Snibe Diagnostic

CE 0123 REF 130262005M:100 tests/kit
130662005M: 50 tests/kit

# MAGLUMI® CMV IgG (CLIA)

## INTENDED USE

The kit is an *in vitro* chemiluminescence immunoassay for the quantitative determination of CMV IgG in human serum and plasma using the MAGLUMI series Fully-auto chemiluminescence immunoassay analyzer and Biolumi series Integrated System, and the assay is used for an aid in the diagnosis of individuals with suspected or confirmed CMV infection, assess the serological status of an individual and used for pre-natal screening of women.

## SUMMARY

Human cytomegalovirus (CMV) is a ubiquitous double-stranded DNA virus belonging to the β-subgroup of the herpesvirus family[1], with a global seroprevalence of 60–90%[2]. CMV infection is more prevalent in underdeveloped countries and among lower socioeconomic groups in developed countries[3]. CMV is transmitted person-to-person via close non-sexual contact, sexual activity, breastfeeding, blood transfusions, and organ transplantation[4].

CMV infection can be primary or secondary[5,6]. Individuals without CMV infection may acquire primary infection, and those with prior infection (seropositive) may reactivate latent CMV or may become reinfected with a new strain of CMV[5]. Moreover,the fetus can also be infected by reactivation of latent maternal infection or by maternal reinfection with a new strain of CMV[6]. Following primary infection, CMV enters a latency phase[7].

In immunocompetent individuals primary CMV infection is usually mild or asymptomatic[2,8]. Patients commonly present with a mononucleosis-like syndrome, including fever, sore throat, cervical lymphadenopathy, malaise, headache and joint pains[9]. The majority of babies born with congenital CMV infection are asymptomatic at birth[10]. Approximately 10% of congenitally infected infants exhibit symptoms of infection[2,10]. In infants with symptomatic congenital CMV infection, the most commonly observed physical findings are petechial rash, jaundice and hepatosplenomegaly with neurologic abnormalities such as microcephaly and lethargy[11]. Ophthalmologic examination reveals chorioretinitis and/or optic atrophy in approximately 10% of symptomatic infants[11]. Recurrent infections are common in immunocompromised patients[12]. For example, clinical symptoms in transplant recipients include pneumonia, gastritis, colitis, hepatitis and retinitis[13]; Common manifestations of CMV disease in AIDS patients are retinitis, esophagitis and colitis; case reports have also documented encephalitis, neuropathy, polyradiculoneuritis, pneumonitis, gastritis, and liver dysfunction[2].

Recent or prior CMV infection can be diagnosed by measuring the presence of anti-CMV IgM and IgG[14]. Typically, CMV infection induces IgM production first, followed by an IgG response[14]. The presence of anti-CMV-IgM antibodies is suggestive of acute, recent or ongoing infection[15]. While presence of IgM alone traditionally indicates acute infection, IgM can persist for months following primary infection and can be detectable during reactivation or reinfection[14]. Diagnosis of primary infection cannot be based on the presence of IgM alone[14]. For further analysis of a primary CMV infection the determination of the CMV IgG avidity is used as an aid[16,17]. The anti-CMV IgG avidity test is currently the most reliable procedure to identify primary infection in pregnant Women[15,18]. A positive IgM result in combination with a low avidity index for IgG is a strong indication of a recent primary CMV infection[14,15,17]. High IgG avidity suggests that CMV infection occurred more than five months earlier.Therefore, a high IgG avidity result during the first trimester of pregnancy suggests that CMV infection occurred before conception, risk of vertical transmission may be low[19]. However, high IgG avidity during the second or third trimester cannot rule out primary infection during pregnancy[14].

## TEST PRINCIPLE

Indirect chemiluminescence immunoassay.

