Elecsys TSH K190773
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 TSH.

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Date Prepared	March 25, 2019
Proprietary Name	Elecsys TSH
Common Name	TSH
Classification Name	Radioimmunoassay, thyroid-stimulating hormone
Product Codes, Regulation Numbers	JLW, 21CFR862.1690
Predicate Device(s)	Elecsys TSH (current version)
Establishment Registration	For the Elecsys TSH, 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 TSH immunoassay makes use of a sandwich test principle using monoclonal antibodies specifically directed against human TSH. The antibodies labeled with ruthenium complex) consist of a chimeric construct from human and mouse specific components. The Elecsys TSH immunoassay is used for the in vitro quantitative determination of thyroid stimulating hormone in human serum and plasma. It is intended for use on the **cobas e** immunoassay analyzers.

1.1. Reagents

The reagent working solutions include: Rack Pack (kit placed on the analyzer)

- M: Streptavidin-coated microparticles, 1 bottle, 14.1 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative.
- R1: Anti-TSH-Ab~biotin, 1 bottle, 15.8 mL: Biotinylated monoclonal anti TSH antibody (mouse) 2.0 mg/L; phosphate buffer 100 mmol/L, pH 7.2; preservative.
- R2: Anti-TSH-Ab~Ru(bpy), 1 bottle, 13.9 mL: Monoclonal anti TSH antibody (mouse/human) labeled with ruthenium complex 1.5 mg/L; phosphate buffer 100 mmol/L, pH 7.2; preservative.

The following changes are proposed to block the interference of biotin with the Elecsys TSH assay. Briefly, Roche is taking a two-step approach by adding an antibody to bind free biotin in the sample, and changing the linker on the biotinylated capture antibody.

For the neutralization of free biotin in serum and plasma, Roche developed an antibody which binds to free biotin. The antibodies are specific for free biotin and do not bind to, or interact with, the biotin-linker conjugates.

In the updated biotinylated antibody conjugate, the distance between biotin and the reactive MEA group is elongated by a PEG spacer which provides the coupled biotin more flexibility for the interaction with the Streptavidin matrix. No change is made to the antibody (immunologically reactive component) which still recognizes the same epitope.

2. INDICATIONS FOR USE

Immunoassay for the in vitro quantitative determination of thyrotropin in human serum and plasma. Measurements of TSH are used in the diagnosis of thyroid and pituitary disorders.

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

3. TECHNOLOGICAL CHARACTERISTICS

The following table compares the Elecsys TSH (K190773) with its predicate device, Elecsys TSH (K162606).

Feature	Elecsys TSH (K162606)	Elecsys TSH (K190773)
Intended Use/Indications for Use	Elecsys TSH immunoassay is intended for the in vitro quantitative determination of thyrotropin in human serum and plasma. Measurements of TSH are used in the diagnosis of thyroid and pituitary disorders. The Elecsys TSH immunoassay is an electrochemiluminescence immunoassay "ECLIA", which is intended for use on the **cobas e** immunoassay analyzers.	Same.
Detection Method	Electrochemiluminescence "ECLIA"	Same
Applications/Test Time	18 minute	Same
Test Format	Sandwich	Same
Instrument Platform	**cobas e** immunoassay analyzers	Same
Test Type	Quantitative	Same
Assay Protocol	R1+R2+sample, incubation, +beads, incubation	Same
Handling of R1 and R2	Liquid, ready to use	Same
Pipetting volume	50 µL	Same
Sample Type/Matrix	Human serum, plasma	Same
Sample Anticoagulants	Li-heparin, K_2-EDTA and K_3-EDTA plasma.	Same
Calibrator	TSH CalSet	Same
Calibration Method	2-point calibration	Same

Feature	Elecsys TSH (K162606)	Elecsys TSH (K190773)
Calibration Interval	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.	Same
Controls	PreciControl Universal and PreciControl TS	Same
Traceability/ Standardization	2nd IRP WHO Reference Standard 80/558	Same
Reagent Stability	Store at 2 8 °C. Do not freeze. Store the **cobas e** pack upright in order to ensure complete availability of the microparticles during automatic mixing prior to use. Unopened at 2-8°C – up to stated expiration date On the **cobas e** 801 analyzer – 16 weeks	Same
Limitations	Biotin ≤ 102 nmol/L or ≤ 25 ng/mL Samples should not be taken from patients receiving therapy with high biotin doses (i.e. > 5 mg/day) until at least 8 hours following the last biotin administration.	Two-step approach adding an antibody to bind free biotin in the sample and changing the linker on the biotinylated capture antibody. Biotin ≤ 4912 nmol/L or ≤ 1200 ng/mL **Biotin interference** This assay has no biotin interference in serum concentrations up to 1200 ng/mL. Some studies have shown that serum concentrations of biotin can reach up to 355 ng/mL within the first hour after biotin ingestion for subjects consuming supplements of 20 mg biotin per day and up to 1160 ng/mL for subjects after a single dose of 300 mg biotin.
Measuring Range	0.005-100 µIU/mL	Same

4. NON-CLINICAL PERFORMANCE EVALUATION

The non-clinical performance studies for the Elecsys TSH are summarized below.

