Elecsys Anti-TSHR

cobas®

REF		Σ	SYSTEM
08496609190	08496609500	100	**cobas e** 411 **cobas e** 601 **cobas e** 602

English

System information

For **cobas e** 411 analyzer: test number 1830
For **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number 488

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 as an aid in the differential diagnosis of Graves' disease.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on **cobas e** immunoassay analyzers.

Summary

Hyperthyroidism in Graves' disease (autoimmune hyperthyroidism) is typically caused by autoantibodies to the thyroid stimulating hormone receptor (TSHR), and measurement of these TSHR antibodies (TRAb) can be useful in disease diagnosis and management.[1,2,3,4,5]

TSH autoantibodies can be classified as stimulating, blocking or neutral depending on their mechanism of action. Despite having actions similar to TSH, TSHR stimulating antibodies are not subject to the negative feedback mechanisms associated with TSH, leading to prolonged activation of the TSHR. This results in the elevated thyroid hormone levels and clinical thyrotoxic state associated with Graves' disease.[6,7]

Indications for TRAb determination include:

- the detection or exclusion of autoimmune hyperthyroidism and its differentiation from disseminated autonomy of the thyroid gland. The presence of TRAb indicates that the patient's thyrotoxicosis is of autoimmune etiology rather than due to toxic nodular goiter.[8,9] Because the aim of treatment for Graves' disease may differ from the treatment of other forms of thyrotoxicosis, an initial TRAb determination is clearly of value.
- monitoring the therapy of Graves' disease patients and prediction of relapse, thereby constituting an important decision-making aid in treatment management. TRAb levels tend to fall during antithyroid drug therapy for Graves' disease. Low levels or the absence of TRAb after a course of drug treatment may indicate disease remission, and therefore the withdrawal of therapy can be considered.[10,11,12]
- TRAb measurement during the last trimester of pregnancy. Because TRAb are IgG-class antibodies, they cross the placenta and can cause neonatal thyroid disease. The measurement of TRAb during pregnancy in patients with a history of thyroid disease is therefore important in assessing the risk of thyroid disease in the neonate.[13,14]

Over the last few decades there has been a substantial improvement in TRAb detection methodologies in clinical practice and the available assays have undergone several important modifications. Available second generation assays using coated plate or tube technique with antibody-immobilized human or porcine TSHR determine the ability of serum TRAb to inhibit the binding of labeled TSH to the receptor.[15,16] The sensitivity and predictive value of these assays in Graves' disease patient management are independent of whether human recombinant or native porcine TSHR is used.[13,17,18,19,20]

The availability of a human thyroid stimulating monoclonal antibody (M22)[20,21] has allowed the development of a third generation TRAb assay system in which patient serum autoantibodies inhibit the binding of the labeled thyroid stimulating antibody (rather than labeled TSH) to the TSHR.[22] These new assays show excellent reproducibility, sensitivity and specificity for detecting Graves' disease and discriminating from other thyroid diseases, as well as a similar or improved performance compared with established second generation assays.[23,24,25,26,27]

The availability of fully automated TRAb assays has allowed to reduce manual procedures and integration of this assay into the workflow on routine laboratory analyzers.[25,27]

Solubilized porcine TSH receptor (pTSHR) immunocomplexed with a biotinylated mouse monoclonal antibody to the porcine TSH receptor C-terminus and human monoclonal autoantibody M22 as a ruthenium[a)] labeled assay ligand are used in the Elecsys Anti-TSHR assay.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

Test principle

Competition principle. Total duration of assay: 27 minutes.

