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

**A. 510(k) Number:**

k103627

**B. Purpose for Submission:**

New device

**C. Measurand:**

Carbamazepine

**D. Type of Test:**

Quantitative immunoassay

**E. Applicant:**

Abbott Laboratories

**F. Proprietary and Established Names:**

ARCHITECT iCarbamazepine reagents and calibrators

**G. Regulatory Information:**

1. Regulation section:

   21 CFR 862.3645, Neuroleptic drugs radioreceptor assay test system

   21 CFR 862.3200, Clinical toxicology calibrator

2. Classification:

   Both Class II

3. Product code:

   KLT, Enzyme Immunoassay, Carbamazepine

   DKB, Clinical Toxicology Calibrator

4. Panel:

   Toxicology (91)

## H. Intended Use:

1. Intended use(s):

   See indication(s) for use below

2. Indication(s) for use:

   Reagents: The ARCHITECT *i*Carbamazepine assay is an *in vitro* chemiluminescent microparticle immunoassay (CMIA) for the quantitative measurement of carbamazepine, an anticonvulsant drug, in human serum or plasma collected in lithium heparin, sodium heparin, dipotassium EDTA or sodium EDTA tubes on the ARCHITECT *i* System with STAT protocol capability. The measurements obtained are used in monitoring levels of carbamazepine to help ensure appropriate therapy.

   Calibrators: The ARCHITECT *i*Carbamazepine Calibrators are for the calibration of the ARCHITECT *i* System with STAT protocol capability when used for the quantitative measurement of carbamazepine, an anticonvulsant drug, in human serum or plasma.

3. Special conditions for use statement(s):

   For prescription use only

4. Special instrument requirements:

   Abbott ARCHITECT *i* $2000_{SR}$ System

## I. Device Description:

The ARCHITECT *i*Carbamazepine assay consists of the *i*Carbamazepine Reagent Kit and six calibrators A through F. Calibrators contain carbamazepine and preservatives in a human serum matrix. Other reagents such as trigger solution and wash buffer are required but not provided. All individual materials derived from human source were tested with FDA cleared/approved methods and found nonreactive for HBsAg, HIV-1 Ag or HIV-1 RNA, anti-HCV, HCV RNA, and anti-HIV-1/HIV-2.

## J. Substantial Equivalence Information:

1. Predicate device name(s):

Abbott AxSYM Carbamazepine

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

   k935374

3. Comparison with predicate:

| **Similarities** | | |
|---|---|---|
| Item | Device | Predicate |
| Indications for Use | Same | Immunoassay for the quantitative measurement of carbamazepine in human serum or plasma |
| Calibrators (µg/mL) | Same | A (0.0), B (2.0), C (4.0), D (8.0), E (12.0), F (20.0) |
| Measuring Range (µg/mL) | 2.0 – 15.0 | 0.5 – 20.0 |

| **Differences** | | |
|---|---|---|
| Item | Device | Predicate |
| Analyzer | Abbott ARCHITECT *i* System | Abbott AxSym |
| Methodology | Chemiluminescent microparticle immunoassay (CMIA) | Fluorescence Polarization Immunoassay (FPIA) |
| Detection Limit (µg/mL) | LoQ: 0.3 | 0.5 |
| Controls (µg/mL) | Not provided with the reagent kit | L (3.0), M (6.0), H (16.0) |

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

CLSI EP5-A2; Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline – Second Edition

CLSI EP6-A; Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline

CLSI EP7-A2; Interference Testing in Clinical Testing; Approved Guideline – Second Edition

CLSI EP9-A2; Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline – Second Edition

CLSI EP17-A; Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline

Points to Consider for Collection of Data in Support of In-Vitro Device Submissions for 510(k) Clearance

Format for Traditional and Abbreviated 510(k)s - Guidance for Industry and FDA Staff

**L. Test Principle:**

The ARCHITECT *i*Carbamazepine assay is a one-step immunoassay for the quantitative measurement of carbamazepine in human serum or plasma using CMIA technology, with flexible assay protocols, referred to as Chemiflex.