4.1. Repeatability and Intermediate Precision

Precision of the Elecsys TSH assay was evaluated on one **cobas e** 801 immunoassay analyzer with one reagent lot. The protocol consisted of testing 2 replicates of each control (PreciControl Universal and PC Thyro Sensitive) 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 all native, single donors as well as pools. 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 the Elecsys TSH.

cobas e 801 analyzer					
		Repeatability		**Intermediate precision**	
Sample	Mean µIU/mL	SD µIU/mL	CV %	SD µIU/mL	CV %
Human serum 1	0.015	0.001	3.4	0.002	11.2
Human serum 2	0.281	0.003	1.1	0.005	1.8
Human serum 3	4.09	0.030	0.7	0.090	2.2
Human serum 4	59.8	0.494	0.8	1.10	1.8
Human serum 5	95.6	0.706	0.7	3.81	4.0
PC[b)] Universal 1	1.39	0.013	1.0	0.021	1.5
PC Universal 2	7.99	0.064	0.8	0.132	1.6
PC Thyro Sensitive	0.176	0.002	1.2	0.004	2.1

4.2. Lot-to-Lot Reproducibility

Lot-to-lot reproducibility of the Elecsys TSH assay was evaluated on one **cobas e** 801 analyzer using three reagent lots. A precision study was performed for a total of 21 days (7 days for each lot, n = 28 determinations per lot), 2 replicates of each human sera (HS) per run, 2 runs per day. The samples were run in randomized order on the analyzer. Human serum samples used were all native, single donors (human serum 1) as well as pools (human serum 2-5).

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.

4.3. Limit of Blank (LoB)

LoB of the Elecsys TSH was determined according to CLSI EP17-A2. The experimental design included three reagent lots evaluated on one **cobas e** 801 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 0.0025 µIU/mL.

4.4. Limit of Detection (LoD)

LoD of the Elecsys TSH was determined according to CLSI EP17-A2. The experimental design included three reagent lots evaluated on one **cobas e** 801 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 0.005 µIU/mL.

4.5. Limit of Quantitation (LoQ)

LoQ of the Elecsys TSH was determined according to CLSI EP17-A2. The experimental design included three reagent lots evaluated on one **cobas e** 801 analyzer for 5 days, one run per day. There were 25 replicates per sample per reagent lot. The LoQ claim in the labeling will be set to 0.005 µIU/mL.

4.6. Linearity/Assay Reportable Range

Linearity of the Elecsys TSH assay was assessed on the **cobas e** 801 analyzer according to CLSI EP06-A. Three high analyte human serum samples were diluted and concentrations covering the measuring range were measured. Samples were assayed in 3-fold determination within a single run. All deviations were within predetermined acceptance criteria. Linearity for serum samples was confirmed in the range from 0.004 – 102 µIU/mL.

4.7. High Dose Hook Effect

The high-dose hook effect of the Elecsys TSH assay was assessed on the **cobas e** 801 analyzer in one-fold determination. Three human serum samples were spiked with analyte to achieve high TSH concentrations. For each sample, a dilution series was performed. No hook effect up to 1000 µIU/mL TSH.

4.8. Endogenous Interference

The purpose of this study was to evaluate endogenous substances for potential interference with the parameters measured with the Elecsys TSH on the **cobas e** 801 analyzer.

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. The claim in the package insert will be set to ≤ 1200 ng/mL.

Lipemia (Intralipid): 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. The claim in the package insert will be set to ≤ 1500 mg/dL.

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 claim in the package insert will be set to ≤ 1000 mg/dL.

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. The claim in the package insert will be set to ≤ 41 mg/dL.

Rheumatoid Factor (RF): 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. The claim in the package insert will be set to ≤ 1500 IU/mL.

Immunoglobulin (IgG, IgM) Interference: One aliquot of each serum sample was spiked with the interfering substance (lyophilisate). In this case, another aliquot without any additives (since the interfering substance is a lyophilisate) is used as 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. The claim in the package insert will be set to ≤ 2 g/dL for IgG and ≤ 0.5 g/dL for IgM.

4.8.1. Summary of Endogenous Interference Results

Interferent	Specification	Interfering substance measured up to		No interference seen up to	
Intralipid® (Lipemia)	≤ 1500	2000	mg/dL	2000	mg/dL
Biotin	≤ 1200	3600	ng/mL	1200	ng/mL
Bilirubin	≤ 41	66	mg/dL	66	mg/dL
Hemoglobin	≤ 1000	1000	mg/dL	1000	mg/dL
Rheumatic Factor	≤ 1500	1500	IU/mL	1500	IU/mL
Human IgG	≤ 2	7	g/dL	3.98	g/dL
Human IgM	≤ 0.5	1	g/dL	0.72	g/dL

4.9. Analytical Specificity/Cross-Reactivity

The effect on quantitation of analyte in the presence of potential cross-reacting compounds using the Elecsys TSH was determined on the **cobas e** 801 analyzer using a native human serum sample pool. For each potential cross-reacting compound a human serum sample with a low concentration level of TSH 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.

