

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY**

A. 510(k) Number:

k080092

B. Purpose for Submission:

New Device

C. Measurand:

TSH receptor autoantibodies

D. Type of Test:

Quantitative immunoassay

E. Applicant:

Roche Diagnostics

F. Proprietary and Established Names:

Elecsys Anti-TSHR Immunoassay

Elecsys PreciControl ThyroAB

G. Regulatory Information:

Regulation Section	Classification	Product code	Panel
21 CFR 866.5870 Thyroid autoantibody immunological test system	Class II	JZO, System, Test, Thyroid Autoantibodies	Immunology (82)
21 CFR 862.1660 Quality control material (assayed and unassayed)	Class I	JJX, Single (specified) analyte controls (assayed and unassayed)	Chemistry (75)

H. Intended Use:

1. Intended Use(s):

Elecsys Anti-TSHR Immunoassay is an 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.

Elecsys PreciControl ThyroAB is used for the quality control of the Elecsys Anti-TSHR immunoassay on the Elecsys and cobas e immunoassay analyzers.

2. Indication(s) for Use:

Same as Intended Use

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

Elecsys 2010, MODULAR ANALYTICS E170, cobas e 411, cobas e 601

I. Device Description:

The Elecsys Anti-TSHR reagent kit consists of a Reagent Pack (R1, R2, and Microparticles), lyophilized calibrators 1 and 2, and a Pretreatment Pack (PT1, PT2, PTR, PTB).

The Elecsys PreciControl ThyroAB is a lyophilized product consisting of human serum with added Anti-TSHR antibody (human) in two concentration ranges. During manufacture, the antibody is spiked into the matrix at the desired concentration levels.

J. Substantial Equivalence Information:

1. Predicate device name(s):
BRAHMS LUMItest TRAK human Assay
2. Predicate 510(k) number(s):
k033454
3. Comparison with predicate:

Similarities		
Feature	New Device	Predicate
	Elecsys Anti-TSHR Immunoassay	BRAHMS LUMItest TRAK human Assay
Intended Use / Indication for Use	Quantitative determination of autoantibodies to TSH receptor in human serum using a thyroid stimulating monoclonal antibody. Used in the assessment of patients with suspect Graves' disease (autoimmune hyperthyroidism).	Same
Assay Protocol	Competition principle	Same
Sample type	Serum	Same
Limit of Quantitation	0.9 IU/L	Same
Controls	Two levels using human serum	Same

Differences		
Feature	New Device	Predicate
Detection Protocol	Electrochemiluminescence immunoassay (ECLIA)	Luminescence receptor assay (LRA)
Platform	Elecsys 2010, MODULAR ANALYTICS E170, cobas e 411, cobas e 601	Luminometer
Expected Values	Positive: > 1.75 IU/L	Negative: < 1 IU/L Equivocal: 1 – 2 IU/L Positive: > 2 IU/L
Measuring Range	0.8 – 40 IU/L	0.9 – 40 IU/L
Limit of Blank	≤ 0.5 IU/L	0.4 IU/L

Differences		
Feature	New Device	Predicate
Precision	<p>Elecsys 2010 and cobas e 411: Sample concentrations = 1.73 IU/L – 25.5 IU/L Within-run % CV = 1.3% - 5.9% Total 9.7% CV = 1.8% - 9.7%</p> <p>E170 and cobas e 601: Sample concentrations = 1.71 IU/L – 24.6 IU/L Within-run % CV = 0.9% - 7.6% Total % CV = 1.9% - 8.7%</p>	<p>Interassay Precision: Sample means 0.6 IU/L – 20.3 IU/L %CV = 4.1 – 35.1%</p> <p>Intra-assay Precision: Sample means 0.9 IU/L – 101.7 IU/L % CV = 2.3 – 24.2%</p>
Calibrator	2 levels	6 levels
Traceability	Standardized against NIBSC 1 st IS 90/672 Standard	WHO 1 st International reference material, 90/672 for TSAb