In the ARCHITECT *i*Carbamazepine assay, the sample, anti-carbamazepine (mouse, monoclonal) coated paramagnetic microparticles, and carbamazepine acridinium-labeled conjugate are combined to create a reaction mixture. The anti-carbamazepine coated microparticles bind to carbamazepine present in the sample and to the carbamazepine acridinium-labeled conjugate. After washing, pre-trigger and trigger solutions are added to the reaction mixture. The resulting chemiluminescent reaction is measured as relative light units (RLUs). An indirect relationship exists between the amount of carbamazepine in the sample and the RLUs detected by the ARCHITECT *i* System optics.

**M. Performance Characteristics (if/when applicable):**

1. <u>Analytical performance:</u>

   *a. Precision/Reproducibility:*

   Precision was evaluated by analyzing two control levels and two serum panels. Testing was performed on three ARCHITECT *i* 2000SR using two lots each of ARCHITECT *i*Carbamazepine Reagents and Calibrators (for a total of two reagent lot/calibrator lot combinations) and one lot of commercially available controls. A single calibration per reagent lot was performed on each instrument and used for the duration of the study. The controls and panels were tested in replicates of two, twice per day (separated by a minimum of two hours), for a total of 20 testing days. The mean concentration, within-run SD and % CV, between-run SD and % CV were calculated for the controls and panels for each reagent lot/instrument combination. The total (within-laboratory) SD and % CV were estimated using the summation of the within-run, between-run, and between-day variance components.

| | | | Within-Run | | Between-Run | | Within-Laboratory | | Overall | |
|---|---|---|---|---|---|---|---|---|---|---|
| Sample | N | Mean (µg/mL) | SD | CV% | SD | CV% | SD | CV% | SD | CV% |
| Low Control | 720 | 3.93 | 0.066 | 1.7 | 0.053 | 1.4 | 0.095 | 2.4 | 0.133 | 3.4 |
| Medium Control | 720 | 9.65 | 0.179 | 1.9 | 0.124 | 1.3 | 0.233 | 2.4 | 0.313 | 3.2 |
| Panel 2 | 720 | 2.20 | 0.046 | 2.1 | 0.033 | 1.5 | 0.063 | 2.9 | 0.094 | 4.3 |
| Panel 3 | 720 | 12.55 | 0.247 | 2.0 | 0.193 | 1.5 | 0.371 | 3.0 | 0.472 | 3.8 |

*b. Linearity/assay reportable range:*

*Linearity*

To evaluate linearity, high and low concentration carbamazepine samples were prepared and combined in a dilution series to produce 7 sample pools with an expected carbamazepine concentration between approximately 1 and 16 µg/mL. Pools were tested in replicates of four on one ARCHITECT *i* 2000SR using one lot each of ARCHITECT *i*Carbamazepine Reagents and Calibrators and one lot of commercially available controls. All samples were tested as a set within a single run.

Linear regression analysis produced the following:

| | |
|---|---|
| slope: | 0.969 |
| y-intercept | -0.21 |
| $r^2$ | 0.999 |

The sponsor claims a reportable range of 2.0 – 15.0 µg/mL, based on the linearity and LoQ data.

*Recovery*

The purpose of this study was to evaluate the ability of the ARCHITECT *i*Carbamazepine assay to recover known concentrations of carbamazepine spiked into human specimens.

Varying concentrations of carbamazepine ranging from approximately 2 to 12 µg/mL were spiked into 50 separate serum samples that did not contain carbamazepine.

Samples were tested in replicates of 4 on one ARCHITECT *i* 2000SR using one lot each of ARCHITECT *i*Carbamazepine Reagents and Calibrators and one lot of commercially available controls. The mean of the four replicates was compared to the amount of carbamazepine spiked into each sample to calculate the recovery. For samples with target values of <5 µg/mL biases were ± 0.49 µg/mL or less. For samples with target values ≥ 5 µg/mL, the recoveries ranged from 96 – 108%.

