

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

A. 510(k) Number:

K151578

B. Purpose for Submission:

New device

C. Measurand:

Carbamazepine

D. Type of Test:

Quantitative Immunoassay

E. Applicant:

Roche Diagnostics Operations

F. Proprietary and Established Names:

ONLINE TDM Carbamazepine Gen.4

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
KLT	II	21 CFR § 862.3645 Neuroleptic drugs radioreceptor assay test system	Toxicology (91)

H. Intended Use:

1. Intended use(s):

See indications for use below.

2. Indication(s) for use:

In vitro test for the quantitative determination of carbamazepine in serum and plasma on Roche/Hitachi cobas c systems. 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:

Roche/Hitachi cobas c501 system

I. Device Description:

Carbamazepine Gen 4 assay kit is supplied in ready-to-use liquid form. The kit consists of two reagents that are packaged in a cassette.

Reagent R1: Anti-carbamazepine antibody (sheep monoclonal); MESa) buffer, pH 6.4; preservative.

Reagent R2: Carbamazepine biotinylated hapten; streptavidin coated latex microparticles: 0.1%; HEPES buffer, pH 7.4; preservative

J. Substantial Equivalence Information:

1. Predicate device name(s):

ONLINE TDM Carbamazepine

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

K031902

3. Comparison with predicate:

Similarities and Differences		
Item	New Device	ONLINE TDM Carbamazepine (Predicate)
Intended Use	In vitro test for the quantitative determination of carbamazepine in serum and plasma on Roche/Hitachi cobas c systems.	The ONLINE TDM Carbamazepine assay is for the quantitative determination of carbamazepine in human serum or plasma on automated clinical chemistry analyzers.
Methodology	Same	Homogeneous microparticle agglutination immunoassay
Reagent Shelf Life	Same	2 - 8° C until expiration date
Sample Matrix	Same	Human serum and plasma

Analyzer	Roche/Hitachi cobas c501 system	Roche Hitachi analyzers
Measuring Interval	2-20 µg/mL	0.2-20 µg/mL
Calibrators	Preciset TDM I calibrators	COBAS-FP Carbamazepine calibrators
Controls	Same	TDM Control Set, levels I, II and III

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

CLSI EP05-A2: *Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline -Second Edition*

CLSI EP06-A: *Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach*

CLSI EP17-A2: *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline*

L. Test Principle:

The Carbamazepine Generation 4 assay is for the quantitative determination of carbamazepine in human serum or plasma on automated clinical chemistry analyzers. It is a homogeneous microparticle agglutination immunoassay based on the kinetic interaction of microparticles in solution. Biotinylated drug hapten serves as the binding partner to anti-carbamazepine antibody and streptavidin coated latex beads. A competitive reaction to a limited amount of specific anti-carbamazepine antibody takes place between the hapten and free carbamazepine in the sample. A decrease in the apparent signal produced by the microparticle agglutination is proportional to the amount of drug present in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Precision was evaluated following the CLSI EP5-A2 guidance. A total of 8 samples, 5 human serum samples and 3 control samples, were tested at five and three carbamazepine levels, respectively. Testing was performed at one site on a cobas c 501 clinical chemistry analyzer using three lots of reagent. Each carbamazepine sample was assayed in replicates of two, twice a day for 21 days and n=84. The mean, within-run and total-run SD, and within-run and total-run %CV were calculated. The results obtained are as shown in the table below:

Sample	Mean (mg/dL)	Repeatability (N=4)		Total Precision (N=84)	
		SD	%CV	SD	%CV
Control 1	3.4	0.08	2.2	0.10	2.8
Control 2	9.7	0.14	1.4	0.22	2.3
Control 3	15.7	0.20	1.3	0.28	1.8

Human Serum 1	2.9	0.08	2.7	0.10	3.3
Human Serum 2	4.2	0.09	2.1	0.12	2.9
Human Serum 3	9.4	0.17	1.8	0.25	2.6
Human Serum 4	14.6	0.19	1.3	0.36	2.4
Human Serum 5	19.5	0.27	1.4	0.56	2.9

b. *Linearity/assay reportable range:*

The claimed assay range is 2.0 to 20 µg/mL. To evaluate linearity, a series of carbamazepine concentrations in serum and plasma were prepared by diluting the high concentration serum and plasma pool with analyte free serum to obtain 11 levels spanning the assay range, in accordance with CLSI EP6-A. Serum carbamazepine concentrations ranged from 2.32. to 21.9 µg/mL, and plasma carbamazepine concentrations ranged from 2.09 to 21.1 µg/mL. In addition, values slightly outside the measuring range of 2 - 20 µg/mL were used per CLSI EP6-A. Three replicates were measured for each concentration and the mean of the measured concentration was compared with its expected concentration. The expected concentration was based on dilutions of the high sample concentration sample. The concentration of the high sample was determined by chromatographic testing traceable to purified carbamazepine.

