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

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

k123518

**B. Purpose for Submission:**

New device

**C. Measurand:**

Carbamazepine

**D. Type of Test:**

Quantitative immunoassay

**E. Applicant:**

Microgenics Corporation

**F. Proprietary and Established Names:**

Abbott Carbamazepine Assay

**G. Regulatory Information:**

1. Regulation section:

   21 CFR 862.3645, Neuroleptic drugs radioreceptor assay test system

2. Classification:

   Class II

3. Product code:

   KLT, Enzyme Immunoassay, Carbamazepine

4. Panel:

   Toxicology (91)

**H. Intended Use:**

1. Intended use(s):

   See indication(s) for use below

2. Indication(s) for use:

   The Abbott Carbamazepine Assay is used for the in vitro quantitative measurement of carbamazepine in human serum or plasma on the ARCHITECT cSystems. The measurements obtained are used in monitoring levels of carbamazepine to help ensure appropriate therapy.

3. Special conditions for use statement(s):

   For prescription use only

4. Special instrument requirements:

   ARCHITECT c8000 System

## I. Device Description:

The Carbamazepine Assay kit is supplied ready-to-use in liquid form, for storage at 2 to 8°C. Each Carbamazepine Assay kit contains three bottles of Antibody Reagent (R1; 3 x 27mL), three bottles of Microparticle Reagent (R2; 3 x 9mL), and the package insert. Each kit is sufficient for 300 tests. The R1 antibody reagent contains <1.0% anti-carbamazepine monoclonal antibody (mouse) in Bis-Tris buffer and <0.09% $NaN_3$ as preservative. The R2 microparticle reagent contains <1.0% carbamazepine-coated microparticles in Tris buffer and <0.09% $NaN_3$ as preservative.

## J. Substantial Equivalence Information:

1. Predicate device name(s):

   Abbott Aeroset® Carbamazepine Assay

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

   K993028

3. Comparison with predicate:

| Item | Candidate device: Abbott Carbamazepine Assay (k123518) | Predicate device: Abbott Aeroset® Carbamazepine Assay (k993028) |
|---|---|---|
| Intended Use | The Abbott carbamazepine assay is used for the in vitro quantitative measurement of carbamazepine in human serum or plasma on the ARCHITECT cSystems. The measurements obtained are used in monitoring levels of carbamazepine to help ensure appropriate therapy. | Same |

| | | |
|---|---|---|
| Methodology | Homogenous particle-enhanced turbidimetric inhibition immunoassay (PETINIA). | Homogeneous enzyme immunoassay based on competition for antibody binding sites between the analyte drug in the specimen and exogenous drug labeled with the enzyme glucose-6-phosphate dehydrogenase (G6PDH). |
| Sample Matrix | Human serum or human plasma (including Li heparin, Na heparin, K EDTA, Na citrate, Na fluoride/K oxalate ) | Same |
| Reagent | Liquid ready-to-use | Same |
| Analyzer | Architect cSystems | Abbott Aeroset analyzer |
| Claimed Assay range | 1.9 to 20.0 µg/mL | 0.5 to 20.0 µg/mL |
| Calibrators | Liquid ready-to-use, six levels (0, 2, 4, 8, 12 and 20 µg/mL) Not provided with the kit. | Liquid ready-to-use, six levels (0, 2, 4, 8, 12 and 20 µg/mL) Provided with the kit. |

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

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

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

CLSI EP17-A2; Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition

**L. Test Principle:**

The Abbott carbamazepine assay is a homogenous particle-enhanced turbidimetric inhibition immunoassay (PETINIA) used for the analysis of carbamazepine in serum or plasma. The assay is based on competition between drug in the sample and drug coated onto a microparticle of antibody binding sites of the carbamazepine antibody reagent. The carbamazepine-coated microparticle reagent is rapidly agglutinated in the presence of the anti-carbamazepine antibody reagent and in the absence of any competing drug in the sample. The rate of absorbance change is measured photometrically, and is directly proportional to the rate of agglutination of the particles. When a sample containing carbamazepine is added, the agglutination reaction is partially inhibited, slowing down the rate of absorbance change. A concentration-dependent classic agglutination inhibition curve can be obtained, with maximum rate of agglutination at the lowest carbamazepine concentration and the

lowest agglutination rate at the highest carbamazepine concentration.

