DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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October 22, 2015

ROCHE DIAGNOSTICS OPERATIONS (RDO)
DAVID TRIBBETT
REGULATORY AFFAIRS PRINCIPAL
9115 HAGUE ROAD
INDIANAPOLIS IN 46250

Re: K151578
Trade/Device Name: ONLINE TDM Carbamazepine Gen 4
Regulation Number: 21 CFR 862.3645
Regulation Name: Neuroleptic drugs radioreceptor assay test system
Regulatory Class: II
Product Code: KLT
Dated: September 21, 2015
Received: September 22, 2015

Dear Mr. Tribbett:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Courtney H. Lias -S

Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
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Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K151578

Device Name
ONLINE TDM Carbamezapine Gen.4

Indications for Use *(Describe)*
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.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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ONLINE TDM Carbamazepine Gen. 4
510(k) Summary

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of 21 CFR 807.92.

Submitter Name	Roche Diagnostics Operations (RDO)
Address	9115 Hague Road Indianapolis, IN, 46250, USA
Contact	David Tribbett Phone: (317)-521-2964 FAX: (317)-521-2324 Email: david.tribbett@roche.com
Date Prepared	October 22, 2015
Proprietary Name	ONLINE TDM Carbamazepine Gen. 4
Common Name	Enzyme immunoassay, Carbamazepine
Classification Name	Neuroleptic drugs radioreceptor assay test system
Product Codes	KLT, 21 CFR § 862.3645
Predicate Devices	ONLINE TDM Carbamazepine, K031902
Establishment Registration	1823260, Roche Diagnostics Corporation

1. DEVICE DESCRIPTION

The ONLINE TDM Carbamazepine Gen. 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 (KIMS). 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.

2. INDICATIONS 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. TECHNOLOGICAL CHARACTERISTICS

The ONLINE TDM Carbamazepine Gen. 4 assay is a homogeneous microparticle agglutination immunoassay.
It is a two-reagent system used for the detection of carbamazepine in serum. Kinetic interaction of microparticles in solution (KIMS) will be measured using automated analyzers. In this technology biotinylated drug hapten attached to streptavidin coated latex beads serves as the binding partner to anti-carbamazepine antibody. A competitive reaction to a limited amount of specific anti-carbamazepine antibody takes place between the latex bound hapten and free carbamazepine in the serum sample. A decrease in the apparent signal is proportional to the amount of drug present in the sample.

Reagents - working solutions which are ready for use, are packaged in a cassette labeled with their instrument positioning B (Reagent 1) and C (Reagent 2).

- R1, Anti-carbamazepine antibody (sheep monoclonal); MES[a)] buffer, pH 6.4; preservative
- R2, Carbamazepine biotinylated hapten; streptavidin coated latex microparticles: 0.1 %; HEPES[b)] buffer, pH 7.4; preservative

a. 2‑(N‑Morpholino) ethanesulfonic acid

b. N‑(2‑Hydroxyethyl)piperazine-N'‑(2‑ethanesulfonic acid)

The following table compares the similarities and differences of the candidate device to the predicate device.

