ARK Diagnostics, Inc.

ARK™ *Lamotrigine Assay*

This ARK Diagnostics, Inc. package insert for the ARK Lamotrigine 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 SER-

ARK Diagnostics, Inc.
48089 Fremont Blvd
Fremont, CA 94538 USA
Tel: 1-877-869-2320
Fax: 1-510-270-6298
customersupport@ark-tdm.com
www.ark-tdm.com

CE EC REP
Emergo Europe
Molenstraat 15
2513 BH The Hague
The Netherlands
Tel: (31) (0) 70 345-8570
Fax: (31) (0) 70 346-7299

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

1 NAME

ARK™ *Lamotrigine Assay*

2 INTENDED USE

The ARK Lamotrigine Assay is a homogeneous enzyme immunoassay intended for the quantitative determination of lamotrigine in human serum or plasma on automated clinical chemistry analyzers. Lamotrigine concentrations can be used as an aid in management of patients treated with lamotrigine.

3 SUMMARY AND EXPLANATION OF THE TEST

Lamotrigine (LAMICTAL®, 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine) is an anti-convulsant drug approved for use in the treatment of epilepsy and is often prescribed as monotherapy or as one component of a multiple anti-epileptic drug therapy. [1]

4 PRINCIPLES OF THE PROCEDURE

ARK Lamotrigine Assay is a homogeneous immunoassay based on competition between drug in the specimen and lamotrigine 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 coenzyme NAD functions only with the bacterial enzyme used in the assay.

5 REAGENT

REF	Product Description	Quantity/Volume
5023-0001-00	**ARK Lamotrigine Assay** **Reagent R1 – Antibody/Substrate** rabbit polyclonal antibodies to lamotrigine, glucose-6-phosphate, nicotinamide adenine dinucleotide, bovine serum albumin, preservatives, and stabilizers	1 X 28 mL
	Reagent R2 – Enzyme Lamotrigine labeled with bacterial G6PDH, buffer, bovine serum albumin, preservatives, and stabilizers	1 X 14 mL

Reagent Handling and Storage

ARK Lamotrigine 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.**

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.

7 SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

- Serum or plasma is required. For consistency, using the same specimen matrix for individual patients is a good practice. A steady state, trough (pre-dose) sample is generally accepted as most consistent for therapeutic drug monitoring of lamotrigine. Time of blood draw since last dose should be noted.
- Whole blood cannot be used. The following anticoagulants may be used with this assay.
  - Sodium heparin
  - Lithium heparin
  - Potassium EDTA
- DO NOT USE GEL SEPARATORS. 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 may be stored frozen (≤ -10°C) up to four weeks prior to being tested (acceptance criterion ± 10%). Care should be taken to limit the number of freeze-thaw cycles. Specimens were shown to withstand 3 freeze-thaw cycles when stored at -20°C.
- **Handle all patient specimens as if they were potentially infectious.**

8 PROCEDURE

Materials Provided

ARK Lamotrigine Assay – REF 5023-0001-00

Materials Required – Provided Separately
ARK Lamotrigine Calibrator – REF 5023-0002-00
Quality Controls – ARK Lamotrigine Control – REF 5023-0003-00

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 Lamotrigine Calibrators A, B, C, D, E, and F; test calibrators in duplicate. Calibration is required with each new reagent kit lot number. 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.

When to Re-Calibrate
- Whenever a new lot number of reagents is used
- Whenever indicated by quality control results
- Whenever required by standard laboratory protocols

Quality Control (QC)
Laboratories should establish QC procedures for the ARK Lamotrigine Assay. All quality control requirements and testing should be performed in conformance with local, state and/or federal regulations or accreditation requirements.

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). Multiply the assayed result by the dilution factor. A four-fold dilution factor is suggested.

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

9 RESULTS

Report result units as µg/mL or µmol/L. To convert results from µg/mL lamotrigine to µmol/L lamotrigine, multiply µg/mL by 3.90. The lamotrigine 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.

10 LIMITATIONS OF PROCEDURE

This assay is designed for use with serum or plasma only; refer to the sections **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.

11 EXPECTED VALUES

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.