The prediluted sample, buffer, magnetic microbeads coated with CMV antigen are mixed thoroughly, incubating and performing a wash cycle after a precipitation in a magnetic field. ABEI labeled with anti-human IgG monoclonal antibody are then added and incubated, reacting to form immuno-complexes. After precipitation in a magnetic field, the supernatant is decanted and then a wash cycle is performed. Subsequently, the Starter 1+2 are added to initiate a chemiluminescent reaction. The light signal is measured by a photomultiplier as relative light units (RLUs), which is proportional to the concentration of CMV IgG present in the sample.

## REAGENTS

**Kit Contents**

| Component | Description | 100 tests/kit | 50 tests/kit |
|---|---|---|---|
| **Magnetic Microbeads** | Magnetic microbeads coated with CMV antigen (~6.00 μg/mL) in PBS buffer, $NaN_3$ (<0.1%). | 2.5 mL | 1.5 mL |
| **Calibrator Low** | A low concentration of CMV IgG in PBS buffer, $NaN_3$ (<0.1%). | 1.0 mL | 1.0 mL |
| **Calibrator High** | A high concentration of CMV IgG in PBS buffer, $NaN_3$ (<0.1%). | 1.0 mL | 1.0 mL |
| **Buffer** | BSA, $NaN_3$ (<0.1%). | 22.5 mL | 12.0 mL |
| **ABEI Label** | ABEI labeled with anti-human IgG monoclonal antibody (~25.0 ng/mL) in Tris-HCl buffer, $NaN_3$ (<0.1%). | 22.5 mL | 12.0 mL |
| **Diluent** | PBS buffer, $NaN_3$ (<0.1%). | 25.0 mL | 13.5 mL |
| **Negative Control** | PBS buffer, $NaN_3$ (<0.1%). | 1.0 mL | 1.0 mL |
| **Positive Control** | A high concentration of CMV IgG (3.00 IU/mL) in PBS buffer, $NaN_3$ (<0.1%). | 1.0 mL | 1.0 mL |
| All reagents are provided ready-to-use. | | | |

**Warnings and Precautions**

- For *in vitro* diagnostic use.
- For professional use only.
- Exercise the normal precautions required for handling all laboratory reagents.
- Personal protective measures should be taken to prevent any part of the human body from contacting samples, reagents, and controls, and should comply with local operating requirements for the assay.
- A skillful technique and strict adherence to the package insert are necessary to obtain reliable results.
- Do not use kit beyond the expiration date indicated on the label.
- Do not interchange reagent components from different reagents or lots.
- Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).
- All waste associated with biological samples, biological reagents and disposable materials used for the assay should be considered potentially infectious and should be disposed of in accordance with local guidelines.
- This product contains sodium azide. Sodium azide may react with lead or copper plumbing to form highly explosive metal azides. Immediately after disposal, flush with a large volume of water to prevent azide build-up.
- The safety data sheet is available on request.
- Note: If any serious incident has occurred in relation to the device, please report to Shenzhen New Industries Biomedical Engineering Co., Ltd. (Snibe) or our authorized representative and the competent authority of the Member State in which you are established.

**Reagent Handling**

- To avoid contamination, wear clean gloves when operating with a reagent kit and sample. When handling reagent kit, replace the gloves that have been in contact with samples, since introduction of samples will result in unreliable results.
- Do not use kit in malfunction conditions; e.g., the kit leaking at the sealing film or elsewhere, obviously turbid or precipitation is found in reagents (except for Magnetic Microbeads) or control value is out of the specified range repeatedly. When kit in malfunction conditions, please contact Snibe or our authorized distributor.
- To avoid evaporation of the liquid in the opened reagent kits in refrigerator, it is recommended that the opened reagent kits to be sealed with reagent seals contained within the packaging. The reagent seals are single use, and if more seals are needed, please contact Snibe or our authorized distributor.
- Over time, residual liquids may dry on the septum surface. These are typically dried salts and have no effect on assay efficacy.
- Do not transfer opened integral reagents between instruments.
- For magnetic microbeads mixing instructions, refer to the Preparation of the Reagent section of this package insert.
- For further information about the reagent handing during system operation, please refer to Analyzer Operating Instructions.

