Bar code

Biotest logo

Instructions for use
Megalotect CP 100 U/ml solution for infusion

Active substance
Human cytomegalovirus immunoglobulin (CMVIG)

Composition
One ml contains:
Human plasma protein 50mg (of which at least 96 % is immunoglobulin G, with a content of antibodies against cytomegalovirus (CMV) of 100 U*.
*Units of the Paul-Ehrlich-Institut reference preparation

Distribution of the IgG subclasses (approx.. values):
IgG1 65 %
IgG2 30 %
IgG3 3 %
IgG4 2 %

The immunoglobin A (IgA) content is ≤ 2000 micrograms/ml.

Excipients:
Glycine, water for injections.

Pharmaceutical form
Solution for infusion
Clear or slightly opalescent and colourless or pale yellow solution with a pH of 5.0 – 5.6 and an osmolality of 250 – 350 mOsm/kg.

Presentations
10 ml or 50 ml of ready-for-use solution for intravenous infusion in vial (type II glass) with a stopper (bromobutyl) and a cap (aluminium).

Each vial with 10ml contains: 500mg human plasma protein (of which at least 96 % is immunoglobulin G), with a content of antibodies against CMV of 1,000 U.
Each vial with 50ml contains: 2,500mg human plasma protein (of which at least 96 % is immunoglobulin G), with a content of antibodies against CMV of 5,000 U.

Pharmacotherapeutic group
Human cytomegalovirus immunoglobulin for intravenous administration

Name and address of manufacturer
Biotest Pharma GmbH
Landsteinerstraße 5
63303 Dreieich, Germany

Indications
Prophylaxis of clinical manifestations of cytomegalovirus infection in patients receiving immunosuppressive therapy, particularly in transplant recipients.

The concomitant use of adequate virostatic agents should be considered for CMV-prophylaxis.

Contraindications

- Hypersensitivity to the active substance (human cytomegalovirus immunoglobulin) or to any of the excipients listed above.
- Patients with selective IgA deficiency who developed antibodies to IgA, as administering an IgA-containing product can result in anaphylaxis.

Fertility, Pregnancy and lactation

Pregnancy

The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women and breast-feeding mothers. IVIg products have been shown to cross the placenta, increasingly during the third trimester. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are expected.

Breast-feeding

Immunoglobulins are excreted into human milk. No negative effects on the breastfed newborns/infants are anticipated.

Fertility

Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.

Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Precautions for use

Potential complications can often be avoided by ensuring that patients:

- are not sensitive to human immunoglobulin by initially injecting the product slowly (0.08 ml/kg body weight/hour),
- are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive to human immunoglobulin, patients switched from an intravenous human immunoglobulin IVIg product, or when there has been a long interval since the previous infusion, should be monitored at the hospital during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration.

In all patients, intravenous immunoglobulin administration requires:

- adequate hydration prior to the initiation of the infusion of intravenous immunoglobulin,
- monitoring of urine output
- monitoring of serum creatinine levels (a indicator of renal function)
- avoidance of concomitant use of loop diuretics.

In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the adverse reaction.

Infusion reaction

Certain adverse reactions (e.g. headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea and hypotension) may be related to the rate of infusion. The recommended infusion rate

given under section **Posology and method of administration** must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Adverse reactions may occur more frequently

- in patients who receive human immunoglobulin for the first time or, in rare cases, when the human immunoglobulin product is switched or when there has been a long interval since the previous infusion
- in patients with an untreated infection or underlying chronic inflammation

Hypersensitivity

Hypersensitivity reactions are rare.

Anaphylaxis can develop in patients

- with undetectable IgA who have anti-IgA antibodies
- who had tolerated previous treatment with human immunoglobulin

IVIg is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern.

In case of shock, standard medical treatment for shock therapy should be implemented.

Thromboembolism

There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, cerebrovascular accident (including stroke), pulmonary embolism and deep vein thromboses which is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin in at-risk patients. Caution should be exercised in prescribing and infusing IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolemic patients, patients with diseases which increase blood viscosity).

