Elecsys Toxo IgM

cobas®

REF		Σ	SYSTEM
04618858190	04618858500	100	**cobas e** 411 **cobas e** 601 **cobas e** 602

English

System information

For **cobas e** 411 analyzer: test number 530
For **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number 95

Intended use

Immunoassay for the in vitro qualitative determination of IgM antibodies to *Toxoplasma gondii* in human serum and plasma.

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

Summary

Qualitative detection of IgM antibodies to Toxoplasma gondii in human serum and plasma with this assay, may be used as an aid in the diagnosis of an acute or recent Toxoplasma gondii infection in suspected patients and pregnant women.

Toxoplasmosis is a relatively common infection caused by the protozoan parasite *Toxoplasma gondii*.

The infection is mainly acquired by ingestion of food or water contaminated by mature oocysts shed by cats or by undercooked meat containing tissue cysts.[1,2,3,4] Infection can also be transmitted congenitally if a woman is newly infected during, or just prior to pregnancy, and also via organ transplant or blood transfusion from an infected donor.[4]

Primary, acute infection in healthy individuals is mostly mild or asymptomatic and is followed by life-long latency.[3,4] Reactivation of a latent Toxoplasma infection can occur as a result of immunosuppression (e.g. in organ transplant recipients, patients with cancer receiving chemotherapy or with advanced HIV infection) and can be associated with high morbidity and mortality.[3,4] Reactivated disease in immunocompromised hosts frequently presents with brain lesions, especially in patients with advanced HIV-related immunosuppression.[3,4,5]

Primary maternal Toxoplasma infection occurring during pregnancy may have significant implications for the fetus as the parasite can be transmitted across the placenta.[3,6] The majority of infants with congenital infection do not present with clinical symptoms at birth but may develop severe sequelae later in life such as chorioretinitis, intellectual and psychomotor disabilities, visual and hearing impairment.[3,6,7,8] The fetal infection rate increases with gestational age but, the risk of severe clinical manifestations is higher in the case of early maternal infection.[3,6,7,8]

Early identification of infection and initiation of appropriate drug therapy in acute infection during pregnancy can prevent congenital damage or ameliorate the severity of clinical manifestations.[6,7]

The diagnosis of Toxoplasma infection is most commonly made by the detection of anti-Toxoplasma-specific IgG and IgM antibodies.[3,4,9]

The presence of IgG antibodies to *Toxoplasma gondii* indicates that infection has occurred but does not distinguish between latent and acute infection.[9] IgM is typically a marker of acute infection, but residual, long-lasting IgM can be detected months or even years after the primary infection.[9] To differentiate between a recently acquired and past infection, specimens that are positive for IgM may be tested for IgG avidity. A high avidity index for IgG antibodies indicates that the infection occurred at least 4 months ago.[9] No clinical interpretation can be deduced from a low avidity result.[9]

The diagnosis of the acute acquired infection during pregnancy is established by a seroconversion or a significant rise in antibody titers (IgG and/or IgM) in serial samples.[8,9]

Test principle

µ-Capture test principle. Total duration of assay: 18 minutes.

- 1st incubation: 10 µL of sample are automatically prediluted 1:20 with Diluent Universal. *T. gondii*-specific recombinant antigen labeled with a ruthenium complex[a)] is added. Anti-Toxo IgM antibodies present in the sample react with the ruthenium-labeled *T. gondii*-specific recombinant antigen.
- 2nd incubation: Biotinylated monoclonal h-IgM-specific antibodies and streptavidin-coated microparticles are added. 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 automatically by the software by comparing the electrochemiluminescence signal obtained from the reaction product of the sample with the signal of the cutoff value previously obtained by calibration.

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

Reagents - working solutions

The reagent rackpack (M, R1, R2) is labeled as TOXIGM.

