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

A. 510(k) Number:

k153596

B. Purpose for Submission:

New Device

C. Measurand:

Oxcarbazepine Metabolite

D. Type of Test:

Homogenous enzyme immunoassay

E. Applicant:

ARK Diagnostics, Inc.

F. Proprietary and Established Names:

ARK Oxcarbazepine Metabolite Assay

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
POX	II	862.3645 - Neuroleptic drugs radioreceptor assay test system.	91 - Toxicology
DLJ	II	862.3200 - Clinical toxicology calibrator	91 - Toxicology
LAS	I, reserved	862.3280 - Clinical toxicology control material	91 - Toxicology

H. Intended Use:

1. Intended use(s):

   See indications for use.

2. Indication(s) for use:

   The ARK Oxcarbazepine Metabolite Assay is a homogeneous enzyme immunoassay intended for the quantitative determination of Oxcarbazepine Metabolite in human serum on automated clinical chemistry analyzers. The measurements obtained are used in monitoring levels of Oxcarbazepine Metabolite to help ensure appropriate therapy.

   The ARK Oxcarbazepine Metabolite Calibrator is intended for use in calibration of the ARK Oxcarbazepine Metabolite Assay.

   The ARK Oxcarbazepine Metabolite Control is an assayed quality control material intended for use in quality control of the ARK Oxcarbazepine Metabolite Assay.

3. Special conditions for use statement(s):

   For prescription use only

4. Special instrument requirements:

   The assay was validated on the Beckman Coulter AU480 automated clinical chemistry analyzer.

I. Device Description:

The ARK Oxcarbazepine Metabolite Assay is a homogeneous immunoassay based on competition between drug in the specimen and Oxcarbazepine Metabolite labeled with the enzyme glucose-6-phosphate dehydrogenase (G6PDH) for binding to the antibody reagent. The ARK Oxcarbazepine Metabolite Assay consists of reagents R1 (anti-Oxcarbazepine Metabolite polyclonal antibody with substrate) and R2 (Oxcarbazepine Metabolite labeled with bacterial G6PDH enzyme).

ARK Oxcarbazepine Metabolite Calibrator is comprised of a synthetic protein matrix and consists of a six-level set to calibrate the assay.

The ARK Oxcarbazepine Metabolite Control is comprised of a synthetic protein matrix and consists of a three level set used for quality control of the assay.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Emit 2000 Carbamazepine Assay, ARK Topiramate Calibrator, ARK Topiramate Control

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

   k010814 (assay); k083799 (calibrator and control)

3. Comparison with predicate:

Assay Similarities		
Item	**Candidate Device (ARK Oxcarbazepine Assay)**	**Predicate Device (Emit 2000 Carbamazepine Assay, k010814)**
Intended Use/Indications for Use	The ARK Oxcarbazepine Metabolite Assay is intended for the quantitative determination of Oxcarbazepine Metabolite in human serum on automated clinical chemistry analyzers. The measurements obtained are used in monitoring levels of Oxcarbazepine Metabolite to help ensure appropriate therapy.	The Emit® 2000 Carbamazepine Assay is a homogeneous enzyme immunoassay intended for use in the quantitative analysis of carbamazepine in human serum or plasma. The results obtained helps physicians individualize dosage regimens.
Sample Type	Serum	Serum or plasma
Methodology	Homogenous enzyme immunoassay (EIA)	Same
Reagent components	Two (2) reagent system: Anti- Oxcarbazepine Metabolite Antibody/Substrate Reagent (R1) containing rabbit polyclonal antibodies to Oxcarbazepine Metabolite, glucose-6- phosphate, nicotinamide adenine dinucleotide, bovine serum albumin, sodium azide, and stabilizers Enzyme Reagent (R2) containing Oxcarbazepine Metabolite labeled with bacterial G6PDH, buffer, bovine serum albumin, sodium azide, and stabilizers	Two (2) reagent system: Antibody/Substrate Reagent (R1) containing mouse monoclonal antibodies to carbamazepine, glucose-6-phosphate, nicotinamide adenine dinucleotide. Enzyme Reagent (R2) containing carbamazepine labeled with bacterial G6PDH, buffer. Sodium azide, buffer, preservatives, and stabilizers
Testing environment	Routine clinical laboratory	Same
Reagent condition and	Liquid, 2-8°C	Same

