February 27, 2018

Roche Diagnostics
Adennis Cora
Regulatory Affairs Consultant
9115 Hague Road
Indianapolis, Indiana 46250

Re: K171605
Trade/Device Name: Elecsys CA 15-3 II
Regulation Number: 21 CFR 866.6010
Regulation Name: Tumor-associated antigen immunological test system
Regulatory Class: Class II
Product Code: MOI
Dated: May 26, 2017
Received: June 1, 2017

Dear Adennis Cora:

This letter corrects our substantially equivalent letter of February 20, 2018.

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 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 Part

801 and Part 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.

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.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Kelly Oliner -S

For
Lea Carrington
Director
Division of Immunology
and Hematology 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: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K171605

Device Name
Elecsys CA 15-3 II

Indications for Use *(Describe)*

Immunological in vitro assay for quantitative determination of CA 15-3 in human serum and Li-heparin plasma to aid in the management of breast cancer patients. In conjunction with other clinical and diagnostic procedures, serial testing with this assay is an aid

- in the early detection of recurrence in previously treated stage II and III breast cancer patients
- for monitoring response to therapy in metastatic breast cancer patients

The electrochemiluminescence immunoassay "ECLIA" is intended for use on cobas e immunoassay analyzers.

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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Elecsys CA 15-3 II
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.

In accordance with 21 CFR 807.87, Roche Diagnostics hereby submits official notification as required by Section 510(k) of the Federal Food, Drug and Cosmetics Act of our intention to market the device described in this Premarket Notification 510(k).

The purpose of this Traditional 510(k) Premarket Notification is to obtain FDA review and clearance for the Elecsys CA 15-3 II.

Submitter Name	Roche Diagnostics
Address	9115 Hague Road P.O. Box 50416 Indianapolis, IN 46250-0457
Contact	Adennis Cora Phone: (317) 521-3915 FAX: (317) 521-2324 Email: adennis.cora_gress@roche.com
Date Prepared	April 14, 2017
Proprietary Name	Elecsys CA 15-3 II
Common Name	Elecsys Cancer Antigen 15-3 II
Classification Name	System, Test, Immunological, Antigen, Tumor
Product Codes, Regulation Numbers	MOI, 866.6010
Predicate Devices	CA 15-3 II Assay (K001468)
Establishment Registration	For the Elecsys CA 15-3 II, the establishment registration number for Roche Diagnostics GmbH in Mannheim, Germany is 9610126, and for Penzberg, Germany, 9610529. The establishment registration number for Roche Diagnostics in the United States is 1823260.

1. DEVICE DESCRIPTION

The Elecsys CA 15-3 II Test System is a two-step sandwich immunoassay with streptavidin microparticles and electrochemiluminescence detection for the quantitative determination of CA 15-3 in human serum and plasma. It is intended for use on the **cobas e** 411 immunoassay analyzer. The **cobas e** family of analyzers employs the electrochemiluminescence "ECLIA" technology.

Results are determined using a calibration curve that is generated specifically on each instrument by a 2-point calibration and a master curve provided with the reagent barcode.

1.1. Reagents

The **cobas e** pack includes:

- Streptavidin-coated microparticles
- Reagent 1 (Biotinylated monoclonal antibody (115D8; mouse) 1.75 mg/L)
- Reagent 2 (Monoclonal anti-CA 15-3 antibody (DF3; mouse) labeled with ruthenium complex 10 mg/L)

1.2. Calibration

Traceability: This method has been standardized against the Elecsys CA 15 3 assay. This in turn has been standardized against the Enzymun Test CA 15 3 method and CA 15 3 RIA by Fujirebio Diagnostics. The predefined master curve is adapted to the analyzer using the relevant CalSet. Calibration frequency: Calibration must be performed once per reagent lot using fresh reagent (i.e. not more than 24 hours since the **cobas e** pack was registered on the analyzer). Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

1.3. Control

PreciControl Tumor Marker is used for the quality control verification of the performance of the assay on the **cobas e** analyzers.