Cross-reactant	Concentration tested (µU/mL)	Cross-reactivity %
LH	10000	0.000
FSH	10000	0.000
hGH	1000	n.d.
hCG	50000	0.000

n.d. = not detectable

4.10. 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** 801 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.

Table 1: Common Drugs

Potential interfering commonly used drugs	**Highest interferent concentration tested at which no significant interference was observed (mg/L)**
Acetylcysteine	150
Acetylsalicylic acid	30
Ampicilin-Na	75
Ascorbic acid	52.5
Cefoxitin	750
Doxycycline	18
Heparin	3300 IU/L
Levodopa	7.5
Methyldopa	22.5
Metronidazole	123

Potential interfering commonly used drugs	Highest interferent concentration tested at which no significant interference was observed (mg/L)
Rifampicin	48
Acetaminophen	156
Cyclosporine	1.8
Ibuprofen	219
Theophylline	60
Phenylbutazone	321
Itraconazole	10

Table 2: Special Drugs

Drug	Concentration tested mg/L
Iodide	0.2
Carbimazole	30
Methimazole	80
Propylthiouracil	60
Perchlorate	2000
Propranolol	240
Amiodarone	200
Prednisolone	100
Hydrocortisone	200
Fluocortolone	100
Octreotide	0.3
Levothyroxine	0.25
Liothyronine	0.075

4.11. Sample Matrix Comparison

The effect on quantitation of analyte in the presence of anticoagulants with the Elecsys TSH immunoassay was determined by comparing values obtained from samples (native human serum samples, single donors as well as pools) drawn into serum and Li-Heparin, K_2-EDTA, K_3-EDTA

plasma tubes. A minimum of 56 serum/plasma pairs per sample material were tested in singleton with one reagent lot on one **cobas e** 801 analyzer. Data were evaluated using a regression analysis according to Passing/Bablok.

Serum/Li-heparin	
	Passing/Bablok
N	56
Range	0.009 – 96.2 µIU/mL
Slope	0.983
Intercept	-0.0006
Correlation coefficient r	0.999
Bias at 0.2 µIU/mL	-1.9 %
Bias at 2.5 µIU/mL	-1.7 %
Serum/K_2-EDTA	
N	58
Range	0.009 – 96.2 µIU/mL
Slope	0.976
Intercept	-0.0006
Correlation coefficient r	1.00
Bias at 0.2 µIU/mL	-2.6 %
Bias at 2.5 µIU/mL	-2.4 %
Serum/K_3-EDTA	
N	58
Range	0.009 – 96.2 µIU/mL
Slope	0.981
Intercept	-0.021
Correlation coefficient r	1.00
Bias at 0.2 µIU/mL	-9.7 %
Bias at 2.5 µIU/mL	-2.4 %

Plasma/Serum separation tubes (PST/SST) from 3 separate manufacturers and blood from five donors were used. Measurements were performed in duplicate with one reagent lot and evaluated on the basis of recovery relative to the serum/plasma tube without separating gel (reference).

The resulting data support the package insert claim that the following sample types are acceptable to use for Elecsys TSH assay: Serum collected using standard serum tubes or tubes containing separating gel, Li-Heparin, K_2-EDTA, K_3-EDTA plasma and Plasma tubes containing separating gel.

4.12. Method Comparison to Predicate

A method comparison was performed using the Elecsys TSH updated assay (candidate device, Y) and the Elecsys TSH current assay (predicate device, X) to assess the bias between the two assays. A total of 138 samples (129 native human serum samples and 9 diluted human serum samples, single donors as well as pools diluted) were measured in singleton on the **cobas e** 801 analyzer in one run covering the entire measuring range. Results for the method comparison are summarized in the following table, all data met predefined acceptance criteria:

	Passing-Bablok	**Linear Regression***
N	138	
Range (µIU/mL)	0.006 – 99.2	
Slope (LCL / UCL)	0.974 (0.958 / 0.984)	0.944 (0.936 / 0.952)
Intercept (µIU/mL) (LCL / UCL)	-0.0002 (-0.0019 / 0.0022)	0.089 (-0.106 / 0.284)
Correlation coefficient Pearson (r) Kendall (tau)	 0.999 -	 - 0.972
Bias at 0.27 µIU/mL (LCL / UCL) Bias at 4.2 µIU/mL (LCL / UCL)	-2.7 (-3.8 / -1.8) -2.6 (-4.2 / -1.7)	27.3 (-44.5 / 99.1) -3.5 (-7.9 / 0.9)

*not specified

4.13. Stability

The stability studies were performed and the pre-specified acceptance criteria were met. The stability data supports Roche Diagnostic's claims as reported in the package inserts.

4.14. Substantial Equivalence

The Elecsys TSH immunoassay (updated assay, Mat. No. 08443432190) is substantially equivalent to the Elecsys TSH immunoassay (current assay, Mat. No. 07028091190).