ms_04618793190V7.0

# Rubella IgG

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**IgG antibodies to Rubella virus**

| REF | Σ | SYSTEM |
|---|---|---|
| **04618793** 190 | 100 | Elecsys 2010<br>MODULAR ANALYTICS E170<br>**cobas e** 411<br>**cobas e** 601<br>**cobas e** 602 |

**English**

**Please note**

The measured anti-Rubella IgG value of a patient's sample can vary depending on the testing procedure used. The laboratory finding must therefore always contain a statement on the Rubella IgG assay used.

Anti-Rubella IgG values determined on patient samples by different testing procedures cannot be directly compared with one another and could be the cause of erroneous medical interpretations.

Therefore, the results reported by the laboratory to the physician should include:

"The following results were obtained with the Elecsys Rubella IgG assay. Results from assays of other manufacturers cannot be used interchangeably."

**Intended use**

Immunoassay for the in vitro quantitative determination of IgG antibodies to Rubella virus 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**

References[1,2,3,4,5,6,7]

Rubella virus is the etiological agent of German measles, a commonly mild rash disease which occurs usually during childhood. It is spread by small droplets via the respiratory route. Postnatal acquired infection is seldom associated with complications.

However, Rubella can be a serious disease when a pregnant woman becomes infected especially during the first trimester of pregnancy. Rubella virus can be transmitted through the placenta and can result in fetal death or may cause severe malformations to the fetus, commonly summarized as congenital Rubella syndrome (CRS). CRS is an important cause of blindness, deafness, congenital heart disease and mental retardation. Today infant vaccination programs and the vaccination of women in child-bearing age who are susceptible to Rubella infection have considerably reduced the incidence of acute Rubella infection and the incidence of CRS.

The detection of Rubella-specific antibodies is used to determine the immune status of an individual and to aid in the diagnosis of acute Rubella infection.

The presence of IgG antibodies to Rubella virus indicates a previous exposure either by vaccination or prior Rubella infection and is indicative of presumptive immunity.

The detection of Rubella-specific IgM antibodies is used as an aid in the diagnosis of acute Rubella infection. Seroconversion of specific Rubella antibodies or a significant rise of the IgG antibody titer from a first to a second sample may support the diagnosis of acute Rubella infection.

Recombinant Rubella-like particles (RLP) have proven to replace authentic Rubella virus as an antigen in diagnostic assays. A recombinant part of the E1 (envelope1) protein of Rubella virus is used to supplement the assay.

The quantitative determination of Rubella IgG is used as an aid in the determination of the immune status to Rubella and the diagnosis of acute infection.

**Test principle**

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 10 µL of sample are incubated with biotinylated monoclonal anti-human IgG antibody, RLP (Rubella-like particles) and a ruthenylated monoclonal anti-Rubella antibody fragment. In addition a biotinylated Rubella virus-specific recombinant antigen E1 (E. coli) and E1 labelled with ruthenium complex[a)] react with anti-Rubella IgG from the sample to form a sandwich complex.
- 2nd incubation: Addition of streptavidin-coated microparticles.
- 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.

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

**Reagents - working solutions**

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

M Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-h IgG-Ab~biotin (gray cap), 1 bottle, 10 mL: Biotinylated monoclonal anti-h IgG antibody (mouse), RLP, phosphate buffer pH 6.8; preservative.

R2 Anti-Rubella-Ab-fragment~$Ru(bpy)_3^{2+}$, recombinant E1~biotin, recombinant E1~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 10 mL: Ruthenylated monoclonal anti-Rubella antibody fragment, biotinylated recombinant E1, ruthenylated recombinant E1, phosphate buffer pH 6.8; preservative.

RUBIGG Cal1 Negative calibrator 1 (white cap), 2 bottles of 1.0 mL each: Human serum, non-reactive for anti-Rubella IgG; preservative.

RUBIGG Cal2 Positive calibrator 2 (black cap), 2 bottles of 1.0 mL each: Anti-Rubella IgG approx. 400 IU/mL in human serum; preservative.

**Precautions and warnings**

For in vitro diagnostic use.

Exercise the normal precautions required for handling all laboratory reagents.

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

Safety data sheet available for professional user on request.

All human material should be considered potentially infectious.

The negative calibrator (RUBIGG Cal1) has been prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV.

Positive calibrator (RUBIGG Cal2): Materials of human origin were tested for HIV and hepatitis C. The findings were negative.

The testing methods applied were FDA-approved or cleared in compliance with the European Directive 98/79/EC, Annex II, List A.

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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.[8,9]

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.

Elecsys 2010 and **cobas e** 411 analyzers: The calibrators should only be left on the analyzers during calibration at 20-25 °C. After use, close the bottles as soon as possible and store at 2-8 °C.

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

MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers: Unless the entire volume is necessary for calibration on the analyzers, 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.

**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<br>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 Elecsys 2010 and **cobas e** 411 at 20-25 °C | up to 5 hours |
| on MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 | use only once |

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

**Specimen collection and preparation**

Only the specimens listed below were tested in a sufficient number and found acceptable.

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

Li-heparin, $K_3$-EDTA and sodium citrate plasma. Do not use plasma treated with sodium fluoride and potassium oxalate.