2. INDICATIONS FOR USE

Immunological in vitro assay for quantitative determination of CA 15-3 in human serum and Li-heparin plasma to aid in the management of breast cancer patients. In conjunction with other clinical and diagnostic procedures, serial testing with this assay is an aid

- in the early detection of recurrence in previously treated stage II and III breast cancer patients
- for monitoring response to therapy in metastatic breast cancer patients.

The electrochemiluminescence immunoassay "ECLIA" is intended for use on **cobas e** immunoassay analyzers.

3. TECHNOLOGICAL CHARACTERISTICS

The following table compares the Elecsys CA 15-3 II with its predicate device, CA 15-3 (K001468). In summary, the Elecsys CA15-3 II described in this submission is substantially equivalent to the predicate device.

Feature	CA 15-3 II (Cleared K001468)	Elecsys CA 15-3 II
Intended use	For the quantitative determination of CA 15-3 in human serum and plasma.	for quantitative determination of CA 15□3 in human serum and Li-heparin plasma
Indication for use	To aid in the management of breast cancer patients. In conjunction with other clinical and diagnostic procedures, serial testing with CA 15-3 assay is an aid in the early detection of recurrence in previously treated Stage II and III breast cancer patients. For monitoring response to therapy in metastatic breast cancer patients.	Same
Sample Type	Human serum and plasma treated with heparin (Li-, Na-) or K3-EDTA plasma	human serum and Li-heparin plasma
Analytical Specificity	Based on monoclonal 115D8 and DF3 antibodies available from Centocor	Same

Feature	CA 15-3 II (Cleared K001468)	Elecsys CA 15-3 II
Instrument Platform	Elecsys 2010 MODULAR *ANALYTICS* E170 **cobas e** 411 **cobas e** 601 **cobas e** 602	**cobas e** 801
Measuring Range	1.0 – 300 U/mL Determined by LDL (2SD)	3 – 300 U/mL Determined by LOQ (Per EP17-A2)
Biotin	Added to R2	Same
Prewash	No Prewash	Prewash Added
Sample Dilution	1:10	1:20
LoD	< 1.0 U/mL	1.5 U/mL
LoB	N/A	1.0 U/mL
LoQ	N/A	3 U/mL
Lower Detection Limit	< 1.00 U/mL	N/A

4. NON-CLINICAL PERFORMANCE EVALUATION

Non-clinical performance evaluation for the Elecsys CA 15-3 II are briefly summarized below:

4.1. Precision

Precision of the Elecsys CA 15-3 II assay was evaluated on one **cobas e** 801 Immunoassay Analyzer according to CLSI EP5-A3 guideline. One reagent lot was evaluated.

The protocol consisted of testing 2 replicates of each control (PC Tumor Marker = PreciControl Tumor Marker) and five pooled human sera (HS) samples per run, 2 runs per day for 21 days. The samples were run in randomized order on the **cobas e** 801 analyzer. To obtain samples with higher concentration, low sample pools were spiked with a high concentrated native sample (pool)..

4.2. Analytical Sensitivity

4.2.1. Limit of Blank (LoB)

LoB of the Elecsys CA 15-3 II assay on the **cobas e** 801 Immunoassay Analyzer has been determined according to CLSI EP17-A2.

Limit of Blank determines the highest observed measurement values for samples free of analyte. The Limit of Blank was determined as the 95th percentile of measurements of blank samples. The Limit of Blank was determined by performing one run per day from three reagent lots on one **cobas e** 801 instrument, over six days. The testing included one blank sample with ten replicates per run for a total of sixty total blank replicates per reagent lot.

4.2.2. Limit of Detection (LoD)

LoD of the Elecsys CA 15-3 assay on the **cobas e** 801 Immunoassay Analyzer has been determined according to CLSI EP17-A2.

