February 27, 2020

Roche Diagnostics
Reanna Toney
Principal, Regulatory Affairs
9115 Hague Road
Indianapolis, Indiana 46250

Re: K193313
Trade/Device Name: Elecsys Anti-TSHR
Regulation Number: 21 CFR 866.5870
Regulation Name: Thyroid autoantibody immunological test system
Regulatory Class: Class II
Product Code: JZO
Dated: November 26, 2019
Received: November 29, 2019

Dear Reanna Toney:

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. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. 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) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; 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 https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). 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 (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Carolina Kagan, M.Sc.
Acting Chief
Division of Immunology
and Hematology Devices
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
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)*
K193313

Device Name
Elecsys Anti-TSHR

Indications for Use *(Describe)*
Immunoassay for the in vitro quantitative determination of autoantibodies to thyroid stimulating hormone (TSH) receptor in human serum using a human thyroid stimulating monoclonal antibody. The anti-TSH receptor determination is used in the assessment of patients suspected of Graves' disease (autoimmune hyperthyroidism).
The electrochemiluminescence immunoassay "ECLIA" is intended for use on cobas e 601 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 Anti-TSHR
510(k) Summary
K193313

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 Anti-TSHR.

Submitter Name	Roche Diagnostics
Address	9115 Hague Road P.O. Box 50416 Indianapolis, IN 46250-0457
Contact	Reanna Toney Phone: (317) 521-4516 FAX: (317) 521-2324 Email: reanna.toney@roche.com Secondary Contact: Tammy Dean Phone: (317) 521-3978 FAX: (317) 521-2324 Email: tammy.dean@roche.com
Date Prepared	February 26, 2020
Proprietary Name	Elecsys Anti-TSHR CalSet Anti-TSHR PreciControl ThyroAB
Common Name	anti-TSHR
Classification Name	System, Test, Thyroid Autoantibody Calibrator, Secondary Single (specified) analyte controls (assayed and unassayed)
Product Codes, Regulation Numbers	JZO, 21 CFR 866.5870 JIT, 21CFR862.1150, EXEMPT JJX, 21CFR862.1660, EXEMPT
Predicate Devices	Elecsys Anti-TSHR Immunoassay (K080092)
Establishment Registration	For the Elecsys Anti-TSHR, 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 Anti-TSHR is used for the in vitro quantitative determination of autoantibodies to TSHR receptor in human serum using a human thyroid stimulating monoclonal antibody. It is intended for use on the **cobas e** 601 immunoassay analyzer. The **cobas e** family of analyzers uses electrochemiluminescence immunoassay "ECLIA" technology.

1.1. Reagents

The reagent working solutions include:

Reagent rackpack (kit placed on the analyzer)

- M Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative.
- R1 Buffer solution (gray cap), 1 bottle, 7 mL: Phosphate buffer 20 mmol/L, pH 7.4; stabilizers, preservative.
- R2 Anti TSHR~Ru(bpy) (black cap), 1 bottle, 7 mL: Monoclonal anti TSHR antibody M22 (human) labeled with ruthenium complex approximately 0.3 mg/L; phosphate buffer 20 mmol/L, pH 7.4; stabilizers, preservative.

Pretreatment rackpack

- PT1 Pretreatment buffer solution (black cap), 1 bottle, 4 mL: Phosphate buffer 20 mmol/L, pH 7.4; stabilizers, preservative.
- PT2 Empty bottle (white cap) for pretreatment reagent (PTR) reconstituted with pretreatment buffer (PTB).k Pack
- PTR Pretreatment reagent, pTSHR-anti-pTSHR-Ab~biotin complex (white cap), 1 bottle for 4 mL of PTB: Phosphate buffer 40 mmol/L, pH 7.2; stabilizers.
- PTB Pretreatment buffer (white cap), 1 bottle, 5 mL:Reconstitution medium for PTR; phosphate buffer 10 mmol/L, pH 7.2; stabilizer.

2. INDICATIONS FOR USE

Immunoassay for the in vitro quantitative determination of autoantibodies to thyroid stimulating hormone (TSH) receptor in human serum using a human thyroid stimulating monoclonal antibody. The anti-TSH receptor determination is used in the assessment of patients suspected of Graves' disease (autoimmune hyperthyroidism).

The electrochemiluminescence immunoassay "ECLIA" is intended for use on the **cobas e** 601 immunoassay analyzers.