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

Stable for 3 weeks at 2-8 °C, 3 days at 25 °C, 3 months at -20 °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 altered subsequently with additives (biocides, anti-oxidants or substances possibly changing the pH 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 frozen samples before performing the assay. Lyophilized samples, and samples and controls stabilized with azide (up to 1 %) can be used.

Do not use heat-inactivated samples.

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 04618807190, PreciControl Rubella IgG, 8 x 1 mL each of PreciControl Rubella IgG 1 and 2
- 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
- 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, Elecsys SysClean, 5 x 100 mL system cleaning solution

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**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 approx. 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 (MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers).

**Calibration**

Traceability: This method has been standardized against the 1st International Standard for Anti-Rubella Immunglobulin, human, code RUBI-1-94, from the National Institute for Biological Standards and Control (NIBSC), Hertfordshire, UK, formerly refered to as proposed 3rd WHO Reference Standard Preparation.

Every Elecsys Rubella IgG 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 RUBIGG Cal1 and RUBIGG Cal2.

*Calibration frequency:* Calibration must be performed once per reagent lot using RUBIGG Cal1, RUBIGG Cal2 and 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 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 with PreciControl Rubella IgG outside the defined limits
- more frequently when this is required by pertinent regulations

**Quality control**

For quality control, use PreciControl Rubella IgG.

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.

**Calculation**

The analyzer automatically calculates the analyte concentration of each sample in IU/mL.

*Interpretation of the results*

Results obtained with the Elecsys Rubella IgG assay can be interpreted as follows:

Non-reactive: < 10 IU/mL

Reactive: ≥ 10 IU/mL

The NCCLS subcommittee on Rubella Serology recommended 10 IU/mL as the cutoff level.[6]

A result < 10 IU/mL is considered to be non-reactive.

A result ≥ 10 IU/mL is considered to be positive for IgG antibody to Rubella virus.

The presence of IgG antibodies to Rubella virus is an indication of previous exposure to the virus, either by prior infection or by vaccination.

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

Therefore, the results reported by the laboratory to the physician should include: "The following results were obtained with the Elecsys Rubella IgG assay. Results from assays of other manufacturers cannot be used interchangeably."

Patients suspected of acute Rubella infection should be tested for the presence of Rubella-specific IgM. The diagnosis of acute Rubella infection may be supported by a significant increase of the Rubella IgG antibody titer from a first to a second sample.

**Limitations - interference**

A test result < 10 IU/mL does not completely rule out the possibility of an acute Rubella infection. Specimens taken very early in the acute phase of infection may not contain any detectable amounts of Rubella IgG antibodies or may have an antibody concentration < 10 IU/mL.

The presence of IgG antibodies in a single sample is not sufficient to distinguish between an acute or past infection.

The lack of a significant increase of the Rubella IgG antibody titer (e.g. within 3-4 weeks) may not completely exclude acute Rubella infection.

When monitoring the Rubella-specific IgG antibody titer it is recommended that serial samples be tested by parallel measurements.

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.

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 < 513 µmol/L or < 30 mg/dL), hemolysis (Hb < 3.47 mmol/L or < 5.6 g/dL), lipemia (Intralipid < 1500 mg/dL) and biotin (< 205 nmol/L or < 50 ng/mL).

Criterion: Mean recovery of positive samples within ± 20 % of initial 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 6210 IU/mL.

In vitro tests were performed on 18 commonly used pharmaceuticals and in addition on folic acid. 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.

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**

0.17-500 IU/mL (defined by the lower detection limit and the maximum of the master curve). Values below the lower detection limit are reported as < 0.17 IU/mL. Values above the measuring range are reported as > 500 IU/mL (or up to 10000 IU/mL for 20-fold diluted samples).

**Lower limits of measurement**

*Detection limit*

Detection limit: 0.17 IU/mL

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The detection limit represents the lowest measurable analyte level that can be distinguished from zero. It is calculated as the value lying two standard deviations above that of the negative calibrator (negative calibrator + 2 SD, repeatability study, n = 21).

**Dilution**

Samples with anti-Rubella concentrations above the measuring range can be diluted with Diluent Universal. The recommended dilution is 1:20 (either automatically by the MODULAR ANALYTICS E170, Elecsys 2010 or **cobas e** analyzers or manually). The concentration of the diluted sample must be > 10 IU/mL.

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

After dilution by the analyzers, the MODULAR ANALYTICS E170, Elecsys 2010 and **cobas e** software automatically takes the dilution into account when calculating the sample concentration.

Manual dilution can also be performed using human serum negative for IgG antibodies to Rubella.

*Note:* Antibodies to Rubella are heterogenous. A non-linear dilution behavior is frequently observed.

A similar dilution behavior within the measuring range was shown when serial samples from the same individual were diluted. Serial samples of n = 12 individuals were examined. In a panel consisting of 33 samples with a concentration within the measuring range, no higher Elecsys Rubella IgG values were found upon dilution (when the dilution factor has not been taken into account).

