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

A. 510(k) Number:
k101305

B. Purpose for Submission:
New assay, calibrator and control

C. Analyte:
Lamotrigine

D. Type of Test:
Homogeneous Enzyme Immunoassay (EIA)

E. Applicant:
ARK Diagnostics, Inc.

F. Proprietary and Established Names:
ARK™ Lamotrigine Assay, Calibrator and Control

G. Regulatory Information:

1. Regulation section:

   21 CFR 862.3350 – Diphenylhydantoin test system

   21 CFR 862.3200 – Clinical toxicology calibrator

   21 CFR 862.3280 – Clinical toxicology control material

2. Classification:

   Class II (assay), Class II (calibrator), Class I, reserved (control)

3. Product code:

   ORH (assay), DLJ (calibrator), LAS (control)

4. Panel:

   91 Toxicology

H. Intended Use:

1. Intended use(s):

   See indications for use, below.

2. Indication(s) for 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.

The ARK™ Lamotrigine Calibrator is intended for use in calibration of the ARK Lamotrigine Assay.

The ARK™ Lamotrigine Control is intended for use in quality control of the ARK Lamotrigine Assay.

3. Special conditions for use statement(s):

   This assay is designed for use with serum or plasma only. The sponsor notes in the labeling that 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 variability. Also see precautions in the Expected Range Section, below.

4. Special instrument requirements:

   The Lamotrigine assay has been validated on the Roche/Hitachi 917 analyzer.

I. Device Description:

The ARK Lamotrigine Assay consists of reagents R1 anti-lamotrigine rabbit polyclonal antibody with substrate and R2 lamotrigine labeled with bacterial G6PDH enzyme. The ARK Lamotrigine Calibrator consists of a six-level (1.0, 2.5, 5.0, 11.0, 15.0, 30.0 and 40.0 µg/mL) set to calibrate the assay, and the ARK Lamotrigine Control consists of a three-level set (2.0, 12.0 and 25.0 µg/mL) used for quality control of the assay. The ARK Lamotrigine Calibrator and the ARK Lamotrigine Control matrix are comprised of a synthetic proteinaceous matrix with buffer, bovine serum albumin and preservatives.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   QMS Lamotrigine, Calibrators and Controls

2. Predicate 510(k) number(s):
   k062966

3. Comparison with predicate:

Characteristic	**Device** ARK™ Lamotrigine Assay	**Predicate** QMS® Lamotrigine K062966
Intended Use/ Indications for Use	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.	Same
Sample	Serum or plasma	Same
Methodology	Homogenous enzyme immunoassay (EIA)	Homogeneous particle-enhanced turbidimetric immunoassay (particle agglutination)
Reagent Components	Two (2) reagent system: • Anti-Lamotrigine Antibody/Substrate Reagent (R1) containing rabbit polyclonal antibodies to lamotrigine, glucose-6-phosphate, nicotinamide adenine dinucleotide, bovine serum albumin, preservatives, & stabilizers • Enzyme Reagent (R2) containing lamotrigine labeled with bacterial G6PDH, buffer, bovine serum albumin, preservatives, and stabilizers	Two (2) reagent system: • Anti-Lamotrigine Antibody Reagent (R1) in buffers containing stabilizers with sodium azide • Lamotrigine-coated Microparticle Reagent (R2) in buffer containing stabilizers with sodium azide
Platform required	Roche/Hitachi 917 analyzer	Same
Accessory reagents	Calibrators (six levels) and controls (three levels)	Same
Testing environment	Routine clinical laboratory	Same

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

CLSI documents: "Evaluation of Precision Performance of Clinical Chemistry Devices", EP5; "Evaluation of the Linearity of Quantitative Measurement", EP6;

"Interference Testing in Clinical Chemistry", EP7; "Method Comparison and Bias Estimation Using Patient Samples", EP9, "Protocols for Determination of Limits of Detection and Limits of Quantitation", EP 17-A.

L. Test Principle:

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.

M. Performance Characteristics (if/when applicable):

Performance was validated on the Roche/Hitachi 917 clinical chemistry analyzer.

1. Analytical performance:

a. Precision

Precision was determined as described in CLSI Protocol EP5-A2. Data were collected on a Hitachi 917 analyzer over twenty (20) non-consecutive days. Multiple calibrations were performed during this interval to provide variation, although each calibration was performing in a stable manner. Three levels of both control materials and human serum samples were tested in each run. Each level was assayed in quadruplicate twice a day for 20 days. Calibrator/Control matrix and pooled human serum were also tested in quadruplicate twice a day for 5 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.