Table 1: Substantial Equivalence – Assay Similarities and Differences

Assay Comparison Similarities		
Feature	**Predicate Device: ONLINE TDM Carbamazepine (K031902)**	**Candidate Device: ONLINE TDM Carbamazepine Gen. 4**
Intended Use	The ONLINE TDM Carbamazepine assay is for the quantitative determination of carbamazepine in human serum or plasma on automated clinical chemistry analyzers.	In vitro test for the quantitative determination of carbamazepine in serum and plasma on Roche/Hitachi **cobas c** systems.
Sample Types	Serum: Collect serum using standard sampling tubes. Plasma: Potassium EDTA, sodium or lithium heparin plasma.	Serum: Collect serum using standard sampling tubes. Plasma: K2‑ and K3‑EDTA, sodium or lithium heparin plasma.
Test Principle	Homogeneous microparticle agglutination immunoassay.	Same
Reagent Shelf Life Stability	2-8 ºC until expiration date	2-8 ºC until expiration date
Reagent On-Board Stability	30 days opened and refrigerated on the analyzer. Do not freeze.	On‑board in use and refrigerated on the analyzer: 4 weeks
Measuring Range	0.2-20 µg/mL	2‑20 µg/mL (8.5‑85 µmol/L)
Traceability	This method has been standardized against USP reference standards.	Same
Calibrator	COBAS-FP Carbamazebine Calibrator, CAL A-F	Preciset TDM I, calibrators B-F (Previously cleared 510(k): K031856)
Calibration frequency	After reagent cassette change, after reagent lot change and as required following quality control procedures	After reagent lot change and as required following quality control procedures
Controls	TDM Control Set, levels I, II and III	Same

Assay Comparison Similarities		
Feature	**Predicate Device:** **ONLINE TDM Carbamazepine (K031902)**	**Candidate Device:** **ONLINE TDM Carbamazepine Gen. 4**
Lower Limits of Measurement	Lower Detection Limit = 0.2 µg/mL (0.81 µmol/L)	LoB = 0.3 µg/mL (1.3 µmol/L) LoD = 0.5 µg/mL (2.1 µmol/L) LoQ = 1.4 µg/mL (5.9 µmol/L)
Test Principle	The ONLINE TDM Carbamazepine assay is a homogeneous microparticle agglutination immunoassay. It is a two-reagent system used for the detection of carbamazepine in serum. Kinetic interaction of microparticles in solution (KIMS) will be measured using RD/Hitachi families of automated analyzers. In this technology blotinylated drug hapten serves as the binding partner to 1) anti-carbamazepine antibody and 2) 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 serum sample. A decrease in the apparent signal is proportional to the amount of drug present in the sample.	The ONLINE TDM Carbamazepine Gen. 4 assay is a homogeneous microparticle agglutination immunoassay. It is a two-reagent system used for the detection of carbamazepine in serum. Kinetic interaction of microparticles (KIMS) will be measured using automated analyzers. In this technology biotinylated drug hapten attached to streptavidin coated latex beads serves as the binding partner to anti-carbamazepine antibody. A competitive reaction to a limited amount of specific anti-carbamazepine antibody takes place between the latex bound hapten and free carbamazepine in the serum sample. A decrease in the apparent signal is proportional to the amount of drug present in the sample.
Reagent Composition	**R1** Conjugate Reagent/Buffer Carbamazepine biotinylated hapten; 2-(N-Morpholino) ethanesulfonic acid (MES) buffer, pH 6.4; preservative; surfactant **R2** Latex-Antibody Reagent/Buffer Anti-carbamazepine antibody (mouse monoclonal); streptavidin coated latex microparticles: 0.08%; N-(2-Hydroxyethyl) piperazine•N'-(2-ethanesulfonlc acid) (HEPES) buffer, pH 7.5; preservative	**R1** Anti-carbamazepine antibody (sheep monoclonal); MESa) buffer, pH 6.4; preservative **R2** Carbamazepine biotinylated hapten; streptavidin coated latex microparticles: 0.1 %; HEPESb) buffer, pH 7.4; preservative

4. NON-CLINICAL PERFORMANCE EVALUATION

The following performance data were provided in support of the substantial equivalence determination:

Detection Limit: LoB, LoD and LoQ according to CLSI EP17-A2

Precision according to CLSI EP5-A2

Linearity according to CLSI EP6-A

Matrix Comparison - Anticoagulants

Interferences - H, L and I Indices

Interference - Drugs

Method Comparison to Predicate

4.1. Detection Limit

LoB, LoD, and LoQ studies were performed based upon CLSI EP17-A2.

LoB:

The diluent is measured with 10-fold determinations per run on one instrument. Six runs distributed over 3 days are performed. Data analysis will be based on determination of the 95th percentile of the 60 measured values.

