ARK Diagnostics, Inc.

ARK™ *Oxcarbazepine Metabolite Assay*

This ARK Diagnostics, Inc. package insert for the ARK Oxcarbazepine Metabolite Assay must be read carefully prior to use. Package insert instructions must be followed accordingly. Reliability of the assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.

CUSTOMER SERVICE

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KEY TO SYMBOLS USED

LOT	Batch code	YYYY-MM-DD	Use by/Expiration date
REF	Catalog Number		Manufacturer
EC REP	Authorized Representative	CE	CE Mark
IVD	In Vitro Diagnostic Medical Device		Temperature limitation
	Consult Instructions for Use	R1 R2	Reagent 1/ Reagent 2
Rx Only	For Prescription Use Only		

1 NAME

ARK™ *Oxcarbazepine Metabolite Assay*

2 INTENDED 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.

Caution: Federal Law restricts this device to sale by or on the order of a licensed practitioner.

3 SUMMARY AND EXPLANATION OF THE TEST

Oxcarbazepine [10, 11-dihydro-10-oxo-5H-dibenzo[b,f]azepine-5-carboxamide] and eslicarbazapine acetate [(S)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine- 5-carboxamide] are prodrugs that are metabolized to an active metabolite (10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide). Oxcarbazepine Metabolite is often called 10-monohydroxy derivative (MHD) or referred to as licarbazepine. Oxcarbazepine (Trileptal, Novartis)[1] is metabolized to two enantiomers (S)-MHD and (R)-MHD at a metabolite ratio of approximately 4:1, respectively[2].

Eslicarbazepine acetate (Aptiom, Sunovion Pharmaceuticals)[3] is prescribed as adjunctive therapy for partial-onset seizures associated with epilepsy in adults. Metabolism of eslicarbazepine acetate to (S)-MHD is favored such that the metabolite ratio of (S)-MHD to (R)-MHD is approximately 19:1.

4 PRINCIPLES OF THE PROCEDURE

ARK Oxcarbazepine Metabolite Assay is a homogeneous enzyme 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.

5 REAGENTS

REF	Product Description	Quantity/Volume
5032-0001-00	**ARK Oxcarbazepine Metabolite Assay** **Reagent R1 – Antibody/Substrate** Rabbit polyclonal antibodies to Oxcarbazepine Metabolite, glucose-6-phosphate, nicotinamide adenine dinucleotide, bovine serum albumin, sodium azide and stabilizers	1 X 28 mL
	Reagent R2 – Enzyme Oxcarbazepine Metabolite labeled with bacterial G6PDH, buffer, bovine serum albumin, sodium azide and stabilizers	1 X 14 mL

Reagent Handling and Storage

ARK Oxcarbazepine Metabolite Assay reagents are provided liquid, ready to use and may be used directly from the refrigerator. When not in use, reagents must be stored at 2–8°C (36–46°F), upright and with screw caps tightly closed. If stored as directed, reagents are stable until the expiration date printed on the label. Do not freeze reagents. Avoid prolonged exposure to temperatures above 32°C (90°F). **Improper storage of reagents can affect assay performance.**

ARK Oxcarbazepine Metabolite products contain ≤0.09% sodium azide. As a precaution, affected plumbing including instrumentation should be flushed adequately with water to mitigate the potential accumulation of explosive metal azides. No special handling is required regarding other assay components.

6 WARNINGS AND PRECAUTIONS

- For In Vitro Diagnostic Use. For prescription use only.
- Reagents R1 and R2 are provided as a matched set and should not be interchanged with reagents from different lot numbers.
- Reagents contain ≤0.09% sodium azide.

7 SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

- Serum is required. A steady state, trough (pre-dose) sample is generally accepted as most consistent for therapeutic drug monitoring (TDM). Time of blood draw since last dose should be noted.

- Blood collection must be performed with collection tubes compatible for use with therapeutic drug monitoring (TDM).
- Do not induce foaming and avoid repeated freezing and thawing to preserve the integrity of the specimen from the time it is collected until the time it is assayed.
- Fibrin, red blood cells, and other particulate matter may cause an erroneous result. Ensure adequate centrifugation.
- Clarified specimens 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 (≤ -20°C) up to four weeks prior to being tested. Care should be taken to limit the number of freeze-thaw cycles.
- **Handle all patient specimens as if they were potentially infectious**.

