

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

A. 510(k) Number:

k081338

B. Purpose for Submission:

New Device

C. Measurand:

Human IgG autoantibodies to cyclic citrullinated peptides

D. Type of Test:

Semi-quantitative immunoassay

E. Applicant:

Roche Diagnostics

F. Proprietary and Established Names:

Elecsys Anti-CCP Immunoassay

Elecsys PreciControl Anti-CCP

G. Regulatory Information:

1. Regulation section:

21 CFR 866.5775 Rheumatoid factor immunological test system

21 CFR 862.1660 Quality control material (assayed and unassayed)

2. Classification:

Class II (Device)

Class I (Quality control)

3. Product codes:

NHX, Antibodies, anti-cyclic citrullinated peptide

JJX, Single (specified) analyte controls (assayed and unassayed)

4. Panel:

Immunology

H. Intended Use:

1. Intended use(s):

See Indication for use

2. Indication(s) for use:

Elecsys Anti-CCP Immunoassay

Immunoassay for the in vitro semi-quantitative determination of human IgG autoantibodies to cyclic citrullinated peptides in human serum and plasma. The results of the assay are intended to be used as an aid in the diagnosis of rheumatoid arthritis in combination with other clinical and laboratory findings.

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

Elecsys PreciControl Anti-CCP

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

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

Elecsys 2010, MODULAR ANALYTICS E170, **cobas e** 411 and **cobas e** 601.

I. Device Description:

The Elecsys Anti-CCP reagent kit consists of a Reagent Pack (R1 and R2) and lyophilized calibrators 1 and 2.

The Elecsys PreciControl Anti-CCP is a lyophilized product consisting of human serum with added Anti-CCP 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):
Eurodiagnostica IMMUNOSCAN RA Anti-CCP Test Kit
2. Predicate K number(s):
k052133
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
	Elecsys Anti-CCP Immunoassay	Eurodiagnostica IMMUNOSCAN RA Anti-CCP
Intended Use / Indication for Use	Immunoassay for the in vitro semi-quantitative determination of human IgG autoantibodies to cyclic citrullinated peptides in human serum and plasma. The results of the assay are intended to be used as an aid in the diagnosis of rheumatoid arthritis in combination with other clinical and laboratory findings	Same

Differences		
Item	Device	Predicate
	Elecsys Anti-CCP Immunoassay	Eurodiagnostica IMMUNOSCAN RA Anti-CCP
Detection Protocol	Electrochemiluminescence	ELISA
Sample Type	Human serum and plasma	Human serum
Platform	Elecsys 2010, MODULAR ANALYTICS E170, cobas e 411, cobas e 601	Spectrophotometer
Measuring Range	8-1000 U/mL	1.6-1600 U/mL
Expected Values	Positive: ≥ 17 U/mL	Negative: < 25 U/mL Positive: ≥ 25 U/mL

Differences		
Item	Device	Predicate
Precision	Elecsys 2010 and cobas e 411: Anti-CCP: 16.9 - 356 U/mL Total %CV: 2.5% - 4.5% Within-run %CV: 0.6% - 2.3%	Intra-assay: Anti-CCP: 33.6 – 1007.4 U/mL %CV: 4.3% - 12.8% Inter-assay: Anti-CCP: 33.3 – 1105.9 U/mL %CV: 6.0% - 17.7%
Calibrator	Two levels	Five levels
Control	Two levels	Reference, positive, and negative controls supplied with kit

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-CCP immunoassay is a two step IgG-capture test 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 a 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-CCP 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 (PC = PreciControl) or sample (HS = human serum) per run, 2 runs per day for 21 days. Within run precision and total precision was calculated according to EP5-A2.

Sample	Anti-CCP (U/mL)	Within-run%CV	Total%CV
1	16.9	0.6	3.1
2	24.6	1.0	3.0
3	137	1.4	2.5
4	356	2.3	4.5

A 10 day inter-assay precision study with a sample at 664 U/mL was also performed to support high end precision. Results are acceptable with %CV of 3.4%.

b. *Linearity/assay reportable range:*

The linearity of the Elecsys® Anti-CCP was evaluated on the Elecsys® 2010/**cobas e**® 411 Immunoassay Analyzer by diluting three high through medium analyte level serum sample pools with varying amounts of low-level serum. Pure samples (0% and 100%) were run n=6 with mean measured value reported. The regression equations of the three pools are as follows:

Sample 1: $y=1.0029x-4.1733$; $r^2=0.9992$

Sample 2: $y=0.9913x+0.5146$; $r^2=0.9992$

Sample 3: $y=1.0261x+5.4971$; $r^2=0.9944$

The measuring range is 8-1000 U/mL (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. Roche has performed linearity testing to cover the low end of the measuring range. The linear regression is $y=0.9338x+1.2276$; $r^2=0.9904$.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

There is no recognized material for anti-CCP. The Elecsys® Anti-CCP test is standardized against a commercially available anti-CCP assay.