LoD:

The 5 samples with low analyte content spiked with Carbamazepine (with concentrations ranging from LoB to approx. 4 times specified LoB) are measured with 2-fold determination per run. Six runs distributed over 3 days are performed.

LoD is defined as the concentration, at which there is a 95% probability that a sample contains analyte.

LoQ is the lowest amount of analyte in a sample that can be detected quantitatively within specified precision and accuracy ranges.

Nine samples are prepared which cover the concentration range between LoB and 2x LoQ. Those samples are tested in two aliquots over at least three days on one analyzer, 2 runs per day for 3 lots.

Expected or target value is determined with LC/MS.

Table 2: LoB, LoD, and LoQ Experimental Determination

	Representative Result (µg/mL)	Claimed in labeling (µg/mL)
Limit of Blank (LoB)	0.3	0.5
Limit of Detection (LoD)	0.5	1.0
Limit of Quantitation (LoQ)	1.4	2.0

4.1. Precision according to CLSI EP5-A

Two runs per day for ≥ 21 days on the same analyzer. Repeatability (within run precision) and intermediate precision (within lab precision) is calculated. The samples have to be randomized in each run separately.

The data set has to be complete for the 21 days.

Table 3: Repeatability Summary

Specimen	Mean (µg/mL)	SD (µg/mL)	CV (%)
TDM Control 1	3.4	0.08	2.2
TDM Control 2	9.7	0.14	1.4
TDM Control 3	15.7	0.20	1.3
Human Serum 1	2.9	0.08	2.7
Human Serum 2	4.2	0.09	2.1
Human Serum 3	9.4	0.17	1.8
Human Serum 4	14.6	0.19	1.3
Human Serum 5	19.5	0.27	1.4

Table 4: Intermediate Precision Summary

Specimen	Mean (µg/mL)	SD (µg/mL)	CV (%)
TDM Control 1	3.4	0.10	2.8
TDM Control 2	9.7	0.22	2.3
TDM Control 3	15.7	0.28	1.8
Human Serum 1	2.9	0.10	3.3
Human Serum 2	4.2	0.12	2.9
Human Serum 3	9.4	0.25	2.6
Human Serum 4	14.6	0.36	2.4
Human Serum 5	19.5	0.56	2.9

4.2. Linearity according to CLSI EP6-A

A dilution series was prepared from a human serum sample pool and diluent (Analyte-free serum). The dilution series are prepared to obtain eleven levels (including the high concentration pool and diluent). The diluted samples shall span the measuring range including a sample at the lower end of the measuring range, a sample over the measuring range and samples at the medical decision points. The process was repeated for plasma samples.

The calculation is according to the CLSI guideline EP6-A. All measurement data of the dilution steps are calculated by regression.

Table 5: Linearity Results

Sample Type	Linear Regression Equation	Claimed Measuring Range
Serum	y = 1.000x – 0.0 Pearson correlation coefficient (R) = 0.997	2.0 to 20.0 µg/mL
K2-EDTA, Plasma	y =1.013x – 0.195 Pearson correlation coefficient (R) = 0.999	2.0 to 20.0 µg/mL

4.3. Matrix Comparison - Anticoagulants

Each pair of serum and plasma of a single donor are spiked with carbamazepine. Included in the data are 33 full tubes as described below.

A matrix comparison is executed by taking the serum as reference. Only samples within the limit of icteric, lipemic and hemolytic interference are allowed to be used. Samples cover the measuring range.