8 PROCEDURE

Materials Provided

ARK Oxcarbazepine Metabolite Assay – REF 5032-0001-00

Materials Required – Provided Separately

ARK Oxcarbazepine Metabolite Calibrator – REF 5032-0002-00
Quality Controls – ARK Oxcarbazepine Metabolite Control – REF 5032-0003-00

Instruments

Reagents R1 and R2 may need to be transferred to analyzer-specific reagent containers prior to use. Avoid cross-contamination of R1 and R2 .

Assay Sequence

To run or calibrate the assay, see the instrument-specific operator's manual.

Calibration

Perform a full calibration (6-point) procedure using the ARK Oxcarbazepine Metabolite Calibrators A, B, C, D, E, and F; test calibrators in duplicate. Verify the calibration curve with at least two levels of quality controls according to the established laboratory quality assurance plan. CAL A is the calibration blank.

Recalibrate whenever a new lot of reagents is used or as indicated by quality control results (See Quality Control below). Acceptable quality control results are needed to validate a new calibration curve. If a new set of reagents with the same lot number is used, validate the system by assaying controls.

A stored calibration curve was effective up to 15 days based on supporting data.

Quality Control (QC)

Laboratories should establish QC procedures for the ARK Oxcarbazepine Metabolite Assay. All quality control requirements and testing should be performed in conformance with local, state and/or federal regulations or accreditation requirements. Ensure that the quality control results meet the acceptance criteria before reporting patient results.

Good laboratory practice suggests that at least two levels (low and high medical decision points) of quality control be tested each day patient samples are assayed and each time a calibration is performed. Monitor the control values for any trends or shifts. If any trends or shifts are detected, or if the control does not recover within the specified range, review all operating parameters according to your clinical laboratory quality procedures. Contact Customer Service for further assistance.

Manual Dilution Protocol

To estimate drug levels in specimens exceeding the upper limit of quantitation, manually dilute the specimen with zero calibrator (CAL A) to achieve a concentration within the measurement range. Multiply the assayed result by the dilution factor.

$$\text{Manual Dilution Factor} = \frac{\text{(Specimen Volume + Volume of CAL A)}}{\text{Specimen Volume}}$$

9 RESULTS

Report result units as µg/mL or µmol/L. To convert results from µg/mL to µmol/L Oxcarbazepine Metabolite, multiply µg/mL by 3.933. The Oxcarbazepine Metabolite value from this assay should be used in conjunction with other clinical information. Refer to the instrument specific operator's manual for any result error codes.

A wide range of MHD serum concentrations (3-35 µg/mL) have been observed in most patients treated with therapeutic doses of oxcarbazepine[7,8]. The reference range of drug concentrations which is quoted should only imply a lower limit below which a therapeutic response is relatively unlikely to occur, and an upper limit above which toxicity is relatively likely to occur in the specific patient populations studied. **Refer to Expected Values.**

10 LIMITATIONS OF PROCEDURE

This assay is designed for use with serum; refer to the section **Specimen Collection and Preparation for Analysis**. It is generally good practice to use the same method (as well as matrix) consistently for individual patient care due to the potential for method-to-method variabilities. See the section **Expected Values** below.

Patient sera from patients treated with eslicarbazepine acetate were not evaluated. A range of ratios for the enantiomers (S)-MHD to (R)-MHD was studied by the ARK Oxcarbazepine Metabolite Assay. Individual patient sera from patients treated with oxcarbazepine may contain a metabolite S:R ratio of 4:1, while sera from patients treated with eslicarbazepine acetate may contain a metabolite S:R ratio of 19:1.

Eslicarbazepine acetate and carbamazepine were observed to cross react (see Performance Characteristics - Specificity). Transitioning of treatment[4,5] from carbamazepine or eslicarbazepine acetate to oxcarbazepine (or vice versa) may lead to falsely elevated or low results.

See the section on **Performance Characteristics - Specificity**. Secondary metabolites include the glucuronide of MHD and the dihydroxy-derivative of oxcarbazepine DHD. Levels of MHD-Glucuronide and DHD may increase during renal impairment and may cause falsely elevated results or interference. See the section on **Expected Values**.

