

REF



SYSTEM

07027117119

07027117500

300

cobas e 801

English

System information

Short name	ACN (application code number)
CMVIGG	10070

Please note

The measured CMV 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 CMV IgG assay method used. CMV 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 CMV 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 cytomegalovirus in human serum and plasma.

Results with this assay are used to indicate past or recent infection with CMV.

The electrochemiluminescence immunoassay "ECLIA" is intended for use on the **cobas e 801** immunoassay analyzer.

Note: Please note that the catalogue number appearing on the package insert retains only the first 8 digits of the licensed 11-digit Catalogue Number: 07027117190 for the Elecsys CMV IgG assay. The last 3 digits -190 have been replaced by -119 for logistic purposes.

Summary

Cytomegalovirus (CMV), a member of the herpes virus family, is ubiquitous in all human populations, causing infections which are followed by life-long latency in the host with occasional reactivations.^{2,3} The seroprevalence of antibodies in adults ranges from 40-100 % with inverse correlation to socioeconomic status.^{2,3,4} CMV is transmitted through body fluids, including blood, genital secretions and breast milk. Saliva and urine of infected individuals also represent a prominent source of infection, and children, especially those attending day care facilities, are a major vector for viral spread.^{3,4,5,6,7} In immunocompetent individuals primary CMV infection is usually mild or asymptomatic.^{3,6} Patients commonly present with a mononucleosis-like syndrome, including fever, sore throat, cervical lymphadenopathy, malaise, headache, muscle ache and joint pains.^{3,4,5,6,8} During pregnancy, CMV can cause congenital infection which may result in permanent physical and/or neurological sequelae in the child.⁹ CMV infection can be primary, i.e. newly acquired, or secondary, i.e. due to reactivation of the latent virus or re-infection with a different viral strain.^{4,6} Primary CMV infection is reported in 1-4 % of seronegative women during pregnancy and the risk of transmission to the fetus is estimated to be about 30-40 %.^{4,5} Reactivation of CMV infection during pregnancy is reported in 10-30 % of seropositive women and, in this circumstance, the risk of transmission of the virus is about 1-3 %.^{4,5,6} Overall, prenatal CMV infection occurs in 0.6-0.7 % of all life births in the developed world.^{5,6,9} The majority of babies born with congenital CMV infection are asymptomatic at birth.^{9,10,11} Of these 5-15 % still develop irreversible impairments, most frequently hearing loss, that can occur several months or even years after birth.^{8,9,10,11} For babies symptomatic at birth prognosis is very poor as they are likely to develop severe mental impairment and/or hearing loss.^{6,9,10,11} Different studies have shown that the risk of symptomatic congenital disease in the fetus or newborn infant is high, when maternal primary infection takes place in early pregnancy before week 20 of gestation, and lower thereafter.^{5,6} The congenital CMV infection caused by recurrent maternal infection seldom leads to symptomatic disease at birth.^{5,6}

At risk for CMV infection and disease are also immunocompromised patients such as transplant recipients and HIV infected patients where the virus can cause life-threatening diseases.^{12,13} The CMV status of transplant donors and recipients is very important, as it will determine prophylactic and

pre-emptive treatment strategies against CMV. CMV-negative transplant recipients should receive donations from CMV-negative individuals or leukocyte depleted blood products. During latency, CMV resides in infected cells and the free viral DNA load is usually low. The CMV status can still be determined by testing for CMV IgG antibodies.

Within the appropriate clinical context, the first step in diagnosing acute primary CMV infection is most commonly made by the detection of anti-CMV-specific IgG and IgM antibodies.⁶ Samples being reactive for IgM antibodies indicate an acute, recent or reactivated infection.^{3,5,6,13} For further analysis of a primary CMV infection the determination of the CMV IgG avidity is used as an aid.^{3,5,6,13} A positive IgM result in combination with a low avidity index for IgG is a strong indication of a recent primary CMV infection.^{5,6,13} Seroconversion to CMV IgM and IgG may also indicate a recent CMV infection.^{3,4,5,6,13}

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 12 µL of sample, biotinylated recombinant CMV-specific antigens, and CMV-specific recombinant antigens labeled with a ruthenium complex^{a)} form a sandwich complex.
- 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 II 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 **cobas link**.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex (Ru(bpy)₃²⁺)

Reagents - working solutions

The **cobas e** pack (M, R1, R2) is labeled as CMVIGG.

- M Streptavidin-coated microparticles, 1 bottle, 14.1 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.
- R1 CMV-Ag-biotin, 1 bottle, 18.8 mL:
Biotinylated CMV-specific antigen (recombinant, E. coli), > 400 µg/L,
2-(N-morpholino)ethanesulfonic acid (MES) buffer 50 mmol/L, pH 6.5;
preservative.
- R2 CMV-Ag-Ru(bpy)₃²⁺, 1 bottle, 18.8 mL:
CMV-specific antigen (recombinant, E. coli) labeled with ruthenium
complex > 400 µg/L; MES buffer 50 mmol/L, pH 6.5; preservative.
- CMVIGG Cal1 Negative calibrator 1, 1 bottle of 1.0 mL:
Human serum, non-reactive for anti-CMV IgG; buffer;
preservative.
- CMVIGG Cal2 Positive calibrator 2, 1 bottle of 1.0 mL:
Human serum, reactive for anti-CMV IgG, approximately
40 U/mL; buffer; 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.

