Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Megalotect 100 U/mL solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human cytomegalovirus immunoglobulin (CMVIG)

One mL contains:
Human plasma protein..... 50 mg (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

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

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

The immunoglobulin A (IgA) content is limited to ≤ 2 000 micrograms/mL.

Produced from the plasma of human donors.

For the full list of excipients, see section 6.1.

3 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.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of clinical manifestations of cytomegalovirus infection in patients subjected to immunosuppressive therapy, particularly in transplant recipients.

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

4.2 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 sero-positive patients. A total of at least 6 single doses at 2 to 3 weeks' intervals should be given.

Paediatric population
The posology in children and adolescents (0-18 years) is not different to that of adults as the posology for each indication is given by body weight and adjusted to the clinical outcome of the above mentioned conditions.

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

Renal impairment
No dose adjustment unless clinically warranted, see section 4.4.

Elderly
No dose adjustment unless clinically warranted, see section 4.4.

Method of administration
Intravenous use
Megalotect should be infused intravenously at an initial rate of 0.08 mL/kg BW/hr for 10 minutes. See section 4.4. 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.

4.3 Contraindications

- Hypersensitivity to the active substance (human cytomegalovirus immunoglobulin) or to any of the excipients listed in section 6.1.
- Patients with selective IgA deficiency who developed antibodies to IgA, as administering an IgA-containing product can result in anaphylaxis.

4.4 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, IVIg administration requires:

- adequate hydration prior to the initiation of the infusion of IVIg,
- monitoring of urine output,
- monitoring of serum creatinine levels,
- avoidance of concomitant use of loop diuretics (see section 4.5)

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 4.2 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

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

Thromboembolism
There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, cerebral vascular 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 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 causes 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 4.8.)

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 [Transfusion 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 pulmonary 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.

Paediatric population
The special warnings and precautions for use mentioned for the adults should also be considered for the paediatric population.

4.5 Interaction 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, 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 diuretics
Avoidance of concomitant use of loop diuretics.

Paediatric population
It is expected that the same interaction mentioned for the adults may also occur in the paediatric population.

4.6 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 further confirmed from data concerning CMVIG administration 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.

4.7 Effects on ability to drive and use machines

Megalotect 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.

4.8 Undesirable effects

Summary of the safety profile
Adverse reactions caused by human normal immunoglobulins (in decreasing frequency) encompass (see also section 4.4):

- 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)

For safety information with respect to transmissible agents, see section 4.4.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients or patients with cardiac or renal impairment (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins, specific immunoglobulins, ATC code: J06BB09.

Megalotect 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 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 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 is the binding of circulating virus. These CMV-specific antibodies block the infection of different cell types including all CMV genotypes and of virus variants that are resistant to virostatics. Furthermore, Megalotect 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.

Clinical efficacy and safety
The clinical efficacy of CMVIG was investigated in different settings, including patients who received solid organ and stem cell transplants. In renal transplantation, CMVIG reduced the incidence of CMV infection from 41.7% (control group) to 21.1% (Biotest CMVIG group). Other examples include lung transplantation, where the incidence of CMV disease was reduced from 43.3% (control group) to 13.2% (Biotest CMVIG group), and bone marrow transplantation, where the incidence of interstitial pneumonitis was reduced from 26.1% to 3.8%.

Renal transplantation
A prospective, randomized controlled study investigated the efficacy of hyperimmunoglobulin prophylaxis for CMV infection in renal transplant patients. 74 patients were enrolled who received a cadaveric kidney for the first time. The mean follow-up was 45 months. Patients received immunosuppressive regimen consisting of methylprednisolone and cyclosporin A. In the treatment group 38 patients received a dose of 2 mL/kg Biotest CMVIG i.v. just before transplantation and then on days 1, 2, 4,

18, 32, 46, 60, 74 and 88 after transplantation. The control group consisted of 36 patients who did not receive Biotest CMVIG. In the treatment group overall 8/38 patients (21.1%) had CMV infection and 5/38 patients (13.2%) had CMV disease, whereas in the control group overall 15/36 patients (41.7%) had CMV infection and 6/36 patients (16.7%) had CMV disease.

Paediatric population
A retrospective study investigated the efficacy and safety of acyclovir plus Biotest CMVIG prophylaxis and early therapy with ganciclovir in CMV high-risk renal transplant paediatric patients (79 patients with a mean age of 14.1 ± 4.9 years, range 2.5 – 20). The minimum follow-up period was 12 months. The immunosuppressive regimen included cyclosporin A and steroids, with the addition of azathioprine in 4 patients who received a living donor-related kidney. Acute rejection episodes were treated with i.v. methylprednisolone pulses. 39 R- patients received 150 mg/kg Biotest CMVIG on the first postoperative day, 100 mg/kg on days 15 and 30 and 50 mg/kg on days 45, 60 and 120 after transplantation and oral acyclovir. 40 R+ patients received only oral acyclovir at the same dosage as R- patients. In the presence of CMV infection, 10 mg/kg body weight per day i.v. ganciclovir was administered for at least 2 weeks, or until negative antigenemia was obtained. In the R- group receiving Biotest CMVIG treatment, of the 33 CMV seronegative recipients (R-) who received the graft from a CMV seropositive donor (D+) 18 (54.5 %) experienced a CMV infection and in 6 CMV seronegative recipients (R-) who received the graft from a CMV negative donor no infection occurred. In the R+ group only receiving acyclovir, of the 28 CMV R +, who received a graft from a CMV D+, 11 (39.3 %) experienced CMV infection and of the 12 R +, who received a graft from a CMV D- donor one recipient experienced a CMV infection (8.3%).