Structural similarity of Oxcarbazepine Metabolite with related antiepileptic drugs explains crossreactivity. The parent drug oxcarbazepine is crossreactive, but is not expected to reach clinically significant levels. The concentration of oxcarbazepine in serum may vary according to individual pharmacokinetic behavior of each patient and time of blood collection. Trough levels of the parent drug are usually <1 µg/mL[2]. Time of blood collection relative to the previous dose should be monitored. A trough sample prior to the next morning dose is recommended.

11 EXPECTED VALUES

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[6,7,8]. Higher levels have been reported for pediatric patients (15-55 µg/mL)[9]. Adverse effects being more commonly observed at concentrations exceeding 30 µg/mL[10]. Changes that might alter MHD clearance including pregnancy[11], concomitant use of liver enzyme inducing drugs, or renal insufficiency may justify TDM. Drug-drug interactions should be considered including those with oral contraceptives[12,13]. Acute overdoses have been observed with MHD reaching approximately 60 µg/mL[14,15]. Serum concentrations of parent drug and secondary metabolites may also be elevated in the case of overdose or renal impairment[16].

Other clinical information should be considered. The reference range of drug concentrations which is quoted should only imply a lower limit below which a therapeutic response is relatively unlikely to occur, and an upper limit above which toxicity is relatively likely to occur in the specific patient populations studied. 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. Sampling time should be standardized such that trough serum concentrations are measured just before the next dosage, preferably in the morning.

12 SPECIFIC PERFORMANCE CHARACTERISTICS

Each laboratory is responsible for verification of performance using instrument parameters established for their analyzer. The following performance characteristics were obtained on the Beckman Coulter AU480® automated clinical chemistry analyzer. Unless otherwise stated, a metabolite S:R ratio of 9:1 was used to evaluate performance.

Sensitivity

Limit of Quantitation (LOQ)

The LOQ of the ARK Oxcarbazepine Metabolite Assay was determined according to CLSI EP17-A2 and is defined as the lowest concentration for which acceptable inter-assay precision and recovery is observed (≤20% CV with ±15% recovery). The LOQ was determined to be 1.0 µg/mL, and may depend on analyzer-specific performance.

Measurement Range

The measurement range of the ARK Oxcarbazepine Metabolite Assay is 1.0 to 37.0 µg/mL based on clinical concentrations tested. Report results below this range as <1.0 µg/mL or below the analyzer-specific lower LOQ established in your laboratory. Report results above this range as >37.0 µg/mL or test a diluted specimen having a concentration within the measurement range.

Recovery

Analytical recovery throughout the measurement range was assessed by adding concentrated Oxcarbazepine Metabolite into human serum negative for Oxcarbazepine Metabolite. The S:R ratio of each enantiomer was varied. The mean of six (6) replicate measurements of Oxcarbazepine Metabolite was tabulated as a function of the enantiomer ratio.

Theoretical Concentration (µg/mL)	Mean Recovered Concentration (µg/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