Assay Similarities		
Item	**Candidate Device (ARK Oxcarbazepine Assay)**	**Predicate Device (Emit 2000 Carbamazepine Assay, k010814)**
storage		

Assay Differences		
Item	**Candidate Device (ARK Oxcarbazepine Assay)**	**Predicate Device (ARK Topiramate Assay, k083799)**
Analyte	Oxcarbazepine metabolite	Carbamazepine

Controls: Similarities and Differences		
Item	**Candidate Device (ARK Oxcarbazepine Control)**	**Predicate Device (ARK Topiramate Control; k083799)**
Intended Use/Indications for Use	The ARK Oxcarbazepine Metabolite control is an assayed quality control material intended for use in quality control of the ARK Oxcarbazepine Metabolite Assay.	The ARK Topiramate Control is intended for use in quality control of the ARK Topiramate Assay.
Matrix	Synthetic protein matrix (buffer, bovine serum albumin, preservatives)	Same
Levels	3 (LOW, MID, HIGH)	Same

Calibrators: Similarities and Differences		
Item	**Candidate Device (ARK Oxcarbazepine Calibrator)**	**Predicate Device (ARK Topiramate Calibrator; k083799)**
Intended Use/Indications for Use	ARK Oxcarbazepine Metabolite Calibrator is intended for use in calibration of the ARK Oxcarbazepine Metabolite Assay.	The ARK Topiramate Calibrator is intended for use in calibration of the ARK Topiramate Assay.
Matrix	Synthetic protein matrix (buffer, bovine serum albumin, preservatives)	Same
Levels	6	Same

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

- Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline- Third Edition (EP05-A3)
- Interference Testing in Clinical Chemistry; Approved Guideline - Second Edition (EP07-A2)
- Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline - Third Edition (EP09-A3)
- Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (EP6-A)
- Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline - Second Edition (EP17-A2)

L. Test Principle:

The ARK Oxcarbazepine Metabolite Assay is a homogeneous immunoassay based on competition between drug in the specimen and Oxcarbazepine Metabolite labeled with the enzyme glucose-6-phosphate dehydrogenase (G6PDH) for binding to the antibody reagent. As the latter binds antibody, enzyme activity decreases. In the presence of drug from the specimen, enzyme activity increases and is directly proportional to the drug concentration. Active enzyme converts the coenzyme nicotinamide adenine dinucleotide (NAD) to NADH that is measured spectrophotometrically as a rate of change in absorbance. Endogenous serum G6PDH does not interfere with the results because the coenyzme NAD functions only with the bacterial enzyme used in the assay.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

   Data for the precision evaluation studies (total and within-laboratory precision) were collected on a single Beckman Coulter AU480 automated clinical chemistry analyzer. Each level of control and patient sample was assayed in quadruplicate twice a day over twenty non-consecutive days. A total of 160 determinations were made for each sample. One calibration was performed during this interval. A total of 6 samples (3 levels of human serum pooled specimens containing Oxcarbazepine Metabolite, and 3 levels of ARK Oxcarbazepine Metabolite controls) were used in the study.

   Mean oxcarbazepine metabolite, standard deviation (SD) and coefficients of variation (%CVs) were calculated for within-run, between-day, and total precision.

Sample	N	Mean (g/mL)	Within Run		Between Day		Total	
			SD	CV (%)	SD	CV (%)	SD	CV (%)
ARK Control								
LOW	160	3.0	0.12	4.0	0.12	4.1	0.17	5.7
MID	160	10.1	0.37	3.6	0.33	3.2	0.48	4.8
HIGH	160	30.2	0.99	3.3	1.19	3.9	1.54	5.1
Human Serum								
LOW	160	3.1	0.12	3.9	0.12	4.0	0.17	5.5
MID	160	10.1	0.38	3.8	0.36	3.6	0.55	5.5
HIGH	160	30.4	1.10	3.6	1.11	3.7	1.55	5.1

b. *Linearity/assay reportable range:*

Linearity was evaluated according to the CLSI EP6-A standard. A series of 8 concentrations (1.00, 3.00, 5.00, 10.00, 20.00, 30.00, 40.00, and 50.00 g/mL) in human serum were prepared by proportionally diluting a spiked high Oxcarbazepine Metabolite concentration serum sample pool with a negative serum pool.