**Storage and Stability**

- Do not freeze the integral reagents.
- Store the reagent kit upright to ensure complete availability of the magnetic microbeads.
- Protect from direct sunlight.

| **Stability of the Reagents** | |
|---|---|
| Unopened at 2-8°C | until the stated expiration date |
| Opened at 2-8°C | 6 weeks |
| On-board | 4 weeks |

| **Stability of Controls** | |
|---|---|
| Unopened at 2-8°C | until the stated expiration date |
| Opened at 10-30°C | 6 hours |
| Opened at 2-8°C | 6 weeks |
| Frozen at -20°C | 3 months |
| Frozen and thawed cycles | no more than 3 times |



## SPECIMEN COLLECTION AND PREPARATION

**Specimen Types**

Only the specimens listed below were tested and found acceptable.

| Specimen Types | Collection Tubes |
|---|---|
| **Serum** | Tubes without additive, or tubes containing clot activator or clot activator with gel |
| **Plasma** | K2-EDTA, Li-heparin or Na-heparin |

- 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. Follow tube manufacturers' instructions carefully when using collection tubes.

**Specimen Conditions**

- Do not use heat-inactivated samples or grossly hemolyzed/hyperlipidaemia specimens and specimens with obvious microbial contamination.
- Ensure that complete clot formation in serum specimens has taken place prior to centrifugation. Some serum specimens, especially those from patients receiving anticoagulant or thrombolytic therapy, may exhibit increased clotting time. If the serum specimen is centrifuged before a complete clotting, the presence of fibrin may cause erroneous results.
- Samples must be free of fibrin and other particulate matter.
- To prevent cross contamination, use of disposable pipettes or pipette tips are recommended.

**Preparation for Analysis**

- Inspect all specimens for foam. Remove foam with an applicator stick before analysis. Use a new applicator stick for each specimen to prevent cross contamination.
- Frozen specimens must be completely thawed before mixing. Mix thawed specimens thoroughly by low speed vortexing or by gently inverting. Visually inspect the specimens. If layering or stratification is observed, mix until specimens are visibly homogeneous. If specimens are not mixed thoroughly, inconsistent results may be obtained.
- For reliable results, specimens should be free of fibrin, red blood cells, or other particulate matter. Specimens must be centrifuged prior to testing, transfer clarified specimen to a sample cup or secondary tube for testing. For centrifuged specimens with a lipid layer, transfer only the clarified specimen and not the lipemic material.
- The sample volume required for a single determination of this assay is 10 μL.

**Specimen Storage**

Specimens removed from the separator, red blood cells or clot may be stored up to 2 days at 10-30°C or 2 weeks at 2-8°C, or 6 months frozen at -20°C. Frozen specimens subjected to up to 5 freeze/thaw cycles have been evaluated.

**Specimen Shipping**

- Package and label specimens in compliance with applicable local regulations covering the transport of clinical specimens and infectious substances.
- Do not exceed the storage limitations listed above.

**Specimen Dilution**

- Samples, with CMV IgG concentrations above the analytical measuring interval, can be diluted with Diluent either by following automated dilution protocol or manual dilution procedure. The recommended dilution ratio is 1:10(sample volume:total volume). The concentration of the diluted sample must be >6.00 IU/mL.
- For manual dilution, multiply the result by the dilution factor. For dilution by the analyzers, the analyzer software automatically takes the dilution into account when calculating the sample concentration.

## PROCEDURE

**Materials Provided**

CMV IgG (CLIA) assay, control barcode labels.