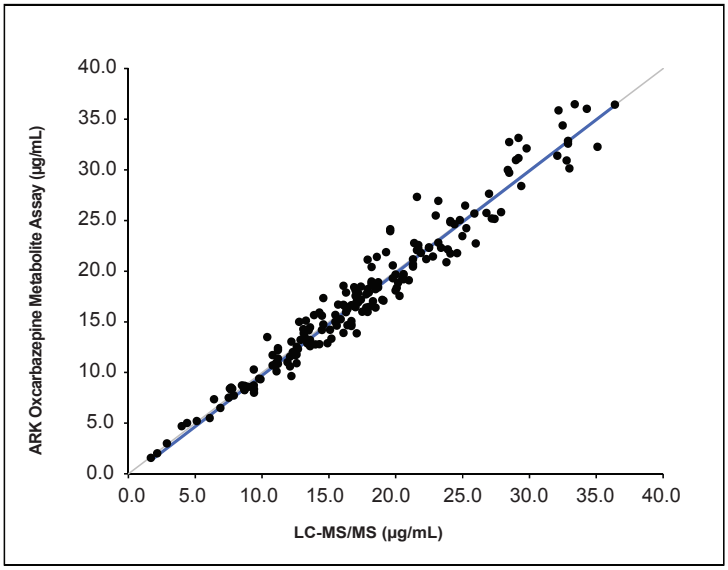
Linearity

Linearity studies were performed as suggested in CLSI/NCCLS Protocol EP6-A. A 60.0 µg/mL serum sample was prepared and dilutions were made proportionally with human serum negative for Oxcarbazepine Metabolite. Oxcarbazepine Metabolite concentrations ranged from 1.0 to 50.0 µg/mL. Linearity at specific dilutions was considered acceptable if the percent difference was ±10% between the predicted 1st and 2nd order regressed values or ≤ 0.20 µg/mL below 2.0 µg/mL. A linear relationship was demonstrated between 1.0 and 50.0 µg/mL (y = 1.0388x – 0.0693). Results are shown below.

Estimated Value (µg/mL)	Results (µg/mL)	1st Order Predicted Results (µg/mL)	2nd Order Predicted Results (µg/mL)	Difference
1.00	1.00	0.97	1.11	0.14 µg/mL
3.00	3.19	3.05	3.11	2.2 %
5.00	5.14	5.12	5.12	0.0 %
10.00	10.26	10.32	10.18	-1.3 %
20.00	21.01	20.71	20.41	-1.4 %
30.00	29.88	31.09	30.80	-0.9 %
40.00	41.92	41.48	41.36	-0.3 %
50.00	52.13	51.87	52.07	0.4 %

Method Comparison

Correlation studies were performed using CLSI Protocol EP9-A3. Results from the ARK Oxcarbazepine Metabolite Assay were compared with results from LC-MS/MS. The Oxcarbazepine Metabolite concentrations ranged from 1.7 µg/mL to 36.4 µg/mL. Results of the Passing-Bablok[17] regression analysis for the study are shown below (with 95% confidence limits).



Slope	1.01 (0.98 to 1.04)
y-intercept	-0.38 (- 0.84 to 0.12)
Correlation Coefficient (r^2)	0.95 (0.94 to 0.97)
Number of Samples	190

Precision

Precision was determined as described in CLSI Protocol EP5-A3. Tri-level controls and three human serum pooled specimens containing Oxcarbazepine Metabolite were used in the study. Each level was assayed in quadruplicate twice a day for 20 days. Each of the runs per day was separated by at least two hours. The within-run, between-day, total SD, and percent CVs were calculated. Acceptance criterion: ≤10% CV.

Sample	N	Mean (µg/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

Interfering Substances

Interference studies were conducted using CLSI/NCCLS Protocol EP7-A2 as a guideline. Clinically high concentrations of the following potentially interfering substances in serum with known levels of Oxcarbazepine Metabolite (approximately 3 and 30 µg/mL) were evaluated. Each sample was assayed using the ARK Oxcarbazepine Metabolite Assay, along with a serum control of Oxcarbazepine Metabolite. Measurement of Oxcarbazepine Metabolite resulted in ≤10% error in the presence of interfering substances at the levels tested.

Interfering Substance	Interferent Concentration	Percentage Recovery	
		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	93.1	93.1
Hemoglobin	1000 mg/dL	105.7	100.7
Rheumatoid Factor	1000 IU/mL	101.0	103.9
Triglycerides	1000 mg/dL	96.6	94.3
Uric Acid	30 mg/dL	107.5	95.5

Specificity

MHD-Glucuronide and Dihydro-dihydroxy-carbamazepine (synonymous with dihydroxy-derivative of oxcarbazepine or DHD) are secondary metabolites of Oxcarbazepine Metabolite (MHD). Oxcarbazepine and Eslicarbazepine acetate are parent drugs for MHD. Carbamazepine and its metabolites (Dihydro–carbamazepine and Carbamazepine-epoxide) are compounds structurally similar to MHD. All were tested for crossreactivity at the concentrations listed in the presence of MHD (20 µg/mL) in serum. MHD-Glucuronide levels may appear in serum greater than MHD in cases of renal impairment[16]. MHD-Glucuronide and DHD levels are not crossreactive.