The following matrix comparisons are provided:

- Gel separation tubes
- K2-EDTA plasma vs serum
- K3-EDTA plasma vs serum
- Li-Heparin plasma vs serum
- Na-Heparin plasma vs serum

Table 6: Matrix Comparison

Anticoagulant	Correlation
Serum vs. Serum Gel Separation	y = 1.01x + 0.177, r = 0.989
Serum vs. Li-heparin	y = 1.01x -0.290, r = 0.991
Serum vs. Na-heparin	y = 1.02x -0.382, r = 0.990
Serum vs. K2-EDTA	y = 1.02x -0.059, r = 0.988
Serum vs. K3-EDTA	y = 0.993x + 0.147, r = 0.994

4.4. Interferences - H, L and I Indices

The effect on quantitation of analyte in the presence of endogenous interfering substances is determined at two carbamazepine concentrations and a dilution set of the added interfering substances. The following lists the potential interfering substances evaluated and the highest concentration which was shown to not interfere with the assay:

Hemolysis: up to an H index of 1000 (approximate hemoglobin concentration 1000 mg/dL)

Icterus/Bilirubin: up to an I index of 50 (approximate bilirubin concentration 50 mg/dL)

Lipemia: up to an L index of 2000 (approximate triglyceride concentration up to 1000 mg/dL)

Cholesterol: up to 600 mg/dL

Rheumatoid Factor: up to 1200 IU/mL

Total Protein: up to 13 g/dL

Test procedure:

High concentrated stock solutions of the interference substances are prepared in a suitable solvent. Two human sample pools are spiked with the defined carbamazepine concentrations and each divided into two aliquots. The potential interfering substance is added to one aliquot of each pool, while the other aliquot is mixed with the same amount of solvent without the interfering substance. A dilution series is prepared with at least 10 dilution steps for each interferent by mixing the two aliquots.

The parts containing the interfering substance have the same carbamazepine concentrations as the aliquots containing no interfering substance. When diluting those two aliquots, the carbamazepine concentration remains constant while the concentration of interferent varies. Thus, the effect of increasing concentrations of interferent can be determined.

Median of the measured results is compared to the expected result (aliquot with no interfering substance) and the recovery is determined (paired difference testing).

This procedure is repeated for each of the interfering substances.

4.5. Interferences – Drugs

Sixteen commonly used drugs were examined for potential interference on measurement with ONLINE TDM Carbamazepine Gen. 4.

Two human sample pools spiked with the defined carbamazepine concentrations are divided into two aliquots. One aliquot of each concentration is used as the reference sample for carbamazepine concentration and is not spiked with the drugs but the solvent for the drug.

The other aliquots, with either the high or low carbamazepine concentration, are spiked with the respective amount of drug. The carbamazepine concentration of the spiked aliquots is determined in triplicate and compared to the carbamazepine concentration determined for the reference aliquot.

The defined pharmaceutical compounds are spiked into samples with concentrations according to EP7-A2 or higher concentrations. The mean values are calculated as well as the % deviations from the interference samples compared to the reference sample (paired difference testing).

Table 7: Common Drug Interferences

Drug	Highest Concentration Shown Not to Interfere with Carbamazepine (drug concentrations in (mg/L))
Acetylcysteine	1660
Ampicillin-Na	1000
Ascorbic acid	300
Cefoxitin	2500
Heparin	5000 U/L
Levodopa	20
Methyldopa	20
Metronidazol	200
Doxycyclin	50
Acetylsalicylic Acid	1000
Rifampicine	60
Cyclosporine	5
Acetaminophen	200
Ibuprofen	500
Phenylbutazone	400
Theophyllin	100

4.6. Cross-reactivity

The following compounds were tested for cross-reactivity at low (3 µg/mL) and high (12 µg/mL) carbamazepine concentration:

Table 8: Cross-reactivity Testing

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

4.7. Method Comparison to Predicate

One hundred single native human samples of patients taking carbamazepine covering the reportable range are tested.

The samples are tested in singlicate on the candidate and predicate device (**cobas c** 501).

The data was evaluated using Deming Regression analysis.

$y = 0.994x - 0.054$ µg/mL

$r = 0.993$

5. CONCLUSIONS

The submitted information in this premarket notification supports a substantial equivalence decision.