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Cortisol II

cobas®

Cortisol

REF	Σ	SYSTEM
06687733 190	100	MODULAR ANALYTICS E170 **cobas e** 411 **cobas e** 601 **cobas e** 602

English

Intended use

Immunoassay for the in vitro quantitative determination of cortisol in human serum, plasma and saliva. The determination of cortisol is used for the recognition and treatment of functional disorders of the adrenal gland.

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

Summary

Cortisol (hydrocortisone) is quantitatively the major glucocorticoid product of the adrenal cortex.[1] The main reason to measure cortisol is to diagnose human diseases which are caused by the overproduction of cortisol in Cushing's syndrome (CS), deficiency of adrenal steroid excretion in Addison's disease, and for therapy monitoring (e.g. dexamethasone suppression therapy in Cushing's syndrome and hormone replacement therapy in Addison's disease).[1] Cortisol plays an important role in the regulation of many essential physiological processes, including energy metabolism, maintenance of electrolyte balance and blood pressure, immunomodulation and stress responses, cell proliferation as well as cognitive functions. The major fraction of cortisol circulates bound to plasma proteins as corticosteroid binding globulin and albumin.[2] The biologically active free fraction comprises only 2-5 % of the total hormone concentration.[1,2]

Elevated serum levels can be found in stress responses, psychiatric diseases, obesity, diabetes, alcoholism and pregnancy, which may cause diagnostic problems in patients with Cushing's syndrome. Low levels of cortisol are seen in patients with rare adrenal enzyme defects and after long-lasting stress. For diagnostic purposes the following analyses are used: Total and free cortisol in serum and midnight saliva.[1]

The secretion of cortisol is mainly controlled by the hypothalamic-pituitary-adrenal axis (HPA). When cortisol levels in the blood are low, a group of cells in a region of the brain called the hypothalamus release corticotropin-releasing hormone (CRH) which causes the pituitary gland to secrete another hormone, adrenocorticotropic hormone (ACTH), into the bloodstream. High levels of ACTH are detected in the adrenal glands and stimulate the secretion of cortisol, causing blood levels of cortisol to rise. As the cortisol levels rise, they start to block the release of CRH from the hypothalamus and ACTH from the pituitary.[2]

Normally, the highest cortisol secretion happens in the second half of the night with peak cortisol production occurring in the early morning. Following this, cortisol levels decline throughout the day with lowest levels during the first half of the night.[3] Therefore the circadian variations of cortisol secretion and the influence of stress have to be considered for the sampling conditions of cortisol in serum, plasma and saliva.[4]

The Elecsys Cortisol II assay makes use of a competition test principle using a monoclonal antibody which is specifically directed against cortisol. Endogenous cortisol in the sample which has been liberated from binding proteins with danazol competes with exogenous cortisol derivative in the test which has been labeled with ruthenium complex[a)] for the binding sites on the biotinylated antibody.

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

Test principle

Competition principle. Total duration of assay: 18 minutes.

- 1st incubation: 10 µL of sample is incubated with a cortisol-specific biotinylated antibody and a ruthenium complex labeled cortisol derivative. Depending on the concentration of the analyte in the sample and the formation of the respective immune complex, the labeled antibody binding site is occupied in part with sample analyte and in part with ruthenylated hapten.
- 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.

Reagents - working solutions

The reagent rackpack is labeled as CORT II.

M Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL:

Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-cortisol-Ab~biotin (gray cap), 1 bottle, 10 mL:

Biotinylated monoclonal anti-cortisol antibody (ovine) 20 ng/mL; danazol 20 µg/mL; MES[b)] buffer 100 mmol/L, pH 6.0; preservative.

R2 Cortisol-peptide~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 10 mL:

Cortisol derivative (synthetic), labeled with ruthenium complex 20 ng/mL; danazol 20 µg/mL; MES buffer 100 mmol/L, pH 6.0; preservative.

b) MES = 2-morpholino-ethane sulfonic acid

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 the analyzers	8 weeks

Specimen collection and preparation

Only the specimens listed below were tested.

Serum and plasma:

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

Li-heparin, K_2-EDTA and K_3-EDTA plasma as well as plasma tubes containing separating gel.

Criterion serum/plasma: Recovery 90-110 %. Below 50 nmol/L, recovery ± 5 nmol/L.