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

1. Analytical performance:

All studies were performed on the Architect c8000.

*a. Precision/Reproducibility:*

Precision was evaluated following the CLSI EP5-A2 guidance. Pooled patient samples at five carbamazepine concentrations and negative serum pools spiked with carbamazepine stock solution (1 mg/mL) at five carbamazepine concentrations were tested. Testing was performed at two locations (an internal and an external site) on an Architect c8000 clinical chemistry analyzer using one lot each of the reagents and the calibrators. Each carbamazepine sample was assayed in replicates of two, twice a day for 20 days with a total of 40 runs and n=80. Each run per day was separated by at least two hours. The mean, within-run and total-run SD, and with-run and total-run %CV were calculated. The results obtained are as shown in the table below:

| Sample | Mean (µg/mL) | Within-run | | Total | |
|---|---|---|---|---|---|
| | | SD | %CV | SD | %CV |
| Internal Site | | | | | |
| Spike 1 | 2.25 | 0.05 | 2.1 | 0.09 | 3.9 |
| Spike 2 | 3.49 | 0.07 | 2.1 | 0.1 | 2.8 |
| Spike 3 | 8.18 | 0.13 | 1.6 | 0.2 | 2.4 |
| Spike 4 | 15.27 | 0.24 | 1.5 | 0.48 | 3.1 |
| Spike 5 | 17.19 | 0.31 | 1.8 | 0.33 | 1.9 |
| Patient 1 | 1.93 | 0.06 | 3.0 | 0.12 | 6.3 |
| Patient 2 | 3.99 | 0.07 | 1.6 | 0.1 | 2.6 |
| Patient 3 | 8.15 | 0.08 | 1.0 | 0.18 | 2.1 |
| Patient 4 | 12.05 | 0.18 | 1.5 | 0.24 | 2.0 |
| Patient 5 | 18.09 | 0.31 | 1.7 | 0.39 | 2.2 |
| External Site | | | | | |
| Spike 1 | 2.32 | 0.06 | 2.7 | 0.1 | 4.1 |
| Spike 2 | 3.17 | 0.07 | 2.2 | 0.09 | 2.9 |
| Spike 3 | 7.94 | 0.09 | 1.1 | 0.12 | 1.6 |
| Spike 4 | 13.46 | 0.32 | 2.4 | 0.38 | 2.8 |
| Spike 5 | 15.15 | 0.16 | 1.1 | 0.25 | 1.7 |

*b. Linearity/assay reportable range:*

The claimed assay range is 1.9 to 20 ug/mL. To evaluate linearity, a series of carbamazepine concentrations in serum were prepared by spiking into negative serum and diluting the high sample to ten concentrations spanning (and exceeding) the assay range. Concentrations included carbamazepine ranged from 1.24 to 20.6 ug/mL. Four replicates were measured for each

concentration and the mean of measured concentration was compared with its expected concentration. The expected concentration was based on dilution factors and the high sample concentration. The concentration of the high sample was determined by chromatographic testing traceable to purified carbamazepine.

The linear regression results are:

| Study Site | Slope | Intercept | $R^2$ |
|---|---|---|---|
| Manufacturer Site | 1.073 | 0.029 | 0.9990 |
| External Site | 0.983 | 0.065 | 0.9984 |

Recoveries relative to the target concentrations were within ±10% or within ± 0.4 ug/mL.

This evaluation supports linearity across the claimed measuring range of 1.9 to 20.0 ug/mL.