A therapeutic range for lamotrigine has not been well established. Some reports in the literature suggest a target range for steady-state concentrations of 3 to 15 µg/mL.[2-5] However, there is not a clear relationship between lamotrigine serum concentrations and clinical response.[2-5] Due to individual patient differences and other co-administered medications, considerable overlap in lamotrigine concentrations has been observed between serum responders and non-responders as well as between serum levels associated with seizure control and adverse effects.[1-14] In one study, the highest mean serum level (trough) reported was 8.8 µg/mL, and less than 15% of patients reported an adverse event at serum concentrations less than 10 µg/mL.[15] Mild to moderate adverse effects are more commonly associated with patients with lamotrigine concentrations above 15 µg/mL.[2,5,14]

Co-medications affect clearance of lamotrigine with enzyme-inducers increasing and valproic acid decreasing clearance.[16] Lamotrigine clearance is higher in children than in adults[17,18] and moderately reduced in the elderly.[18] Clearance may be increased during pregnancy,[19-22] but such increase is attenuated in women co-medicated with valproic acid.[20] Acute overdoses associated with serum levels above 40 µg/mL (156 µmol/L) have been reported.[23,24]

Lamotrigine 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 initiation and dosage adjustments. Multiple measurements of lamotrigine may be needed.

12 SPECIFIC PERFORMANCE CHARACTERISTICS

The following performance characteristics were obtained on the Roche/Hitachi 917 System. Each laboratory is responsible for verification of performance using instrument parameters established for their analyzer.

Sensitivity
Limit of Quantitation (LOQ)

The LOQ of the ARK Lamotrigine Assay was determined according to CLSI EP17-A 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 0.85 µg/mL, and may depend on analyzer-specific performance.

Assay Range
The range of the assay is 0.85 to 40.00 µg/mL. Report results below this range as <0.85 µg/mL or below the analyzer-specific lower LOQ established in your laboratory. Report results above this range as >40.00 µg/mL or above the analyzer-specific upper LOQ established in your laboratory.

Recovery
Accuracy (analytical recovery) was performed by adding concentrated lamotrigine drug into human serum negative for lamotrigine. A stock concentrate of highly pure lamotrigine was added volumetrically to human serum negative for lamotrigine, representing drug concentrations across the assay range. Six replicates of each sample were assayed on an automated clinical chemistry analyzer. The results were averaged and compared to the target concentration and percent recovery calculated. Results are shown below.

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

Theoretical Concentration (µg/mL)	Mean Recovered Concentration (µg/mL)	Percent Recovery
0.85	0.84	98.2
1.00	0.99	99.2
2.50	2.48	99.3
5.00	5.25	105.1
11.00	10.97	99.7
15.00	14.80	98.7
30.00	29.16	97.2
40.00	38.33	95.8

Mean percent recovery: 99.2

Linearity
Linearity studies were performed as suggested in CLSI/NCCLS Protocol EP6-A. A 48.00 µg/mL serum sample was prepared and dilutions were made proportionally with human serum negative for lamotrigine. Lamotrigine concentrations ranged from 1.00 to 48.00 µg/mL. Linearity at specific dilutions was considered acceptable if the percent difference was ±10% between the predicted 1st and 2nd order regressed values. Results are shown below.