Two analytical runs of three replicates of each sample (6 replicates total) were measured for each concentration, and the mean of the measured concentration was compared to the theoretical expected Oxcarbazepine Metabolite concentrations based on the first order and second order linear regression analysis.

The linear regression results using the sample concentrations listed above are:

Analyzer	Slope	Intercept	R^2
AU480	1.0388	-0.0693	0.9994

This evaluation supports linearity within the claimed measuring range of 1.0 to 37.0 g/mL.

Recovery

An analytical recovery study was conducted on the Beckman Coulter AU480 to determine the effect of differing ratios of Oxcarbazepine Metabolite enantiomers (S- or R- enantiomer; ratio hereafter S:R) on recovery by spiking Oxcarbazepine Metabolite into human serum negative for Oxcarbazepine Metabolite. The results are as follows:

	Mean Recovered Concentration (g/mL)			
Theoretical Concentration (g/mL)	**S:R 1:1**	**S:R 4:1**	**S:R 9:1**	**S:R 19:1**
1.0	0.77	0.93	0.98	0.95
4.0	3.78	3.92	3.94	3.86
8.0	7.47	8.18	8.16	7.82
15.0	14.10	15.80	14.91	15.42
20.0	19.03	21.69	19.81	21.02
35.0	33.74	34.71	33.52	36.16
45.0	42.89	46.88	44.63	49.46

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

Traceability and Value Assignment:

ARK Oxcarbazepine Metabolite Calibrators and ARK Oxcarbazepine Metabolite Controls are traceable to a commercial product, and are value assigned by gravimetric dilution.

Stability:

Shelf life: Accelerated and real-time shelf-life stability study protocols and acceptance criteria were reviewed and found to be adequate. Accelerated stability studies were performed to support a shelf-life stability claim until the expiration date for the ARK Oxcarbazepine Metabolite Calibrators and Controls when stored unopened at 2-8°C. Real time stability studies to support shelf-life stability claims are ongoing.

Open vial: The Sponsor's open vial stability study protocols and acceptance criteria were reviewed and found to be adequate. Real-time testing for opened vial ARK Oxcarbazepine Metabolite Calibrators and Controls stability was performed and supports stability claims of up to 12 months when stored opened at 2 - 8°C.

d. Detection limit:

The LoB was determined using pooled human serum negative for oxcarbazepine metabolite as the blank sample. A single concentration of oxcarbazepine metabolite (0.3 g/mL) in serum was tested to assess LoD. To determine the LoB and LoD, twenty (20) replicates of each sample were tested in each of three (3) runs to yield sixty (60) replicates of each sample tested, in a single day. The grand mean, standard deviation, and coefficient of variation for each test sample were calculated to determine inter-assay precision.

The LOQ of the ARK Oxcarbazepine Metabolite Assay was determined as the lowest concentration for which acceptable inter-assay precision and recovery is observed

(≤20% CV with ±15% recovery). Multiple low concentration Oxcarbazepine Metabolite serum samples were prepared gravimetrically. Eight (8) replicates of each sample were tested in each of five (5) runs to give a minimum of 40 replicates of each LOQ sample tested. The grand mean, standard deviation, and coefficient of variation for each test sample were calculated to determine inter-assay precision.