K. Standard/Guidance Document Referenced (if applicable):

CLSI EP17-A: “Protocol for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline”

CLSI EP5-A2: “Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second Edition”

L. Test Principle:

The Elecsys Anti-TSHR immunoassay is a three step competition principle immunoassay with streptavidin-coated microparticles and electrochemiluminescence detection. Results are determined using a calibration curve that is generated specifically on each instrument by a 2 point calibration and master curve provided with the reagent bar code.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Precision of the Elecsys® Anti-TSHR Test System was evaluated on Elecsys® 2010/cobas e® 411 Immunoassay Analyzer according to CLSI EP5-A2 guideline. The protocol consisted of testing 2 replicates of each control (PeciControl 1 and PeciControl 2) and 2 replicates each of 4 human serum samples per run, 2 runs per day for 21 days (2 replicates x 2 runs per day x 21 days = 84) Within run precision and total precision was calculated according to EP5-A2.

Within Run precision was:

Concentrations of 1.5 - 5 IU/L: CV < 10 %

Concentrations of 5 - 20 IU/L: CV < 3 %

Concentrations of 20 - 40 IU/L: CV < 4 %

Total precision was:

Concentrations of 1.5 - 5 IU/L: CV < 13 %

Concentrations of 5 - 20 IU/L: CV < 5 %

Concentrations of 20 - 40 IU/L: CV < 6 %

b. Linearity/assay reportable range:

The measuring range is 0.8 – 40 IU/L (defined by the limit of detection and the maximum of the master curve). Performance information at the low end of the assay range is summarized in the Detection Limit section below.

c. Traceability, Stability, Expected values:

Standardized against NIBSC 1st IS 90/672 Standard. Stability for controls and calibrators is 15 months at 2-8° C

d. Detection limit:

The limit of blank and limit of detection were determined in accordance with the CLSI EP17-A requirements.

The limit of blank (LoB)(≤ 0.5 IU/L) is the 95th percentile value from $n \geq 60$ measurements of analyte free samples over several independent series. The limit of blank corresponds to the concentration below which analyte-free samples are found with a probability of 95%.

The limit of detection (LoD)(≤ 0.8 IU/L) is determined based on the limit of blank and the standard deviation of low concentration samples. The limit of detection corresponds to the lowest analyte concentration which can be detected (value above the limit of blank with a probability of 95%).

The limit of quantitation (LoQ)(0.9 IU/L) is the lowest analyte concentration that can be reproducibly measured with a between-run coefficient of variation of $\leq 20\%$. It has been determined using low concentration anti-TSHR samples.

Because the %CV of low concentration samples is high, values below the LoQ should be reported with caution. The package insert states: “When reporting values < 0.9 IU/L, the client report should be annotated with the following information. ‘Values < 0.9 IU/L are not reliable as the between-run coefficient of variation is > 20%.’”

e. Analytical specificity:

The specificity of the Elecsys Anti-TSHR was determined using human serum samples spiked with potential cross-reactant compounds. The results obtained:

No cross-reactivity observed with:

- Anti-TG if less than 4000 IU/mL

- Anti-TPO if less than 600 IU/mL
- Human TSH if less than 1000 mIU/L
- Human LH if less than 10,000 mIU/mL
- Human FSH if less than 10,000 mIU/mL
- hCG if less than 50,000 mIU/mL

f. Interferences:

Effect on quantitation of analyte in the presence of endogenous interfering substances using the Elecsys® Anti-TSHR Immunoassay was determined on Elecsys® 2010/**cobas e**® 411 Immunoassay Analyzer using natural (low analyte concentration) and spiked serum sample pools. The assay is unaffected by:

- Bilirubin: < 25 mg/dL
- Hemoglobin: < 0.4 g/dL
- Intralipid: < 1500 mg/dL
- Biotin: < 10 ng/mL
- rheumatoid factors: < 600 IU/mL

g. Assay cut-off:

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 cut-off of 1.75 IU/L was determined. At this cut-off the sensitivity was calculated at 97% and the specificity at 99%. The calculated receiver operating characteristic (ROC) curve had an area under the curve (AUC) of 0.99.

