DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
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Silver Spring, MD 20993-0002

ROCHE DIAGNOSTICS OPERATIONS (RDO)
NOEL MENCIAS
REGULATORY AFFAIRS CONSULTANT
9115 HAGUE ROAD
INDIANAPOLIS MD 46250

May 25, 2016

Re: K160570
Trade/Device Name: Creatine Kinase
Regulation Number: 21 CFR 862.1215
Regulation Name: Creatine phosphokinase/creatine kinase or isoenzymes test system
Regulatory Class: II
Product Code: JHS
Dated: February 26, 2016
Received: February 29, 2016

Dear Noel Mencias:

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,

Katherine Serrano -S

For: Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

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)*
k160570

Device Name
Creatine Kinase

Indications for Use *(Describe)*
Creatine Kinase is an in vitro test for the quantitative determination of creatine kinase (CK) in human serum and plasma on Roche/Hitachi cobas c systems. The determination of CK and CK isoenzyme activities is utilized in the diagnosis and monitoring of myocardial infarction and myopathies such as the progressive Duchenne muscular dystrophy.

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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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	Noel B. Mencias Phone: (317) 521-3172 FAX: (317) 521-2324 Email: noel.mencias@roche.com
Date Prepared	February 26, 2016
Proprietary Name	Creatine Kinase
Common Name	Creatine Kinase
Classification Name	Creatine phosphokinase/creatine kinase or isoenzymes test system
Product Codes	JHS, 21 CFR § 862.1215
Predicate Devices	Creatine Kinase, K951595
Establishment Registration	1823260, Roche Diagnostics Corporation

1. DEVICE DESCRIPTION

The Creatine Kinase assay is a two reagent assay for the quantitative determination of creatine kinase (CK) in human serum and plasma on automated clinical chemistry analyzers. Photometrically measured NAPDP formation is directly proportional to CK activity in a human sample.

2. INDICATIONS FOR USE

Creatine Kinase is an in vitro test for the quantitative determination of creatine kinase (CK) in human serum and plasma on Roche/Hitachi **cobas c** systems. The determination of CK and CK isoenzyme activities is utilized in the diagnosis and monitoring of myocardial infarction and myopathies such as the progressive Duchenne muscular dystrophy.

Measurements of creatine phosphokinase and its isoenzymes are used in the diagnosis and treatment of myocardial infarction and muscle diseases such as progressive, Duchenne-type muscular dystrophy.

3. TECHNOLOGICAL CHARACTERISTICS

The Creatine Kinase assay is a UV test for the quantitative determination of creatine kinase (CK) in human serum and plasma on Roche/Hitachi **cobas c** systems. The CK is activated by N-acetylcysteine (NAC). In a primary reaction, the activated CK catalyzes the dephosphorylation of creatine phosphate. In a coupled reaction, catalyzed by hexokinase (HK), glucose is phoshorylated by the ATP formed in the primary reaction to form D-glucose-6-phosphate (G6P). Finally D-glucose-6-phosphate dehydrogenase (G6PDH) catalyzes the oxidation of G6P by NADP to form D-6-phosphogluconate and NADPH. The rate of NADPH formation is directly proportional to catalytic CK activity. It is determined by measuring the increase in absorbance at 340nm (main) and 546nm (sub).

Roche Diagnostics claims substantial equivalence to COBAS INTEGRA Creatine Kinase cleared in K951595 on the COBAS INTEGRA analyzer. The reagent was applied to **cobas c** 501 (**c** 501) following the 2003 FDA Policy document "Replacement Reagent and instrument family Policy." A comparison of the similarities and differences between the candidate device and the

predicate device is provided in the following table. There are no prior submissions for the candidate device.