*Spike/Recovery*
Purified carbamazepine was gravimetrically spiked into negative human serum at 2, 8 and 18µg/mL. Twenty one replicates for each sample were tested in the assay. The average measured concentration was compared to its expected concentration for each spiked sample, as determined by a chromatographic method. The percent recoveries were less than ±10% for the mid and high samples (8 and 18µg/mL) and were within 0.4µg/mL for samples < 4µg/mL.

To validate labeling recommendations for dilution of high samples, high concentration carbamazepine samples were prepared by adding reference material to serum. Samples were manually diluted into Calibrator 1 or saline. Three high sample concentrations (20, 25, and 30 ug/mL) were tested with three replicates and two separate 4-fold dilutions each for a total of 18 measurements diluted into saline and 18 measurements diluted into Calibrator 1. Recoveries ranged from 101-107% of expected. The automated dilution into saline was similarly tested and recoveries were within 95-101% of expected.

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

Calibrators were previously cleared under k120936. See k120936 for traceability, stability, and expected values information on calibrators.

*d. Detection limit:*

The sponsor performed a study following CLSI EP17 guidelines to determine the LoB and LoQ of the Abbott Carbamazepine assay on the Architect c8000 analyzer. The LoB was calculated to be 0.1018µg/mL.

Precision and bias at the LoQ were evaluated by adding reference material to carbamazepine-free serum and carbamazepine- free plasma to attain concentrations ranging from 0.5 to 3.2 ug/mL. Four replicates per day were measured over 17 days with 2 lots of reagent. At the claimed lower limit of 1.9 ug/mL the upper 95% confidence limit of the CV was within <7%, and bias relative to the known concentration was within ± 0.4 ug/mL.

*e. Analytical specificity:*

Interference by metabolites, drugs, and endogenous compounds was tested by spiking the potential interferents into human serum containing carbamazepine at concentrations of 4, 8, and 12 ug/mL. Corresponding control samples were prepared by adding the equal volume of solvent that was in the stock solution of the compound tested. Samples were measured in duplicate by the carbamazepine assay. The compounds listed below did not interfere at the concentrations shown below in the table. Recoveries were all within ± 6% of expected.

| **Compound tested for interference** | **Concentration (µg/mL)** |
|---|---|
| 5-(p-Hydroxyphenyl-5-phenylhydantoin | 1000 |
| Acetaminophen | 200 |
| N-acetylcysteine | 150 |
| Acetylsalicylic acid | 1000 |
| Amitriptyline | 2 |
| Amobarbital | 50 |
| Ampicillin-Na | 100 |
| Ascorbic acid | 30 |
| Cefoxin | 2500 |
| Cetirizine dihydrochloride | 3 |
| Chlordiazepoxide | 30 |
| Chlorpromazine | 100 |
| Clonazepam | 12 |
| Cyclosporine | 5 |
| Desipramine | 3 |
| Diazepam | 25 |
| Ethosuximide | 1000 |
| Ethotoin | 50 |
| Glutethimide | 50 |
| Hydroxyzine Dihydrochloride | 1 |
| Ibuprofen | 500 |
| Imipraminee | 6 |

| | |
|---|---|
| besilate (hydroquinonesulfonic acid potassium salt) | 200 |
| Levodopa (3,4-Dihydroxy-L-phenylalanine) | 20 |
| Mephenytoin | 150 |
| Methsuximide | 50 |
| Methyldopa sesquihydrate ((−)-3-(3,4- Dihydroxyphenyl)-2-methyl-L-alanine sesquihydrate) | 20 |
| Metronidazole | 200 |
| Nortriptyline | 1 |
| Phenobarbital | 500 |
| Phenothiazine | 200 |
| Phenylbutazoneeeee | 16 |
| Phenytoin | 1000 |
| Primidone | 1000 |
| Probenecid | 500 |
| Promethazine | 100 |
| Probenecid | 60 |
| Secobarbital | 50 |
| Tetracycline | 50 |
| Theophylline | 100 |
| Valproic Acid | 1000 |