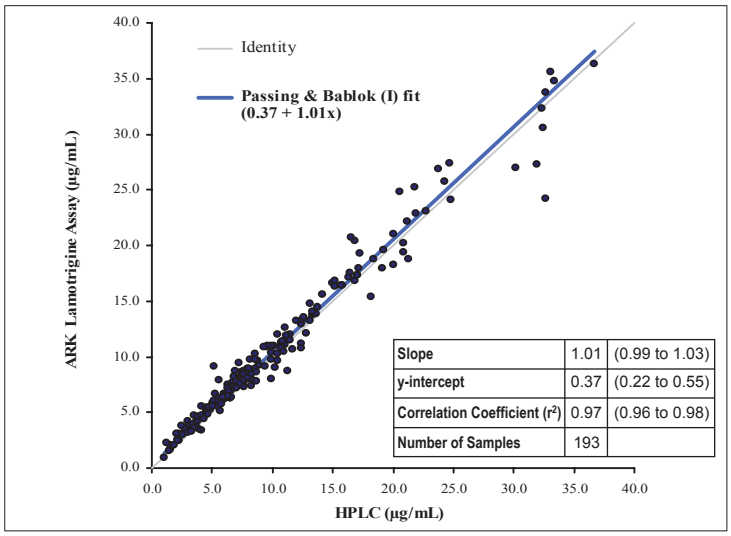
Estimated Value (µg/mL)	Results (µg/mL)	1st Order Predicted Results	2nd Order Predicted Results	% Difference
1.00	0.96	1.13	1.21	7.1
2.00	2.08	2.11	2.17	3.1
4.00	4.16	4.06	4.10	0.9
8.00	8.18	7.97	7.96	-0.1
12.00	12.01	11.88	11.83	-0.4
16.00	16.18	15.78	15.72	-0.4
24.00	22.78	23.60	23.53	-0.3
32.00	30.84	31.41	31.39	-0.1
40.00	40.13	39.23	39.30	0.2
48.00*	46.88	47.04	47.27	0.5

*Concentration exceeds the reportable limit.

Method Comparison
Correlation studies were performed using CLSI/NCCLS Protocol EP9-A2. Results from the ARK Lamotrigine Assay were compared with results from high performance liquid chromatography (HPLC, Study 1) and a turbidimetric immunoassay (Study 2).

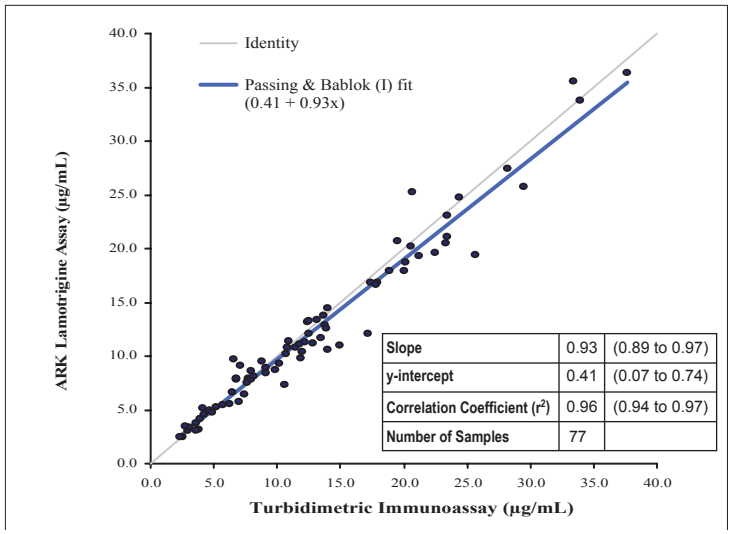
Study 1

Lamotrigine concentrations by HPLC ranged 1.00 to 36.70 µg/mL. ARK lamotrigine values ranged 0.97 to 36.32 µg/mL. Results of the Passing-Bablok[25] regression analysis for the study are shown below (with 95% confidence limits).



Study 2

Lamotrigine concentrations by the turbidimetric immunoassay ranged from 2.28 µg/mL to 37.70 µg/mL. ARK lamotrigine values ranged 2.51 to 36.32 µg/mL. Results of the Passing-Bablok[25] regression analysis for the study are shown below (with 95% confidence limits).



Precision

Precision was determined as described in CLSI/NCCLS Protocol EP5-A2. Tri-level controls and three human serum pooled specimens containing lamotrigine 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. Results are shown below. Acceptance criteria: ≤10% total CV.