*Manual Dilution*

To evaluate the manual dilution feature, serum samples that did not contain carbamazepine were spiked with carbamazepine to target concentrations of 22, 30, 50, and 60 µg/mL. Three samples were prepared at each of the four levels. A manual dilution (1:4) of each spiked sample was prepared by adding 50 µL of the prepared sample to 150 µL of Calibrator A (0.00 µg/mL). The spiked samples and manual dilutions were tested in a minimum of two replicates on one ARCHITECT i 2000SR using one lot each of ARCHITECT *i*Carbamazepine Reagents and Calibrators, and one lot of commercially available controls. The manually diluted concentration was then compared to the target concentration. The individual percent recovery results ranged from 91.6% to 94.2%.

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

*Traceability*

Calibrators are traceable to a USP certified Carbamazepine Reference Standard. The sponsor estimates the uncertainty of the assigned values to be ≤ ± 2.2% compared to the Reference Standard.

The sponsor manufactures internal reference standards (designated Primary Calibrators) for this assay using Carbamazepine Reference Standard (USP). Carbamazepine calibrators (market calibrators) are manufactured gravimetrically and tested against these internal reference standards.

Primary Calibrator A is prepared with normal human serum with a carbamazepine concentration of 0.00 µg/mL. Preservatives are added and Primary Calibrator A is stored at -20°C or colder. Primary Calibrators B through F are prepared from Primary Stock Standard. The Primary Stock Standard (at 40 µg/mL) is prepared as follows: A super stock solution is prepared gravimetrically using Carbamazepine USP Reference Standard powder, and the material is mixed. Primary Calibrator A is gravimetrically added, and the solution is mixed. To prepare the Primary Stock Standard, the super stock solution is gravimetrically diluted to batch size with Primary Calibrator A to a concentration of 40 µg/mL, and the material is mixed and stored. Each Primary Calibrator B through F is gravimetrically prepared with Primary Stock Standard and Primary Calibrator A to a target concentration of

2.00, 4.00, 8.00, 12.00, and 20.00 µg/mL, respectively. The material is mixed, filled into final containers, labeled, and stored at -20°C or colder.

Preparation of Market Calibrator A. Preservatives are added to normal human serum not containing carbamazepine, and the material is mixed, filtered, added to final containers, and stored at 2 to 8°C.

Preparation of Market Calibrators B through F. Preparation of Stock Standard: Anhydrous methyl alcohol is added to a gravimetrically measured amount of Carbamazepine USP grade powder, and the material is mixed. The solution is gravimetrically diluted to batch size with serum not containing carbamazepine, and the material is mixed. Concentration determination testing is performed. Each Calibrator B through F is gravimetrically prepared with stock standard and negative serum to a target concentration of 2.0, 4.0, 8.0, 12.0, and 20.0 µg/mL, respectively. The material is mixed.

*Stability*

The closed-vial (shelf life) stability claim is 12 months at 2 – 8° C, as demonstrated by accelerated stability testing. Protocols and acceptance criteria were reviewed and found to be acceptable. Real-time stability testing is ongoing. The open-vial stability claim is 12 months at 2 – 8° C, as demonstrated by accelerated stability testing. Protocols and acceptance criteria were reviewed and found to be acceptable. Real-time stability testing is ongoing.

*Value Assignment*

Each Calibrator B through F is tested by Relative Light Units (RLU) by matching against the corresponding primary calibrator by analyzing multiple replicates on the ARCHITECT *i* System instrument. The on-test calibrator is compared to the corresponding primary calibrator using a sample/reference ratio of the mean RLU results. If necessary, the concentration is adjusted by adding either stock standard or negative serum and the material is mixed. The material is filled into final containers, labeled, and stored at 2 to 8 C.

Customer Release Testing is performed with the ARCHITECT *i*Carbamazepine Calibrators A through F. The calibrators and reference high and low panels are tested in multiple replicates in one run on each of two ARCHITECT *i* System instruments. The calibrators generate the calibration curve used to calculate the panel concentration results. For each panel, the mean concentration is calculated for each instrument, and the grand mean concentration is calculated from the two instrument mean concentrations. The grand mean concentration values are evaluated against the acceptance criteria. The components are kit packed and stored at 2 to 8° C.

