LPA2

cobas®

Tina-quant Lipoprotein (a) Gen.2

REF		CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
08106126190	08106126500	Tina-quant Lipoprotein (a) Gen.2 (150 tests)	System-ID 2086 001	**cobas c** 303, **cobas c** 503

Materials required (but not provided):

05852641190	Preciset Lp(a) Gen.2 (5 × 1 mL)	Codes 20962-20966	
05852650190	PreciControl Lp(a) Gen.2 Level Low (2 × 1 mL) Level High (2 × 1 mL)	 Code 20137 Code 20138	
08063494190	Diluent NaCl 9 % (123 mL)	System-ID 2906 001	

English

System information

LPA2: ACN 20860

Intended use

In vitro test for the quantitative determination of lipoprotein (a) in human serum and plasma on **cobas c** systems.

Summary

Lipoprotein (a) [Lp(a)] measurements, performed with this assay in human serum and plasma are used as an aid in evaluating lipid metabolism disorders and assessing atherosclerotic cardiovascular disease, when used in conjunction with clinical evaluation and other lipoprotein tests.

Lp(a) is a class of lipoprotein particles with structural properties similar to low density lipoprotein (LDL).[1,2] Compared to LDL, Lp(a) contains the Lp(a)-specific glycoprotein apolipoprotein(a) [apo(a)]. Apo(a) is a carbohydrate-rich protein and is bound to apoB-100 through a single disulfide bridge.[3] It is highly homologous to plasminogen and contains multiple Kringle domains, which are loop-like structures.[3,4] Kringle IV (KIV) exhibits 10 different types in apo(a), with type 1 and 3 to 10 present as a single copy and type 2 present in a number of variable copies in different individuals. The number of KIV type 2 (KIV-2) are genetically determined by the apo(a) gene LPA on chromosome 6 and may range from 1 to > 40 copies, resulting in multiple different isoforms and thus in a large size heterogeneity of apo(a) size ranging from 250 kDa to > 800 kDa.[5,6] There is a pronounced inverse correlation between the number of KIV 2 repeats and the serum/plasma concentration of Lp(a).[7] Individuals expressing a low number of repeats resulting in small apo(a) isoforms have on average markedly higher serum Lp(a) concentrations, compared with individuals carrying only large apo(a) isoforms.[8]

Lp(a) levels are predominantly genetically determined by the apo (a) gene and are not influenced by age or diet.[9,10] Concentrations may vary among individuals and among populations of different ancestries.[11]

The variable number of identical KIV-2 repeats may interfere with the accurate measurement of Lp(a) in serum and plasma: Lp(a) with a lower number of KIV repeats might be underestimated and Lp(a) with a larger number of KIV repeats might be overestimated by KIV-2 dependent methods.[2,3] Due to this pronounced size heterogeneity, accurate quantification of the mass of Lp(a) is problematic because the size of the molecule in the samples may be greatly different than the size in the assay calibrators. For this reason, the scientific community recommends the use of Lp(a) assays not affected or minimally affected by apo(a) size variation and calibrated in nmol/L.[12,13,14] In addition, the value of the present WHO/IFCC reference material for Lp(a) and that of the new reference material being prepared by the current IFCC Standardization group, are expressed in nmol/L.[3,12]

Assays that provide measurements in nmol/L require standardization against an apo(a) size independent method. For this assay, the standardization process is performed by comparison to an ELISA method based on a monoclonal antibody that detects a single epitope per Lp(a) molecule located at the Kringle IV type 9, allowing for the reporting of measurements in nmol/L.[2,3] The comparability of the Roche assay against this apo(a) size independent ELISA reference method is constantly assessed through a certification process repeated for every master calibrator.

There is strong evidence that a statistically significant, independent relationship exists between increased Lp(a) concentrations and an increased risk of atherosclerotic cardiovascular disease.[15,16,17] High Lp(a) concentrations in serum correlate with premature manifestation of atherosclerosis and strokes.[15] Lp(a) is also a risk for aortic valve stenosis.[15]

A high Lp(a) concentration should be interpreted in the context of other risk factors and absolute global cardiovascular risk.[15]

Multiple national and international societies have incorporated recommendations for Lp(a) testing into their guidelines.[15,18,19,20,21,22, 23,24] The Canadian Cardiovascular Society and the European Atherosclerosis Society (EAS) recommend all adults be tested for elevated Lp(a) at least once in their lifetime.[21,23] According to the EAS, Lp(a) measurements should also be considered in selected cases with a family history of premature cardiovascular disease.[21] The ACC/AHA considers Lp(a) an ASCVD risk enhancer and recommends screening in selected individuals with borderline or intermediate risk.[20]

Test principle

Particle enhanced immunoturbidimetric assay.[25]

Human lipoprotein (a) agglutinates with latex particles coated with anti-Lp(a) antibodies. The precipitate is determined turbidimetrically.