			Within Run		Between Day		Total	
Sample	**N**	**Mean (µg/mL)**	**SD**	**CV (%)**	**SD**	**CV (%)**	**SD**	**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

b. Linearity/assay reportable range:

The manufacturer's claimed assay reportable range is 0.85 to 40.0 µg/mL. The assay range was established based on the linearity, together with limit of quantitation (LOQ) and recovery/linearity studies. Method comparison evaluated specimens near the upper quantitative limit. (See respective sections below for specific information on performance).

Samples for the recovery/linearity study were prepared by gravimetric addition of lamotrigine (USP > 99.9% purity) stock solution to human serum negative for lamotrigine. Drug concentrations across the assay range (0.85, 1.0, 2.5, 5.0, 11.0, 15.0, 30.0 and 40.0 µg/mL) were tested. Each sample was assayed in triplicate in each of two separately calibrated runs for a total of six replicates. The results at each separate level were averaged and compared to the target concentration (based on spiked concentrations of USP materials) and the percentage recovery was calculated.

% Recovery = [100 X Mean recovered concentration]/Theoretical concentration

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

Regression analysis of the data yields the equation, y(observed result) = 0.96 x (target concentration) + 0.22, and regression coefficient r = 0.99.

High Sample Carryover

The impact of high lamotrigine concentration specimens on the measurement of Lamotrigine in specimens with lower concentrations (high sample carryover) was evaluated by assaying a series of high 100.0 µg/mL spiked serum sample followed by a series of low 2.0 µg/mL spiked serum sample. No carryover was observed from the High 100.0 µg/mL sample to the Low 2.0 µg/mL sample.

Manual Dilution Protocol

The manufacturer recommends that samples with concentrations exceeding 40.0 µg/mL should be diluted 4-fold with zero calibrator. Samples spiked with lamotrigine and patient samples containing lamotrigine (with initial concentrations ranging from 47.0 to 100 µg/mL) were diluted 4-fold with zero calibrator and results using the ARK method were compared to the target level (for spiked samples) and the HPLC-determined level (for neat samples). In some cases natural patient samples containing lower levels of lamotrigine were spiked to achieve higher concentrations for this evaluation. Concentrations tested ranged from 47-100 µg/mL. Recoveries versus expected values using the dilution procedure ranged from 93% to 96%.

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

Traceability and Value Assignment of Calibrators and Controls

ARK Lamotrigine Calibrators and ARK Lamotrigine Controls are prepared by gravimetric dilution of high purity lamotrigine (USP > 99.9 % purity) into a synthetic proteinaceous matrix free of lamotrigine. Each calibrator and control level is then qualified versus a master calibrator lot. Calibrator and control production lots must demonstrate comparison to the master lot within 5% at each positive calibrator and control level.

Quality control (QC) ranges were established using three runs with four replicates tested per run (n=12 for each control level) and the mean lamotrigine level of each control was calculated. Control ranges were set at ± 15% around the mean level tested. The package insert notes that each laboratory should establish its own ranges for each new lot of controls.

Specimen Stability

Stability of stored specimens (frozen storage and refrigerated exposure) and the effect of freezing/thawing on the measurement of lamotrigine by the ARK™ Lamotrigine Assay were evaluated. Clarified serum specimens were shown to be stable for at least four weeks frozen at ≤ -10 °C, and for a week when refrigerated (2-8 °C). The manufacturer's acceptance criteria for this evaluation are recovery within ±10%. No trend was observed in the stability data. The manufacturer notes that 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.

The ARK Lamotrigine Calibrator and the ARK Lamotrigine Control are comprised of a synthetic proteinaceous matrix with buffer, bovine serum albumin and preservatives. To evaluate recovery and matrix equivalence, synthetic calibrator/control matrix (Calibrator A) and pooled human serum were supplemented with lamotrigine to achieve 1.0, 2.5, 5.0, 11.0, 15.0, 30.0 and 40.0 µg/mL levels. Multiple replicates and runs were performed and the mean

recovery (of replicates) was calculated for each level and each matrix. All levels tested in the calibrator matrix recovered within 96% of the serum lamotrigine levels. Recoveries (percentage of nominal level) ranged from 96% to 104% for the calibrator/control matrix and from 96% to 105% for the serum matrix (95.8% to 105.1%).