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

2-methyl-2H-isothiazol-3-one hydrochloride

EUH 208 May produce an allergic reaction.

Product safety labeling follows EU GHS guidance.

All human material should be considered potentially infectious.

The calibrators (CMVIGG Cal1, CMVIGG Cal2) have been 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-CMV IgG (CMVIGG Cal2) was sterile filtered.

The testing methods used assays approved by the FDA or cleared in compliance with the European Directive 98/79/EC, Annex II, List A.

However, as no testing method can rule out the potential risk of infection with absolute certainty, the material should be handled with the same level of care as a patient specimen. In the event of exposure, the directives of the responsible health authorities should be followed.^{14,15}

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

Reagent handling

The reagents (M, R1, R2) in the kit are ready-for-use and are supplied in **cobas e** packs.

Calibrators

The calibrators are supplied ready-for-use in bottles compatible with the system.

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 available via the **cobas** link.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the **cobas e** pack **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability of the cobas e pack:	
unopened at 2-8 °C	up to the stated expiration date
on the cobas e 801 analyzer	16 weeks

Stability of the calibrators:	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	16 weeks
on the cobas e 801 analyzer at 20-25 °C	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 and found acceptable.

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

Li-heparin, Na-heparin, K₂-EDTA, K₃-EDTA, Na-Citrate, CPD, CP2D, CPDA-1 and ACDA plasma.

Criterion: Mean recovery of serum value: negative/borderline samples ± 0.2 U/mL; reactive samples: 80-120 % for samples containing solid anticoagulants and 55-95 % for samples containing liquid anticoagulants.

Sampling devices containing liquid anticoagulants have a dilution effect resulting in lower values (U/mL) for individual patient specimens.

In order to minimize dilution effects it is essential that respective sampling devices are filled completely according to manufacturer's instructions.

Stability:

Stable for 7 days at 20-25 °C, 28 days at 2-8 °C, 6 months at -20 °C (± 5 °C). The samples may be frozen 5 times.

The sample types listed were tested with a selection of sample collection tubes or systems 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/collection system 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.

Heat-inactivated and reconstituted lyophilized samples can be used.

Ensure the samples and calibrators are at 20-25 °C prior to measurement.

Due to possible evaporation effects, samples and calibrators on the analyzers should be analyzed/measured within 2 hours.

The performance of the Elecsys CMV IgG assay has not been established with cadaveric samples or body fluids other than serum and plasma.

Materials provided

See "Reagents – working solutions" section for reagents.

Materials required (but not provided)

- [REF] 04784600190, PreciControl CMV IgG, 16 x 1.0 mL
 - [REF] 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles
 - [REF] 07299001190, Diluent Universal, 45.2 mL sample diluent
 - General laboratory equipment
 - **cobas e** 801 analyzer
- Additional materials for the **cobas e** 801 analyzer:
- [REF] 06908799190, ProCell II M, 2 x 2 L system solution
 - [REF] 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
 - [REF] 07485409001, Reservoir Cup, 8 cups to supply ProCell II M and CleanCell M
 - [REF] 06908853190, PreClean II M, 2 x 2 L wash solution
 - [REF] 05694302001, Assay Tip/Assay Cup tray, 6 magazines x 6 magazine stacks x 105 assay tips and 105 assay cups, 3 wasteliners
 - [REF] 07485425001, Liquid Flow Cleaning Cup, 2 adaptor cups to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning Detection Unit
 - [REF] 07485433001, PreWash Liquid Flow Cleaning Cup, 1 adaptor cup to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning PreWash Unit
 - [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.

Place the cooled (stored at 2-8 °C) **cobas e** pack on the reagent manager. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the **cobas e** pack.

Calibrators:

Place the calibrators in the sample zone.

Read in all the information necessary for calibrating the assay.

Calibration

Traceability: This method has been standardized against the internal Roche standard for CMV IgG. No international standard is available for CMV.

The predefined master curve is adapted to the analyzer using CMVIGG Cal1 and CMVIGG Cal2.

Calibration frequency: Calibration must be performed once per reagent lot using CMVIGG Cal1, CMVIGG Cal2 and fresh reagent (i.e. not more than 24 hours since the **cobas e** pack 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 12 weeks when using the same reagent lot
- after 28 days when using the same **cobas e** pack on the analyzer
- as required: e.g. quality control findings outside the defined limits

Quality control

For quality control, use PreciControl CMV 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 **cobas e** pack, 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 U/mL, and adds the qualitative interpretation.