Reagents - working solutions

R1 Glycine buffer: 170 mmol/L, pH 7.0; stabilizers; BSA; rabbit serum 0.1 %, preservative

R3 Latex particles coated with polyclonal anti-human lipoprotein(a) antibodies (rabbit); glycine buffer: 170 mmol/L, pH 7.3, BSA; preservative

R1 is in position B and R3 is in position C.

Precautions and warnings

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

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.

Reagent handling

Ready for use

Carefully invert reagent container several times prior to use to ensure that the reagent components are mixed.

Storage and stability

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label.
On-board in use and refrigerated on the analyzer:	26 weeks

Specimen collection and preparation

For specimen collection and preparation only use suitable tubes or collection containers.

Only the specimens listed below were tested and found acceptable.
Serum
Plasma: Li-heparin or K_2-EDTA and K_3-EDTA plasma.

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.

With K_3-EDTA tubes pay particular attention that the tubes are adequately filled.

Centrifuge samples containing precipitates before performing the assay.

See the limitations and interferences section for details about possible sample interferences.

Stability:

If samples are not assayed within 8 hours, samples should be stored at 2-8 °C.[26]

If samples are not assayed within 48 h,[26] samples should be stored frozen at -70 °C (± 10 °C) or below.[27,28] Frozen samples should be thawed only once. Analyte deterioration may occur in samples that are repeatedly frozen and thawed.

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

See "Order information" section

General laboratory equipment

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.

The performance of applications not validated by Roche is not warranted and must be defined by the user.

Application for serum and plasma

Test definition

Reporting time	10 min		
Wavelength (sub/main)	800/660 nm		
Reagent pipetting		Diluent (H_2O)	
R1	100 µL	–	
R3	25 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	*Diluent (NaCl)*
Normal	1.5 µL	–	–
Decreased	6.0 µL	8 µL	88 µL
Increased	1.5 µL	–	–

For further information about the assay test definitions refer to the application parameters screen of the corresponding analyzer and assay.

Calibration

Calibrators	S1: H_2O S2-S6: Preciset Lp(a) Gen.2
Calibration mode	Non-linear
Calibration frequency	Automatic full calibration - after reagent lot change Full calibration - as required following quality control procedures

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

Traceability: This method has been standardized against the IFCC reference material SRM2B for nmol/L.[29]

Quality control

For quality control, use control materials as listed in the "Order information" section. In addition, other suitable control material can be used.

The control intervals and limits should be adapted to each laboratory's individual requirements. It is recommended to perform quality control always after lot calibration and subsequently at least every 26 weeks.

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

cobas c systems automatically calculate the analyte concentration of each sample in the unit nmol/L (mg/dL).

Conversion factor:[30] mg/dL = (nmol/L + 3.83) × 0.4587

Limitations – interference

Criterion: Recovery within ± 6 nmol/L of initial values of samples ≤ 60 nmol/L and within ± 10 % for samples > 60 nmol/L.

Icterus:[31] No significant interference up to an I index of 60 for conjugated and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 1026 µmol/L or 60 mg/dL).

Hemolysis:[31] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 621 µmol/L or 1000 mg/dL).

Lipemia (Intralipid):[31] No significant interference up to an L index of 2000. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Rheumatoid factors: No significant interference from rheumatoid factors up to a concentration of 1200 IU/mL.

Plasminogen: No significant cross-reactivity in the tested concentration range (up to 150 mg/dL).

Apolipoprotein B: No significant cross-reactivity in the tested concentration range (up to 200 mg/dL).