The LoD was determined as the lowest amount of analyte in a sample that can be detected with 95% probability. The Limit of Detection was determined by performing one run per day from three reagent lots on one **cobas e** 801 instrument, over six days. The testing included two replicates per sample (5 samples) per run for a total of sixty total blank replicates per sample per reagent lot.

4.2.3. Limit of Quantitation (LoQ)

The LoQ of the Elecsys CA 15-3 II assay was determined on the **cobas e** 801 Immunoassay Analyzer according to CLSI Guideline EP17-A2.

A set of ten human serum samples (single donors, native as well as diluted) with concentrations in the specified LoQ-area was evaluated for each of 3 reagent lots.

The mean value and the intermediate precision as coefficient of variation (CV) and standard deviation (SD) for each LoQ sample were calculated. The Limit of Quantitation was determined by performing one run per day from three reagent lots on one **cobas e** 801 instrument, over five days. The testing included ten samples, each with five replicates per daily run over 5 days for a total of twenty five replicates per sample per reagent lot.

4.3. High-Dose Hook Effect

The high-dose hook effect of the Elecsys CA 15-3 II assay was assessed on the **cobas e** 801 analyzer in three-fold determination. Two samples were spiked with analyte to achieve high CA 15-3 concentrations. For each sample, a dilution series was performed using native human

serum. The hook concentration reported corresponds to the highest analyte concentration that generates a signal ≥10% above the upper limit of the measuring range.

4.4. Linearity/Assay Reportable Range

Linearity of the Elecsys CA 15-3 II assay was evaluated using the **cobas e** 801 Immunoassay Analyzer according to CLSI EP6-A.

Three high analyte serum samples and three high analyte plasma samples (serum/plasma pool, spiked) were diluted with Elecsys Universal Diluent. 15 concentrations (dilutions) throughout the measuring range were prepared. Samples were assayed in 3-fold determination within a single run.

The linearity data were analyzed with regards to linear, quadratic and cubic polynomials according to CLSI EP6-A. In a first step, a linearity check was performed with a first order (linear) regression and then with higher order models (quadratic and cubic).

All deviations were within predetermined acceptance criteria.

4.5. Endogenous Interferences

The effect on quantitation of analyte in the presence of endogenous interfering substances using the Elecsys CA 15-3 II was determined on the **cobas e** 801 Immunoassay analyzer using human serum samples.

For each interfering substance three human serum samples containing low (pooled sera), mid (pooled spiked sera) and high (pooled spiked sera) concentrations of CA 15-3 were tested.

4.6. Hemolysis/Bilirubin/Lipemia/Biotin

Biotin:

One aliquot of each serum sample was spiked with the interfering substance, another aliquot was spiked with the same volume of isotonic NaCl solution (dilution pool). The interfering pool was then diluted into the dilution pool in 10% increments.

The recovery for each sample was calculated by comparison to the reference (unspiked) sample.

In conclusion, the specification was met for all substances tested, as each substance was found to be non-interfering at the spiked concentration.

Lipemia:

One aliquot of each serum sample was spiked with the interfering substance, and another aliquot was spiked with the same volume of isotonic NaCl solution (dilution pool). The interfering pool was then diluted into the dilution pool in 10% increments.

The recovery for each sample was calculated by comparison to the reference (unspiked) sample.

In conclusion, the specification was met for all substances tested, as each substance was found to be non-interfering at the spiked concentration.

Hemoglobin:

Fresh hemolysate was prepared from fresh EDTA or heparin blood. One aliquot of each serum sample was spiked with the hemolysate (interfering pool), another aliquot was spiked with the same volume of isotonic NaCl solution (dilution pool). The interfering pool was then diluted into the dilution pool in 10% increments. The recovery for each sample was calculated by comparison to the reference (unspiked) sample.

In conclusion, the specification was met for all substances tested, as each substance was found to be non-interfering at the spiked concentration.

