ms_04388780190V12.0

Anti-TSHR

cobas®

Antibodies to TSH receptor

REF	Σ	SYSTEM
04388780 190	100	Elecsys 2010 MODULAR ANALYTICS E170 **cobas e** 411 **cobas e** 601 **cobas e** 602

English

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 Elecsys and **cobas e** immunoassay analyzers.

Summary

Hyperthyroidism in Graves' disease (autoimmune hyperthyroidism) is caused by autoantibodies to the TSH receptor (TSHR), and measurement of these TSHR antibodies (TRAb) can be useful in disease diagnosis and management. The majority of TSH receptor antibodies mimic the action of TSH. Because they are not controlled by the negative feedback system, the stimulation of the thyroid often leads to the clinical thyrotoxic state of Graves' disease.[1,2,3,4,5,6]

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. 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 the management of the treatment.[7,8,9] 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.
- 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 history of thyroid disease is therefore important in assessing the risk of thyroid disease in the neonate.

Detection of TRAb in clinical routine is performed by second generation assays using coated plate or tube technique with antibody-immobilized human or porcine TSHR.[10,11] Such TSH binding inhibition assays determine the ability of serum TRAb to inhibit the binding of labeled TSH to the immobilized TSH receptor. Sensitivity and predictive value in Graves' disease patient's management is independent on the fact if the assay uses human recombinant or native porcine TSH receptor.[12,13,14]

With the availability of a human thyroid stimulating monoclonal antibody (M22)[15,16] a TRAb assay system in which patient serum autoantibodies inhibit the binding of a labeled thyroid stimulating antibody (rather than labeled TSH) to the TSH receptor could be developed.[17]

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

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.

Reagents - working solutions

The reagent rackpack (M, R1, R2) is labeled as A-TSHR.

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 approx. 0.3 mg/L; phosphate buffer 20 mmol/L, pH 7.4; stabilizers, preservative.

Calibrators

A-TSHR Cal1 Anti-TSHR calibrator 1 (white cap), 1 bottle (lyophilized) for 2.0 mL:
Anti-TSHR antibody (human) approx. 1.0 IU/L in a human serum matrix.

A-TSHR Cal2 Anti-TSHR calibrator 2 (black cap), 1 bottle (lyophilized) for 2.0 mL:
Anti-TSHR antibody (human) approx. 25 IU/L in a human serum matrix.

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.
Exercise the normal precautions required for handling all laboratory reagents.

Anti-TSHR

Antibodies to TSH receptor

Disposal of all waste material should be in accordance with local guidelines. 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

H319	Causes serious eye irritation.

Prevention:

P264	Wash skin thoroughly after handling.
P280	Wear protective gloves/ protective clothing/ eye protection/ face protection.

Response:

P305 + P351 + P338	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P337 + P313	If eye irritation persists: Get medical advice/attention.

Product safety labeling primarily 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 applied were FDA-approved or cleared in compliance with the European Directive 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.[18,19]

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

Reagent handling

Reagent rackpack

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

Calibrators

Carefully dissolve the contents of one bottle by adding exactly 2.0 mL of distilled or deionized water and allow to stand closed for 15 minutes to reconstitute. Mix carefully, avoiding foam formation.

Transfer aliquots of the reconstituted calibrators into empty labeled snap-cap bottles (CalSet Vials). Attach the supplied labels to the additional bottles. Store the aliquots immediately at -20 °C.

Perform **only one** calibration procedure per aliquot.

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

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.

Important note

Elecsys 2010 analyzer:
The pretreatment and reagent rackpacks provided in the same Elecsys Anti-TSHR reagent kit belong together and must be handled as one set. To avoid any mix-ups please clearly mark each set of pretreatment and reagent rackpacks immediately after opening the Elecsys Anti-TSHR reagent kit (e.g. using a water-resistant permanent marker). Only one set of pretreatment/reagent rackpacks can be placed on the analyzer.

