of reagents. One hundred fifty unaltered clinical samples ranging in concentration from 0.65 µg/mL to 23.50 µg/mL were analyzed using the ARK Lacosamide Assay in singlicate, and the results were compared to a validated LC-MS/MS method. Results of the Passing-Bablok regression analysis are shown below.

Analyzer	Slope (95% CI)	Intercept (95% CI)	N	R^2 (95% CI)	Sample Range Tested
AU680	1.01 (0.99 to 1.04)	0.03 (-0.10 to 0.15)	150	0.98 (0.98 to 0.99)	0.65-23.50 µg/mL

2. Matrix Comparison:

Not applicable. The assay is only intended for use with serum samples.

C Clinical Studies:

1. Clinical Sensitivity:

Not applicable.

2. Clinical Specificity:

Not applicable.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

Not applicable.

D Clinical Cut-Off:

Not applicable.

E Expected Values/Reference Range:

The package insert includes the following statement:

"Therapeutic drug monitoring of antiepileptic drug (AED) is used worldwide as an aid to individualize drug therapy, and various guidelines have been published that highlight the particular properties of AEDs and the features of epilepsy that make TDM useful.[1-4] Observational studies have suggested reference ranges for lacosamide concentrations, with dosage as a contributing factor. Recommended reference ranges vary from 2.2 to 20 mg/L,[5] and ranges of 5 µg/mL to 10 µg/mL[6] or 10 µg/mL to 20 µg/mL[7] have also been proposed. Altered serum lacosamide disposition may result in serum concentrations that are too low to maintain efficacy, or elevated with the increased potential to cause adverse effects or toxicity, suggesting the potential need for TDM. Factors that may affect lacosamide pharmacokinetics include renal function, pregnancy status, age, and critical illness.[5]

Steady state concentrations may be achieved after 3 days of treatment.[8] Lacosamide concentrations in serum increased dose dependently, were age independent, and were higher in women compared with men.[9] Monitoring lacosamide may benefit retention of therapy among patients with intellectual disability.[10] Coadministration of carbamazepine and phenytoin (inducers of drug-metabolizing enzymes) may decrease serum concentrations of lacosamide substantially.[9,11]

Case reports associated with lacosamide toxicity have included: (1) a 70-year-old female experienced life-threatening ventricular tachycardia,[12] (2) a 26-year-old male, who after ingestion of 6,000 mg of lacosamide in a suicide attempt, a 10 h post-ingestion was well above the reference range at 44.5 µg/mL,[13] and (3) another case in which mental status changes and abnormal ECG occurred and for which hemodialysis brought the patient back to baseline.[14]

Generally, clinicians using reference ranges such as these should be aware that, because of individual variation, patients may achieve therapeutic benefit with serum drug concentrations outside of these ranges and may experience toxicity with levels below the lower limit of the reference range. Lacosamide 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 and dosage adjustments."

[1]Johannessen, S.I. et al. 2003. Therapeutic drug monitoring of the newer antiepileptic drugs. Ther Drug Monit **25**:347-363.

[2]Patsalos, P.N. et al. 2008. Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE commission on therapeutic strategies. Epilepsia **49**:1239-1276.

[3]Krasowski, M. 2010. Therapeutic drug monitoring of the newer anti-epilepsy medications. Pharmaceuticals (Basel) **3**:1909-1935.

[4]Brandt, C. and T.W. May. 2011. Therapeutic drug monitoring of newer antiepileptic drugs. J Lab Med **35**:161-169.

[5]Schultz, L. and Mahmoud, S.H. 2020. Is Therapeutic Drug Monitoring of Lacosamide Needed in Patients with Seizures and Epilepsy? *Eur J Drug Metab Pharmacokinet.* **45**(3):315-349. Doi: 10.1007/s13318-019-00601-8. PMID: 31950342.

[6]Kellinghaus, C. 2009. Lacosamide as a treatment for partial epilepsy: Mechanisms of action, pharmacology, effects, and safety. Ther Clin Risk Manag **5**:757-766.

[7]Greenaway, C. et al. 2010. A high-performance liquid chromatography assay to monitor the new antiepileptic drug lacosamide in patients with epilepsy. Ther Drug Monit **32**:448-452.

[8]Chung, S.S. 2010. Lacosamide: new adjunctive treatment option for partial-onset seizures. Expert Opin Pharmacother **11**:1595-1602.

[9]Markoula, S. et al. 2014. Lacosamide serum concentrations in adult patients with epilepsy: The Influence of Gender, Age, Dose, and Concomitant Antiepileptic Drugs. Ther Drug Monit **36**:494-498.

[10]Svendsen, T. et al. 2020. Clinical experience combined with therapeutic drug monitoring of lacosamide. *Acta Neurol Scand* **141**:279-286.

[11]Contin, M. and F. Albani. 2013. Lacosamide therapeutic monitoring in patients with epilepsy: Effect of concomitant antiepileptic drugs. *Ther Drug Monit* **35**:849-52.

[12]Berei, T.J. et al. 2018. Lacosamide-induced recurrent ventricular tachycardia in the acute care setting. *J Pharm Pract* **31**(2):222-6.

[13]Deslandes, G. et al. 2015. Status epilepticus following self-poisoning of lacosamide and lamotrigine: a case report with follow-up of drug serum concentrations. *Toxicol Anal Clin* **27**(2):88-90.

[14]Kiernan, E. et al. 2019. Hemodialysis: the final frontier for acute lacosamide toxicity? *J Med Toxicol* **15**(2):63.

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

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