Table 1: Substantial Equivalence – Assay Similarities

Assay Comparison Similarities		
Feature	**Predicate Device:** COBAS INTEGRA Creatine Kinase (K951595)	**Candidate Device: Creatine Kinase**
Intended Use	The COBAS INTEGRA Creatine Kinase (CK) contains an in vitro diagnostic reagent system intended for use on COBAS INTEGRA for the quantitative determination of the catalytic activity of CK (EC 2.7.3.2: adenosine triphosphate: creatine N-phosphotransferase) in serum and plasma (test CKL, 0-039).	In vitro test for the quantitative determination of creatine kinase (CK) in human serum and plasma on Roche/Hitachi cobas c systems.
Sample Types	Serum and plasma, free from hemolysis. Acceptable anticoagulants are heparin and EDTA.	Serum: Non hemolyzed serum is the specimen of choice and also recommended by IFCC. Plasma: Li-Heparin, K2-, K3-EDTA.
Test Principle	The CK is activated by N-acetylcysteine (NAC). In a primary reaction the activated CK catalyzes the dephosphorylation of creatine phosphate. In a coupled reaction catalyzed by hexokinase (HK) glucose is phoshorylated by the ATP formed in the primary reaction to form D-glucose-6-phosphate (G6P). Finally D-glucose-6-phosphate dehydrogenase (G6PDH) catalyzes the oxidation of G6P by NADP to form D-6-phosphogluconate and NADPH. The rate of NADPH formation is directly proportional to catalytic CK activity. It is determined by measuring the increase in absorbance at 340nm.	The CK is activated by N-acetylcysteine (NAC). In a primary reaction the activated CK catalyzes the dephosphorylation of creatine phosphate. In a coupled reaction catalyzed by hexokinase (HK) glucose is phoshorylated by the ATP formed in the primary reaction to form D-glucose-6-phosphate (G6P). Finally D-glucose-6-phosphate dehydrogenase (G6PDH) catalyzes the oxidation of G6P by NADP to form D-6-phosphogluconate and NADPH. The rate of NADPH formation is directly proportional to catalytic CK activity. It is determined by measuring the increase in absorbance at 340nm (main) and 546nm (sub).
Reagent Shelf Life Stability	+ 2 to +8 ºC until expiration date	2-8 ºC until expiration date
Reagent On-Board Stability	On-board in use at +8ºC: 4 weeks	On-board in use and refrigerated on the analyzer: 8 weeks

Assay Comparison Similarities		
Feature	**Predicate Device:** COBAS INTEGRA Creatine Kinase (K951595)	**Candidate Device:** **Creatine Kinase**
Sample Stability	CK activity in serum remains stable for 24h at +22 ºC or 10 days at +4 ºC and -20 ºC.	Stability in serum: 2 days at 20-25 °C 7 days at 4-8 °C 4 weeks at -20 °C Stability in EDTA/heparin plasma: 2 days at 15-25 °C 7 days at 2-8 °C 4 weeks at (-15)-(-25) °C
Measuring Range	0 – 2000 U/L (0 -33.4 µkat/L)	7 – 2000 U/L (0.12-33.4 µkat/L)
Traceability	Traceable to IFCC	This method has been standardized against the IFCC Method for Creatine Kinase
Calibrator	Calibrator (human)	Calibrator for automated systems (C.f.a.s.) (k101456)
Calibration frequency	Each lot	After reagent lot change and as required following quality control procedures
Controls	Control Serum N (human) Control Serum P (human)	Precinorm U plus/Precipath U Plus (k042389) Precinorm CK-MB/Precipath CK-MB (k062972) PreciControl ClinChem Multi 1 and 2 (k102016)
Lower Limits of Measurement	LDL = 0 U/L	LoB = 7 U/L (0.12 µkat/L) LoD = 7 U/L (0.12 µkat/L) LoQ = 7 U/L (0.12 µkat/L)
Reagent Composition	**3 Reagents** R1 liquid, and R2 and SR granulates **R1**: Buffer in vial A (15.8 mL). **R2**: Enzyme granulate in vial B (0.5 g for 12.3 mL). **R3** = SR: Creatine phosphate granulate in vial C (0.7 g for 5 mL).	**2 Reagents** **R1** Imidazole buffer: 123 mmol/L, pH 6.5 (37 °C); EDTA: 2.46 mmol/L; Mg2+: 12.3 mmol/L; ADP: 2.46 mmol/L; AMP: 6.14 mmol/L; diadenosine pentaphosphate: 19 µmol/L; NADP+ (yeast): 2.46 mmol/L; N-acetylcysteine: 24.6 mmol/L; HK (yeast): ≥ 36.7 µkat/L; G6PDH (E. coli): ≥ 23.4 µkat/L; preservative; stabilizers; additives. **R2** CAPSO* buffer: 20 mmol/L, pH 8.8 (37 °C); glucose: 120 mmol/L; EDTA: 2.46 mmol/L; creatine phosphate: 184 mmol/L; preservative; stabilizers. *CAPSO:3(-cyclohexylamine)-2-hydroxy-1-propanesulfonic acid