The linear regression results using the sample concentrations listed above were:

Sample Type	Slope	Intercept	R
Serum	1.000	0	0.997
Plasma	1.013	-0.195	0.999

This evaluation supports linearity across the claimed measuring range of 2.0 to 20.0 ug/mL.

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

Calibrators were previously cleared under k031856. See k031856 for traceability, stability, and expected values information on calibrators.

d. *Detection limit:*

Analytical sensitivities were determined following CLSI EP17-A2 guidelines. LoB was determined using 0.9% saline with 3 lots of reagent on cobas c 501 analyzer in 2 runs per day for 3 days, and 10 replicates per run. LoD was determined using 6 serum samples spiked with carbamazepine levels ranging from LoB to approximately 4 times specified LoB (n=60). For limit of quantitation (LoQ), nine serum samples that cover the range between LoB and 2x LoQ were prepared. All samples were measured in replicates of 4 using three reagent lots over a period of 3 days. LoQ is defined as the lowest analyte concentration where %Total Error is ≤20%.

The results are summarized in the below table.

	LoB (ug/mL)	LoD (ug/mL)	LoQ (ug/mL)
Lot 1	0.34	0.51	1.24
Lot 2	0.28	0.45	1.38
Lot 3	0.31	0.48	1.23
Claimed	0.5	1.0	2.0

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 3 and 12 µg/mL on a cobas c 501 analyzer. 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 ± 10% of expected.

Compound tested for interference	Concentration
Hemoglobin	1000 mg/dL
Triglycerides	1000 mg/dL
Cholesterol	600 mg/dL
Unconjugated bilirubin	50 mg/dL
Conjugated bilirubin	50 mg/dL
Rheumatoid Factors	1200 IU/mL
Total Protein	13 g/dL

16 drugs were tested for interference and the results are presented below:

Drugs tested	Concentration (mg/L)
Acetylcysteine	1660
Ampicillin-Na	1000
Ascorbic acid	300
Cefoxitin	2500
Heparin	5000 U/L
Levodopa	20
Methyldopa	20

Drugs tested	Concentration (mg/L)
Metronidazol	200
Doxycyclin	50
Acetylsalicylic Acid	1000
Rifampicine	60
Cyclosporine	5
Acetaminophen	200
Ibuprofen	500
Phenylbutazone	400
Theophylline	100

Twenty-seven substances were tested for cross-reactivity at two different carbamazepine concentrations in serum:

Compound	Concentration tested ($\mu\text{g/dL}$)	%Cross reactivity at 3 $\mu\text{g/mL}$	% Cross reactivity at 12 $\mu\text{g/ml}$
Carbamazepine-10,11-epoxide	29.6 $\mu\text{g/mL}$	2.87	1.4
Oxcarbazepine (Oxc)	100 $\mu\text{g/mL}$	0.88	0.2
10-Hydroxycarbamazepine (MHD)	100 $\mu\text{g/mL}$	0.63	0.2
Nortriptyline	50 $\mu\text{g/mL}$	0	0.3
Amitriptyline	100 $\mu\text{g/mL}$	0	0
Imipramine	200 $\mu\text{g/mL}$	0	0
Phenothiazine	200 $\mu\text{g/mL}$	0	0
Phenylbutazone	450 $\mu\text{g/mL}$	0.05	0
Promethazine	1000 $\mu\text{g/mL}$	0.02	0
Phenytoin	1000 $\mu\text{g/mL}$	0	0
Mephenytoin	1000 $\mu\text{g/mL}$	0.5	0.1
2-Phenyl-2-ethylmalonamide	1000 $\mu\text{g/mL}$	0.31	0.2
Ethotoin	1000 $\mu\text{g/mL}$	0.12	0.10
Valproic acid	1000 $\mu\text{g/mL}$	0.02	0
Amobarbital	1000 $\mu\text{g/mL}$	0	0
Chlordiazepoxide	30 $\mu\text{g/mL}$	0.33	0.4
Clonazepam	12 $\mu\text{g/mL}$	0.44	0.3
Ethosuximide	1000 $\mu\text{g/mL}$	0.01	0
Diazepam	25 $\mu\text{g/mL}$	0.21	0.4