2. Comparison studies:

a. Method comparison with predicate device:

A method comparison study was performed to compare the Elecsys Anti-TSHR values obtained with both the Elecsys® 2010/**cobas e**® 411 and MODULAR ANALYTICS E170/**cobas e**® 601 Immunoassay Analyzer (Y-axis) to the values obtained with the predicate device BRAHMS LUMItest TRAK human (X-axis). The results were calculated using the Passing/Bablok.

Cohort:

The cohort consisted of 350 individuals who were clinically classified as having various thyroid disease states, Graves' disease (mostly treated for longer than 6 months), Hashimoto thyroiditis, chronic thyroiditis (goiter, non autoimmune thyroiditis), adenomas or other thyroid diseases.

138 samples were outside the reportable range of the BRAHMS LUMItest TRAK human assay (< 1 IU/L or > 40 IU/L) and/or samples outside the reportable range of the Elecsys Anti-TSHR assay (< 0.8 IU/L or > 40 IU/L) and were therefore excluded from the regression analysis.

The analysis of the 138 samples which were outside of the measuring range of the predicate device (< 1 IU/L or > 40 IU/L) and/or outside of the measuring range of the Elecsys Anti-TSHR immunoassay (< 0.8 IU/L or > 40 IU/L) shows the following distribution:

BRAHMS LUMItest TRAK (Predicate Device) Values	Elecsys Anti-TSHR (New Device) Values
Samples < 1 IU/L (n = 109)	n = 90 with values < 1 IU/L; n = 19 with values ≥ 1 IU/L, range = 1.02 – 2.6 IU/L
Samples ≥ 1 IU/L and ≤ 40 IU/L (n = 17)	n = 7 with values < 1 IU/L; range not known because values were outside of measuring range (< 0.8 IU/L). n = 10 with values > 40 IU/L range not known because outside of measuring range (> 40 IU/L)
Samples > 40 IU/L (n = 12)	n = 10 with values > 40 IU/L; n = 2 with values ≤ 40 IU/L, range = 32.49 – 37.48 IU/L

The regression statistics for the 212 samples are as follows:

	Passing/Bablok
N	212
Range	1.1 to 40.0 IU/L
Slope	1.183 (95%CI 1.108 to 1.273)
Y intercept	- 0.316 (95% CI -0.633 to -0.079)

Concordance analysis:

	BRAHMS LUMItest TRAK		
	< 1.0 IU/L	1.0 – 2.0 IU/L	> 2.0 IU/L
Elecsys	7	11	199
Anti-	102	31	0
TSHR	109	42	199

Of the 11 samples positive for anti-TSHR but equivocal for TSAb, two had anti-TSHR values from 1.75-2 IU/L and nine had values above 2 IU/L. Of the 31 anti-TSHR negative but TSAb equivocal samples, 11 had values below 1 IU/L and 20 had values from 1- 1.75 IU/L.

Agreement Classification	Numerator/Denominator	Percent Agreement (%)	95% Confidence Interval (%)
Negative agreement	102/109	93.6	87.2 to 97.4
Positive agreement	199/199	100	98.2 to 100

- b. Matrix comparison:*
Serum is the only recommended matrix.
 3. Clinical studies:
 - a. Clinical Sensitivity:*
Not available
 - b. Clinical specificity:*
Not available
 - c. Other clinical supportive data (when a. and b. are not applicable):*
Not applicable
 4. Clinical cut-off:
Results above 1.75 IU/L are considered positive; see assay cut off.
 5. Expected values/Reference range:
(see assay cut off)
- N. Proposed Labeling:**
The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.
- O. Conclusion:**
The submitted information in this premarket notification is complete and supports a substantial equivalence decision.