MODULAR ANALYTICS E170, **cobas e** 411, **cobas e** 601 and **cobas e** 602 analyzers:
Depending on the software version more than one set of pretreatment/reagent rackpacks can be placed on the analyzers. Pretreatment/reagent rackpack link feature is available on

- MODULAR ANALYTICS E170 analyzer from software version 08-07 onwards
- **cobas e** 411 analyzer from software version 02-04 onwards
- **cobas e** 601 analyzer from software version 05-02 onwards
- **cobas e** 602 analyzer from software version 04-01 onwards

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: Both the vial labels, and the additional labels (if available) contain 2 different barcodes. The barcode between the yellow markers is for **cobas** 8000 systems only. If using a **cobas** 8000 system, please turn the vial cap 180° into the correct position so the barcode can be read by the system. Place the vial on the instrument 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 calibrators	
lyophilized calibrators	up to the stated expiration date
reconstituted calibrators at -20 °C	3 months (freeze only once)
on the analyzers at 20-25 °C	3 hours
after thawing	use only once

Store calibrators **upright** in order to prevent the calibrator solution from adhering to the snap-cap.

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 3 days at 2-8 °C, at least 1 month at -20 °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.

Anti-TSHR

Antibodies to TSH receptor

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.

- 2 x 6 bottle labels

Materials required (but not provided)

- REF 05042666191, PreciControl ThyroAB, for 2 x 2 mL each of PreciControl Thyro 1 and 2
- REF 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles
- General laboratory equipment
- Elecsys 2010, MODULAR ANALYTICS E170 or **cobas e** analyzer

Accessories for Elecsys 2010 and **cobas e** 411 analyzers:

- 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, Elecsys 2010 AssayCup, 60 x 60 reaction vessels
- REF 11706799001, Elecsys 2010 AssayTip, 30 x 120 pipette tips

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 Combimagazine M, 48 magazines x 84 reaction vessels 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.

MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers: PreClean M solution is necessary.

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.

Place the reconstituted calibrators in the sample zone. Perform **only one** calibration procedure per aliquot.

Calibration

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

Every Elecsys Anti-TSHR 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 A-TSHR Cal1 and A-TSHR Cal2.

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

Renewed calibration on all analyzers:

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

Quality control

For quality control, use PreciControl ThyroAB.

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.

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 assay is unaffected by icterus (bilirubin < 427 µmol/L or < 25 mg/dL), hemolysis (Hb < 0.248 mmol/L or < 0.4 g/dL), lipemia (Intralipid < 1500 mg/dL) and biotin (< 41 nmol/L or < 10 ng/mL).

Criterion: Recovery within ± 15 % of initial value.

Elevated results are obtained when using samples with biotin concentrations > 41 nmol/L or > 10 ng/mL.

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 600 IU/mL.

In vitro tests were performed on 20 commonly used pharmaceuticals. No interference with the assay was found except for sodium heparin. Do not use samples from patients under sodium heparin treatment. Fractionated heparin (Clexane) showed no interference up to a concentration of 5 IU/mL.

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

0.3-40 IU/L (defined by the lower detection limit and the maximum of the master curve). Values below the lower detection limit are reported as < 0.3 IU/L. Values above the measuring range are reported as > 40 IU/L.

Lower limits of measurement

Lower detection limit of the test

Lower detection limit: approximately 0.3 IU/L

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 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.

Anti-TSHR

Antibodies to TSH receptor

cobas®

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 96 % 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 1.58 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 (EP5-A2) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplication each for 21 days (n = 84). The following results were obtained:

Elecsys 2010 and **cobas e** 411 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean IU/L	SD IU/L	CV %	SD IU/L	CV %
Human serum 1	1.73	0.102	5.9	0.168	9.7
Human serum 2	2.57	0.113	4.4	0.173	6.7
Human serum 3	6.57	0.178	2.7	0.254	3.9
Human serum 4	25.5	0.323	1.3	0.470	1.8
PC[a)] THYRO1	4.09	0.144	3.5	0.190	4.6
PC THYRO2	16.4	0.220	1.3	0.300	1.8

a) PC = PreciControl

MODULAR ANALYTICS E170, **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	1.71	0.129	7.6	0.195	11.4
Human serum 2	2.16	0.110	5.1	0.187	8.7
Human serum 3	5.92	0.112	1.9	0.222	3.8
Human serum 4	24.6	0.233	0.9	0.469	1.9
PC THYRO1	4.05	0.139	3.4	0.144	3.5
PC THYRO2	16.4	0.258	1.6	0.304	1.9

Method comparison

A comparison of the Elecsys Anti-TSHR assay (y) with an established commercially available anti-TSHR radioimmunoassay method (x) using clinical samples gave the following correlations:

Number of samples measured: 221

Passing/Bablok[20]	Linear regression
y = 1.10x + 0.02	y = 0.95x + 0.76
τ = 0.789	r = 0.939

The sample concentrations were between approximately 1.0 and 34.6 IU/L.