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Criterion saliva: Average difference of samples between 5 and 15 nmol/l is < 3 nmol/L.

Please note: Due to the circadian rhythm of cortisol levels in serum and plasma, the sample collection time must be noted.

Stable for 24 hours at 20-25 °C, 4 days at 2-8 °C, 12 months at -20 °C. Freeze only once.

Saliva:

Collect a saliva sample using a Salivette device.

Do not use vials containing citric acid.

Remove the swab from the suspended insert and gently chew for about 2 minutes to thoroughly saturate the swab with saliva. Replace the swab into the suspended insert and close the tube. Centrifuge the Salivette for 2 minutes at 1000 g to separate off the saliva into the outer tube. Use the clear supernatant for the Elecsys Cortisol II assay. Use saliva samples in the same way as serum or plasma specimens.

Please note: If no instructions have been given, saliva should be collected before brushing teeth in the morning. During the day, saliva should be collected no earlier than 30 minutes after eating or drinking.

The centrifuged saliva sample is stable for 24 hours at 20-25 °C, 4 days at 2-8 °C, 12 months at -20 °C. Freeze only once.

The sample types listed (serum and plasma) 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 06687750190, Cortisol II CalSet, for 4 x 1 mL
- REF 11731416190, PreciControl Universal, for 4 x 3 mL
  REF 06687768190, PreciControl Cortisol Saliva, for 4 x 1 mL
- REF 05192943190, Diluent Universal 2, 2 x 36 mL sample diluent
- General laboratory equipment
- MODULAR ANALYTICS E170 or **cobas e** analyzer

Additionally required for the determination of cortisol in saliva:

- Salivette, sample collection tube, Sarstedt, Nümbrecht, Germany, REF 51.1534

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, 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.

Calibration

Traceability: This method has been standardized against the IRMM (Institute for Reference Materials and Measurements)/IFCC-451 panel (ID-GC/MS, isotope dilution-gas chromatography/mass spectrometry).[5]

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). 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 Cortisol Saliva.

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.

PreciControl Cortisol Saliva:

Note: The controls are not barcode-labeled and therefore have to be run like external controls. All values and ranges have to be entered manually. Please refer to the section "QC" in the operator's manual or to the online help of the instrument software.

Non-barcode labeled controls: Only one target value and range for each control level can be entered in the analyzer. The reagent lot-specific target values have to be re-entered each time a specific reagent lot with different control target values and ranges is used. Two reagent lots with different control target values and ranges cannot be used in parallel in the same run.

The exact lot-specific target values and ranges are printed on the enclosed (or electronically available) value sheet in the reagent kit or PreciControl kit.

Please make sure that the correct values are used.

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Calculation

The analyzer automatically calculates the analyte concentration of each sample (either in nmol/L, µg/dL or µg/L).

Conversion factors:
nmol/L x 0.03625 = µg/dL
nmol/L x 0.3625 = µg/L
µg/dL x 27.586 = nmol/L
µg/L x 2.7586 = nmol/L

Limitations - interference

When performed in serum and plasma, the assay is unaffected by icterus (bilirubin ≤ 428 µmol/L or ≤ 25 mg/dL), hemolysis (Hb ≤ 0.311 mmol/L or ≤ 0.5 g/dL), lipemia (Intralipid ≤ 1500 mg/dL), biotin (≤ 123 nmol/L or ≤ 30 ng/mL), IgG ≤ 50 g/L, IgA ≤ 10 g/L and IgM ≤ 10 g/L.

Criterion: Recovery within ± 10 % of initial value for samples > 50 nmol/L and ± ≤ 5 nmol/L for samples ≤ 50 nmol/L.

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 16 commonly used pharmaceuticals. No interference with the assay was found.

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.

Pregnancy, contraceptives and estrogen therapy give rise to elevated cortisol concentrations.

In samples from patients who have been treated with prednisolone, 6-α-Methylprednisolone or prednisone, falsely elevated concentrations of cortisol may be determined.

During metyrapon tests, 11-deoxycortisol levels are elevated. Falsely elevated cortisol values may be determined due to cross reactions (see section on analytical specificity).

Patients suffering from 21-hydroxylase deficiency exhibit elevated 21-deoxycortisol levels and this can also give rise to falsely elevated cortisol results.