Interpretation of the results

Numeric result	Result message	Interpretation/further steps
< 0.5 U/mL	Non-reactive	Not infected with CMV and therefore susceptible to primary infection.
≥ 0.5 to < 1.0 U/mL	Borderline	Samples should be retested. In case the result is still borderline, a second sample should be collected (e.g. within 2 weeks) and testing should be repeated.
≥ 1.0 U/mL	Reactive	Positive for CMV IgG-specific antibodies indicating either acute or past infection. Such individuals are potentially at risk of transmitting the virus (e.g. mother to fetus) but are at current not necessarily contagious.*

* For the diagnosis of acute CMV infection further tests have to be performed e.g. CMV IgM and CMV IgG avidity. A positive IgM result in combination with a low avidity index for IgG is a strong indication of a primary CMV infection within the last 4 months.

The diagnosis may be supported by a significant increase of the CMV IgG antibody titer from a first to a second sample taken e.g. within 3-4 weeks. Note: A borderline or low positive result may already indicate an early acute CMV infection (also if the sample is non-reactive for CMV IgM antibodies).

The anti-CMV IgG results 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 CMV IgG assay. Results from assays of other manufacturers cannot be used interchangeably."

Limitations - interference

The effect of the following endogenous substances and pharmaceutical compounds on assay performance was tested. Interferences were tested up to the listed concentrations and no impact on results was observed.

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 1129 μmol/L or ≤ 66 mg/dL
Hemoglobin	≤ 0.310 mmol/L or ≤ 500 mg/dL
Intralipid	≤ 2000 mg/dL
Biotin	≤ 368 nmol/L or ≤ 90 ng/mL
Rheumatoid factors	≤ 1500 IU/mL

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

A negative test result does not completely rule out the possibility of an infection with CMV. Individuals may not exhibit any detectable IgG antibodies at the early stage of acute infection.

The detection of CMV-specific IgG antibodies in a single sample indicates a previous exposure to CMV but is not always sufficient to distinguish between an acute or latent infection (irrespective of the level of the IgG antibody titer).

In rare cases of primary CMV infection IgG antibody may be present before a specific IgM antibody response is detected. It is recommended that a follow-up sample be tested after 2 weeks. If the CMV IgG antibody titer remains stable, a primary infection can be excluded.^{17,18}

Elecsys CMV IgG results should be used in conjunction with the patient's medical history, clinical symptoms and other laboratory tests, e.g. CMV-specific IgM results, CMV IgG avidity results.

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.

There is no high-dose hook effect at CMV IgG concentrations up to 2500 U/mL.

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

Pharmaceutical substances

In vitro tests were performed on 16 commonly used pharmaceuticals. No interference with the assay was found.

In addition, the following special anti-viral drugs were tested. No interference with the assay was found.

Special anti-viral drugs

Drug	Concentration tested
Ganciclovir	≤ 800 mg/L
Valganciclovir	≤ 900 mg/L

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.

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

0.25-500 U/mL (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Blank are reported as < 0.15 U/mL. Values above the Limit of Blank but below the Limit of Detection will not be flagged by the instrument. Values above the measuring range are reported as > 500 U/mL (or up to 10000 U/mL for 20-fold diluted samples).

Lower limits of measurement

Limit of Blank, Limit of Detection

Agreement to comparative assays

Site	N	Agreement ^{h)} %	Concordant reactive	Concordant non-reactive	Discrepant
1 ⁱ⁾	181	96.1	172	2	7
2 ^{j)}	57	96.5	52	3	2
3	40 ^{k)}	97.5	39	0	1
	36 ^{l)}	94.4	34	0	2
4 ^{m)}	54	90.7	43	6	5

h) All indeterminate samples counted positive.

i) 6 samples were found discordant positive with the Elecsys CMV IgG assay; 1 sample was found discordant negative with the Elecsys CMV IgG assay.

j) 1 sample was found discordant positive with the Elecsys CMV IgG assay; 1 sample was found discordant negative with the Elecsys CMV IgG assay.

k) 1 sample was found discordant negative with the Elecsys CMV IgG assay.

l) 1 sample was found discordant negative with the Elecsys CMV IgG assay and indeterminate with the comparison assay.

m) 4 samples were found discordant negative with the Elecsys CMV IgG assay; 1 sample was found discordant indeterminate with the Elecsys CMV IgG assay; the comparison assay was negative.

Agreement in past infection

A total of 158 frozen samples from pregnant women with past CMV infection analyzed by commercially available CMV IgG assays were tested with the Elecsys CMV IgG assay at 4 different sites. A 100 % agreement for the Elecsys CMV IgG assay was found with the competitor assays.

Agreement in pre-selected negative samples

A total of 161 frozen samples from pregnant women in which a CMV infection was excluded and analyzed by commercially available CMV IgG assays were tested with the Elecsys CMV IgG assay at 4 different sites. In 3 sites a 100 % agreement of the Elecsys CMV IgG assay was found with the competitor assays, whereas at site 4 the Elecsys CMV IgG assay showed 1 discrepant positive and 1 discrepant indeterminate result (agreement 96 %).

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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 (for USA: see dialog.roche.com for definition of symbols used):

	Contents of kit
	Analyzers/Instruments on which reagents can be used
	Reagent
	Calibrator
	Volume after reconstitution or mixing
	Global Trade Item Number

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