**Materials Required (But Not Provided)**

- General laboratory equipment.
- Fully-auto chemiluminescence immunoassay analyzer Maglumi 600, Maglumi 800, Maglumi 2000, Maglumi 2000 Plus, Maglumi 4000 Plus, MAGLUMI X3, MAGLUMI X6, MAGLUMI X8, MAGLUMI X10, or Integrated System Biolumi CX8.
- For Reaction Module, Starter 1+2, Wash Concentrate, Light Check, Tip, and Reaction Cup, please refer to corresponding Analyzer Operating Instructions for catalogue number.
- Please use accessories specified by Snibe to ensure the reliability of the test results.

**Assay Procedure**

Preparation of the Reagent

- Take the reagent kit out of the box and visually inspect the integral vials for leaking at the sealing film or elsewhere. If there is no leakage, please tear off the sealing film carefully.
- Open the reagent area door; hold the reagent handle to get the RFID label close to the RFID reader (for about 2s); the buzzer will beep; one beep sound indicates successful sensing.
- Keeping the reagent straight insert to the bottom along the blank reagent track.
- Observe whether the reagent information is displayed successfully in the software interface, otherwise repeat the above two steps.
- Resuspension of the magnetic microbeads takes place automatically when the kit is loaded successfully, ensuring the magnetic microbeads are totally resuspended homogenous prior to use.

Assay Calibration

- Select the assay to be calibrated and execute calibration operation in reagent area interface. For specific information on registrating calibrations, refer to the calibration section of Analyzer Operating Instructions.
- Execute recalibration according to the calibration interval required in this package insert.

Quality Control

- When new lot used, check or edit the quality control information.
- Scan the control barcode, choose corresponding quality control information and execute testing. For specific information on registrating quality controls, refer to the quality control section of the Analyzer Operating Instructions.

Sample Testing

- After successfully loading the sample, select the sample in interface and edit the assay for the sample to be tested and execute testing. For specific information on registrating samples, refer to the sample section of the Analyzer Operating Instructions.

To ensure proper test performance, strictly adhere to Analyzer Operating Instructions.

**Calibration**

Traceability: This method has been standardized against the WHO 1st International Standard 136616/17

Test of assay specific calibrators allows the detected relative light unit (RLU) values to adjust the master curve.

Recalibration is recommended as follows:

- Whenever a new lot of Reagent or Starter 1+2 is used.
- Every 28 days.
- The analyzer has been serviced.
- Control values lie outside the specified range.

**Quality Control**

Controls are recommended for the determination of quality control requirements for this assay and should be run in singlicate to monitor the assay performance. Refer to published guidelines for general quality control recommendations, for example Clinical and Laboratory Standards Institute (CLSI) Guideline C24 or other

published guidelines[20].

Quality control is recommended once per day of use, or in accordance with local regulations or accreditation requirements and your laboratory's quality control procedures, quality control could be performed by running the CMV IgG assay:

- Whenever the kit is calibrated.
- Whenever a new lot of Starter 1+2 or Wash Concentrate is used.

The first seven digits of the lot number on the controls must match those of the corresponding reagent kit. For each target value and range refer to the label.

The performance of other controls should be evaluated for compatibility with this assay before they are used. Appropriate value ranges should be established for all quality control materials used.

Control values must lie within the specified range, whenever one of the controls lies outside the specified range, calibration should be repeated and controls retested. If control values lie repeatedly outside the predefined ranges after successful calibration, patient results must not be reported and take the following actions:

- Verify that the materials are not expired.
- Verify that required maintenance was performed.
- Verify that the assay was performed according to the package insert.
- If necessary, contact Snibe or our authorized distributors for assistance.

If the controls in kit are not enough for use, please order CMV IgG (CLIA) Controls (REF: 160201477MT) from Snibe or our authorized distributors for more.

## RESULTS

**Calculation**

The analyzer automatically calculates the CMV IgG concentration in each sample by means of a calibration curve which is generated by a 2-point calibration master curve procedure. The results are expressed in IU/mL. For further information please refer to the Analyzer Operating Instructions.