Drugs: No interference was found at therapeutic concentrations using common drug panels.[32, 33]

High dose hook-effect: No false result occurs up to a lipoprotein (a) concentration of 450 nmol/L.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[34]

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

ACTION REQUIRED

Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on **cobas c** systems. All special wash programming necessary for avoiding carry-over is available via the **cobas** link. The latest version of the carry-over evasion list can be found with the NaOHD/SMS/SCCS Method Sheet. For further instructions refer to the operator's manual.

Limits and ranges

Measuring range

Measuring range: 7-240 nmol/L

Determine samples having higher concentrations via the rerun function. Dilution of samples via the rerun function is a 1:3 dilution. Results from samples diluted using the rerun function are automatically multiplied by a factor of 3.

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank	= 6 nmol/L
Limit of Detection	= 7 nmol/L
Limit of Quantitation	= 7 nmol/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 a total error of 20 %. It has been determined using low concentration lipoprotein (a) samples.

Expected values

A Lp(a) concentration of 30 mg/dL corresponding to the 75th percentile in a male Caucasian reference population is widely used as cut-off point or threshold value.[35,36]

The European Atherosclerosis Society recommends screening for elevated Lp(a) in those at intermediate or high CVD/CHD risk and defines a desirable Lp(a) level ≤ 50 mg/dL.[37]

However the NHLBI recommends to stop using data for total Lp(a) mass, and to use nmol/L units instead, which consider the number of particles. Additionally they recommend to use assays independent from apo(a) size and standardized according to the IFCC reference material SRM2B.[38]

Based on the evaluation of Framingham data values above 75 nmol/L are regarded as a cut-off value for the presence of an increased risk.[38]

Elevated Lp(a) levels can be found in most racial/ethnicity groups, with the prevalence being lowest in whites and Asians. The median Lp(a) levels in black subjects and in Asian Indians from southern locations are 2- to 4-fold higher compared with whites, and up to 68 % of blacks have Lp(a) levels > 75 nmol/L, whereas levels above this threshold are present in around 25 % of whites.[39]

Therefore reference ranges have not been established for this assay for different ethnic populations or disease states. Since Lp(a) levels are largely influenced by hereditary factors and vary with ethnic populations it is recommended that each laboratory establish own expected values.

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. These data represent the performance of the analytical procedure itself.

Results obtained in individual laboratories may differ due to heterogenous sample materials, aging of analyzer components and mixture of reagents running on the analyzer.

Precision

Precision was determined using human samples and controls in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP05-A3 requirements with repeatability (n = 84) and intermediate precision (2 aliquots per run, 2 runs per day, 21 days). Results for repeatability and intermediate precision were obtained on the **cobas c** 503 analyzer.

Repeatability	*Mean* *nmol/L*	*SD* *nmol/L*	*CV* *%*
Lp (a) Control Level Low	35.2	0.412	1.2
Lp (a) Control Level High	97.7	0.435	0.4
Human serum 1	19.7	0.414	2.1
Human serum 2	49.3	0.516	1.0
Human serum 3	80.5	0.434	0.5
Human serum 4	120	0.546	0.5
Human serum 5	203	0.794	0.4

Intermediate precision	*Mean* *nmol/L*	*SD* *nmol/L*	*CV* *%*
Lp (a) Control Level Low	35.1	0.562	1.6
Lp (a) Control Level High	99.0	1.14	1.2
Human serum 1	19.7	0.508	2.6
Human serum 2	49.3	0.676	1.4
Human serum 3	80.5	0.831	1.0
Human serum 4	119	1.14	1.0
Human serum 5	203	1.33	0.7

The data obtained on **cobas c** 503 analyzer(s) are representative for **cobas c** 303 analyzer(s).

Method comparison

Lipoprotein (a) values for human serum and plasma samples obtained on a **cobas c** 503 analyzer (y) were compared with those determined using the corresponding reagent on a **cobas c** 501 analyzer (x).

Sample size (n) = 99

Passing/Bablok[40]	Linear regression
y = 1.019x + 0.878 nmol/L	y = 1.010x + 1.34 nmol/L
τ = 0.988	r = 1.000

The sample concentrations were between 7.34 and 235 nmol/L.

Lipoprotein (a) values for human serum and plasma samples obtained on a **cobas c** 303 analyzer (y) were compared with those determined using the corresponding reagent on a **cobas c** 501 analyzer (x).