*d. Detection limit:*

The sponsor performed a study based on guidance from the CLSI document EP17-A to determine the Limit of Quantitation (LoQ) of the ARCHITECT iCarbamazepine assay on the ARCHITECT *i* $2000_{SR}$. The LoQ was calculated to be 0.30 µg/mL. The % CV at the LoQ was 11.3 % with a recovery ranging from 104 – 112%.

The sponsor claims 2.0 µg/mL as the lowest reportable value.

*e. Analytical specificity:*

Potential interference from drugs was evaluated at carbamazepine concentrations of 4 and 12 µg/mL.

Normal human serum was used as the zero-level carbamazepine sample. The low-level and high-level carbamazepine samples were each prepared by spiking carbamazepine stock solution into normal human serum to target the lower (4 µg/mL) and upper (12 µg/mL) therapeutic medical decision points.

Compounds with structures similar to carbamazepine or likely to be co-administered were obtained from commercial vendors.

Test samples were prepared by spiking each drug at the concentration level listed below into an aliquot of each level of carbamazepine.

Reference samples were prepared by adding diluent to an aliquot of each level of carbamazepine. The diluent that was used to prepare the reference samples was the same as the diluent used to prepare the drug stock and was added at the same volume as was used to prepare the test samples.

The test and reference samples were tested with multiple replicates on one ARCHITECT *i* 2000SR using one lot each of ARCHITECT *i*Carbamazepine Reagents and Calibrators and one lot of commercially available controls.

All of the drugs in the table below caused a bias of 10% or less at the concentrations tested:

| Drug | Concentration (µg/mL) |
|---|---|
| 10-Hydroxycarbamazepine | 22 |
| 5-(p-Hydroxyphenyl-5-phenylhydantoin | 1000 |
| Acetaminophen | 200 |
| Acetylcysteine | 150 |
| Acetylsalicylic acid | 1000 |

| Drug | Concentration (μg/mL) |
|---|---|
| Amitriptyline | 100 |
| Amobarbital | 50 |
| Ampicillin-Na | 100 |
| Ascorbic acid | 30 |
| Carbamazepine-10,11- epoxide | 6 |
| Cefoxitin | 2500 |
| Cetirizine dihydrochloride | 3 |
| Chlordiazepoxide | 30 |
| Chlorpromazine | 100 |
| Clonazepam | 12 |
| Cyclosporine | 5 |
| Desipramine | 5 |
| Diazepam | 25 |
| Eslicarbazepine | 170 |
| Ethosuximide | 1000 |
| Ethotoin | 50 |
| Glutethimide | 50 |
| Ibuprofen | 500 |
| Imipramine | 200 |
| K-Dobesilate (hydroquinonesulfonic acid potassium salt) | 200 |
| Levodopa | 20 |
| Mephenytoin | 150 |
| Methsuximide | 50 |
| Methyldopa sesquihydrate | 20 |
| Metronidazole | 200 |
| Nortriptyline | 50 |
| Oxcarbazepine | 10 |
| Phenobarbital | 50 |
| Phenothiazine | 200 |
| Phenylbutazone | 400 |
| Phenytoin | 1000 |
| p-Hydroxyphenobarbital | 50 |
| Primidone | 1000 |
| Probenecid | 500 |
| Promethazine | 1000 |
| Rifampicin | 60 |
| Secobarbital | 50 |
| Tetracycline | 50 |
| Theophylline | 100 |
| Valproic acid | 1000 |

One drug, Hydroxyzine dihydrochloride, showed interference of up to -15% when tested at a concentration of 1 µg/mL.

Potential interference from endogenous substances was evaluated at carbamazepine concentrations of 4 and 12 µg/mL. The potential interferents evaluated were bilirubin (conjugated and unconjugated), hemoglobin, total protein, and triglycerides.

The test and reference samples were tested with multiple replicates on one ARCHITECT *i* 2000SR using one lot each of ARCHITECT *i*Carbamazepine Reagents and Calibrators and one lot of commercially available controls.