Heart transplantation
An open-label, comparative, retrospective study investigated the combined prophylaxis of Biotest CMVIG plus ganciclovir versus Biotest CMVIG alone in 207 adult high-risk heart transplant recipients (mean age 52.2 years) receiving an allograft from seropositive donors (D+/R-). All patients received polyclonal rabbit antithymocyte globulin as induction therapy. Cyclosporin A, azathioprine, and prednisone were used as maintenance immunosuppressive therapy. Acute allograft rejection episodes were treated with a daily bolus of prednisone for 3 consecutive days. In group A 96 patients received Biotest CMVIG alone and in group B 111 patients received Biotest CMVIG with ganciclovir. 100 mg/kg Biotest CMVIG were administered i.v. before transplantation and on postoperative days 1, 7, 14, 21 and 28. Patients with CMV disease were treated with ganciclovir for 21 days in combination with a reduction of the immunosuppressive therapy. Additional Biotest CMVIG was administered at weekly intervals. In group A 53.1% had CMV infection and 32.3% (31/96 patients) had CMV disease. In group B 65.8% had CMV infection and 11.7% (13/111 patients) had CMV disease. Four CMV-associated deaths were observed in group A; 3 patients died of severe CMV sepsis, and 1 patient died of CMV encephalitis. There were no CMV-associated deaths observed in group B, which reflects a statistically significant benefit of combined Biotest CMVIG and ganciclovir versus sole Biotest CMVIG prophylaxis (P=0.0326).

An open-label, single center study investigated the passive immunisation against CMV in adult allograft recipients (146 patients who underwent heart transplantation between 1984 and 1991 with a median age of 47 years). The follow-up period ranged from 13 to 73 months (median 43 months). Maintenance immunosuppression consisted of cyclosporin A and prednisone. Azathioprine was added to this regimen in 11 patients because of recurrent rejection within the first year. In the treatment group 65 CMV (R-) patients received 150 mg/kg Biotest CMVIG during the operation and 100 mg/kg Biotest CMVIG at days 2, 7, 14, 28, 42, 56 and 72 after transplantation, whereas the control group consisted of 81 CMV (R+) patients who did not receive CMV prophylaxis. In the treatment group 21/65 (R-) patients (32.3%) had CMV infection and 11/65 (R-) patients (16.9%) had CMV disease. In the control group 40/81 (R+) patients (49.4%) had CMV infection and 10/81 (R+) patients (12.3%) had CMV disease.

Lung transplantation
A retrospective, single center study investigated CMV immunoglobulin for prophylaxis and treatment of CMV infection (156 adult patients who received a lung transplant between 2007 and 2011 with a mean age of 52 years (range 17-67 years) were analyzed). The median duration of follow-up was 19.2 months. All patients received basiliximab induction, and a triple immunosuppression (tacrolimus, mycophenolate mofetil, methylprednisolone followed by prednisolone). Ganciclovir i.v. was initiated in all at-risk patients (D+/R– or R+) during the first week post-transplant. In the treatment group 23 D+/R– patients received 2 mL/kg Biotest CMVIG on days 1, 4, 8, 15, and 30 post-transplant, then monthly for a further year and valganciclovir for 6 months. In the control group 133 R+ patients received valganciclovir for 3 months. In the treatment group 14/23 (D+/R-) patients (61%) had CMV infection and 4/23 (D+/R-) patients (17.4%) had CMV disease, whereas in the control group 46/133 (R+) patients (35%) had CMV infection and 6/133 (R+) patients (4%) had CMV disease. The mortality was 4/23 (D+R-) patients (17.4%) in the treatment group and 40/133 (R+) patients (30%) in the control group.

A comparative, retrospective study investigated the combined CMV prophylaxis after lung transplantation in 68 adult lung-transplant patients (mean age 55.8 years in the treatment group and 49.2 years in the control group) with CMV seropositive allograft. The median follow-up period was 16.5 months in the control group (5.3 to 69.5 months) and 23.8

months in the study group (11.9 to 35 months). In the control group 30 patients (transplanted from 1994 to 2000) received ganciclovir alone for the first 3 postoperative months, in the treatment group 38 patients (transplanted from 2000 to 2004) received additional treatment with 1 mL/kg Biotest CMVIG in 7 doses within the first post-transplant month.