M	Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative.
R1	Toxoplasma-Ag~$Ru(bpy)_3^{2+}$ (gray cap), 1 bottle, 9 mL: Toxoplasma-antigen labeled with ruthenium complex > 1 mg/L; MES[b)] buffer 50 mmol/L, pH 6.0; preservative.
R2	Anti-h-IgM-Ab~biotin (black cap), 1 bottle, 9 mL: Biotinylated monoclonal anti-h-IgM antibody (mouse) > 500 µg/L; HEPES[c)] buffer 50 mmol/L, pH 7.2; preservative.

b) MES = 2-morpholino-ethane sulfonic acid

c) HEPES = [4-(2-hydroxyethyl)-piperazine]-ethane sulfonic acid

TOXIGM Cal1	Negative calibrator 1 (white cap), 2 bottles of 0.67 mL each: Human serum, negative for anti-Toxo IgM; preservative.
TOXIGM Cal2	Positive calibrator 2 (black cap), 2 bottles of 0.67 mL each: Anti-Toxo IgM (human) approximately 130 U/mL (Roche units) in human serum; preservative.

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.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Warning

H317	May cause an allergic skin reaction.

Prevention:

P261	Avoid breathing mist or vapours.

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P272 Contaminated work clothing should not be allowed out of the workplace.

P280 Wear protective gloves.

Response:

P333 + P313 If skin irritation or rash occurs: Get medical advice/attention.

P362 + P364 Take off contaminated clothing and wash it before reuse.

Disposal:

P501 Dispose of contents/container to an approved waste disposal plant.

Product safety labeling 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 use assays that have been approved or cleared by the FDA or that are in compliance with the legal rules of the European Union (IVDR 2017/746/EU, IVDD 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.[10,11]

All products derived from human blood (TOXIGM Cal1, TOXIGM Cal2) are prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV.

The serum containing anti-Toxo IgM (TOXIGM Cal2) was 0.2 micron filtrated.

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

Reagent handling

The reagents in the kit are ready-for-use and are supplied in bottles compatible with the system.

cobas e 411 analyzer: The calibrators should only be left on the analyzer during calibration at 20-25 °C. After use, close the bottles as soon as possible and store upright at 2-8 °C.

Due to possible evaporation effects, not more than 5 calibration procedures per bottle set should be performed.

cobas e 601 and **cobas e** 602 analyzers: Unless the entire volume is necessary for calibration on the analyzer, transfer aliquots of the ready-for-use calibrators into empty snap-cap bottles (CalSet Vials). Attach the supplied labels to these additional bottles. Store the aliquots at 2-8 °C for later use.

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

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

Please note for **cobas e** 602 analyzers: Both the vial labels, and the additional labels (if available) contain 2 different barcodes. Please turn the vial cap 180° into the correct position so that the barcode between the yellow markers can be read by the system. Place the vial on the analyzer 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
after opening at 2-8 °C	12 weeks
on the analyzers	2 weeks or 12 weeks if stored alternately in the refrigerator and on the analyzers (up to 84 hours)

Stability of the calibrators	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	8 weeks
on **cobas e** 411 at 20-25 °C	up to 5 hours
on **cobas e** 601 and **cobas e** 602 at 20-25 °C	use only once

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

Materials required (but not provided)

- REF 04618866190, PreciControl Toxo IgM, 16 x 0.67 mL
- REF 11732277122, Diluent Universal, 2 x 16 mL sample diluent or REF 03183971122, Diluent Universal, 2 x 36 mL sample diluent
- REF 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles
- General laboratory equipment
- **cobas e** analyzer

Additional materials for the **cobas e** 411 analyzer:

- REF 11662988122, ProCell, 6 x 380 mL system buffer
- REF 11662970122, CleanCell, 6 x 380 mL measuring cell cleaning solution
- REF 11930346122, Elecsys SysWash, 1 x 500 mL washwater additive
- REF 11933159001, Adapter for SysClean
- REF 11706802001, AssayCup, 60 x 60 reaction cups
- REF 11706799001, AssayTip, 30 x 120 pipette tips
- REF 11800507001, Clean-Liner

Additional materials for **cobas e** 601 and **cobas e** 602 analyzers:

- REF 04880340190, ProCell M, 2 x 2 L system buffer
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 03023141001, PC/CC-Cups, 12 cups to prewarm ProCell M and CleanCell M before use
- REF 03005712190, ProbeWash M, 12 x 70 mL cleaning solution for run finalization and rinsing during reagent change
- REF 12102137001, AssayTip/AssayCup, 48 magazines x 84 reaction cups or pipette tips, waste bags
- REF 03023150001, WasteLiner, waste bags
- REF 03027651001, SysClean Adapter M

Additional materials for all analyzers:

- REF 11298500316, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution

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_3-EDTA and Na-citrate plasma.

Criterion: Mean recovery of positive samples within 80-120 % of serum value.

Stable for 3 weeks at 2-8 °C, 3 days at 20-25 °C, 3 months at -20 °C (± 5 °C). The samples may be frozen 6 times.

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.

Specimens should not be subsequently altered with additives (e.g. biocides, anti-oxidants or substances that could possibly change the pH or ionic strength of the sample) in order to avoid erroneous findings.

Pooled samples and other artificial material may have different effects on different assays and thus may lead to discrepant findings.

Centrifuge samples containing precipitates and thawed samples before performing the assay.

Lyophilized samples, heat-inactivated samples and samples and controls stabilized with azide (up to 1 %) can be used.

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 2 bottle labels

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.

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 calibrators in the sample zone.

All the information necessary for calibrating the assay is automatically read into the analyzer.

After calibration has been performed, store the calibrators at 2-8 °C or discard (**cobas e** 601 and **cobas e** 602 analyzers).

Calibration

Traceability: This method has been standardized against a Roche standard. The units have been selected arbitrarily.

Calibration frequency: Calibration must be performed once per reagent lot using TOXIGM Cal1, TOXIGM Cal2 and fresh reagent (i.e. not more than 24 hours since the reagent kit was registered on the analyzer).

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

Renewed calibration is recommended as follows:

- after 1 month (28 days) 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
- more frequently when this is required by pertinent regulations

Range for the electrochemiluminescence signals (counts) for the calibrators:
Negative calibrator (TOXIGM Cal1): 400-2500
Positive calibrator (TOXIGM Cal2): 4500-35000

Quality control

Use PreciControl Toxo IgM or other suitable controls for routine quality control procedures.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per reagent kit, and following each calibration.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

If necessary, repeat the measurement of the samples concerned.

Follow the applicable government regulations and local guidelines for quality control.

Note:
For technical reasons re-assigned target values valid only for a specific reagent and control lot combination must be entered manually on all analyzers (except for the **cobas e** 602 analyzer). Therefore always refer to the value sheet included in the reagent kit or PreciControl kit to make sure that the correct target values are used.
When a new reagent or control lot is used, the analyzer will use the original values encoded in the control barcodes.

Calculation

The analyzer automatically calculates the cutoff based on the measurement of TOXIGM Cal1 and TOXIGM Cal2. The result of a sample is given either as reactive or non-reactive as well as in the form of a cutoff index (signal sample/cutoff).

Interpretation of the results

Results obtained with the Elecsys Toxo IgM assay can be interpreted as follows:

Non-reactive: < 0.8 COI

Indeterminate: ≥ 0.8 - < 1.0 COI

Reactive: ≥ 1.0 COI

Samples with a cutoff index < 0.8 are non-reactive in the Elecsys Toxo IgM assay.

Samples with a cutoff index between ≥ 0.8 and < 1.0 are considered indeterminate. The sample should be retested. In case the result is still indeterminate, a second sample should be tested e.g. within 2-3 weeks. Samples with a cutoff index ≥ 1.0 are reactive in the Elecsys Toxo IgM assay.

The magnitude of the measured result above the cutoff is not indicative of the total amount of antibody present in the sample.

The anti-Toxoplasma IgM results in a given specimen, as determined by assays from different manufacturers, can vary due to differences in assay and reagent methods.