The time of sample collection must be taken into account when interpreting results due to the cortisol secretion circadian rhythm. Severe stress can also give rise to elevated cortisol levels.

Saliva samples contaminated with blood have to be discarded.

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

1.5-1750 nmol/L or 0.054-63.4 µg/dL (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 1.5 nmol/L (< 0.054 µg/dL). Values above the measuring range are reported as > 1750 nmol/L (> 63.4 µg/dL) (or up to 17500 nmol/L or 634 µg/dL for 10-fold diluted samples).

Lower limits of measurement

Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ)

Limit of Blank = 1.0 nmol/L (0.036 µg/dL)

Limit of Detection = 1.5 nmol/L (0.054 µg/dL)

Limit of Quantitation = 3.0 nmol/L (0.109 µg/dL) with a total allowable error of ≤ 30 %

The Limit of Blank, Limit of Detection and Limit of Quantitation were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A 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 defined as the lowest amount of analyte in a sample that can be accurately quantitated with a total allowable error of ≤ 30 %.

Dilution

Serum and plasma samples with cortisol concentrations above the measuring range can be diluted with Diluent Universal 2. The recommended dilution is 1:10 (either automatically by the MODULAR ANALYTICS E170 or **cobas e** analyzers or manually). The concentration of the diluted sample must be > 150 nmol/L or > 5 µg/dL.

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

After dilution by the analyzers, the MODULAR ANALYTICS E170 and **cobas e** software automatically takes the dilution into account when calculating the sample concentration.

Expected values

Cortisol in serum and plasma

In studies with the Elecsys Cortisol II assay, the following values were determined using samples from 150 self-reported healthy individuals, aged 21 years or older. Exclusion criteria were: pregnancy, lactation, use of oral contraceptives and medication with cortisone/cortisol (5th-95th percentile):

Morning hours 6-10 a.m.: 172-497 nmol/L (6.24-18.0 µg/dL), n = 146

Afternoon hours 4-8 p.m.: 74.1-286 nmol/L (2.69-10.4 µg/dL), n = 150

No statistical difference was observed between males and females.

Cortisol in saliva

In studies with the Elecsys Cortisol II assay, the following values were determined using saliva samples from the same 150 individuals described above. Again, no gender specific differences were seen (5th-95th percentile):

Morning hours 6-10 a.m.: < 21.6 nmol/L (< 0.783 µg/dL), n = 147
3.4 % < 1.50 nmol/L, n = 5

Afternoon hours 4-8 p.m.: < 6.70 nmol/L (< 0.243 µg/dL), n = 149
24.8 % < 1.50 nmol/L, n = 37

Midnight ± 30 minutes: < 5.74 nmol/L (< 0.208 µg/dL), n = 150
72.0 % < 1.50 nmol/L, n = 108

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, human sera and controls in accordance with 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:

cobas e 411 analyzer					
		Repeatability		**Intermediate precision**	
Sample	Mean nmol/L (µg/dL)	SD nmol/L (µg/dL)	CV %	SD nmol/L (µg/dL)	CV %
Human serum 1	3.09 (0.112)	0.219 (0.008)	7.1	0.392 (0.014)	12.7
Human serum 2	35.8 (1.30)	0.718 (0.026)	2.0	1.36 (0.049)	3.8
Human serum 3	283 (10.3)	7.29 (0.264)	2.6	9.39 (0.340)	3.3
Human serum 4	548 (19.9)	10.4 (0.377)	1.9	17.4 (0.631)	3.2
Human serum 5	1592 (57.7)	29.3 (1.06)	1.8	42.7 (1.55)	2.7

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cobas e 411 analyzer					
		Repeatability		**Intermediate precision**	
Sample	Mean nmol/L (µg/dL)	SD nmol/L (µg/dL)	CV %	SD nmol/L (µg/dL)	CV %
PreciControl Universal 1	308 (11.2)	4.33 (0.157)	1.4	8.35 (0.303)	2.7
PreciControl Universal 2	719 (26.1)	10.4 (0.377)	1.4	18.0 (0.653)	2.5

MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean nmol/L (µg/dL)	SD nmol/L (µg/dL)	CV %	SD nmol/L (µg/dL)	CV %
Human serum 1	3.62 (0.131)	0.195 (0.007)	5.4	0.366 (0.013)	10.1
Human serum 2	37.6 (1.36)	0.908 (0.033)	2.4	1.06 (0.038)	2.8
Human serum 3	319 (11.6)	4.81 (0.174)	1.5	7.00 (0.254)	2.2
Human serum 4	551 (20.0)	9.37 (0.340)	1.7	12.8 (0.464)	2.3
Human serum 5	1660 (60.2)	26.8 (0.972)	1.6	32.4 (1.17)	1.9
PreciControl Universal 1	310 (11.2)	4.91 (0.178)	1.6	5.96 (0.216)	1.9
PreciControl Universal 2	734 (26.6)	12.2 (0.442)	1.7	15.5 (0.562)	2.1

Precision was determined using Elecsys reagents, saliva samples and saliva controls in accordance with 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:

cobas e 411 analyzer					
		Repeatability		**Intermediate precision**	
Sample	Mean nmol/L (µg/dL)	SD nmol/L (µg/dL)	CV %	SD nmol/L (µg/dL)	CV %
Human saliva 1	3.77 (0.137)	0.230 (0.008)	6.1	0.446 (0.016)	11.8
Human saliva 2	9.29 (0.337)	0.346 (0.013)	3.7	0.657 (0.024)	7.1
Human saliva 3	30.7 (1.11)	1.02 (0.037)	3.3	1.35 (0.049)	4.4
Human saliva 4	84.1 (3.05)	2.08 (0.075)	2.5	2.99 (0.108)	3.6
PreciControl Cortisol Saliva 1	9.08 (0.329)	0.437 (0.016)	4.8	0.551 (0.020)	6.1
PreciControl Cortisol Saliva 2	28.8 (1.04)	0.907 (0.033)	3.1	1.46 (0.053)	5.1

MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers					
		Repeatability		**Intermediate precision**	
Sample	Mean nmol/L (µg/dL)	SD nmol/L (µg/dL)	CV %	SD nmol/L (µg/dL)	CV %
Human saliva 1	2.57 (0.093)	0.239 (0.009)	9.3	0.366 (0.013)	14.2
Human saliva 2	9.09 (0.330)	0.281 (0.010)	3.1	0.409 (0.015)	4.5
Human saliva 3	27.9 (10.1)	0.701 (0.025)	2.5	0.907 (0.033)	3.2
Human saliva 4	77.7 (2.82)	1.29 (0.047)	1.7	1.98 (0.072)	2.5
PreciControl Cortisol Saliva 1	9.79 (0.355)	0.379 (0.014)	3.9	0.478 (0.017)	4.9
PreciControl Cortisol Saliva 2	28.5 (1.03)	0.634 (0.023)	2.2	0.956 (0.035)	3.4

Method comparison

Serum:

A) A comparison of the Elecsys Cortisol II assay (y) with ID-GC/MS (x) using the IRMM/IFCC-451 panel gave the following correlations (nmol/L):

Number of samples measured: 34

Passing/Bablok[6]	Linear regression
y = 1.00x + 4.96	y = 1.02x + 1.38
τ = 0.975	r = 0.998

The sample concentrations were between 83.0 and 764 nmol/L or 3.01 and 27.7 µg/dL (ID-GC/MS).

B) A comparison of the Elecsys Cortisol II assay (y) with Elecsys Cortisol (x) gave the following correlations (nmol/L):

Number of samples measured: 536

Passing/Bablok[6]	Linear regression
y = 0.758x + 10.1	y = 0.786x - 1.85
τ = 0.872	r = 0.968

The sample concentrations were between 9.21 and 1680 nmol/L or 0.33 and 60.9 µg/dL.

Analytical specificity

For the Elecsys Cortisol II assay, the following cross-reactivities were found (in %):

a) Substance added in a concentration of 10 µg/mL:

11-Deoxycorticosterone	0.640
11-Deoxycortisol	4.90
17-α-Hydroxyprogesterone	0.080
Corticosterone	2.48
Cortisone	6.58
Dexamethasone	n. d.[c)]
Fludrocortisone	0.200
Prednisone	2.23
Progesterone	0.035

b) Substance added in a concentration of 1 µg/mL:

21-Deoxycortisol	2.40

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c) Substance added in a concentration of 0.1 µg/mL

Prednisolone	7.98
6-α-Methylprednisolone	12.0

c) n. d. = not detectable

References

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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

CE

Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim
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