3. TECHNOLOGICAL CHARACTERISTICS

The following table lists the technical characteristics from the Elecsys Anti-TSHR method sheet.

Table 1: Elecsys Anti-TSHR Technical Characteristics

Feature	Elecsys Anti-TSHR
Technology	ECLIA
Application/test time	18 minutes
Instrument platform	**cobas e** 601 immunoassay analyzers
Test format	Competition
Test type	Quantitative
Assay protocol	Sample+PT1+PT2, incubation, +R1, incubation, + R2
Handling of R1 and R2	Liquid, Ready for use
Sample Type/Matrix	serum
Measuring Range	0.8 – 40 IU/L

Table 2: Substantial Equivalency

Item	Elecsys Anti-TSHR (K080092)	Elecsys Anti-TSHR (K193313)
Proprietary name	Elecsys Anti-TSHR Immunoassay	Elecsys Anti-TSHR
Catalog number	04388780 160	08496609 190
Intended use	Immunoassay for the in vitro quantitative determination of autoantibodies to TSH receptor in human serum using a human thyroid stimulating monoclonal antibody. The anti-TSH receptor determination is used in the assessment of patients with suspect Graves' disease (autoimmune hyperthyroidism). The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and **cobas e** immunoassay analyzers.	Immunoassay for the in vitro quantitative determination of autoantibodies to thyroid stimulating hormone (TSH) receptor in human serum using a human thyroid stimulating monoclonal antibody. The anti-TSH receptor determination is used in the assessment of patients suspected of Graves' disease (autoimmune hyperthyroidism). The electrochemiluminescence immunoassay "ECLIA" is intended for use on the **cobas e** 601 immunoassay analyzer.
Technology	ECLIA	Same
Test format	Competitive	Same
Test type	Quantitative	Same
Assay protocol	sample+PT1+PT2, incubation, +R1, incubation, +beads+R2, incubation	Same
Pipetting volume sample	50 µL	Same
Pretreatment buffer solution (PT1)	10 µL	Same
Pretreatment reagent buffer (PT2)	20 µL	Same
Pipetting volume M (beads)	30 µL	Same
Pipetting volume R1	40 µL	Same
Pipetting volume R2	50 µL	Same
Handling of PT1	Liquid, ready to use	Same
Handling of PT2	Mix pretreatment reagent (PTR) + 4 mL of pretreatment buffer (PTB)	Same
Handling of R1 and R2	Liquid, ready to use	Same
Measuring range	0.800 – 40.0 IU/L	Same
Biotin tolerance	Up to 10 ng/mL	Up to 600 ng/mL

Expected values	In an external study using the Elecsys Anti-TSHR assay on samples from 436 apparently healthy individuals, 210 patients with thyroid diseases* without diagnosis of Graves' disease, and 102 patients with untreated Graves' disease an optimal cutoff of 1.75 IU/L was determined. At this cutoff the sensitivity was calculated at 96 % and the specificity at 99 %.	In an external study using the Elecsys Anti-TSHR assay on samples from 436 apparently healthy individuals, 210 patients with thyroid diseases* without diagnosis of Graves' disease, and 102 patients with untreated Graves' disease an optimal cutoff of 1.75 IU/L was determined. Assay values less than or equal to the cut-off, 1.75 IU/L, are considered negative. Values greater than the cut-off are considered positive. At this cutoff the sensitivity was calculated at 96 % and the specificity at 99 %.
Buffer composition R1	Phosphate buffer 20 mmol/L	Same
Biotinylated antibody	MAK<TSHR>M-4E31-IgG-Bi (DDS* mono)	MAK<TSHR>M-4E31-IgG-Bi(PEG**, mono)
Buffer composition R2	Phosphate buffer 20 mmol/L	Same
	-	Anti-Biotin Antibody; specific for free, unconjugated biotin ("scavenger antibody")

4. NON-CLINICAL PERFORMANCE EVALUATION

The non-clinical performance studies for Elecsys Anti-TSHR are summarized below.

4.1. Precision

4.1.1. Repeatability and Intermediate Precision

Precision of the Elecsys Anti-TSHR assay was evaluated on one **cobas e** 601 immunoassay analyzer with one reagent lot. The protocol consisted of testing 2 replicates of each control level and human sera (HS) per run, 2 runs per day for 21 days. The samples were run in randomized order on the analyzer. Human serum samples used were native human serum pools (human serum 1-4) and spiked human serum (human serum 5). Repeatability and Intermediate imprecision were calculated according to EP05-A3. All samples met the predetermined acceptance criterion.