The following compounds were tested for cross-reactivity at the following three serum carbamazepine concentrations. Results are shown in the table:

| | Percent Bias/Recovery | | | %-Cross-reactivity | | |
|---|---|---|---|---|---|---|
| Compound | 4 ug/mL CBMZP | 8 ug/mL CBMZP | 12 ug/mL CBMZP | 4 ug/mL CBMZP | 8 ug/mL CBMZP | 12 ug/mL CBMZP |
| Eslicarbazepine | 4.3% | 5% | 1% | 9.0% | 20% | 6% |
| Carbamazepine-10,11-epoxide | 15.2% | .9 | 8.2 | 31.5% | 35% | 549.8 |
| 10-Hydroxycarbamazepine | 6.2% | 6.3 | -1.3% | 12.8% | 24% | -8% |
| Oxcarbazepine | 3.5% | 3.9 | 8.2 | 7.2% | 15% | 49.8% |

Potentially interfering endogenous compounds were spiked at the highest possible

concentrations expected from the intended use population into human serum pool containing approximately 4, 8, and 12 µg/mL of carbamazepine. The potential interference of Rheumatoid Factor (RF) and triglyceride was assessed using RF patient specimens and two triglyceride specimens naturally high in these substances and then spiking with carbamazepine at approximately 8µg/mL. Corresponding control samples were prepared by supplementing the human serum pool with the equal volume of solvent that was in the stock solution of the compound tested or by spiking carbamazepine into negative human serum. Each prepared sample and its control solution were measured in replicates of three. The following compounds at listed concentrations cause minimal interference to the assay. Carbamazepine recoveries observed were within ±3% of expected, and no trends were observed.

| Compound | Concentration tested |
|---|---|
| Bilirubin, unconjugated | 60.0 mg/dL |
| Bilirubin, conjugated | 30.0 mg/dL |
| Hemoglobin | 800.0 mg/dL |
| Triglycerides | 1000.0 mg/dL |
| Cholesterol | 500.0 mg/dL |
| Human serum albumin (HSA) | 7.5 g/dL |
| Gamma globulin (IgG) | 12.0 g/dL |
| HAMA | 400.0 ng/mL |
| Rheumatoid factor (RF) | 919.0 IU/mL |

Recoveries for the potential interferents above at all carbamazepine concentrations were within +/- 8% of expected values and no trends were observed.

*f. Assay cut-off:*

Not applicable

2. Comparison studies:

*a. Method comparison with predicate device:*

Two correlation studies were performed using a modified CLSI guideline EP9-A2 to evaluate the accuracy of the Abbott's Carbamazepine Assay by comparing patient sample measurements to the predicate Abbott Aeroset Carbamazepine Assay. In the first study, 103 serum samples with carbamazepine concentrations ranging from 2.2 to 18.2 ug/mL were tested by the candidate carbamazepine assay (on-test) and Abbott Aeroset Carbamazepine assay. In the second study, a different set of 105 serum samples ranging from approximately 2-15 ug/mL were evaluated with the candidate carbamazepine assay (on-test) and Abbott Aeroset Carbamazepine assay.

Data analysis was performed using Passing-Bablok regression model. Results are summarized below:

| Comparative Methods | N | Slope (95% CI) | Intercept (95% CI) | Correlation Coeff. (R) |
|---|---|---|---|---|
| Manufacturer Site | | | | |
| On-test vs. Abbott Aeroset assay | 103 | 0.905 (0.857 – 0.960) | 0.564 (0.202 – 1.00) | 0.9675 |
| External Laboratory | | | | |
| On-test vs. Abbott Aeroset assay | 105 | 0.956 (0.923 – 0.989) | 0.013 (-0.208 – 0.283) | 0.9827 |

*b.* *Matrix comparison:*

Matrix comparison studies were performed to evaluate the performance of the following: serum in plastic, serum separator tubes (SST) in plastic, plasma with sodium fluoride/potassium oxalate in plastic, plasma with sodium heparin in plastic and glass, plasma with lithium heparin in plastic with or without gel, plasma with K3 EDTA in glass and plastic, plasma with K2 EDTA in plastic, and sodium citrate in plastic and glass, compared to the control matrix (serum in glass) in the candidate carbamazepine assay.