Calibration Stability on the analyzer

ARK provided a study on calibration stability on the analyzer. This study supports the stable operation of the assay over an extended period based on one calibration. Up to 30 days of calibration curve stability and in-use stability of reagents, calibrators and controls were observed for the study as tested.

Calibrator and Control material Stability

1. The calibrators and controls are stable until the expiration date printed on the vial when stored unopened and opened at 2-8 °C.
2. Real time stability studies are ongoing for both unopened and opened calibrators and controls. Stability testing protocols and acceptance criteria were reviewed and found to be acceptable.

d. Detection Limit:

Accuracy and precision studies near the low range of the assay were conducted to determine the manufacturer's claimed lower limit of quantitation (LOQ) according to CLSI Guideline EP-17. Three levels were tested below the lowest positive calibrator concentration (1.0 µg/mL). Samples were prepared by gravimetric addition of lamotrigine (USP > 99.9% purity) to human serum negative for lamotrigine to give concentrations of 0.5, 0.75 and 0.85 µg/mL. Eight replicates of each sample were tested in each of five runs on five separate days to give a minimum of 40 replicates of each sample per reagent lot. A total of three reagent lots were used for the study. The LOQ of the ARK Lamotrigine Assay is defined as the lowest concentration for which acceptable inter-assay precision (≤ 20% CV) and recovery (± 15%) is observed. The criteria of LOQ were met at 0.85 µg/mL; the precision was 2.9 %CV and the recovery was 90.1%.

e. Analytical Specificity:

Studies included testing for interference from endogenous compounds, metabolite, and commonly co-administered and other anti-epileptic drugs.

Endogenous Interfering Substances

Serum samples with clinically high concentrations of the potential endogenous interfering substances were tested by ARK Lamotrigine assay in the presence of varying amounts of lamotrigine. Specifically, serum samples tested contained lamotrigine at concentrations of 3.0 µg/mL and 15.0 µg/mL. Each sample containing interferent was assayed, along with a serum control of lamotrigine. No significant interference (defined by the manufacturer as ≤ 10% differences

in detecting lamotrigine) was observed. Results for endogenous compounds are shown below:

Percentage Recovery			
Interfering Substance	**Interferent Concentration**	**3 µg/mL Lamotrigine**	**15 µg/mL Lamotrigine**
Albumin	12 g/dL	101.5 %	103.4 %
Bilirubin - conjugated	70 mg/dL	93.6 %	102.6 %
Bilirubin - unconjugated	70 mg/dL	97.1 %	105.0 %
Cholesterol	342 mg/dL	105.2 %	95.0 %
Gamma-Globulin	12 g/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	618 mg/dL	101.7 %	104.0 %
Uric Acid	30 mg/dL	101.0 %	99.6 %

Metabolite Interference

Lamotrigine-2-N-glucuronide, Lamotrigine-2-N-methyl and Lamotrigine-2-N-oxide 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. The samples were analyzed and the lamotrigine concentrations of samples containing interferent were compared to the serum control. Cross-reactivity to Lamotrigine-2-N-glucuronide ranged from 1.09 to 2.91%, cross-reactivity to Lamotrigine-2-N-methyl ranged from 0.02 to 0.24% and cross-reactivity to Lamotrigine-2-N-oxide ranged from 1.3 to 3.94%.

Metabolite*	Metabolite Concentration (µg/mL)	Percentage Cross-Reactivity Lamotrigine (3 µg/mL)	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	3.69 %	3.63 %
	40	3.94 %	3.64 %
	20	3.72 %	3.14 %
	10	3.88 %	1.30 %

Drugs that Cross-React - Trimethoprim

Cross-reactivity of the antibody to trimethoprim was analyzed from 5.0 to 40.0 µg/mL in the presence of either Low (3 µg/mL) or High (15 µg/mL) concentration of lamotrigine and assayed along with a serum control of lamotrigine. Interference was observed only at the low concentration of lamotrigine. Recovery of lamotrigine ranged 111.2 to 156.0% with increasing concentration of trimethoprim. The manufacturer notes in the package insert that care should be taken when interpreting ARK Lamotrigine results if trimethoprim is also being administered to the patient. 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 %
20.0	5.5 %	4.0 %	134.6 %	105.4 %
10.0	6.5 %	-0.8 %	120.9 %	99.4 %
5.0	6.9 %	8.6 %	111.2 %	103.0 %