Sample	N	Mean (µg/mL)	Within Run SD	Within Run CV (%)	Between Day SD	Between Day CV (%)	Total SD	Total CV (%)
ARK Lamotrigine Control								
LOW	160	2.08	0.07	3.4	0.05	2.5	0.08	4.1
MID	160	11.70	0.42	3.6	0.28	2.4	0.49	4.2
HIGH	160	24.23	0.99	4.1	1.06	4.4	1.47	6.1
Calibrator/Control Matrix	40	38.04	2.05	5.4	0.95	2.5	2.27	6.0
Human Serum								
LOW	160	2.41	0.08	3.5	0.09	3.7	0.12	5.2
MID	160	10.75	0.41	3.8	0.42	3.9	0.59	5.5
HIGH	160	25.84	1.33	5.2	1.12	4.3	1.88	7.3
Pooled Human Serum	40	38.24	2.78	7.3	0.61	1.6	3.38	8.8

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 lamotrigine (approximately 3 and 15 µg/mL) were evaluated. Each sample was assayed using the ARK Lamotrigine Assay, along with a serum control of lamotrigine. Measurement of lamotrigine resulted in ≤10% error in the presence of interfering substances at the levels tested.

		Percentage Recovery	
Interfering Substance	Interferent Concentration	3 µg/mL Lamotrigine	15 µg/mL Lamotrigine
Albumin	12g/dL	101.5	103.4
Bilirubin - conjugated	70 mg/dL	93.6	102.6
Bilirubin - unconjugated	70 mg/dL	97.1	105.0
Cholesterol	623 mg/dL	98.9	103.8
Gamma-Globulin	12g/dL	106.8	104.4
Hemoglobin	1000 mg/dL	98.2	97.0
Intralipid®	1000 mg/dL	94.5	94.3
Rheumatoid Factor	1100 IU/mL	107.3	108.9
Triglycerides	618mg/dL	101.7	104.0
Uric Acid	30 mg/dL	101.0	99.6

Specificity

Lamotrigine's major metabolite, medications that may be routinely co-administered with lamotrigine and other anti-epileptic drugs were tested to determine whether these compounds affect the quantitation of lamotrigine concentrations using the ARK Lamotrigine Assay. High levels of these compounds were spiked into serum pools containing low (3 µg/mL) and high (15 µg/mL) therapeutic levels of lamotrigine. The samples were analyzed and the lamotrigine concentrations of samples containing interferent were compared to the serum control.

Metabolites

Lamotrigine is metabolized predominantly by UDP-glucuronyltransferase to form a pharmacologically inactive metabolite, 2-N-glucuronide.[26-28] Lamotrigine-2-N-methyl has been detected in human plasma by HPLC and capillary electrophoresis.[27,28] Other minor metabolites, lamotrigine-2-N-oxide, and lamotrigine-5-N-glucuronide have been proposed.[26] Lamotrigine-2-N-glucuronide, Lamotrigine-2-N-methyl and Lamotrigine-2-N-oxide metabolites were tested for cross-reactivity. These metabolites were spiked into two separate samples each containing low and high lamotrigine concentrations of 3 and 15 µg/mL, respectively.

Metabolite*	Metabolite Concentration (µg/mL)	Percentage Cross-Reactivity Lamotrigine (3 µg/mL)	Percentage Cross-Reactivity Lamotrigine (15 µg/mL)
Lamotrigine-2-N-glucuronide	50.0	2.41	1.86
	25.0	2.57	1.09
	12.5	2.91	1.92
	9.0	2.15	1.57
Lamotrigine-2-N-methyl	400.0	0.04	0.21
	200.0	0.07	0.02
	80.0	0.10	0.24
Lamotrigine-2-N-oxide	80.0	3.69	3.63
	40.0	3.94	3.64
	20.0	3.72	3.14
	10.0	3.88	1.30

* The literature suggests there is weak evidence for the presence of minor metabolites in human plasma.[25]

Drug that Cross-Reacts

Cross-reactivity of the antibody to trimethoprim at the following concentration was tested. A high concentration was spiked into normal human serum with known levels of lamotrigine (approximately 3 and 15 µg/mL) and assayed along with a serum control of lamotrigine. The results are shown below.

Trimethoprim (µg/mL)	Percent Cross-Reactivity		Percent Recovery	
	Lamotrigine (3 µg/mL)	Lamotrigine (15 µg/mL)	Lamotrigine (3 µg/mL)	Lamotrigine (15 µg/mL)
40.0	4.4	3.0	156.0	108.0

Care should be taken when interpreting ARK Lamotrigine results if trimethoprim is also being administered to the patient.