Limitations - interference

A negative Toxo IgM test result, also in combination with a positive Toxo IgG result, does not completely rule out the possibility of an acute infection with *Toxoplasma gondii:*

- Individuals at the early stage of acute infection may not exhibit detectable amounts of Toxo IgM antibodies. In some of these individuals an indeterminate or low positive result with the Elecsys Toxo IgG assay may be found and indicate an early acute infection. A second sample should be tested e.g. within 2 weeks. The detection of Toxo IgM and/or a significant increase of the Elecsys Toxo IgG antibody titer in the second sample supports the diagnosis of acute Toxoplasma infection.
- In some individuals Toxoplasma IgM-specific antibodies may revert to non-reactive levels within few weeks after infection with *T. gondii.*

A positive Toxo IgM test result in a single sample, also in combination with a negative Toxo IgG result, is not sufficient to prove an acute *Toxoplasma gondii* infection:

- Elevated IgM antibody levels may persist even for years after initial infection.[12,13] Further tests or a combination of test methods should be done for clarification.[1,13,14,15]
- In very rare cases false reactive Toxo IgM results may occur. If Toxo IgM results are inconsistent with clinical evidence, additional testing is suggested to confirm the result. For diagnostic purposes, results should be used in conjunction with other data (e.g. results of other tests such as Toxo IgG and Toxo IgG Avidity), and clinical impressions, that might however be unspecific.
- In diagnosis of Toxoplasma infection, particularly during pregnancy if therapeutic decisions depend on the diagnosis, the current local or if not available global medical guidelines provided by professional medical societies are to be followed.

Early treatment may prevent an increase in antibody production. IgG and IgM levels may remain low and can coexist for years.

The results in HIV patients, in patients undergoing immunosuppressive therapy, or in patients with other disorders leading to immune suppression, should be interpreted with caution.

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Specimens from neonates, cord blood, pretransplant patients or body fluids other than serum and plasma, such as urine, saliva or amniotic fluid have not been tested.

The assay is unaffected by icterus (bilirubin < 684 µmol/L or < 40 mg/dL), hemolysis (Hb < 1.24 mmol/L or < 2 g/dL), lipemia (Intralipid < 2000 mg/dL) and biotin (< 246 nmol/L or < 60 ng/mL).

Criterion: Mean recovery of positive samples within ± 20 % of serum value.

Samples should not be taken from patients receiving therapy with high biotin doses (i.e. > 5 mg/day) until at least 8 hours following the last biotin administration.

No interference was observed from rheumatoid factors up to a concentration of 3720 IU/mL.

The high-dose hook effect does not lead to false-negative results in the Elecsys Toxo IgM assay.

In vitro tests were performed on 18 commonly used pharmaceuticals and in addition on spiramycine, sulfadiazine, folinic acid and pyrimethamine. No interference with the assay was found.

As with many µ-capture assays an interference with unspecific IgM is observed. Increasing amounts of unspecific IgM may lead to a decrease in the recovery of positive samples with the Elecsys Toxo IgM assay.

In rare cases, interference due to extremely high titers of antibodies to immunological components, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.

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

cobas e 411 analyzer						
	Repeatability			**Intermediate precision**		
Sample	Mean COI[d)]	SD COI	CV %	Mean COI	SD COI	CV %
HS[e)], negative	0.109	0.002	2.2	0.103	0.006	5.4
HS, positive	1.37	0.021	1.5	1.33	0.034	2.5
HS, positive	3.78	0.067	1.8	3.70	0.171	4.6
PC[f)] Toxo IgM 1	0.120	0.002	1.6	0.118	0.005	4.1
PC Toxo IgM 2	1.35	0.015	1.1	1.29	0.043	3.3

d) COI = cutoff index

e) HS = human serum

f) PC = PreciControl

cobas e 601 and **cobas e** 602 analyzers						
	Repeatability			**Intermediate precision**		
Sample	Mean COI	SD COI	CV %	Mean COI	SD COI	CV %
HS, negative	0.107	0.002	1.8	0.103	0.002	1.9
HS, positive	1.33	0.011	0.9	1.36	0.023	1.7
HS, positive	3.86	0.034	0.9	3.83	0.061	1.6
PC Toxo IgM 1	0.116	0.002	1.6	0.117	0.002	1.7
PC Toxo IgM 2	1.30	0.015	1.2	1.31	0.032	2.4