The following table summarizes the precision data for Elecsys Anti-TSHR.

		Repeatability		Intermediate Precision	
Sample	Mean IU/L	SD IU/L	CV %	SD IU/L	CV %
Sample 1	1.41	0.105	7.5	0.129	9.1
Sample 2	1.87	0.140	7.5	0.161	8.6
Sample 3	1.99	0.114	5.7	0.144	7.2
Sample 4	22.7	0.252	1.1	0.347	1.5
Sample 5	37.5	0.298	0.8	0.505	1.3
PC ThyroAB 1	4.42	0.145	3.3	0.178	4.0
PC ThyroAB 2	18.1	0.342	1.9	0.397	2.2

4.1.2. FDA requested Lot-to-Lot Reproducibility

Lot-to-lot reproducibility of the Elecsys Anti-TSHR assay was evaluated on one **cobas e** 601 analyzer using three reagent lots. A precision study was performed with 2 replicates of each human sera (HS) per run, 2 runs per day (n = 28 determinations per lot, 3x7x2x2 measurements for each sample). The samples were run in randomized order on the analyzer. Human serum samples used were human serum pools (human serum 1-4) as well as spiked human serum (human serum 5).

Repeatability, Between-Run, Between-Day, Between-Lot and Total imprecision were calculated according to EP05-A3. Calculated SD´s and CV´s for the multiple lot (reproducibility) study are comparable to those of the single lot (intermediate) precision study over 21 days using only one reagent lot indicating that the updated assay performs consistently from lot to lot.

4.2. Analytical Sensitivity

4.2.1. Limit of Blank (LoB)

LoB of the Elecsys Anti-TSHR was determined according to CLSI EP17-A2. The experimental design included three reagent lots evaluated on one **cobas e** 601 analyzer, six runs on ≥ three days, with five blank samples with two replicates each per run. In total, 60 determinations for analyte free samples have been obtained. All lots met the predetermined acceptance criterion. The LoB claim in the labeling will be set to 0.5 IU/L.

4.2.2. Limit of Detection (LoD)

LoD of the Elecsys Anti-TSHR was determined according to CLSI EP17-A2. The experimental design included three reagent lots evaluated on one **cobas e** 601 analyzer, six runs on ≥ three days, with five low analyte samples with two replicates each per run. Sixty (60) replicates per sample per reagent lot were run. All lots met the predetermined acceptance criterion. The LoD claim in the labeling will be set to 0.8 IU/L.

4.2.3. Limit of Quantitation (LoQ)

LoQ of the Elecsys Anti-TSHR was determined according to CLSI EP17-A2. The experimental design included three reagent lots evaluated on one **cobas e** 601 analyzer for 5 days, one run per day. There were 25 replicates per sample per reagent lot. All lots met the predetermined acceptance criterion. The LoQ claim in the labeling will be set to 1.1 IU/L.

4.3. Linearity/Assay Reportable Range

The linearity study was conducted to demonstrate that there exists a mathematically verified linear relationship between the determined values and the true concentrations across the claimed measuring range. The study was performed according to CLSI guideline EP06-A.

Three high analyte human serum samples (serum pools) were diluted with anti-TSHR free serum. 14 concentrations (13 dilutions) throughout the measuring range were prepared. Samples were measured in triplicate 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). If a first order polynomial gives the best fit, the tested measuring range is linear. If a better fit is obtained with a 2nd or 3rd order polynomial, the difference between this polynomial and the 1st order polynomial is calculated. The difference must be within specification across the entire measuring range.

All deviations were within predetermined acceptance criteria. Linearity was confirmed in the range from 0.8 to 40.0 IU/L.

4.4. High Dose Hook Effect

Not Applicable

4.5. Human Anti-Mouse Antibodies (HAMA)

The Elecsys Anti-TSHR is not susceptible to interference from Human Anti-Mouse Antibodies (HAMA).

4.6. Endogenous Interference

The purpose of this study was to evaluate endogenous substances for potential interference with the parameters measured with the Elecsys Anti-TSHR on the **cobas e** 601 analyzer.

4.6.1. 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. The recovery for each sample was calculated by comparison to the reference (unspiked) sample. The claim of package insert has been set to ≤ 600 ng/mL.

4.6.2. Hemolysis

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. The claim of package insert has been set to ≤ 400 mg/dL.