Drug Interference

Lamotrigine-selective antibody did not crossreact with most other anti-epileptic or coadministered drugs tested. Due to structural similarities with lamotrigine, high trimethoprim levels may interfere. A high concentration of each compound was spiked into normal human serum with known levels of lamotrigine (approximately 3 and 15 µg/mL) and assayed along with a serum control of lamotrigine. Measurement of lamotrigine resulted in ≤10% error in the presence of drug compounds at the levels tested.

Compound	Conc. Tested (µg/mL)	Percentage Recovery 3 µg/mL Lamotrigine	15 µg/mL Lamotrigine
Acetaminophen	200	103.7	99.1
Acetazolamide	100	101.2	99.2
Acetylsalicylic acid	1000	100.8	100.7
Amikacin	100	95.7	97.0
Amitriptyline	20	99.0	97.9
Amoxapine	40	104.7	101.2
Amphotericin B	100	94.0	91.6
Ampicillin	100	97.7	94.1
Ascorbic Acid	100	98.5	94.4
Baclofen	100	95.8	90.9
Buproprion	40	98.8	106.2
Caffeine	100	101.3	103.2
Carbamazepine	120	104.3	103.2
Carbamazepine-10, 11 epoxide	120	101.7	99.0
10-Hydroxy carbamazepine	100	96.2	94.3
Chloramphenicol	250	103.7	98.4
Chlorpromazine	20	97.2	95.0
Citalopram	20	98.0	97.5
Clobazam	100	103.4	105.6
Clonazepam	20	97.6	96.4
Cyclosporin A	40	101.7	99.4
Diazepam	20	101.1	97.7
Digoxin	80	103.4	97.6
Doxepin	20	101.6	103.1
Erythromycin	200	103.6	103.9
Ethanol	4000	94.0	98.2
Ethotoin	100	101.3	101.9
Ethosuximide	250	101.0	96.4
Felbamate	250	103.0	101.4
Fluoxetine	20	102.2	97.0
Furosemide	100	99.8	97.1
Gabapentin	200	103.8	98.1
Gentamicin	100	99.8	98.6
Haloperidol	20	104.1	100.3
Heparin	200 U/mL	99.0	100.5
Ibuprofen	500	101.6	96.2
Imipramine	20	99.6	97.7
Kanamycin B	200	98.5	100.5
Levetiracetam	400	103.6	101.9
Lidocaine	100	101.6	101.8
Lincomycin	1000	106.0	99.7
Mephenytoin	100	95.7	103.9
Mesoridazine	40	97.6	101.7
Methicillin	250	95.2	99.4
Naproxen	600	97.3	104.8
Neomycin	1000	100.8	101.6
Niacin	100	97.8	105.8
Nitrazepam	20	101.5	103.9
Nortriptyline	20	96.6	104.9
Olanzapine	20	99.5	102.2
Oxcarbazepine	200	97.3	100.5
Paroxetine	40	101.6	100.0
2-phenyl-ethyl-malonamide (PEMA)	1000	100.1	100.9
Penicillin V	100	100.4	101.4
Perphenazine	100	99.5	103.2
Phenobarbital	200	101.0	98.9
Phenytoin	200	100.0	100.8
Pregabalin	200	99.6	98.4
Primidone	100	98.7	102.5
Procainamide	100	100.6	101.9
Prochlorperazine	40	99.4	90.3
Ranitidine	100	104.0	97.8
Rifampin	100	101.6	97.7
Risperidone	20	98.0	100.2
Sertraline	100	101.5	101.9
Spectinomycin	100	97.7	103.1
Stiripentol	100	102.3	101.6
Sulfamethoxazole	400	99.2	99.2
Theophylline	200	98.7	97.9
Thioridazine	20	102.9	101.3
Tiagabine	200	100.9	97.8
Tobramycin	100	98.8	96.9
Topiramate	250	100.3	96.7
Valproic Acid	600	100.8	96.8
Vancomycin	250	96.5	95.0
Vigabatrin	150	97.8	101.0
Zonisamide	400	97.9	99.6

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14 TRADEMARKS

ARK Diagnostics, Inc.
Fremont, CA 94538 USA

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