In patients at risk for thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.

Acute renal failure

Cases of acute renal failure have been reported in patients receiving IVIg therapy. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant nephrotoxic medicinal products, or age over 65.

Renal parameters should be assessed prior to infusion of IVIg, particularly in patients judged to have a potential increased risk for developing acute renal failure, and again at appropriate intervals. In patients at risk for acute renal failure, IVIg products should be administered at the minimum rate of infusion and dose practicable.

In case of renal impairment, IVIg discontinuation should be considered.

While reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products, containing various excipients such as sucrose, glucose and maltose, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products that do not contain sucrose may be considered. Megalotect CP does not contain sucrose, glucose and maltose.

Aseptic meningitis syndrome (AMS)
Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment. The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm3, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dl. AMS may occur more frequently in association with high-dose (2 g/kg) IVIg treatment.

Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other caused of meningitis.

Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae.

Haemolytic anaemia
IVIg products can contain blood group antibodies which may act as haemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs' test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced red blood cells (RBC) sequestration. IVIg recipients should be monitored for clinical signs and symptoms of haemolysis. (See section **Undesirable effects**)

Neutropenia/Leukopenia
A transient decrease in neutrophil count and/or episodes of neutropenia, sometimes severe, have been reported after treatment with IVIg. This typically occurs within hours or days after IVIg administration and resolves spontaneously within 7 to 14 days.

Transfusion related acute lung injury (TRALI)
In patients receiving IVIg, there have been some reports of acute non-cardiogenic pulmonary oedema [(Transufsion Related Acute Lung Injury(TRALI)). TRALI is characterised by severe hypoxia, dyspnoea, tachypnoea, cyanosis, fever and hypotension. Symptoms of TRALI typically develop during or within 6 hours of a transfusion, often within 1 – 2 hours. Therefore, IVIg recipients must be monitored for and IVIg infusion must be immediately stopped in case of pulomonary adverse reactions. TRALI is a potentially life-threatening condition requiring immediate intensive-care-unit management.

Interference with serological testing
After the administration of immunoglobulin the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing. Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red cell antibodies for example the direct antiglobulin test (DAT, direct Coombs' test).

Transmissible agents
Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and for the non-enveloped hepatitis A

virus (HAV). The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19.

There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety.

Effects on ability to drive and use machines
Megalotect CP may have a minor influence on the ability to drive and use machines. Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines.

Interactions with other medicinal products and other forms of interaction

Live attenuated virus vaccines
Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. After administration of Megalotect CP, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore patients receiving measles vaccine should have their antibody status checked.

Loop diurectics
Avoidance of concomitant use of loop diuretics.

Incompatibilities
Megalotect CP solution must not be mixed with other medicinal products, nor with any other IVIg products.

Posology and method of administration

Posology
The single dose is 1 ml per kg body weight. Administration should be initiated on the day of transplantation. In case of bone marrow transplantation an initiation of prophylaxis up to 10 days before transplantation can also be envisaged, particularly in CMV zero-positive patients. A total of at least 6 single doses at 2 to 3 weeks' intervals should be given.

Hepatic impairment
No evidence is available to require a dose adjustment.

Renal impairment
No dose adjustment unless clinically warranted, see section ‘Special warnings and precautions for use’.

Method of administration

Intravenous use
Megalotect CP should be infused intravenously at an initial rate of 0.08 ml/kg BW/hr for the first 10 minutes. See section **Special warnings and precautions for use**. In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. If well tolerated, the rate of administration may gradually be increased to a maximum of 0.8 ml/kg BW/hr for the remainder of the infusion.

Overdose
Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients or patients with cardiac or renal impairment.