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 (≤ 7 U/mL) 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 distribution of values for five zero-level human serum samples have been determined on two Elecsys® 2010 / **cobas e**® 411 Immunoassay Analyzer over 3 days, 2 runs per day.

The limit of detection (≤ 8 U/mL) 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 distribution of values for five low-level human serum samples have been determined on two Elecsys® 2010 / **cobas e**® 411 Immunoassay Analyzer over 3 days, 2 runs per day.

The limit of quantitation (8 U/mL) 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-CCP samples. Nine human serum sample pools with concentrations ranging from 6.57 to 27.2 U/mL were tested once per day, for 10 days.

e. *Analytical specificity:*

Effect on quantitation of analyte in the presence of endogenous interfering substances using the Elecsys® Anti-CCP 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: < 0.5 g/dL
- Intralipid: < 1500 mg/dL
- Biotin: < 30 ng/mL
- Rheumatoid Factors: < 150 IU/mL

Hook effect:

No hook effect was detected up to concentration of 7000 U/mL.

f. Assay cut-off:

In cohorts of 792 confirmed rheumatoid arthritis patients, 420 asymptomatic healthy individuals and 907 patients with other rheumatic and non-rheumatic disorders, an optimal cut-off of 17 U/mL was determined. At this cut-off the sensitivity was calculated at 67.7% and the specificity at 97.0%. The calculated receiver operating characteristic (ROC) curve had an area under the curve (AUC) of 0.85.

2. Comparison studies:

a. Method comparison with predicate device:

A method comparison study was performed to compare the Elecsys Anti-CCP values obtained with both the Elecsys® 2010/**cobas e**® 411 and MODULAR ANALYTICS E170/**cobas e**® 601 Immunoassay Analyzer to the values obtained with the predicate device Eurodiagnostica IMMUNOSCAN RA Anti-CCP.

Cohort:

Non-RA cohort:

Negative cohort consisting of 319 apparently healthy individuals and 673 patients with non-rheumatoid arthritis diseases; in total 992 patients from two sites.

RA Cohort:

Positive cohort consisting of 614 patients with clinical diagnosis of rheumatoid arthritis based on the ARA (American Rheumatology Association) 1987 Revised Criteria for the Classification of Rheumatoid Arthritis.

1606 samples tested using a cut-off of ≥ 17 U/mL for the Elecsys Anti-CCP assay.

N=1606		Immunoscan Anti-CCP		
		+	-	Total
Elecsys Anti-CCP	+	428	18	446
	-	26	1134	1160
	Total	454	1152	1606

Positive Percent Agreement = 94.3% (95% CI = 91.7-96.2)

Negative Percent Agreement = 98.4% (95% CI = 97.5-99.1)

Total Percent Agreement = 97.3% (95% CI = 96.3-98.0)

b. Matrix comparison:

The effect on quantitation of analyte in the presence of anticoagulants with Elecsys Anti-CCP Immunoassay was determined on Elecsys 2010/cobas e 411 Immunoassay Analyzer by comparing values obtained from samples drawn into Serum, Li- and K3-EDTA-Heparin plasma primary tubes. Potential effects are assessed by Passing/Bablok regression analysis. The following was found:

Serum/K3-EDTA: $y=1.10x-0.977$ (anti-CCP = 8.37-473 U/mL, n=31)

Serum/Li-Heparin: $y=1.03x-0.143$ (anti-CCP = 8.37-769 U/mL, n=33)

3. Clinical studies:

a. Clinical sensitivity and specificity:

The clinical sensitivity and specificity were determined by testing 792 confirmed rheumatoid arthritis patients, 420 asymptomatic healthy individuals and 907 patients with other rheumatic and non-rheumatic disorders. Results showed sensitivity and specificity of 67.7% and 97.0% respectively.

b. Other clinical supportive data (when a. is not applicable):

Not applicable

4. Clinical cut-off:

Results ≥ 17 U/mL are considered positive; see assay cut off

5. Expected values/Reference range:

The expected value in the normal population is negative.

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.