**Interpretation of Results**

The expected results for the CMV IgG assay was obtained by testing 311 CMV IgG positive patients and 221 CMV IgG negative people, gave the following expected value by ROC curve:

- Non-reactive: A result less than 0.800 IU/mL (<0.800 IU/mL ) is considered to be negative.
- Grayzone: A result with in the interval between 0.800 and 1.20 (0.800≤x<1.20 IU/mL) is considered to be equivocal.
- Reactive: A result greater than or equal to 1.20 IU/mL (≥1.20 IU/mL) is considered to be positive.

It is recommended to retest the samples in the greyzone. If the results continue to be unclear, consider taking a second sample within an appropriate period of time (e.g. 2 weeks) and repeating testing.

Results may differ between laboratories due to variations in population and test method. It is recommended that each laboratory establish its own reference interval.

## LIMITATIONS

- The assay is mainly used to prenatal screening and physical examination.
- Results should be used in conjunction with patient's medical history, clinical examination and other findings.
- If the CMV IgG results are inconsistent with clinical evidence, additional testing is needed to confirm the result.
- Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). Such specimens may show either falsely elevated or depressed values when tested with assay kits which employ mouse monoclonal antibodies[21,22]. Additional information may be required for diagnosis.
- Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays. Patients routinely exposed to animals or animal serum products can be prone to this interference and anomalous values may be observed[23].
- Bacterial contamination or heat inactivation of the specimens may affect the test results.
- 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 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.

## SPECIFIC PERFORMANCE CHARACTERISTICS

Representative performance data are provided in this section. Results obtained in individual laboratories may vary.

**Precision**

Precision was determined using the assay, samples and controls in a protocol (EP05-A3,EP05-A2) of the CLSI (Clinical and Laboratory Standards Institute): duplicates at two independent runs per day for 20 days at three different sites using three lots of reagent kits (n=720). The following results were obtained:

| Sample | Mean (IU/mL) (n=720) | Within-Run | | Between-Run | | Reproducibility | |
|---|---|---|---|---|---|---|---|
| | | SD (IU/mL) | %CV | SD (IU/mL) | %CV | SD (IU/mL) | %CV |
| Serum Pool 1 | 0.639 | N/A | N/A | N/A | N/A | N/A | N/A |
| Serum Pool 2 | 1.452 | 0.093 | 6.42 | 0.035 | 2.42 | 0.133 | 9.16 |
| Serum Pool 3 | 5.021 | 0.284 | 5.65 | 0.097 | 1.93 | 0.444 | 8.84 |
| Plasma Pool 1 | 0.648 | N/A | N/A | N/A | N/A | N/A | N/A |
| Plasma Pool 2 | 1.540 | 0.099 | 6.46 | 0.041 | 2.63 | 0.140 | 9.07 |
| Plasma Pool 3 | 5.052 | 0.293 | 5.79 | 0.116 | 2.30 | 0.441 | 8.72 |
| Negative Control | ＜0.560 | N/A | N/A | N/A | N/A | N/A | N/A |
| Positive Control | 3.032 | 0.197 | 6.48 | 0.070 | 2.30 | 0.250 | 8.25 |

Based on internal testing on the MAGLUMI and Biolumi systems, the test results of negative samples should be negative; the overall repeatability (% CV) is estimated to be ≤ 10% for samples tested, the overall reproducibility (%CV) is estimated to be ≤ 15%. Performance of the assay at individual laboratories may vary.

**Linear Range**

0.400-60.0 IU/mL (defined by the Limit of Quantitation and the maximum of the master curve).

**Reportable Interval**

0.300-600 IU/mL (defined by the Limit of Detection and the maximum of the master curve×Recommended Dilution Ratio).

**Analytical Sensitivity**

Limit of Blank (LoB) =0.150 IU/mL.
Limit of Detection (LoD) =0.300 IU/mL.
Limit of Quantitation (LoQ) =0.400 IU/mL.

