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Elecsys TSH

cobas®

REF	Σ	SYSTEM
11731459 122	200	MODULAR ANALYTICS E170 **cobas e** 411 **cobas e** 601 **cobas e** 602

English

System information

For **cobas e** 411 analyzer: test number 010
For MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number 001

Intended use

Immunoassay for the in vitro quantitative determination of thyrotropin in human serum and plasma.

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

Summary

Thyroid-stimulating hormone (TSH, thyrotropin) is a glycoprotein having a molecular weight of approximately 30000 daltons and consisting of two subunits. The β-subunit carries the TSH-specific immunological and biological information, whereas the α-chain carries species-specific information and has an identical amino acid sequence to the α-chains of LH, FSH and hCG.[1]

TSH is formed in specific basophil cells of the anterior pituitary and is subject to a circadian secretion sequence. The hypophyseal release of TSH (thyrotropic hormone) is the central regulating mechanism for the biological action of thyroid hormones. TSH has a stimulating action in all stages of thyroid hormone formation and secretion; it also has a proliferative effect.[1]

The determination of TSH serves as the initial test in thyroid diagnostics. Even very slight changes in the concentrations of the free thyroid hormones bring about much greater opposite changes in the TSH level. Accordingly, TSH is a very sensitive and specific parameter for assessing thyroid function and is particularly suitable for early detection or exclusion of disorders in the central regulating circuit between the hypothalamus, pituitary and thyroid.[2,3,4,5,6]

The Elecsys TSH assay employs monoclonal antibodies specifically directed against human TSH. The antibodies labeled with ruthenium complex[a)] consist of a chimeric construct from human and mouse-specific components. As a result, interfering effects due to HAMA (human anti-mouse antibodies) are largely eliminated.

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

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 50 µL of sample, a biotinylated monoclonal TSH-specific antibody and a monoclonal TSH-specific antibody labeled with a ruthenium complex react to form a sandwich complex.
- 2nd incubation: After addition of streptavidin-coated microparticles, the 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 is labeled as TSH.

M Streptavidin-coated microparticles (transparent cap), 1 bottle, 12 mL:

Streptavidin-coated microparticles 0.72 mg/mL, preservative.

R1 Anti-TSH-Ab~biotin (gray cap), 1 bottle, 14 mL:

Biotinylated monoclonal anti-TSH antibody (mouse) 2.0 mg/L; phosphate buffer 100 mmol/L, pH 7.2; preservative.

R2 Anti-TSH-Ab~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 12 mL:

Monoclonal anti-TSH antibody (mouse/human) labeled with ruthenium complex 1.2 mg/L; phosphate buffer 100 mmol/L, pH 7.2; preservative.

Precautions and warnings

For in vitro diagnostic use.
Exercise the normal precautions required for handling all laboratory reagents.
Disposal of all waste material should be in accordance with local guidelines.
Safety data sheet available for professional user on request.

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

Reagent handling

The reagents in the kit have been assembled into a ready-for-use unit that cannot be separated.

All information required for correct operation is read in from the respective reagent barcodes.

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:	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	12 weeks
on MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602	6 weeks
on **cobas e** 411	8 weeks

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.

Li-, Na-, NH_4^+-heparin, K_3-EDTA, sodium citrate and sodium fluoride/potassium oxalate plasma.

Criterion: Recovery within 90-110 % of serum value or slope 0.9-1.1 + intercept within < ± 2x analytical sensitivity (LDL) + coefficient of correlation > 0.95.

Stable for 7 days at 2-8 °C, 1 month at -20 °C.[7] 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 04738551190, TSH CalSet, 4 x 1.3 mL
- REF 11731416190, PreciControl Universal, for 4 x 3.0 mL
- REF 06445918190, PreciControl Thyro Sensitive, for 4 x 2.0 mL
- REF 03609987190, Diluent MultiAssay, 2 x 16 mL sample diluent
- General laboratory equipment
- MODULAR ANALYTICS E170 or **cobas e** analyzer

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

Accessories for MODULAR ANALYTICS E170, **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

Accessories 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 (except for the **cobas e** 602 analyzer).

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 2nd IRP WHO Reference Standard 80/558.

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 once per reagent lot using fresh reagent (i.e. not more than 24 hours since the reagent kit was registered on the analyzer).

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

Renewed calibration is recommended as follows:

- after 8 weeks when using the same reagent lot
- after 7 days when using the same reagent kit on the analyzer
- as required: e.g. quality control findings outside the defined limits

Quality control

For quality control, use PreciControl Universal or PreciControl Thyro Sensitive.

In addition, other suitable control material can be used.

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 either in µIU/mL or mIU/L (selectable).

Limitations - interference

The assay is unaffected by icterus (bilirubin < 701 µmol/L or < 41 mg/dL), hemolysis (Hb < 0.621 mmol/L or < 1 g/dL), lipemia (Intralipid < 1500 mg/dL), biotin (< 102 nmol/L or < 25 ng/mL), IgG < 2 g/dL and IgM < 0.5 g/dL.

Criterion: Recovery within ± 10 % of initial value.

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.

No interference was observed from rheumatoid factors up to a concentration of 3250 IU/mL and samples from dialysis patients.

There is no high-dose hook effect at TSH concentrations up to 1000 µIU/mL.

In vitro tests were performed on 26 commonly used pharmaceuticals. No interference with the assay was found.