The sponsor determined the LoB, LoD, and LoQ to be the following:

Criterion	**Oxcarbazepine Metabolite Concentration (g/mL)**
Limit of Blank (LoB): N = 60	0.01
Limit of Detection (LoD); N = 60	0.06
Limit of Quantitation (LoQ); N=40	1.0

e. *Analytical specificity:*

Specificity studies were conducted for metabolites of Oxcarbazepine and structurally related compounds (including Oxcarbazepine itself), medications routinely co-administered with Oxcarbazepine, other over-the-counter drugs, and endogenous substances, where Oxcarbazepine Metabolite (20 µg/mL) was present in serum. Concentrations tested and results are tabulated in the sections below.

Oxcarbazepine Metabolites:

Metabolite	**Level Tested (µg/mL)**	**% Cross-Reactivity**	**% Interference**
MHD Glucuronide	20	1.6	1.6
	40	0.0	-0.1
	100	1.5	7.4
	200	1.0	10.5
Dihydro-carbamazepine	5.0	6.0	1.5
Carbamazepine-epoxide	10.0	13.6	6.9
Dihydro-dihydroxy carbamazepine (DHD)	5.0	-11.3	-2.9
Oxcarbazepine	20.0	22.2	22.6
Carbamazepine	20.0	20.4	20.7
Eslicarbazepine acetate	20.0	22.1	22.4

Endogenous Substances:

Endogenous substances were tested at 3 and 30 g/mL Oxcarbazepine Metabolite in serum. No significant interference was observed. Concentrations tested and results are shown below. No significant interference was observed.

		Percentage recovery	
Interfering Substance	**Interferent Concentration**	**3 μg/mL Oxcarbazepine Metabolite**	**30 μg/mL Oxcarbazepine Metabolite**
Human Albumin	12 g/dL	102.2	95.1
Bilirubin (conjugated)	70 mg/dL	108.6	100.2
Bilirubin (unconjugated)	70 mg/dL	102.7	92.4
Cholesterol	602 mg/dL	96.5	103.5
Human IgG	12 g/dL	105.7	100.7
Hemoglobin	1000 mg/dL	101.0	103.9
Rheumatoid Factor	1000 IU/mL	93.1	93.1
Triglycerides	1000 mg/dL	96.6	94.3
Uric Acid	30 mg/dL	107.5	95.5

Co-administered drugs and common OTC drugs:

The sponsor evaluated the effect of co-administered drugs and common over the counter drugs on the measurement of Oxcarbazepine Metabolite in pooled human serum containing either low (3.0 μg/mL) or high (30.0 μg/mL) levels of Oxcarbazepine Metabolite. No significant interference was observed.

#	Compound	Concentration Tested	Percentage Recovery	
			Oxcarbazepine metabolite (3 g/mL)	**Oxcarbazepine metabolite (30 g/mL)**
1	Acetaminophen	200	95.6	97.1
2	Acetazolamide	100	99.9	90.3
3	Acetylsalicylic acid	100	95.1	96.0
4	Amikacin	100	91.7	92.0
5	Amitriptyline	10	105.1	101.1
6	Amoxapine	10	99.3	98.0
7	Amphotericin B	100	93.6	93.2
8	Ampicillin	100	96.5	100.2

#	Compound	Concentration Tested	Percentage Recovery	
			Oxcarbazepine metabolite (3 g/mL)	**Oxcarbazepine metabolite (30 g/mL)**
9	Ascorbic acid	100	92.8	91.1
10	Baclofen	100	91.1	93.5
11	Bupropion	10	109.6	98.8
12	Caffeine	100	98.3	91.7
13	Chloramphenicol	250	93.7	90.3
14	Chlorpromazine	10	98.3	99.7
15	Citalopram	10	102.9	99.3
16	Clobazam	100	98.3	103.2
17	Clonazepam	10	104.6	99.2
18	Cyclosporin A	40	91.2	90.2
19	Diazepam	20	103.1	100.3
20	Digoxin	10	97.3	97.0
21	Doxepin	10	107.4	102.9
22	Erythromycin	200	94.5	94.7
23	Ethanol	4000 (0.4%)	91.6	100.7
24	Ethotoin	100	98.4	96.2
25	Ethosuximide	250	103.2	105.1
26	Felbamate	250	93	93.8
27	Fluoxetine	20	94.9	99.2
28	Furosemide	100	95.2	92.8
29	Gabapentin	200	92.2	104.3
30	Gentamicin	100	95.8	91.2
31	Haloperidol	10	101.2	97.4
32	Heparin	200 U/mL	96.3	92.3
33	Ibuprofen	500	103.3	91.6
34	Imipramine	10	109.4	100.4
35	Kanamycin A	200	93.8	109.0
36	Lamotrigine	400	91.5	97.9
37	Levetiracetam	400	97.7	94.7
38	Lidocaine	100	96.8	97.7
39	Lincomycin	1000	90.7	100.4
40	Mephenytoin	100	100.7	97.3