Bilirubin:

One aliquot of each serum sample was spiked with the interfering substance, and another aliquot with was spiked with the same volume of the solvent (0.1 mol/L NaOH) of the interfering

substance (dilution pool). The interfering pool was then diluted into the dilution pool in 10% increments.

HAMA:

The effect of the presence of human anti-mouse antibodies on the Elecsys CA 15-3 II assay was assessed on the **cobas e** 801 Immunoassay Analyzer.

The specified HAMA-serum with a concentration of 805 ng/mL and the related reference serum (without interferent) was measured in two-fold determination over 3 levels. Recovery of the HAMA-serum compared to the reference serum sample was calculated.

In conclusion, the specification was met for all substances tested, as each substance was found to be non-interfering at the spiked concentration.

Rheumatoid Factors Interference:

One aliquot of each serum sample was spiked with the interfering substance, and another aliquot with the same volume of the solvent (buffer matrix) of the interfering substance (dilution pool). The interfering pool was then diluted into the dilution pool in 10% increments.

The recovery for each sample was calculated by comparison to the reference sample.

In conclusion, the specification was met for all substances tested, as each substance was found to be non-interfering at the spiked concentration.

4.7. Exogenous Interferences – Anticoagulants

The effect on quantitation of analyte in the presence of anticoagulants with the Elecsys CA 15-3 II Immunoassay was determined by comparing values obtained from samples (native) drawn into Serum, and Li-Heparin plasma.

Forty nine native samples were tested with one reagent lot on one **cobas e** 801 Immunoassay Analyzer. Potential effects are assessed by Passing/Bablok regression analysis.

4.8. Method Comparison to cobas e 601 Immunoassay Analyzer

A method comparison was performed using the **cobas e** 601 immunoassay analyzer as predicate device. The study was performed on the **cobas e** 601 immunoassay analyzer (X) and on the **cobas e** 801 analyzer (Y).

A total of 190 human serum samples (all single donors, native samples) were measured with Elecsys CA 15-3 II immunoassay on both analyzers in singleton covering the entire measuring range. Mean values ranges between 5.14 – 290 U/mL for the **cobas e** 601 analyzer and between 4.24 – 273 U/mL for the **cobas e** 801 analyzer.

Evaluation was performed for all samples within the measuring range of both assays and in compliance with Standard Operation Procedures of Roche Diagnostics GmbH. Passing/Bablok and linear regression analysis was performed according to CLSI EP09-A3.

4.9. Reagent Stability

To test reagent stability, two studies were executed with one study completed including:

Study 1. On board reagent stability (16 weeks)

Study 2. A real-time stability study is ongoing to support shelf-life stability claim.

4.9.1. Study 1- Onboard reagent stability (for 16 weeks)

Elecsys CA 15-3 II reagent kits can be stored on board of the analyzers for up to 16 weeks.

A new calibration of the kit kept on-board is recommended every 28 days.

Onboard Reagent Stability and Calibration Stability for the Elecsys CA 15-3 II assay was tested on one **cobas e** 801 Immunoassay Analyzer.

A fresh **cobas e** pack was placed on the analyzer and calibrated. Reference values for the samples tested were determined (day 0). After 5, 9, 13 and 17 weeks the same samples were measured with the same reagent kit kept under onboard condition. Re-calibration was performed at every measuring time point.

Samples tested include six human serum (HS) samples. Each sample was tested in two-fold determination. The human serum samples used were pooled sera for sample ranges low, Decision range 1 and 2, and pooled spiked sera for sample ranges medium and high.

4.9.2. Study 2 - Reagent Real-time Stability

In the real-time stability study, the Elecsys CA 15-3 II reagent was stored at 2-8°C. The stored assay reagents were tested at time point T=0 (after manufacturing) and at specified intervals over the shelf life of the device. Testing was performed using PreciControl Tumor Marker Level 1 and 2 (lyophilized, stored at +2 to +8°C) for lot-numbers 156423, 158287 and 174942.