Sample size (n) = 72

Passing/Bablok[40]	Linear regression
y = 0.984x + 2.00 nmol/L	y = 0.988x + 1.70 nmol/L
τ = 0.990	r = 1.000

The sample concentrations were between 7.07 and 222 nmol/L.

References

1 Kostner KM, Kostner GM. Lipoprotein (a): a historical appraisal. J Lipid Res 2017 Jan;58(1):1-14.

2 Schmidt K, Noureen A, Kronenberg F, et al. Structure, function, and genetics of lipoprotein (a). J Lipid Res 2016 Aug;57(8):1339-59. doi: 10.1194/jlr.R067314. Epub 2016 Apr 13. PMID: 27074913; PMCID: PMC4959873.

3 Marcovina SM, Albers JJ. Lipoprotein (a) measurements for clinical application. J Lipid Res 2016 Apr;57(4):526-537.

4 Maranhão RC, Carvalho PO, Strunz CC, et al. Lipoprotein (a): structure, pathophysiology and clinical implications. Arq Bras Cardiol. 2014 Jul;103(1):76-84.

5 Nordestgaard BG, Langsted A. Lipoprotein (a) as a cause of cardiovascular disease: insights from epidemiology, genetics, and biology. J Lipid Res. 2016 Nov;57(11):1953-1975.

6 Reyes-Soffer G, Ginsberg HN, Ramakrishnan R. The metabolism of lipoprotein (a): an ever-evolving story. J Lipid Res 2017 Sep;58(9):1756-1764.

7 Coassin S, Kronenberg F. Lipoprotein(a) beyond the kringle IV repeat polymorphism: The complexity of genetic variation in the LPA gene. Atherosclerosis. 2022 May;349:17-35.

8 Kronenberg F. Human Genetics and the Causal Role of Lipoprotein(a) for Various Diseases. Cardiovasc Drugs Ther. 2016 Feb;30(1):87-100.

9 Langsted A, Kamstrup PR, Nordestgaard BG. Lipoprotein(a): fasting and nonfasting levels, inflammation, and cardiovascular risk. Atherosclerosis. 2014 May;234(1):95-101.

10 Kronenberg F. Lipoprotein(a) in various conditions: to keep a sense of proportions. Atherosclerosis. 2014 May;234(1):249-251.

11 Reyes-Soffer G. The impact of race and ethnicity on lipoprotein(a) levels and cardiovascular risk. Curr Opin Lipidol. 2021 Jun 1;32(3):163-166.

12 Cobbaert CM, Althaus H, Begcevic Brkovic I, et al. IFCC Working Group for Standardization of Apolipoproteins by Mass Spectrometry. Towards an SI-Traceable Reference Measurement System for Seven Serum Apolipoproteins Using Bottom-Up Quantitative Proteomics: Conceptual Approach Enabled by Cross-Disciplinary/Cross-Sector Collaboration. Clin Chem. 2021 Mar 1;67(3):478-489.

13 Ward NC, Watts GF, Bishop W, et al. Australian Atherosclerosis Society Position Statement on Lipoprotein(a): Clinical and Implementation Recommendations. Heart Lung Circ. 2023 Mar;32(3):287-296.

14 Cegla J, France M, Marcovina SM, et al. Lp(a): When and how to measure it. Ann Clin Biochem. 2021 Jan;58(1):16-21.

15 Kronenberg F, Mora S, Stroes ESG, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. Eur Heart J 2022 Oct 14;43(39):3925-3946.

16 Forbes CA, Quek RG, Deshpande S, et al. The relationship between Lp(a) and CVD outcomes: a systematic review. Lipids Health Dis. 2016 May 17;15:95.

17 Pearson K, Rodriguez F. Lipoprotein(a) and Cardiovascular Disease Prevention across Diverse Populations. Cardiol Ther 2020 Dec;9(2):275-292.

18 Wilson DP, Jacobson TA, Jones PH, et al. Use of Lipoprotein(a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association. J Clin Lipidol 2019 May-Jun;13(3):374-392.

19 Cegla J, Neely RDG, France M, et al. HEART UK Medical, Scientific and Research Committee. HEART UK consensus statement on Lipoprotein(a): A call to action. Atherosclerosis. 2019 Dec;291:62-70.

20 Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACV-PR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 Jun 18;139(25):e1082-e1143.