- 1st incubation: 50 µL of serum sample are incubated with pretreatment buffer solution (PT1) and pretreatment reagent buffer (PT2) consisting of a pre-formed immunocomplex of solubilized porcine TSH receptor (pTSHR) and biotinylated anti-porcine TSH receptor mouse monoclonal antibody. TRAb in patient's sera are allowed to interact with the TSH receptor complex.
- 2nd incubation: After addition of buffer solution, TRAb are allowed to further interact with the TSH receptor complex.
- 3rd incubation: After addition of streptavidin-coated microparticles and a human thyroid stimulating monoclonal autoantibody (M22) labeled with a ruthenium complex, bound TRAb are detected by their ability to inhibit the binding of labeled M22. The entire complex becomes bound to the solid phase via interaction of biotin and streptavidin.
- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the reagent barcode or e-barcode.

Reagents - working solutions

The reagent rackpack (M, R1, R2) is labeled as ATSHR.

Reagent rackpack

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~$Ru(bpy)_3^{2+}$ (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).

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.

Precautions and warnings

For in vitro diagnostic use for laboratory professionals. Exercise the normal precautions required for handling all laboratory reagents.

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Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Warning

H317	May cause an allergic skin reaction.
H319	Causes serious eye irritation.

Prevention:

P261	Avoid breathing mist or vapours.
P280	Wear protective gloves/ eye protection/ face protection.

Response:

P333 + P313	If skin irritation or rash occurs: Get medical advice/attention.
P337 + P313	If eye irritation persists: Get medical advice/attention.
P362 + P364	Take off contaminated clothing and wash it before reuse.

Disposal:

P501	Dispose of contents/container to an approved waste disposal plant.

Hazardous components:

- 2-methyl-2H-isothiazol-3-one hydrochloride

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

All human material should be considered potentially infectious. All products derived from human blood are prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV. The testing methods use assays that have been approved or cleared by the FDA or that are in compliance with the legal rules of the European Union (IVDR 2017/746/EU, IVDD 98/79/EC, Annex II, List A). However, as no testing method can rule out the potential risk of infection with absolute certainty, the material should be handled with the same level of care as a patient specimen. In the event of exposure, the directives of the responsible health authorities should be followed.[28,29]

Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).

Reagent handling

The reagent rackpack (M, R1 and R2) in the kit is ready-for-use and is supplied in bottles compatible with the system.

Pretreatment rackpack

The pretreatment rackpack (bottle PT2) is not ready for use and has to be prepared. See “Preparation of working solutions” for further details.

Preparation of working solutions

Reconstitution of pretreatment reagent (PTR, white cap) with pretreatment buffer (PTB, white cap):

Carefully dissolve the contents of the lyophilized pretreatment reagent (PTR) by adding exactly 4.0 mL of pretreatment buffer (PTB).

Allow to reconstitute closed for 60 minutes by permanent gentle agitation with a rotator until complete solution is obtained.

Pour the working solution of PTR/PTB carefully into the empty bottle (PT2; white cap). Avoid foam formation!

Please note for **cobas e** 602 analyzers: Both the vial labels, and the additional labels (if available) contain 2 different barcodes. Please turn the vial cap 180° into the correct position so that the barcode between the yellow markers can be read by the system. Place the vial on the analyzer as usual.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the Elecsys reagent kit **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability of the reagent rackpack	
unopened at 2-8 °C	up to the stated expiration date
on the analyzers	3 weeks

Stability of the pretreatment rackpack	
unopened at 2-8 °C	up to the stated expiration date
after reconstitution (PT2) at 2-8 °C	3 weeks (see below)
on the analyzers	72 hours if continuously stored onboard (20-25 °C) or 3 weeks including up to 7 x 8 hours in total onboard (20-25 °C) if stored alternately in the refrigerator and on the analyzers

Note: Always store the pretreatment rackpack (PT2 containing the reconstituted PTR) in the refrigerator when not in use.

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

Serum collected using standard sampling tubes or tubes containing separating gel.

Stable for 7 hours at 20-25 °C, 6 days at 2-8 °C, 12 months at -20 °C (± 5 °C). Freeze only once.

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge samples containing precipitates before performing the assay.

Do not use heat-inactivated samples.

Do not use samples and controls stabilized with azide.

Ensure the samples, calibrators and controls are at 20-25 °C prior to measurement.