Undesirable effects
Summary of the safety prpofile
Adverse reactions caused by human normal immunoglobulins (in decreasing frequency) encompass

- chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain
- reversible haemolytic reactions: especially in those patients with blood groups A, B and AB and (rarely) haemolytic anaemia requiring transfusion
- (rarely) a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration
- (rarely) transient cutaneous reactions (including cutaneous lupus erythematosus – frequency unknown)
- (very rarely) thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses
- cases of reversible aseptic meningitis
- cases of increased serum creatinine level and/or occurrence of acute renal failure
- cases of Transfusion Related Acute Lung Injury (TRALI)

Tabulated list of adverse reactions
The table presented below is according to the MedDRA system organ classification (SOC) and Preferred Term (PT) Level.
Frequencies have been evaluated according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, the adverse reactions are presented in the order of decreasing seriousness.

Adverse reactions from clinical trials:
In the clinical trial program (3 clinical trials, single dose) conducted with Biotest CMVIG preparations involving 33 patients in total, no adverse drug rections related to Biotest CMVIG products have been identified.

Adverse reactions from post-marketing experience (frequencies not known – cannot be estimated from the available data):

MedDRA System Organ Class	**Adverse reactions**
Blood and lymphatic system disorders	Haemolytic anaemia
Immune system disorders	Anaphylatic shock, anaphylactic reaction, anaphylactoid reaction, hypersensitivity
Nervous system disorders	Headache, dizziness
Gastrointestinal disorders	Vomiting
Skin and subcutaneous tissue disorders	Rash, erythema, drug eruption, pruritus
Musculoskeletal and connective tissue disorders	Anthralgia

Renal and urinary disorders	Acute renal failure
General disorders and administration site conditions	Chills, pyrexia, fatigue
Investigations	Blood creatinine increased

The patient is requested to inform the doctor or pharmacist of the occurrence of any side effect that is not mentioned in the package insert.

Pharmacological properties

Pharmacodynamic properties
Pharmacotherapeutic group: immune sera and immunoglobulins, specific immunoglobulins, ATC code: J06BB09.
Megalotect CP is an immunoglobulin preparation from plasma of donors with a high antibody titer against the CMV. It has a defined and high titer of high avidity anti-CMV antibodies. It also contains IgG antibodies against other pathogens representative of the large number of normal persons who contributed to the plasma pools from which the product was derived. It has a distribution of IgG subclasses closely proportional to that in native human plasma.

Mechanism of action
Megalotect CP is a CMV-specific polyclonal immunoglobulin preparation that binds to CMV surface antigens thereby neutralizing the potential of CMV from entering host cells and presenting the CMV particle for phagocytosis. Megalotect CP antibodies also modulate and interact with immune cells (dendritic cells, monocytes, B- and T-cells) exerting a positive immunological balance in addition to the virostatic inhibition of CMV replication.

Pharmacodynamic effects
The primary mode of action of Megalotect CP Biotest is the binding of circulating virus. These CMVspecific antibodies block the infection of different cell types including all CMV genotypes and of virus variants that are resistant to virostatics. Furthermore, Megalotect CP can activate CMV-reactive immune cells for long-lasting CMV-specific immune responses. It also has additional immunomodulating properties independent of CMV that have been implicated with a reduction of organ rejection.

Pharmacokinetic properties
Megalotect CP is immediately and completely bioavailable in the recipient's circulation after intravenous administration. It is distributed relatively rapidly between plasma and extravascular fluid; after approximately 3-5 days an equilibrium is reached between the intra- and extravascular compartments. Megalotect CP has a half-life of 25 days. This half-life may vary from patient to patient and depends also on the clinical condition.
IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

Shelf-life and storage
Megalotect CP should not be used after the expiry date indicated on the label.
Store in a refrigerator (2°C - 8°C). Keep vial in the outer carton in order to protect from light.
Do not freeze.

Special precautions for disposal and other handling
The medicinal product should be brought to room or body temperature before use.
Products should be inspected visually for particular matter and discoloration prior to administration. The solution should be clear or slightly opalescent and colourless or pale yellow. Do not use solutions which

are cloudy or which have deposits.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
The medicinal product should be used immediately after first opening.

Date of information
October 2019