4.6.3. Bilirubin

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. The claim of package insert has been set to ≤ 25 mg/dL.

4.6.4. Lipemia

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. The claim of package insert has been set to ≤ 1500 mg/dL.

4.6.5. Rheumatoid Factors (RF) Interference

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. The claim of package insert has been set to ≤ 600 IU/mL.

4.6.6. Summary

Table 3: Summary of Endogenous Interference Results

Potential Interferent	**Concentration**
Hemolysis	400 mg/dL
Bilirubin	25.0 mg/dL
Lipemia	1500 mg/dL
Biotin	600 ng/mL
Rheumatic Factor	600 IU/mL

4.7. Analytical Specificity/Cross-Reactivity

The effect on quantitation of analyte in the presence of potential cross-reacting compounds using the Elecsys Anti-TSHR was determined on the **cobas e** 601 analyzer using a native human serum sample pool. For each potential cross-reacting compound a human serum sample with a low concentration level of anti-TSHR was tested. Results from these spiked serum samples were matched against the unspiked references and the % cross-reactivity was calculated. All cross-reactivities met the predefined acceptance criterion at the specified concentration level of the corresponding cross reactant.

No influence with human autoantibodies to thyroglobulin (< 4000 IU/mL) or anti-TPO (< 600 IU/mL) was detectable.

Cross-reactant	**Concentration tested** **mIU/ML**
Human LH	< 10000
Human FSH	< 10000
hCG	< 50000

4.8. Exogenous Interferences – Drugs

The effect on quantitation of analyte in the presence of drugs was determined by comparing values obtained from samples spiked with 17 commonly and 13 specially used pharmaceutical compounds with the reference sample (unspiked). Two human serum samples (native serum pools) were used and tested on the **cobas e** 601 analyzer. The drug concentrations tested correspond at least to the three times maximum daily doses (or the one-time maximum daily dose, respectively). Drug interferences are measured based on recommendations given in CLSI guidelines EP7-ED3 and EP37-ED1 and other published literature. For all drugs tested, the specification was met as each compound was found to be non-interfering at the drug concentration as listed. The method sheet will include an interference claim for Heparin.

Drug	**Concentration tested** **mg/L**
Amiodarone	≤ 200
Carbimazole	≤ 30
Fluocortolone	≤ 20
Hydrocortisone	≤ 200
Iodide	≤ 0.040
Levothyroxine	≤ 0.250
Liothyronine	≤ 0.015
Thiamazole	≤ 16
Octreotide	≤ 0.300
Perchlorate	≤ 400
Prednisolone	≤ 20
Propranolol	≤ 240
Propylthiouracil	≤ 60

4.9. Method Comparison to Predicate

A method comparison was performed using the Elecsys Anti-TSHR updated assay (candidate device) and the current Elecsys Anti-TSHR immunoassay (predicate device) to assess the bias between the two assays. A total of 260 clinical samples from the intended use population were measured with both assays in singleton on the **cobas e** 601 analyzer covering the entire measuring range. From these measurements, positive percent agreement, negative percent agreement, and total percent agreement were calculated.

Table 4: Agreement between Elecsys Anti-TSHR and Predicate

	% Agreement	**95% Confidence Interval**
Positive Percent Agreement (PPA)	97.37	93.43 – 98.97
Negative Percent Agreement (NPA)	95.37	89.62 – 98.01
Overall Percent Agreement (TPA)	96.54	93.55 – 98.17

An additional method comparison study was performed using the Elecsys Anti-TSHR updated assay (candidate device, Y) and the current Elecsys Anti-TSHR immunoassay (predicate device, X) to assess the bias between the two assays. From the 260 samples collected and analyzed, a subset of 120 samples, evenly distributed across the measuring range, were used for regression analysis (Passing/Bablock method).

N = 120	
Passing/Bablok	95% CI
y = 1.047x-0.068	Slope = 1.029 to 1.064
r = 0.998	Intercept = -0.188 to 0.032

4.10. Stability

The stability studies and acceptance criteria have been reviewed and found to be acceptable. The stability data supports Roche Diagnostic's claims as reported in the package inserts.

5. CONCLUSION

The information provided in this 510(k) Premarket Notification will support a determination of substantial equivalence for the Elecsys Anti-TSHR. The data from the nonclinical tests demonstrate that the device is as safe, as effective, and performs as well as or better than the predicate device.