08443432501V2.0

Elecsys TSH

cobas®

REF		Σ	SYSTEM
08443432190	08443432501	300	**cobas e** 801

English

For use in the USA only

System information

Short name	ACN (application code number)
TSH	10172

Intended 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 **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on **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: 30 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 II 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 **cobas** link.

Reagents - working solutions

The **cobas e** pack is labeled as TSH.

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

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.

For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

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 available via the **cobas** link.

Storage and 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.

Stability:	
unopened at 2-8 °C	up to the stated expiration date
on the **cobas e** 801 analyzer	16 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-heparin, K_2-EDTA and K_3-EDTA plasma.

Plasma tubes containing separating gel can be used.

Criterion: Slope 0.9-1.1 + coefficient of correlation ≥ 0.95 and with a bias ≤ 10 % at medical decision points (0.27 µIU/mL and 4.2 µIU/mL).

Stable for 8 days at 20-25 °C, 14 days at 2-8 °C, 24 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 and calibrators are at 20-25 °C prior to measurement.

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

Sample stability claims were established by experimental data by the manufacturer or based on reference literature and only for the temperatures/time frames as stated in the method sheet. It is the responsibility of the individual laboratory to use all available references and/or its own studies to determine specific stability criteria for its laboratory.

Materials provided

See "Reagents – working solutions" section for reagents.

Elecsys TSH

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Materials required (but not provided)

- REF 08443459160, TSH CalSet, 4 x 1.3 mL
- REF 06445918160, PreciControl TS, for 4 x 2.0 mL
- REF 11731416160, PreciControl Universal, for 4 x 3.0 mL
- REF 07299010190, Diluent MultiAssay, 45.2 mL sample diluent
- General laboratory equipment
- **cobas e** 801 analyzer

Additional materials for the **cobas e** 801 analyzer:

- REF 06908799190, ProCell II M, 2 x 2 L system solution
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 07485409001, Reservoir Cup, 8 cups to supply ProCell II M and CleanCell M
- REF 06908853190, PreClean II M, 2 x 2 L wash solution
- REF 05694302001, Assay Tip/Assay Cup tray, 6 magazines x 6 magazine stacks x 105 assay tips and 105 assay cups, 3 wasteliners
- REF 07485425001, Liquid Flow Cleaning Cup, 2 adaptor cups to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning Detection Unit
- REF 07485433001, PreWash Liquid Flow Cleaning Cup, 1 adaptor cup to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning PreWash Unit
- REF 11298500160, 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.

Place the cooled (stored at 2-8 °C) **cobas e** pack on the reagent manager. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the **cobas e** pack.

Calibration

Traceability: This method has been standardized against the 2nd IRP WHO Reference Standard 80/558.

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 **cobas e** pack 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 12 weeks when using the same reagent lot
- after 28 days when using the same **cobas e** pack on the analyzer
- as required: e.g. quality control findings outside the defined limits

Quality control

For quality control, use PreciControl Universal or PreciControl TS.

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 **cobas e** pack, 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 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	≤ 701 µmol/L or ≤ 41 mg/dL
Hemoglobin	≤ 0.621 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 1500 mg/dL
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL
Rheumatoid factors	≤ 1500 IU/mL
IgG	≤ 2 g/dL
IgM	≤ 0.5 g/dL

Criterion: For concentrations ≤ 0.2 µIU/mL the deviation is ≤ 0.02 µIU/mL. For concentrations > 0.2 µIU/mL the deviation is ≤ 10 %.

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[7] and up to 1160 ng/mL for subjects after a single dose of 300 mg biotin.[8]

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

Pharmaceutical substances

In vitro tests were performed on 17 commonly used pharmaceuticals. No interference with the assay was found.

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
Rifampicin	48
Acetaminophen	156
Cyclosporine	1.8
Ibuprofen	219
Theophylline	60
Phenylbutazone	321
Itraconazole	10

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

Special drugs

Drug	Concentration tested mg/L
Iodide	0.2
Carbimazole	30
Methimazole	80

Elecsys TSH

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

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.

The presence of autoantibodies may induce high molecular weight complexes (macro-TSH) which may cause unexpectedly high values of TSH.[9]

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 Limit of Detection and the maximum of the master curve). Values below the Limit of Detection 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

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank = 0.0025 µIU/mL

Limit of Detection = 0.005 µIU/mL

Limit of Quantitation = 0.005 µIU/mL

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 TSH concentrations above the measuring range can be diluted with Diluent MultiAssay. The recommended dilution is 1:10 (either automatically by the analyzer 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 analyzer, the software automatically takes the dilution into account when calculating the sample concentration.

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.

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 analyzer is given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using Elecsys reagents, samples 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 801 in **cobas pro** integrated solutions					
		Repeatability		**Intermediate precision**	
Sample	Mean µIU/mL	SD µIU/mL	CV %	SD µIU/mL	CV %
Human serum 1	0.0133	0.0008	6.3	0.0016	11.7
Human serum 2	0.262	0.0045	1.7	0.0072	2.8
Human serum 3	3.95	0.0661	1.7	0.123	3.1
Human serum 4	57.3	1.50	2.6	2.24	3.9
Human serum 5	93.1	2.64	2.8	4.29	4.6
PC[b)] Universal 1	1.32	0.0230	1.7	0.0319	2.4
PC Universal 2	8.00	0.142	1.8	0.234	2.9
PC Thyro Sensitive	0.168	0.0027	1.6	0.0049	2.9

b) PC = PreciControl

Method comparison

A comparison of the Elecsys TSH assay, REF 08443432190 on (**cobas e** 801 in **cobas pro** integrated solutions; y) and (**cobas e** 801 in **cobas** 8000; x) gave the following correlations (µIU/mL):

Number of samples measured: 138

Passing/Bablok[10]	Linear regression
y = 1.018x - 0.00177	y = 1.005x + 0.0449
τ = 0.977	r = 0.999

The sample concentrations were between 0.006 and 97.8 µIU/mL.

Analytical specificity

The following cross-reactivities were found, tested with a TSH concentration of approximately 0.35 µIU/mL.

Cross-reactant	Concentration tested mU/mL	Cross-reactivity %
LH	10000	0.000
FSH	10000	0.000
hGH	1000	n. d.[c)]
hCG	50000	0.000

c) n. d. = not detectable

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 Grimsey P, Frey N, Bendig G, et al. Population pharmacokinetics of exogenous biotin and the relationship between biotin serum levels and in vitro immunoassay interference. Int J Pharmacokinet 2017;2(4):247-256.

8 Piketty ML, Prie D, Sedel F, et al. High-dose biotin therapy leading to false biochemical endocrine profiles: validation of a simple method to overcome biotin interference. Clin Chem Lab Med 2017;55(6):817-825.

9 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.

10 Bablok W, Passing H, Bender R, et al. A general regression procedure for method transformation. Application of linear regression procedures for method comparison studies in clinical chemistry, Part III. J Clin Chem Clin Biochem 1988 Nov;26(11):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).

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see dialog.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 for reconstitution
GTIN	Global Trade Item Number

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