Samples were spiked with carbamazepine at multiple concentrations spanning the assay range. Each spiked sample was measured in duplicate by the Carbamazepine Assay. The results of samples prepared in the evaluating matrix were compared to those of serum in glass by determining the slope, intercept, and correlation coefficient, and recovery for each sample relative to expected.

| Matrix Comparison | N | Range µg/mL | Slope | Intercept | Correlation Coeff. (R) |
|---|---|---|---|---|---|
| X: Serum in glass<br>Y: Serum in plastic | 24 | 1.60-19.10 | 0.991 | 0.030 | 0.9982 |
| X: Serum in glass<br>Y: SST in plastic | 24 | 1.60-19.10 | 1.003 | -0.086 | 0.9986 |
| X: Serum in glass<br>Y: Plasma w/ NaF / K Oxalate | 23 | 1.35-19.85 | 0.997 | -0.066 | 0.9987 |
| X: Serum in glass<br>Y: Plasma w/ Na Heparin in glass | 25 | 1.51-18.53 | 1.007 | 0.029 | 0.9986 |
| X: Serum in glass<br>Y: Plasma w/ Na Heparin in plastic | 25 | 1.51-18.53 | 0.969 | 0.196 | 0.9709 |
| X: Serum in glass<br>Y: Plasma w/ Li Heparin w/gel in plastic | 24 | 1.81-19.80 | 0.988 | 0.095 | 0.9986 |
| X: Serum in glass | 24 | 1.81-19.80 | 0.993 | -0.115 | 0.9992 |

| | | | | | |
|---|---|---|---|---|---|
| Y: Plasma w/ Li Heparin w/o gel plastic | | | | | |
| X: Serum in glass<br>Y: Plasma w/ K3 EDTA in glass | 23 | 1.36-18.70 | 1.003 | -0.082 | 0.9982 |
| X: Serum in glass<br>Y: Plasma w/ K3 EDTA in plastic | 23 | 1.52-19.15 | 1.010 | -0.087 | 0.9988 |
| X: Serum in glass<br>Y: Plasma w/ K2 EDTA in plastic | 23 | 1.36-18.70 | 0.988 | 0.115 | 0.9993 |
| X: Serum in glass<br>Y: Plasma w/ Na Citrate in glass | 24 | 1.38-18.61 | 1.042 | -0.302 | 0.9985 |
| X: Serum in glass<br>Y: Plasma w/ Na Citrate in plastic | 24 | 1.38-18.61 | 1.047 | -0.275 | 0.9988 |

Recoveries were largely within ±4% of the expected value (based on serum in glass) and were all within ±8%.

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:

   Therapeutic effect is usually achieved in the serum and plasma carbamazepine concentration range of 4.0 to 12.0 µg/mL (17.0 to 51.0 µmol/L). Peak carbamazepine concentrations above 15.0 µg/mL (63.0 µmol/L) are often associated with toxicity.[1,2]

   In addition, the sponsor has included the following in the labeling: For effective treatment, some patients may require serum levels of carbamazepine outside these ranges. Therefore, the expected range is provided only as a guide, and individual patient results should be interpreted in light of other clinical signs and symptoms.

[1]Levy, R.H., Wilensky, A.J., Freil, P.N. Other antiepileptic drugs. In: Evans, W.E., Schentag, J.J., Jusko, W.J., editors. Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring, 2nd ed. Spokane, W.A.: Applied Therapeutics; 1986: 540-569.

[2]Goldman, L., Ausiello, D.,editors. Cecil Medicine, 23rd ed. Philadelphia, PA: Elsevier Saunders; 2008:2994.

**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**.**