The parent drug oxcarbazepine crossreacted 22.2% (as did Eslicarbazepine Acetate), although neither Oxcarbazepine nor Eslicarbazepine Acetate are expected to be present with MHD at a significant level due to rapid renal clearance. Carbamazepine and its metabolites also crossreacted in the assay; the possibility of co-therapy or transition of therapy should be considered.

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

Drug Interference

Other anti-epileptic or coadministered drugs tested did not crossreact with Oxcarbazepine Metabolite-selective antibody. A high concentration of each compound was spiked into normal human serum with known levels of Oxcarbazepine Metabolite (approximately 3 and 30 µg/mL) and assayed along with a serum control of Oxcarbazepine Metabolite. Measurement of Oxcarbazepine Metabolite resulted in ≤10% error in the presence of drug compounds at the levels tested.

		Percentage Recovery	
Compound	**Level Tested (µg/mL)**	**3 µg/mL Oxcarbazepine Metabolite**	**30 µg/mL Oxcarbazepine Metabolite**
Acetaminophen	200	95.6	97.1
Acetazolamide	100	99.9	90.3
Acetylsalicylic acid	1000	95.1	96.0
Amikacin	100	91.7	92.3
Amitriptyline	10	105.1	101.1
Amoxapine	10	99.3	98.0
Amphotericin B	100	93.6	93.2
Ampicillin	100	96.5	100.2
Ascorbic acid	100	92.8	91.1
Baclofen	100	91.1	93.7
Buproprion	10	109.6	98.8
Caffeine	100	98.3	91.7
Chloramphenicol	250	94.0	90.3
Chlorpromazine	10	98.3	99.7
Citalopram	10	102.9	99.3
Clobazam	100	98.3	103.2
Clonazepam	10	104.6	99.2
Cyclosporin A	40	91.2	90.2
Diazepam	20	103.1	100.3
Digoxin	10	97.3	97.0
Doxepin	10	107.4	102.9
Erythromycin	200	94.5	94.7
Ethanol	4000 (0.4%)	91.6	100.7
Ethotoin	100	98.4	96.2
Ethosuximide	250	103.2	104.9
Felbamate	250	93.0	93.8
Fluoxetine	20	98.1	99.2
Furosemide	100	95.2	93.1
Gentamicin	100	95.8	91.5
Haloperidol	10	101.2	97.3
Ibuprofen	500	103.3	91.8
Imipramine	10	109.4	100.4
Kanamycin A	200	93.8	109.0
Gabapentin	200	92.2	104.3
Lamotrigine	400	91.5	97.9
Levetiracetam	400	97.7	94.7
Lidocaine	100	96.8	97.7
Lincomycin	1000	90.7	100.4
Mephenytoin	100	100.7	97.3
Mesoridazine	10	97.8	99.3
Methicillin	250	93.5	96.2
Naproxen	600	102.2	95.7
Neomycin	1000	95.6	102.9
Niacin	100	93.0	93.9
Nitrazepam	20	106.3	98.5
Nortriptyline	10	104.6	102.0
Olanzapine	10	105.8	100.5
Paroxetine	10	96.7	98.3
2-phenyl-2-ethyl-malonamide (PEMA)	1000	94.6	93.9
Penicillin V	100	95.4	93.8
Perphenazine	50	105.2	100.9
Phenobarbital	200	90.2	94.5
Phenytoin	200	100.1	99.6
Pregabalin	200	91.5	90.2
Primidone	100	95.0	92.4
Procainamide	100	93.3	92.4
Prochloroperazine	10	105.2	101.6
Ranitidine	100	102.1	100.6
Rifampin	100	93.3	92.7
Risperidone	10	100.6	97.7
Sertraline	100	98.9	93.4
Spectinomycin	100	97.2	97.9
Stiripentol	100	93.8	99.7
Sulfamethoxazole	400	98.4	97.5
Theophylline	200	100.5	100.8
Thioridazine	10	103.9	98.0
Tobramycin	100	94.5	101.3
Tiagabine	200	92.1	93.5
Topiramate	250	92.8	91.7
Trimethoprim	40	101.2	93.6
Valproic Acid	600	92.7	93.0
Vancomycin	250	101.3	92.6
Vigabatrin	150	103.2	96.9
Zonisamide	400	92.1	91.4

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14 TRADEMARKS

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