Data for lot no. (in months):

156423 for the time-points at 0, 15, 19, 30

158287 for the time-points at 0, 13, 17, 25

174942 for the time-points at 0, 12, 15, 19

The average on-test recovery value will be calculated as percent recovery compared to the reference value (assigned value for PreciControl Tumor Marker Level 1 and 2).

4.10. Sample Stability

To test sample stability, three studies were completed, including:

Study 1. Sample stability at 2-8°C

Study 2. Sample stability at Room Temperature (20-25°C)

Study 3. Sample stability -20°C (± 5 °C)

4.10.1. Study 1-Sample Stability at 2-8°C

Ten samples for each sample type (Serum, and Li-Heparin plasma) were aliquoted and measured after storage at 2-8°C for 9 days. The aliquot for the reference value was stored at -80°C and measured at the same time point. Measurements were performed with three-fold determination on a **cobas e** 601 Immunoassay Analyzer and recovery was calculated as percent of the reference value. The samples used were all single donors (native, spiked as well as diluted).

4.10.2. Study 2-Sample Stability at Room Temperature (20-25°C)

Ten samples for each sample type (Serum, and Li-Heparin plasma) were aliquoted and measured after storage at 20-25°C for 8 days. The aliquot for the reference value was stored at -80°C and measured at the same time point.

Measurements were performed with three-fold determination on a **cobas e** 601 Immunoassay Analyzer and recovery was calculated as percent of the reference value.

The samples used were all single donors (native, spiked as well as diluted).

4.10.3. Study 3-Sample Stability at -20°C (±5°C)

Ten samples for each sample type (Serum, and Li-Heparin plasma) were aliquoted and measured after storage at - 20°C for 53 weeks. The aliquot for the reference value was stored at -80°C and measured at the same time point.

Measurements were performed with three-fold determination on a **cobas e** 601 Immunoassay Analyzer and recovery was calculated as percent of the reference value.

The samples used were all single donors (native, spiked as well as diluted).

4.11. Calibration Stability

To test calibration stability, two studies were completed, including:

Study 1. Lot calibration stability

Study 2. On-board calibration stability

4.11.1. Study 1-Lot Calibration Stability

Calibration of an Elecsys CA 15-3 II reagent lot is recommended every 12 weeks. During that time period fresh reagent kits of the same lot can be used without calibration using the calibration curve of the Day 0 reagent kit.

Elecsys CA 15-3 II was calibrated with a fresh reagent kit on Day 0 using a **cobas e** 801 Immunoassay Analyzer. After 13weeks a new reagent kit of the same lot was used and recovery of samples was determined using the calibration curve of day 0.

Five human serum (HS) samples were tested; each sample was tested with two-fold determination. The human serum samples used were pooled diluted sera for sample range low, pooled sera for Decision range, and pooled spiked sera for sample ranges medium and high.

4.11.2. Study 2-On-board Calibration Stability

Elecsys CA 15-3 II reagent kits can be stored on board of the analyzers for up to 28 days without a new calibration.

Reagent On-board Calibration stability for the Elecsys CA 15-3 II assay was tested on one **cobas e** 801 Immunoassay Analyzer.

A fresh Reagent **cobas e** pack was placed on the analyzer and calibrated. All samples were measured on day 0. On day 29 the same samples were measured with the same reagent kit kept under on-board conditions using the calibration curve established on day 0.

Samples tested include six human serum (HS) samples. Each sample was tested in two-fold determination. The human serum samples used were pooled diluted sera for sample range low, pooled sera for Decision range, and pooled spiked sera for sample ranges medium and high.

5. CONCLUSIONS

The information provided in this 510(k) Premarket Notification will support a determination of substantial equivalence for the Elecsys CA 15-3 II test system. The data supports a safe, effective device which performs as well as or better than the predicate device.