4. NON-CLINICAL PERFORMANCE EVALUATION

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

Detection Limitaccording 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

All performance specifications were met. Cyanokit (Hydroxocobalamin) at therapeutic concentrations was found to interfere with the test.

4.1. Detection Limits according to CLSI EP17-A2

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

LoB: The concentration at which there is a 95% probability that a sample is analyte-free.

For determination of LoB one analyte free sample was measured with three lots in 10-fold determination in 6 runs, distributed over 3 days, on one **c** 501 analyzer. In total, 60 measurements were obtained per lot. Data analysis is based on determination of the 95th percentile of the 60 measured values.

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

For determination of LoD five samples with low-analyte concentration (approximately up to 4 times the LoB) will be measured with three lots in two-fold determination in 6 runs, distributed over 3 days, on one **c** 501 analyzer. In total 60 measurements will be obtained per lot.

LoQ: The lowest analyte concentration that can be quantitatively determined with a stated acceptable precision and trueness under stated experimental conditions.

A low Level Sample Set was prepared by diluting 5 human serum samples with an analyte free diluent (0.9% NaCl). The Low level Sample Set was tested in 5 replicates per sample on 5 days, one run per day on one **cobas c** 501 analyzer

Table 2: LoB and LoD Results

	Result (U/L)	Claim (U/L)
Limit of Blank (LoB)	0.3	7
Limit of Detection (LoD)	1.0	7
Limit of Quantitation (LoQ)	3.3	7

4.2. Precision according to CLSI EP5-A2

Precision experiments are performed in accordance with CLSI Guideline EP5-A2. Two aliquots per run, two runs per day for ≥ 21 days were performed on the same analyzer using 3 lots of reagent. Repeatability (within run precision) and intermediate precision (within lab precision) were calculated. The samples were randomized in each run separately. For each sample, the following are calculated: mean, repeatability and intermediate precision as CV and SD values, and the upper 95% confidence interval for SD and CV values.

Table 3: Repeatability Summary

Specimen	Mean (U/L)	SD (U/L)	CV (%)
Human Serum 1	18.7	0.6	3.0
Human Serum 2	137	0.8	0.6
Human Serum 3	477	3.0	0.6
Human Serum 4	946	5.3	0.6
Human Serum 5	1816	9.4	0.5
PreciControl ClinChem Multi 1	154	0.9	0.6
PreciControl ClinChem Multi 2	301	1.3	0.4

Table 4: Intermediate Precision Summary

Specimen	Mean (U/L)	SD (U/L)	CV (%)
Human Serum 1	18.7	0.6	3.2
Human Serum 2	137	1.1	0.8
Human Serum 3	477	3.1	0.6
Human Serum 4	946	5.8	0.6
Human Serum 5	1816	10	0.6
PreciControl ClinChem Multi 1	154	1.7	1.1
PreciControl ClinChem Multi 2	301	2.6	0.9

4.3. Linearity according to CLSI EP6-A

Linearity was assessed according to CLSI EP6-A with one batch of reagent, in one run, and with samples measured in triplicate. Two separate dilution series differing by sample type (serum and plasma) were prepared with 14 concentrations. Dilutions were made using 0.9% NaCl.