All of the endogenous substances in the table below caused a bias of 10% or less at the concentrations tested:

| Endogenous substance | Concentration Tested | Recovery observed at 4 ug/mL Carbamazepine | Recovery observed at 12 ug/mL Carbamazepine |
|---|---|---|---|
| Bilirubin (conjugated) | 20 mg/dL | 104% | 103% |
| Bilirubin (unconjugated) | 20 mg/dL | 105 | 105% |
| Hemoglobin | 500 mg/dL | 106% | 104% |
| Total protein | 12 g/dL | 103% | 109% |
| Triglycerides | 3000 mg/dL | 98% | 100% |

Potential interference from clinical conditions was evaluated at carbamazepine concentrations of 4 and 12 µg/mL. The clinical conditions evaluated were Human Anti-Mouse Antibodies (HAMA), Rheumatoid Factor (RF), and Heterophilic Antibodies. Results were as follows:

| **Potentially Interfering Clinical Condition** | **n** | **4 µg/mL carbamazepine** | **12 µg/mL carbamazepine** |
|---|---|---|---|
| Human Anti-Mouse Antibodies (HAMA) | 12 | -6.6% to 7.4% | -7.8% to 13.9% |
| Rheumatoid Factor | 12 | -4.5% to 8.7% | -6.7% to 8.5% |
| Heterophilic Antibody | 12 | -2.5% to 9.8% | -8.4% to 4.3% |

*f. Assay cut-off:*

Not applicable

2. Comparison studies:

*a. Method comparison with predicate device:*

A total of 276 serum samples containing carbamazepine were evaluated with the ARCHITECT *i*Carbamazepine and AxSYM Carbamazepine assays. The concentrations tested ranged from 2.22 – 14.97 µg/mL.

For the ARCHITECT *i*Carbamazepine assay, two lots of ARCHITECT *i*Carbamazepine Reagents, one lot of ARCHITECT *i*Carbamazepine Calibrators, and one lot of commercially available controls were used. The specimens were tested using both lots of reagents on one of two ARCHITECT *i* 2000SR instruments.

For the AxSYM Carbamazepine assay, the specimens were tested in replicates of two on one AxSYM instrument using one lot of reagents, calibrators, and controls. The specimens were tested within 24 hours of each other.

Simple linear regression analysis with 95% confidence intervals produced the following:

| | |
|---|---|
| slope: 0.93 | [0.91 to 0.97] |
| y-intercept: 0.02 | [ -0.2 to 0.3] |
| corr. coeff. (r): 0.95 | |

Passing-Bablok regression analysis with 95% confidence intervals produced the following:

| | |
|---|---|
| slope: 0.97 | [0.93 to 1.00] |
| y-intercept: -0.22 | [-0.48 to 0.03] |
| corr. coeff. (r): 0.95 | |

*b. Matrix comparison:*

A study was performed to evaluate which blood collection tube types are acceptable for use with the ARCHITECT *i*Carbamazepine assay.

There were 50 donors from whom specimens were collected in the following blood collection tube types: plastic plain (serum), glass plain (serum), plastic lithium heparin (plasma), plastic sodium heparin (plasma), plastic dipotassium EDTA (plasma), and glass sodium EDTA (plasma). The approximate concentrations tested were 2, 3, 4, 5, 6, 8, 10, 12, 15 µg/mL.

The prepared samples of each sample set were tested on one ARCHITECT *i* 2000SR in replicates of four using one lot each of ARCHITECT *i*Carbamazepine Reagents and Calibrators and one lot of commercially available controls.

The plain plastic serum tube was used as the control (reference measurement) against which the other tube types were compared. Four tubes of each type were drawn from each donor. Individual replicates of each tube type were compared to the mean of four measurements of the plain plastic serum tube.

99% of the samples had recoveries within ± 10% of the reference tube.

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:

   [1]Therapeutic range: Plasma concentrations between 4 and 12 µg/mL of carbamazepine have been associated with optimal seizure control in adults.

[1]Arroyo S, Sander JWAS. Carbamazepine in comparative trials: pharmacokinetic characteristics too often forgotten. *Neurology* 1999;53(6):1170-1174.

**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.