Gluthethimide	1000 µg/mL	0	0
Methosuximide	100 µg/mL	0.01	0
p-Hydroxypheno- barbital	100 µg/mL	0.05	0.4
5-(p-Hydroxyphenyl)- phenylhydantoin	1000 µg/mL	0.01	0
Phenobarbital	1000 µg/mL	0.01	0
Primidone	1000 µg/mL	0.02	0
Probenecid	500 µg/mL	0.03	0
Secobarbital	1000 µg/mL	0.02	0

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. *Method comparison with predicate device:*

To demonstrate substantial equivalence to the predicate device, one-hundred individual human serum samples ranging in concentration from 2.38 µg/mL to 18.7 µg/mL were measured with one lot of the Carbamezapine Gen 4 assay and compared to the results obtained with the ONLINE TDM Carbamazepine assay on the cobas c 501 analyzer. Results of the Deming regression analysis are presented below:

Carbamezapine Gen 4 assay vs	Slope (95% CI)	Intercept (95% CI)	Std Dev.	R
ONLINE TDM Carbamazepine (k031902)	0.994 (0.972 to 1.016)	0.0536 (-0.0721 to 0.179)	0.04	0.993

The sponsor also compared the same one-hundred samples vs. an LC-MS method, and the results of the Deming regression analysis for that comparison are presented below:

Carbamezapine Gen 4 assay vs	Slope (95% CI)	Intercept (95% CI)	Std Dev.	R
LC-MS	0.935 (0.907 to 0.963)	0.466 (0.277 to 0.654)	0.29	0.991

b. *Matrix comparison:*

Matrix comparison studies were performed to evaluate the performance of the following: serum gel separation tube, K2-EDTA plasma, K3-EDTA plasma, Li-Heparin plasma, Na-Heparin plasma compared to the control matrix (serum from a plastic tube) in the candidate carbamazepine assay.

Thirty-three samples were spiked with carbamazepine at multiple concentrations spanning the assay range. Each spiked sample was measured in duplicate by the ONLINE TDM Carbamazepine Gen.4 assay. The results of samples prepared in the evaluating matrix were compared to those of serum in plastic tubes by determining the slope, intercept, and correlation coefficient, and recovery for each sample relative to expected (y = reference tube, x = tested tube):

Tube Type or anticoagulant (vs. Serum)	Range tested (ug/mL)	Passing Bablok Regression	Correlation Coefficient (R)
Serum Gel Separation tube	2.42-19.5	$y=1.010x+0.177$	0.989
Na-Heparin	2.12-19.0	$y= 1.022x-0.382$	0.990
Li-Heparin	2.23-19.5	$y= 1.010x-0.290$	0.991
K2-EDTA	2.21-20.0	$y=1.024x-0.0593$	0.988
K3-EDTA	2.19-19.7	$y= 0.993x + 0.0147$	0.994

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:

The therapeutic range for Carbamazepine is derived from the relationships among plasma level, seizure control and emergence of side effects. Blood levels vary depending on sex,

race or age. Although other ranges are also quoted, the therapeutic range is often set between 4 and 12 µg/mL. (16.9-50.8 µmol/L).*

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

*Goldman L, Ausiello D, editors. *Cecil Medicine*, 23rd ed. Philadelphia PA: Elsevier Saunders; 2008: 2983-2995.

Lower concentrations may provide effective therapeutic response when other anticonvulsants are used in combination with carbamazepine.

Serum or plasma level monitoring provides an indicator for individual dosage regimen. Some patients may require levels outside these ranges for effective treatment. The ranges are therefore, provided only as a guide for interpretation along with other clinical symptoms, and are not to be taken as the sole indicator for adjustment of dosage. Peak concentrations above 12 µg/mL (50.8 µmol/L) are often associated with toxicity. For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

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.