The presence of autoantibodies may induce high molecular weight complexes (macro-TSH) which may cause unexpected high values of TSH.[8]

In rare cases, interference due to extremely high titers of antibodies to analyte-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

0.005-100 µIU/mL (defined by the lower detection limit and the maximum of the master curve). The functional sensitivity is 0.014 µIU/mL.[6] Values below the lower detection limit are reported as < 0.005 µIU/mL. Values above the measuring range are reported as > 100 µIU/mL (or up to 1000 µIU/mL for 10-fold diluted samples).

Lower limits of measurement

Lower detection limit of the test

Lower detection limit: 0.005 µIU/mL

The lower detection limit represents the lowest analyte level that can be distinguished from zero. It is calculated as the value lying two standard deviations above that of the lowest standard (master calibrator, standard 1 + 2 SD, repeatability study, n = 21).

Dilution

Samples with TSH concentrations above the measuring range can be diluted with Diluent MultiAssay. The recommended dilution is 1:10 (either automatically by the analyzers, or manually). The concentration of the diluted sample must be > 10 µIU/mL.

After manual dilution, multiply the result by the dilution factor.

After dilution by the analyzers, the software automatically takes the dilution into account when calculating the sample concentration.

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Expected values

0.270-4.20 µIU/mL

These values correspond to the 2.5th and 97.5th percentiles of results obtained from a total of 516 healthy test subjects examined.

For detailed information about reference intervals in children, adolescents and pregnant women, refer to the brochure "Reference Intervals for Children and Adults", English: REF 04640292, German: REF 04625889.

This booklet also contains results of a detailed study about influencing factors on thyroid parameters in a well characterized reference group of adults. Different inclusion and exclusion criteria were applied (e.g. sonographic results (thyroid volume and density) as well as criteria according to the guidelines of the National Academy of Clinical Biochemistry - NACB).

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 modified protocol (EP5-A) of the CLSI (Clinical and Laboratory Standards Institute): 6 times daily for 10 days (n = 60); repeatability on MODULAR ANALYTICS E170 analyzer, n = 21. PreciControl TSH was determined once daily for 10 days (n = 10). The following results were obtained:

cobas e 411 analyzer					
		Repeatability		**Intermediate precision**	
Sample	Mean µIU/mL	SD µIU/mL	CV %	SD µIU/mL	CV %
Human serum 1	0.034	0.003	8.6	0.003	8.7
Human serum 2	0.91	0.02	2.1	0.03	3.3
Human serum 3	3.96	0.07	1.8	0.14	3.6
PC[b)] Universal 1	2.45	0.05	1.9	0.05	2.2
PC Universal 2	10.67	0.16	1.5	0.19	1.8
PreciControl TSH	0.084	-	-	0.005	5.4

b) PC = PreciControl

MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers						
	Repeatability			**Intermediate precision**		
Sample	Mean µIU/mL	SD µIU/mL	CV %	Mean µIU/mL	SD µIU/mL	CV %
Human serum 1	0.040	0.001	3.0	0.035	0.003	7.2
Human serum 2	0.092	0.002	2.7	0.151	0.005	3.2
Human serum 3	9.37	0.102	1.1	3.66	0.120	3.3
PC Universal 1	0.959	0.014	1.5	0.915	0.031	3.5
PC Universal 2	8.13	0.098	1.2	7.52	0.316	4.2

Method comparison

A comparison of the Elecsys TSH assay (y) with the Enzymun-Test TSH method (x) using clinical samples gave the following correlations:

Number of samples measured: 109

Passing/Bablok[9]	Linear regression
y = 1.01x + 0.01	y = 0.98x + 0.04
τ = 0.944	r = 0.993

The sample concentrations were between approximately 0 and 19 µIU/mL.

Analytical specificity

For the monoclonal antibodies used, the following cross-reactivities were found:

LH 0.038 %, FSH 0.008 %; hGH and hCG no cross-reactivity.

Functional sensitivity

0.014 µIU/mL

The functional sensitivity is the lowest analyte concentration that can be reproducibly measured with an intermediate precision CV of ≤ 20 %.

References

1 Kronenberg HM, Melmed S, Polonsky KS, et al. Williams Textbook of Endocrinology. Saunders Elsevier, Philadelphia, 12th edition, 2011, chapter 10, p. 301-318.

2 Wu AHB. Tietz Clinical Guide To Laboratory Tests. Saunders Elsevier, Philadelphia, 4th edition, 2006, section II, p. 1040-1043.

3 Surks MI, Chopra IJ, Mariash CN, et al. American Thyroid Association Guidelines for the Use of Laboratory Tests in Thyroid Disorders. JAMA 1990;263:1529-1532.

4 Keffer JH. Preanalytical Considerations in Testing Thyroid Function. Clin Chem 1996;42(1):125-135.

5 Ladenson PW. Optimal laboratory testing for diagnosis and monitoring of thyroid nodules, goiter and thyroid cancer. Clin Chem 1996;42:(1):183-187.

6 Nicoloff JT, Spencer CA. The use and misuse of the sensitive thyrotropin assays. J Clin Endocr Metab 1990;71:553-558.

7 Tietz NW. Clinical Guide to Laboratory Tests, 3rd edition. Philadelphia, Pa. WB Saunders Co. 1995:594.

8 Sakai H, Fukuda G, Suzuki N, et al. Falsely Elevated Thyroid-Stimulating Hormone (TSH) Level Due to Macro-TSH. Endocr J 2009;56(3):435-440.

9 Passing H, Bablok W, Bender R et al. A general regression procedure for method transformation. J Clin Chem Clin Biochem 1988;26:783-790.

For further information, please refer to the appropriate operator's manual for the analyzer concerned, the respective application sheets, the product information 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.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see https://usdiagnostics.roche.com for definition of symbols used):

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume after reconstitution or mixing
GTIN	Global Trade Item Number

CE

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