21 Mach F, Baigent C, Catapano AL, et al. ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020 Jan 1;41(1):111-188.

22 Handelsman Y, Jellinger PS, Guerin CK, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Management of Dyslipidemia and Prevention of Cardiovascular Disease Algorithm - 2020 Executive Summary. Endocr Pract. 2020 Oct;26(10):1196-1224.

23 Pearson GJ, Thanassoulis G, Anderson TJ, et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults. Can J Cardiol 2021 Aug;37(8):1129-1150.

24 Kronenberg F, Mora S, Stroes ESG, et al. Frequent questions and responses on the 2022 lipoprotein(a) consensus statement of the European Atherosclerosis Society. Atherosclerosis. 2023 Jun;374:107-120.

25 Simó JM, Camps J, Gómez F, et al. Evaluation of a Fully Automated Particle-enhanced Turbidimetric Immunoassay for the Meaurement of Plasma Lipoprotein(a). Population-Based Reference Values in an Area with Low Incidence of Cardiovascular Disease. Clin Biochem 2003 Mar;36(2):129-134.

26 National Committee for Clinical Laboratory Standards, Procedures for the handling and Processing of Blood Specimens, Approved Guideline, NCCLS publication H18-A, Villanova, 1990.

27 Simó JM, Camps J, Vilella E, et al. Instability of Lipoprotein (a) in Plasma Stored at -70 °C: Effects of Concentration, Apolipoprotein (a) Genotype, and Donor Cardiovascular Disease. Clin Chem 2001 Sep;47(9):1673-1678.

28 Sgoutas DS, Tuten T. Effect of Freezing and Thawing of Serum on the Immunoassay of Lipoprotein(a). Clin Chem 1992;38(9):1873-1877.

29 Marcovina SM, Albers JJ, Scanu AM, et al. Use of a reference Material Proposed by the International federation of Clinical Chemistry and Laboratory Medicine to Evaluate Analytical methods for the Determination of Plasma Lipoprotein (a). Clin Chem 2000 Dec;46(12):1956-1967.

30 Anne Langsted, Pia R. Kamstrup, Borge G. Nordestgaard. High lipoprotein(a) and high risk of mortality. European Heart Journal (2019) 40:2760-2770.

31 Glick MR, Ryder KW, Jackson SA. Graphical Comparisons of Interferences in Clinical Chemistry Instrumentation. Clin Chem 1986;32:470-475.

32 Breuer J. Report on the Symposium "Drug effects in Clinical Chemistry Methods". Eur J Clin Chem Clin Biochem 1996;34:385-386.

33 Sonntag O, Scholer A. Drug interference in clinical chemistry: recommendation of drugs and their concentrations to be used in drug interference studies. Ann Clin Biochem 2001;38:376-385.

34 Bakker AJ, Mücke M. Gammopathy interference in clinical chemistry assays: mechanisms, detection and prevention. Clin Chem Lab Med 2007;45(9):1240-1243.

35 Marcovina SM, Koschinsky ML. A Critical Evaluation of the Role of Lp(a) in Cardiovascular Disease: Can Lp(a) Be Useful in Risk Assessment? Semin Vasc Med 2002 Aug;2(3):335-344.

36 Shai I, Rimm EB, Hankinson SE, et al. Lipoprotein (a) and Coronary Heart Disease Among Women: Beyond a Cholesterol Carrier? Eur Heart J 2005;26:1633-1639.

37 Nordestgaard BG, Chapman MJ, Ray K, et al. Lipoprotein (a) as a cardiovascular risk factor: current status. Eur Heart J 2010 Dec;31(23):2844-2853.

38 Marcovina SM, Koschinsky ML, Albers JJ, et al. Report of the National Heart, Lung, and Blood Institute Workshop on Lipoprotein (a) and Cardiovascular Disease: Recent Advances and Future Directions. Clin Chem 2003 Nov;49(11):1785-1796.

39 Tsimikas S, Clopton P, Brilakis ES, et al. Relationship of Oxidized Phospholipids on Apolipoprotein B-100 Particles to Race/Ethnicity, Apolipoprotein (a) Isoform Size, and Cardiovascular Risk Factors: Results From the Dallas Heart Study, Circulation 2009 Apr;119(13):1711-1719.

40 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.

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
→	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, D-68305 Mannheim
www.roche.com
+800 5505 6606