Drug Interference

Lamotrigine-selective antibody did not cross-react with most other anti-epileptic or co-administered drugs tested. Due to structural similarities with lamotrigine, high trimethoprim levels may interfere. A high concentration of each compound shown below 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	**Concentration (µg/mL)**	**Percentage Recovery (%)**	
		Lamotrigine (3 µg/mL)	**Lamotrigine (15 µg/mL)**
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

Bupropion	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
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
Gabapentin	200	103.8	98.1
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
Tobramycin	100	98.8	96.9
Tiagabine	200	100.9	97.8
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

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison studies were performed according to CLSI Guideline EP9-A2. Banked samples from patients tested for lamotrigine concentrations were used. Inclusion criteria for the samples measured were based on lamotrigine concentration. No exclusion criteria were used for selection of specimens. The large majority of specimens were in a serum matrix. (See also matrix comparison, below.)

Results from the ARK Lamotrigine Assay were compared with results from the predicate device (QMS) at an external clinical laboratory site. Results compared to high performance liquid chromatography (HPLC) were also included. Assay descriptions and summary validation for the comparative methods were included in the 510(k).

The results are shown below:

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

		95% confidence limits
Slope	0.93	(0.89 to 0.97)
y-intercept	0.41 µg/mL	(0.07 to 0.74)
Correlation Coefficient (r^2)	0.96	(0.94 to 0.97)
Number of Samples		77

Results of the Pearson Bland Altman analysis gave a mean bias of -0.559, SE of 0.1876, and SD of difference as 1.646.

Comparison to an HPLC method
Lamotrigine concentrations by HPLC ranged 1.0 to 36.70 µg/mL. ARK lamotrigine values ranged 0.97 to 36.32 µg/mL. Results of the Passing-Bablok regression analysis for the study are shown below (with 95% confidence limits).

		95% confidence limits
Slope	1.01	(0.99 to 1.03)
y-intercept	0.37 µg/mL	(0.22 to 0.55)
Correlation Coefficient (r^2)	0.97	(0.96 to 0.98)
Number of Samples		193

Results of the Pearson Bland Altman analysis gave a mean bias of 0.42, SE of 0.0934, and SD of difference as 1.298.

b. Matrix Comparison-Serum versus Plasma:

Anticoagulated plasma and serum were evaluated to evaluate equivalency of these matrices for measurement of lamotrigine with the ARK™ Lamotrigine

Assay. Matched samples for serum and plasma from eight (8) subjects (four subjects at 35.0 µg/mL) were evaluated. Blood was collected in three different anticoagulant tubes viz. lithium heparin, potassium EDTA, sodium heparin, and a serum tube to produce a matched set. A lamotrigine stock solution was spiked in each matrix to give a lamotrigine concentration of 35.0, 30.0, 15.0, 3.0 and 0.85 µg/mL. The mean, standard deviation and %CV for six replicates were calculated for each sample. Also, correlation analysis was performed. Percentage recovery of lamotrigine in anticoagulated samples compared to the serum control was calculated for each subject. No significant differences were observed between matrices. The overall percentage of serum levels of lamotrigine in plasma ranged 92.9 to 106.3%, and the slope was 1.0, intercept was -0.02 µg/mL, and correlation was $r^2 = 1.00$.

In addition, the method comparison study (Section a, above) included five plasma samples. In general, no significant differences were observed between the results of these samples and the averaged serum samples.

3. Clinical studies:

   a. Clinical Sensitivity:

   Not applicable. Not typically submitted for this type of assay.

   b. Clinical specificity:

   Not applicable. Not typical for this type of assay.

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

   The sponsor provided a discussion with balanced and representative literature discussing clinical use of lamotrigine measurements.

4. Clinical cut-off:

   See expected values below.

5. Expected values/Reference range:

   In the labeling the manufacturer provides the following information:
   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 3.0 to 15 µg/mL. However, there is not a clear relationship between lamotrigine serum concentrations and clinical response. 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. 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 10.0 µg/mL. Mild to moderate adverse effects are more commonly associated with patients with lamotrigine concentrations above 15.0 µg/mL. Co-medications affect clearance of lamotrigine with enzyme-inducers increasing and valproic acid decreasing clearance. Lamotrigine clearance is higher in children than in adults and moderately reduced in the elderly. Clearance may be increased during pregnancy, but such increase is attenuated in women co-medicated with valproic acid. Acute overdoses associated with serum levels above 40.0 µg/mL (156 µmol/L) have been reported.

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.

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 substantial equivalence decision.