Analytical specificity

No influence with human autoantibodies to thyroglobulin (< 4000 IU/mL) or anti-TPO (< 600 IU/mL) was detectable.

There is no interference with human TSH (< 1000 mIU/L), human LH (< 10000 mIU/mL), human FSH (< 10000 mIU/mL) and hCG (< 50000 mIU/mL).

Functional sensitivity

Approximately 0.9 IU/L

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

References

1 Pfannenstiel P, Saller B. Schilddrüsenkrankheiten – Diagnose und Therapie, 2nd edition. Berliner Medizinische Verlagsanstalt. 1995;28-30,141,169-172,200-201.

2 McIntosh RS, Asghar MS, Weetman AP. The antibody response in human autoimmune thyroid disease. Clin Sci 1997;92:529-541.

3 Schott M, Seißler J, Scherbaum WA. Diagnostic testing for autoimmune thyroid diseases. J Lab Med 2006;34(4):254-257.

4 Feldt-Rasmussen U. Analytical and clinical performance goals for testing autoantibodies to thyroperoxidase, thyroglobulin, and thyrotropin receptor. Clin Chem 1996;42(1):160-163.

5 Farid NR, Szkudlinski MW. Minireview: structural and functional evolution of the thyrotropin receptor. Endocrinology 2004;145(9):4048-4057.

6 Rapoport B, Chazenbalk GD, Jaume JC, et al. The thyrotropin (TSH) receptor: interaction with TSH and autoantibodies. Endocrine Reviews 1998;19(6):673-716.

7 Quadbeck B, Hoermann R, Roggenbuck U, et al. Sensitive thyrotropin and thyrotropin-receptor antibody determinations one month after discontinuation of antithyroid drug treatment as predictors of relapse in Graves' disease. Thyroid 2005;15:1047-1054.

8 Okamoto Y, Tanigawa SI, Ishikawa K, et al. TSH receptor antibody measurements and prediction of remission in Graves' disease patients treated with minimum maintenance doses of antithyroid drugs. Endocr J 2006;53(4):467-472.

9 Zöphel K, Wunderlich G, Kopprasch C, et al. Predictive value of thyrotropin receptor antibodies using the second generation TRAb human assay after radioiodine treatment in Graves' disease. Nuklearmedizin 2003;42:63-70.

10 Bolton J, Sanders J, Oda Y, et al. Measurement of thyroid-stimulating hormone receptor autoantibodies by ELISA. Clin Chem 1999;45:2285-2287.

11 Costagliola S, Morgenthaler NG, Hoermann R, et al. Second generation assay for thyrotropin receptor antibodies has superior diagnostic sensitivity for Graves' disease. J Clin Endocrinol Metab 1999;84:90-97.

12 Kamijo K. TSH receptor antibody measurement in patients with various thyrotoxicosis and Hashimoto's thyroiditis: a comparison of two two-step assays, coated plate ELISA using porcine TSH-receptor and coated tube radioassay using human recombinant TSH-receptor. Endocr J 2003;50(1):113-116.

13 Zöphel K, Wunderlich G. Predictive value of TSH receptor antibody measurement in Graves' disease is independent on the TSH receptor (human or porcine) but depends on the generation of the assay used. Endocr J 2006;53(6):869-870.

14 Zöphel K, von Landenberg P, Roggenbuck D, et al. Are porcine and human TSH receptor antibody measurements comparable? Clin Lab 2008;54(1-2):1-8.

15 Sanders J, Evans M, Premawardhana LDKE, et al. Human monoclonal thyroid stimulating autoantibody. Lancet 2003;362:126-128.

16 Sanders J, Jeffreys J, Depraetere H, et al. Characteristics of a human monoclonal autoantibody to the thyrotropin receptor: sequence, structure and function. Thyroid 2004;14:560-570.

17 Rees Smith B, Bolton J, Young S, et al. A new assay for thyrotropin receptor autoantibodies. Thyroid 2004;14:830-835.

18 Occupational Safety and Health Standards: bloodborne pathogens. (29 CFR Part 1910.1030). Fed. Register.

19 Directive 2000/54/EC of the European Parliament and Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work.

20 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).

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.

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

Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
www.roche.com