#	Compound	Concentration Tested	Percentage Recovery	
			Oxcarbazepine metabolite (3 g/mL)	Oxcarbazepine metabolite (30 g/mL)
41	Mesoridazine	10	97.8	99.4
42	Methicillin	250	93.5	96.2
43	Naproxen	600	102.2	95.7
44	Neomycin	100	95.6	102.9
45	Niacin	100	93	93.9
46	Nitrazepam	20	106.3	98.5
47	Notriptyline	10	104.4	102.0
48	Olanzapine	10	105.8	100.5
49	Paroxetine	10	96.7	98.3
50	2-phenyl-2-ethyl-malonamide (PEMA)	100	94.6	93.9
51	Penicillin V	100	95.4	93.8
52	Perphanazine	50	104.9	100.9
53	Phenobarbital	200	90.2	94.7
54	Phenytoin	200	100.1	99.6
55	Pregabalin	200	91.5	90.2
56	Primidone	100	95	92.4
57	Procainamide	100	93.3	92.4
58	Prochlorperazine	10	105.2	101.6
59	Ranitidine	100	102.1	100.6
60	Rifampin	100	93.3	92.7
61	Risperidone	10	100.6	97.7
62	Sertraline	100	98.9	93.4
63	Spectinomycin	100	97.2	97.9
64	Stiripentol	100	93.8	99.7
65	Sulfamethoxazole	400	100.5	97.5
66	Theopylline	200	100.5	100.8
67	Thioridazine	10	103.9	98.0
68	Tobramycin	100	94.5	101.3
69	Tiagabine	200	91.6	93.5
70	Topiramate	250	92.8	91.7
71	Trimethoprim	40	101.2	93.6
72	Valproic Acid	600	92.7	93.0

#	Compound	Concentration Tested	Percentage Recovery	
			Oxcarbazepine metabolite (3 g/mL)	Oxcarbazepine metabolite (30 g/mL)
73	Vancomycin	250	101.3	92.6
74	Vigabatrin	150	103.2	96.9
75	Zonisamide	400	92.1	91.4

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison studies were performed according to the CLSI EP09-A3. One-hundred-Ninety (190) individual human serum samples ranging in concentration from 1.7 g/mL to 36.4 g/mL were measured using the ARK Oxcarbazepine Metabolite Assay and compared to the results obtained using LC-MS/MS. Results of the Passing Bablock regression analysis are presented below.

Analyzer	Slope (95% CI)	Intercept (95% CI)	N	R^2 (95% CI)	Sample Range Tested
AU480	1.01 (0.96 to 1.04)	-0.38 (-0.84 to 0.12)	190	0.95 (0.94 to 0.97)	1.7-36.4 g/mL

b. Matrix comparison:

Not applicable.

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):

Not applicable

4. Clinical cut-off**:**

Not applicable

5. Expected values/Reference range:

The package insert includes the following statement:

"A reference range for TDM of Oxcarbazepine Metabolite (MHD) has not been well established. A wide range of MHD serum concentrations (3-35 µg/mL) have been observed (established by reference methods) in most patients treated with therapeutic doses of oxcarbazepine[1,2,3]."

[1.] Flesch, G. 2004. Overview of the clinical pharmacokinetics of oxcarbazepine. Clin Drug Invest 24:185-203.

[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.] Borusiak, P. et al. 1998. Oxcarbazepine in treatment of childhood epilepsy: A survey of 46 children and adolescents. J Epilepsy 11:355-360.

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.