Table 1: results of the study

	Treatment group (ganciclovir + Biotest CMVIG) (N=38)	Control group (ganciclovir alone) (N=30)
1-year survival	81.6%	63.3%
3-year survival	71.5%	40%
1-year freedom from CMV reactivation or de novo infection	71.5%	51.1%
3-year freedom from CMV reactivation or de novo infection	66.4%	30%
Development of CMV disease during follow–up	13.2%	43.3%
Development of CMV pneumonitis	13.2%	33.3%
Occurrence of CMV syndrome	0%	10%
1-year freedom from bronchiolitis obliterans syndrome (BOS)	91.0%	69.7%
3-year freedom BOS	82%	54.3%
CMV related death	0%	16.7%

Bone marrow transplantation (BMT)

A randomised comparative study investigated the use of intravenous hyperimmunoglobulin in the prevention of CMV infection in 49 adult patients with leukemia who received allogenic BMT from HLA-matched siblings (mean age 22 (Biotest CMVIG) and 22.5 years (control)). The follow-up was 110 days. All patients were conditioned with cyclophosphamide and total body irradiation. In the treatment group 26 patients received 1 mL/kg Biotest CMVIG, in the control group 23 patients received 2 mL/kg normal immunoglobulin on day -7, and days 13, 33, 73 and 93 after BMT. Within the first 110 days after BMT 1/26 patients (4%) developed CMV-related interstitial pneumonitis in the treatment group and in the control group 6/23 patients (26%). Two patients in the Biotest CMVIG treated group developed CMV-related interstitial pneumonitis after cessation of treatment (Days 143 and 153).

An open-label, non-comparative study investigated the reduction of CMV disease by prophylaxis with CMV hyperimmunoglobulin plus oral acyclovir in 93 adult BMT recipients (median age 22 years, years, range 1-49 years). Acute GVHD was reported for 43 (48.3%) (Grade <II), 18 (20.2%) (Grade II) and 28 (34.3%) (Grade III-IV) patients. Total body irradiation was applied in a fractionated scheme on Days - 3 to -1. 100 mg/kg Biotest CMVIG was given twice before BMT and then every third week through day 100 post BMT. 11/93 patients (11.8%) showed evidence of CMV infection of these 6 patients developed CMV infection during the time they received prophylaxis with CMV hyperimmunoglobulin, and 5 patients reactivated the virus after Biotest CMVIG was stopped. Among the patients suffering from severe GVHD 10/38 patients (26.2%) developed CMV infection, in contrast to only 1/55 patients (1.8%) who experienced mild GVHD.

Results of meta-analyses

Meta-analyses of the literature data on clinical efficacy have been performed to analyze all published data with Biotest CMVIG in the approved indication prophylaxis, independent of their study design. The CMV infection rate was determined as analyzed parameter for the primary endpoint. One meta-analysis covers all studies irrespective of the type of transplantation and one covers only solid organ transplantations (bone marrow transplant/leukaemia not included), results see table 2.

Table 2: results of the meta-analyses:

	Biotest CMVIG n/N % 95% Clopper-Pearson CI	**Control Group** n/N % 95% Clopper-Pearson CI
Meta-analysis (all indications)	422/1137 37.1% 34.3% - 40.0%	286/637 44.9% 41.0% - 48.9%
	2-sided chi-square test: p-value = 0.001	
Meta-analysis (renal, heart and lung transplantations)	390/969 40.2%	283/603 46.9%

	37.1% - 43.4%	42.9% - 51.0%
	2-sided chi-square test: p-value = 0.009	

In both analyses a significant reduction of CMV infection was observed in patients treated with Biotest CMVIG. Including all indications, the CMV infection rate was reduced from 44.9% of patients in the control group to 37.1% of patients in the Biotest CMVIG group (p = 0.001). Looking only at renal, heart and lung transplantations, the reduction was from 46.9% to 40.2% of all patients (p = 0.009).

5.2 Pharmacokinetic properties

Megalotect 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 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.

5.3 Preclinical safety data

Immunoglobulins are normal constituents of the human body. Repeated dose toxicity testing and embryo-foetal toxicity studies are impracticable due to induction of, and interference with antibodies.

Since clinical experience provides no hint for tumorigenic and mutagenic effects of immunoglobulins, experimental studies, particularly in heterologous species, are not considered necessary.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine, water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products, nor with any other IVIg products.

6.3 Shelf life

3 years.

The medicinal product should be used immediately after first opening.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Keep the vial in the outer carton in order to protect from light. Do not freeze.

6.5 Nature and contents of container

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

One box containing:
1 vial with 10 mL (1 000 U) solution for infusion or
1 vial with 50 mL (5 000 U) solution for infusion

Not all pack sizes may be marketed.

6.6 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.

7 MARKETING AUTHORISATION HOLDER

Biotest Pharma GmbH
Landsteinerstrasse 5
D-63303 Dreieich
Germany

8 MARKETING AUTHORISATION NUMBER

PA0592/008/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th October 2022
Date of last renewal: 1st August 2023

10 DATE OF REVISION OF THE TEXT

May 2023