Due to possible evaporation effects, samples, calibrators and controls on the analyzers should be analyzed/measured within 2 hours.

Materials provided

See “Reagents – working solutions” section for reagents.

Materials required (but not provided)

- REF 05042666191, PreciControl ThyroAB, for 4 x 2.0 mL
- REF 08496641190, CalSet Anti-TSHR, for 4 x 2.0 mL
- General laboratory equipment
- **cobas e** analyzer

Additional materials for the **cobas e** 411 analyzer:

- REF 11662988122, ProCell, 6 x 380 mL system buffer
- REF 11662970122, CleanCell, 6 x 380 mL measuring cell cleaning solution
- REF 11930346122, Elecsys SysWash, 1 x 500 mL washwater additive
- REF 11933159001, Adapter for SysClean
- REF 11706802001, AssayCup, 60 x 60 reaction cups

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- REF 11706799001, AssayTip, 30 x 120 pipette tips
- REF 11800507001, Clean-Liner

Additional materials for **cobas e** 601 and **cobas e** 602 analyzers:

- REF 04880340190, ProCell M, 2 x 2 L system buffer
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 03023141001, PC/CC-Cups, 12 cups to prewarm ProCell M and CleanCell M before use
- REF 03005712190, ProbeWash M, 12 x 70 mL cleaning solution for run finalization and rinsing during reagent change
- REF 12102137001, AssayTip/AssayCup, 48 magazines x 84 reaction cups or pipette tips, waste bags
- REF 03023150001, WasteLiner, waste bags
- REF 03027651001, SysClean Adapter M

Additional materials for all analyzers:

- REF 11298500316, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

Resuspension of the microparticles takes place automatically prior to use. Read in the test-specific parameters via the reagent barcode. If in exceptional cases the barcode cannot be read, enter the 15-digit sequence of numbers.

Bring the cooled reagents to approximately 20 °C and place on the reagent disk (20 °C) of the analyzer. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the bottles.

Calibration

Traceability: This method has been standardized against the NIBSC (National Institute for Biological Standards and Control) 1st IS 90/672 Standard.

Every Elecsys reagent set has a barcoded label containing specific information for calibration of the particular reagent lot. The predefined master curve is adapted to the analyzer using the relevant CalSet.

Calibration frequency: Calibration must be performed with every set of reagent/pretreatment rackpack.

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Renewed calibration on all analyzers:

- daily
- as required: e.g. quality control findings outside the defined limits

Quality control

Use PreciControl ThyroAB or other suitable controls for routine quality control procedures.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per reagent kit, and following each calibration.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

If necessary, repeat the measurement of the samples concerned.

Follow the applicable government regulations and local guidelines for quality control.

Calculation

The analyzer automatically calculates the analyte concentration of each sample in IU/L.

Limitations - interference

The effect of the following endogenous substances and pharmaceutical compounds on assay performance was tested. Interferences were tested up to the listed concentrations and no impact on results was observed.

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 427 µmol/L or ≤ 25 mg/dL
Hemoglobin	≤ 0.248 mmol/L or ≤ 400 mg/dL
Intralipid	≤ 1500 mg/dL
Biotin	≤ 2456 nmol/L or ≤ 600 ng/mL
Rheumatoid factors	≤ 600 IU/mL

Criterion: For concentrations of 1.1-5 IU/L the deviation is ≤ ± 0.75 IU/L. For values ≥ 5-40 IU/L the deviation is ≤ 15 %.

The assay result is not affected in samples with biotin concentrations up to 600 ng/mL (2456 nmol/L). 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.[30] Concentrations up to 1160 ng/mL have been described after a single dose of 300 mg biotin used in controlled settings.[31] If the biotin threshold for the assay is exceeded the result will have a positive bias (e.g. 128 % at 675 ng/mL).