**Analytical Specificity**

**Interference**

Interference was determined using the assay, three samples containing different concentrations of analyte were spiked with potential endogenous and exogenous interferents in a protocol (EP7-A2) of the CLSI. The measurement deviation of the interference substance is within ±10%. The following results were obtained:

| Interference | No interference up to | Interference | No interference up to |
|---|---|---|---|
| Hemoglobin | 2400 mg/dL | Ganciclovir | 800 mg/L |
| Intralipid | 3000 mg/dL | Valganciclovir | 900 mg/L |
| Bilirubin | 50 mg/dL | Interferon α | 15000 IU/mL |
| HAMA | 40 ng/mL | Levamisole | 1.5 mg/mL |
| ANA | 398 AU/mL | Acetylsalicylic acid | 0.65 mg/mL |
| Rheumatoid factor | 2000 IU/mL | Ibuprofen | 50 mg/dL |
| Total protein | 12 g/dL | Methylcobalamin | 50 μg/mL |
| Systemic Lupus Erythematosus Plasma | / | Rifampicin | 48 μg/mL |
| Anti-Mitochondrial Antibody | 398 RU/mL | Doxycycline | 18 μg/mL |
| Total IgG | 8000 mg/dL | Cefoxitin | 6600 μg/mL |
| Total IgM | 2500 mg/dL | Cyclosporine | 2 μg/mL |
| K2-EDTA | 22.75 μmol/mL | Metronidazole | 125 μg/mL |
| Heparin sodium salt | 80 IU/mL | Ascorbic acid | 60 μg/mL |
| Heparin lithium salt | 80 IU/mL | Phenylbutazone | 330 μg/mL |
| Biotin | 0.5 mg/dL | Vidarabine | 1000 μg/mL |
| Ribavirin | 2 mg/mL | Acetaminophen | 400 μg/mL |
| Acyclovir | 6.6 mg/dL | Sodium salicylate | 500 μg/mL |

**Cross-Reactivity**

The assay is highly specific for CMV IgG antibodies, with no observed cross reactivity to Toxo IgG, CMV IgM, HSV-1 IgG, HSV-2 IgG, Rubella IgG, HAV IgG, Anti-HBs, HBeAb IgG, HBcAb IgG, Anti-HCV, Anti-HIV, Anti-*Treponema pallidum*, EBV EA IgG, EBV NA IgG, EBV VCA IgG, *M.Pneumoniae* IgG, *C.Pneumoniae* IgG, *Parvovirus B19* IgG, VZV IgG, *Influenza A virus* IgG, *Influenza B virus* IgG, *Parainfluenza virus* IgG, *Adenovirus IgG* and COXB IgG.

**High-Dose Hook**

No high-dose hook effect was seen for CMV IgG concentrations up to 600 IU/mL.

**Relative Sensitivity**

The relative sensitivity of the CMV IgG assay was determined by testing 109 samples collected from expected positive population with commercial assay confirmation of CMV IgG positive result.

| N of samples | Reactive | Relative Sensitivity | 95% CI |
|---|---|---|---|
| 109 | 109 | 100% | 96.60%-100% |

**Relative Specificity**

The relative specificity of the CMV IgG assay was determined by testing 87 samples collected from expected negative population with commercial assay confirmation of CMV IgG negative result.

| N of samples | Non-reactive | Relative Specificity | 95% CI |
|---|---|---|---|
| 87 | 87 | 100% | 95.77%-100% |

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## SYMBOLS EXPLANATIONS

| | | | |
|---|---|---|---|
| | Consult instructions for use | | Manufacturer |
| 2°C 8°C | Temperature limit (Store at 2-8°C) | | Use-by date |
| Σ | Contains sufficient for<n> tests | | Keep away from sunlight |
| | This way up | EC REP | Authorized representative in the European Community |
| IVD | *In vitro* diagnostic medical device | CONTENTS | Kit component |
| REF | Catalogue number | LOT | Batch code |
| CE 0123 | CE marking with notified body ID number | | |



Summary of safety and performance is available at Eudamed.


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