In a first step, a linearity check was performed with first order (linear) regression and then with higher order models (quadratic and cubic). The linear regression was not forced through the origin. The linear regression was weighted.

Table 5: Linearity results

Sample type	Linear Regression
Serum	y=1.001x-0.646 Pearson correlation coefficient (R)=0.9999
Plasma	y=1.002x-1.205 Pearson correlation coefficient (R)=0.9999

4.4. Matrix Comparison - Anticoagulants

The effect of the presence of anticoagulants on analyte recovery was determined by method comparison, obtained from samples drawn into serum and different types of plasma collection tubes (K2 EDTA, K3 EDTA, Li Heparin, and Gel Separation). For each of the four tube types, 30 tubs were filled completely.

Method comparison was executed by using the serum data as the reference. Slope, Intercept and Correlation were calculated.

Table 6: Matrix Comparison

Anticoagulant	Regression
Serum vs. Serum Gel Separation	y = 0.998x + 0.010, r = 0.999
Serum vs. Li-heparin	y = 1.00x – 1.994, r = 0.998
Serum vs. K2-EDTA	y = 0.993x – 2.016, r = 0.998
Serum vs. K3-EDTA	y = 0.981x – 2.671, r = 0.999

4.5. Interferences - H, L and I Indices

The effects of interference by hemoglobin, lipemia (Intralipid), Bilirubin on the CK test system are determined on the **cobas c** 501 analyzer using pooled human serum samples spiked with varying levels of interferent.

The resulting sample series (10 dilution steps per sample) were tested in triplicate and the median values used to calculate % recovery, by comparing the measured concentration to the expected concentration (which is the CK concentration when no interferent was added).

Table 7: Interference – H, L, I Indices

Interferent	No interference up to	Claim
Hemolysis	Level 1: 103 H Index Level 2: 130 H Index	No significant interference up to an H index of 100 (approximate hemoglobin concentration: 62.1 µmol/L or 100 mg/dL). The level of interference may be variable depending on the exact content of erythrocytes.
Lipemia	Level 1: 1356 L Index Level 2: 1143 L Index	No significant interference up to an L index of 1000. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration. Highly lipemic specimens (L index > 1000) may cause high absorbance flagging. Choose diluted sample treatment for automatic rerun.

Interferent	No interference up to	Claim
Unconjugated Bilirubin	Level 1: 67 I Index Level 2: 67 I Index	No significant interference up to an I index of 60 for conjugated and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 1026 µmol/L or 60 mg/dL)
Conjugated Bilirubin	Level 1: 68 I Index Level 2: 76 I Index	

4.6. Interferences – Drugs

Two sample pools containing a low and high concentration of CK were used. These sample pools were divided into an appropriate number of aliquots. One aliquot is not spiked with the drugs and it was used as the reference sample for CK concentration. The CK concentration in the sample was determined with n = 3 measurements on a **cobas c** 501 analyzer.

The other sample aliquots, with either the high or low CK concentrations, were spiked with the respective amount of drug. The CK concentration of the spiked aliquots were determined in triplicate and the mean of the triplicate determinations was compared to the CK concentration determined for the reference aliquot (mean of n=3).

No interference was found at therapeutic concentrations using common drug panels.

Cyanokit (Hydroxocobalamin) at therapeutic concentrations interferes with the test.

4.7. Method Comparison to Predicate

A total of 132 human serum samples were tested in singlicate with the CK assay on **cobas c** 501 and the CKL assay on INTEGRA 800. 9 of the 132 samples were spiked with human recombinant CK MB.

The data were evaluated using Passing Bablok Regression analysis.

$y = 1.021x + 5.88$ U/L

$r = 0.999$

5. CONCLUSIONS

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