Pharmaceutical substances

In vitro tests were performed on 17 commonly used pharmaceuticals. No interference with the assay was found except for sodium heparin. Do not use samples from patients under sodium heparin treatment. Sodium heparin showed no interference up to a concentration of 50 IU/L.

In addition, the following special thyroid drugs were tested. No interference with the assay was found.

Special thyroid drugs

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

Drug interferences are measured based on recommendations given in CLSI guidelines EP07 and EP37 and other published literature. Effects of concentrations exceeding these recommendations have not been characterized.

In rare cases, interference due to extremely high titers of antibodies to test-specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

Limits and ranges

Measuring range

0.8-40 IU/L (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 0.8 IU/L. Values above the measuring range are reported as > 40 IU/L.

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 0.5 IU/L

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Limit of Detection = 0.8 IU/L

Limit of Quantitation = 1.1 IU/L

The Limit of Blank, Limit of Detection and Limit of Quantitation were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A2 requirements.

The Limit of Blank is the 95th percentile value from n ≥ 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 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 is the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of ≤ 20 %.

Dilution

Samples with anti-TSHR concentrations above the measuring range can be diluted manually with anti-TSHR negative serum pool. The recommended dilution is 1:5 to 1:10. The concentration of the diluted sample must be > 4 IU/L. After dilution, multiply the result by the dilution factor.

Please note: The autoantibodies are heterogeneous and this gives rise to non-linear dilution phenomena for certain individual samples.

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 97 % and the specificity at 99 %. The calculated receiver operating characteristic (ROC) curve had an area under the curve (AUC) of 0.99. The upper limits of anti-TSHR values in the cohorts of healthy individuals and patients with thyroid disease without diagnosis of Graves' disease were 1.22 IU/L and 1.53 IU/L, respectively (97.5th percentiles).

*91 subacute thyroiditis, 45 adenomatous goiter, 27 Hashimoto's disease, 32 painless thyroiditis, 7 autonomously functioning thyroid nodules, 1 toxic multinodular goiter, 7 others

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using Elecsys reagents, pooled human sera and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplicate each for 21 days (n = 84). The following results were obtained:

cobas e 411 analyzer					
		Repeatability		**Intermediate precision**	
Sample	Mean IU/L	SD IU/L	CV %	SD IU/L	CV %
Human serum 1	1.38	0.097	7.0	0.170	12.3
Human serum 2	1.82	0.157	8.6	0.187	10.2
Human serum 3	23.0	0.355	1.5	0.419	1.8
Human serum 4	37.2	0.313	0.8	0.487	1.3
PC[b)] ThyroAB 1	4.58	0.155	3.4	0.256	5.6
PC ThyroAB 2	18.1	0.390	2.2	0.513	2.8

b) PC = PreciControl

cobas e 601 and **cobas e** 602 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean IU/L	SD IU/L	CV %	SD IU/L	CV %
Human serum 1	1.41	0.105	7.5	0.129	9.1
Human serum 2	1.87	0.140	7.5	0.161	8.6
Human serum 3	22.7	0.252	1.1	0.347	1.5
Human serum 4	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

Method comparison

A comparison of the Elecsys Anti-TSHR assay, REF 08496609190 (**cobas e** 601 analyzer; y) with the Elecsys Anti-TSHR assay, REF 04388780190 (**cobas e** 601 analyzer; x) gave the following correlations (IU/L):

Number of samples measured: 120

Passing/Bablok[32]	Linear regression
y = 0.983x + 0.328	y = 0.995x + 0.258
τ = 0.927	r = 0.999

The sample concentrations were between 0.824 and 37.5 IU/L.

Analytical specificity

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

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For further information, please refer to the appropriate user guide or operator's manual for the analyzer concerned, the respective application sheets and the Method Sheets of all necessary components (if available in your country).

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard:

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume for reconstitution
GTIN	Global Trade Item Number
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

CE 0123

Roche Diagnostics GmbH
Sandhofer Strasse 116
68305 Mannheim, Germany
www.roche.com
+800 5505 6606

Roche