**Expected values**

The Elecsys Rubella IgG assay was used to test 560 samples from clinical routine in France (site 1) and 1000 samples from clinical routine in Germany (site 2). A distribution of these values is given in the following table.

| IU/mL | Site 1, France, n = 560 | | Site 2, Germany, n = 1000 | |
|---|---|---|---|---|
| | N | % of total | N | % of total |
| < 5 | 32 | 5.7 | 19 | 1.9 |
| 5-< 10 | 5 | 0.9 | 2 | 0.2 |
| 10-< 20 | 13 | 2.3 | 12 | 1.2 |
| 20-< 50 | 34 | 6.1 | 47 | 4.7 |
| 50-< 100 | 56 | 10.0 | 82 | 8.2 |
| 100-< 300 | 244 | 43.6 | 541 | 54.1 |
| 300-< 500 | 105 | 18.8 | 151 | 15.1 |
| > 500 | 71 | 12.7 | 146 | 14.6 |

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 (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:

| Elecsys 2010 and **cobas e** 411 analyzers | | | | | | |
|---|---|---|---|---|---|---|
| | **Repeatability** | | | **Intermediate precision** | | |
| Sample | Mean IU/mL | SD IU/mL | CV % | Mean IU/mL | SD IU/mL | CV % |
| HS[b], negative | 0.000 | - | - | 0.000 | - | - |
| HS, weakly positive | 72.9 | 1.40 | 1.9 | 68.5 | 2.61 | 3.8 |
| HS, positive | 476 | 12.0 | 2.5 | 458 | 15.4 | 3.4 |
| PC[c] Rubella IgG 1 | 3.75 | 0.112 | 3.0 | 3.62 | 0.232 | 6.4 |
| PC Rubella IgG 2 | 67.7 | 2.00 | 3.0 | 69.0 | 2.49 | 3.6 |

b) HS = human serum

c) PC = PreciControl

| MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers | | | | | | |
|---|---|---|---|---|---|---|
| | **Repeatability** | | | **Intermediate precision** | | |
| Sample | Mean IU/mL | SD IU/mL | CV % | Mean IU/mL | SD IU/mL | CV % |
| HS, negative | 0.000 | - | - | 0.000 | - | - |
| HS, weakly positive | 62.8 | 1.64 | 2.6 | 68.7 | 2.28 | 3.3 |
| HS, positive | 427 | 4.82 | 1.1 | 485 | 15.5 | 3.2 |
| PC Rubella IgG 1 | 3.61 | 0.074 | 2.1 | 3.54 | 0.153 | 4.3 |
| PC Rubella IgG 2 | 66.0 | 0.772 | 1.2 | 67.7 | 2.21 | 3.3 |

**Clinical sensitivity**

***Acute Rubella infection***

Of 98 samples from 71 patients with primary Rubella infection (including early and late acute phase), 61 samples were found positive with the Elecsys Rubella IgG assay and 37 samples were found negative.

***Rubella vaccination***

231 samples from 61 individuals vaccinated against Rubella infection were examined with the Elecsys Rubella IgG assay and a comparison test. The average time interval to the first positive bleed was 14.1 days with the Elecsys Rubella IgG assay and 19.7 days with the comparison assay.

**Method comparison**

A total of 1559 fresh samples obtained from clinical routine (antenatal screening) and 989 pre-selected frozen samples were tested at 4 different sites in comparison to commercially available Rubella IgG assays. Discordant results were re-tested by a third commercial Rubella IgG test.

10 specimens with indeterminate results in one of the assays and 3 samples which could not be retested were excluded from the final calculation of sensitivity and specificity (7 samples at site 1, 4 samples at site 2 and 2 samples at site 3).

Relative sensitivity and specificity after resolution

| Study | N | Relative sensitivity (%) | Lower confidence limit (%) | Relative specificity (%) | Lower confidence limit (%) |
|---|---|---|---|---|---|
| 1 | 552 | 100 (514/514) | 99.4 | 97.4 (37/38) | - |
| 2 | 996 | 99.9 (977/978) | 99.5 | 100 (18/18) | - |
| 3 | 198 | 100 (120/120) | 97.5 | 100 (78/78) | 96.2 |
| 4 | 789 | 100 (20/20) | - | 100 (769/769) | 99.6 |

Site 1: Of 17 samples which were initially discordant positive with the Elecsys Rubella IgG assay, 16 samples were also found positive by a third commercial Rubella IgG test.

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Site 2: Of 2 samples which were initially discordant negative with the Elecsys Rubella IgG assay, 1 sample was also found negative by a third commercial Rubella IgG test.

Site 4: Of 20 samples which were initially discordant positive with the Elecsys Rubella IgG assay, 20 samples were also positive by a third commercial Rubella IgG test.

**References**


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6 Detection and Quantitation of Rubella IgG Antibody: Evaluation and Performance Criteria for Multiple Component Test Products, Specimen Handling, and Use of Test Products in the Clinical Laboratory; Approved Guideline. NCCLS document I/LA6-A (ISBN) 1-56238-335-3. NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 1997.

7 Skendzel L. Rubella Immunity. Defining the Level of Protective Antibody. Am J Clin Pathol 1996;106:170-174.

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

9 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.


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 |



CE 0123


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