Method comparison

In study 1 the performance of the Elecsys Toxo IgM assay was determined by testing a total of 826 fresh and frozen samples at two sites in comparison to a commercially available Toxoplasma IgM test.

In study 2 the Elecsys Toxo IgM assay was compared to another commercially available Toxoplasma IgM assay by testing 400 fresh and frozen samples. In both studies all specimens with initially discordant results were re-tested. Resolution of repeatedly discordant samples was done by avidity testing. 51 specimens with indeterminate results in one of the assays were excluded from the final calculation of relative sensitivity and specificity.

Relative sensitivity and specificity after resolution

Study	N	Relative sensitivity %	Lower confidence limit %	Relative specificity %	Lower confidence limit %
1	785	95.3 (162/170)	91.7	98.8 (595/602)	97.8
2	390	98.8 (83/84)	94.5	99.7 (294/295)	98.4

Study 1: Of 21 samples which were initially discordant negative with the Elecsys Toxo IgM assay, 11 samples revealed a high avidity test result, 2 samples were found negative with Toxo ISAGA IgM. 7 discordant negative samples revealed a low avidity test result, 1 sample was found positive with Toxo ISAGA IgM. 5 samples which were discordant positive with the Elecsys Toxo IgM assay revealed a high avidity test result, 2 samples were from individuals without Toxoplasma infection.

Study 2: Of 12 samples which were initially discordant negative with the Elecsys Toxo IgM assay, 11 samples revealed a high avidity test result. 1 sample revealed a low avidity test result. 1 sample which was discordant positive with the Elecsys Toxo IgM assay was from an individual without Toxoplasma infection.

Analytical specificity

455 potentially cross reacting samples were tested with the Elecsys Toxo IgM assay and a comparison Toxo IgM assay comprising specimens:

- containing antibodies against HAV, HBV*, HCV, HIV, CMV, EBV*, HSV, VZV, Rubella, Treponema pallidum, Malaria**, Amebiasis, Chlamydia and Gonorrhea
- containing autoantibodies (AMA*, ANA) and elevated titers of rheumatoid factors
- after vaccination against HBV and Influenza

An overall agreement of 98.9 % (446/451) was found in these specimens using the Elecsys Toxo IgM assay and the comparison test. 444 samples were found concordantly negative and 2 samples were found positive. 4 samples were found indeterminate either by the Elecsys Toxo IgM assay or the comparison test and were excluded.

* 1 discordant sample in each of these groups

** 2 discordant samples

Seroconversion panels

In two studies seroconversion samples obtained during pregnancy screening were tested with the Elecsys Toxo IgM assay in comparison to two different commercially available Toxo IgM assays.

In 24 seroconversion panels comprising 83 samples at the first site, the Elecsys Toxo IgM assay detected 64 samples from 66 samples which were found positive using a comparison test. 2 discordant negative sera were follow-up samples, taken more than 8 weeks after infection.

In 29 seroconversion panels (including 92 samples) at the second site, the Elecsys Toxo IgM assay detected 67 samples from 74 samples which were found positive by a second comparison test. 2 discordant negative sera from the very early phase of infection were also negative by another comparison test. In two panels (comprising 3 and 2 serial bleeds from the very early phase of infection) IgM was not detected, however seroconversion could be demonstrated by the Elecsys Toxo IgG assay.

In both panels discordant negative results for several samples were also found by two other commercial Toxoplasma IgM assays.

References

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

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.

The Summary of Safety & Performance Report can be found here: https://ec.europa.eu/tools/eudamed

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see navifyportal.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
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

CE 0123

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