Package leaflet: Information for the user

Cytotect CP Biotest 100 U/ml solution for infusion
Human cytomegalovirus immunoglobulin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Cytotect CP Biotest is and what it is used for

Cytotect CP Biotest
- belongs to the group of immunoglobulins. These medicines contain antibodies (antibodies are part of the body's immune system).
- contains antibodies against the cytomegalovirus.
- is a solution for infusion that is given as a "drip" (infusion) into a vein.

Cytotect CP Biotest is given to patients receiving immunosuppressive treatment (treatment to suppress the immune system) to prevent the clinical manifestation of cytomegalovirus infection, particularly patients after organ transplantation.

Your doctor will consider the concomitant use of adequate virostatic agents when administering Cytotect CP Biotest.

2. What you need to know before you use Cytotect CP Biotest

Do not use Cytotect CP Biotest
- if you are **allergic** to human cytomegalovirus immunoglobulin or any of the other ingredients of this medicine (listed in section 6).
- if you have an immunoglobulin A (IgA) deficiency, especially if you have antibodies against IgA in your blood because this might lead to anaphylaxis..

Warnings and precautions
Talk to your doctor, pharmacist or nurse before Cytotect CP Biotest is given to you
- if you are being given human immunoglobulin **for the first time or after a long break in treatment** or the **immunoglobulin product is being changed**. In these cases adverse reactions may occur more frequently and your doctor will monitor you closely.

- if you are **allergic** to immunoglobulins (see section "Do not use Cytotect CP Biotest"). You may be allergic to immunoglobulins without knowing it, even if you have previously been given immunoglobulins and have tolerated them well. However, hypersensitivity reactions are rare.
- If you have an untreated infection or underlying long lasting (chronic) inflammation
- if you
  - are **very overweight** or **elderly**,
  - have **high blood pressure** (hypertension), **diabetes** or **vascular disease**,
  - have an **increased tendency for blood clotting**,
  - have been **bedridden** for a long time,
  - have a **low blood volume** (hypovolaemia) or your **blood is thicker than normal**,
  - have pre-existing **kidney disease** or **take medicines that may harm your kidneys**.

  In these cases, there is an increased risk of having side effects. Your doctor may stop the Cytotect CP Biotest therapy or use other precautionary measures (e.g. an especially slow infusion rate).

Infusion reactions
If you experience during the infusion of Cytotect CP Biotest any of the following signs of a reaction, i.e., headache, flushing, chills, muscle pain, wheezing, rapid heart rate, lower back pain, nausea and low blood pressure, immediately inform your doctor.

Tell your doctor immediately if you notice such reactions during the administration of Cytotect CP Biotest. He or she will decide whether to decrease the infusion rate or to stop the infusion completely and to start necessary medical measures to treat this.

Information on safety with respect to infections
Cytotect CP Biotest is made from human plasma (this is the liquid part of blood). When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients through administration of this medicine. All blood donors are tested for viruses and infections. In addition, processing of the blood or plasma includes steps that can inactivate or remove viruses.

Despite these measures, when medicines prepared from human blood or plasma are given, the possibility of passing on infection cannot be totally excluded.

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

The measures taken may be of limited value against viruses such as
- parvovirus B19.

Immunoglobulins have not been associated with hepatitis A or parvovirus B19 infections to date. This is possibly because antibodies, which are contained in Cytotect CP Biotest, are protective against these infections.

It is strongly recommended that every time you are given a dose of Cytotect CP Biotest the name and batch number of the product are recorded. The batch number provides information about the specially used starting materials of your medicine. If necessary a connection between you and the starting material used can thereby be made.

Children and adolescents
The special warnings and precautions for adults also apply to children and adolescents.

Other medicines and Cytotect CP Biotest
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Cytotect CP Biotest may reduce the efficacy of certain **vaccines**, e.g. the efficacy of vaccines against
- **measles**
- **rubella**
- **mumps**
- **chicken pox** (varicella)

After being given Cytotect CP Biotest, you may have to wait up to 3 months before you can have some vaccines and up to a year before you can have a measles vaccine.

Please avoid the concomitant use of loop diuretics (commonly known as water tablets) together with Cytotect CP Biotest.

Children and adolescents
The interactions listed for adults are expected to be the same for children and adolescents.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Your doctor will decide if Cytotect CP Biotest may be used during pregnancy and breast-feeding.

Driving and using machines
Cytotect CP Biotest may have a minor influence on the ability to drive and use machines.. If you experience side effects during treatment you should wait for these to resolve before driving or operating machines.

3. How to use Cytotect CP Biotest

Cytotect CP Biotest is given to you by your treating doctor.
The recommended dose is 1 ml per kg body weight and day for adults, children and adolescents.

You will receive this medicine for at least 6 times in total at an interval of 2 to 3 weeks. Your doctor will decide how many infusions you will need exactly and when to start the treatment.

Cytotect CP Biotest is given to you as a "drip" (infusion) into a vein. The medicinal product should be brought to room or body temperature before use.

If you were given more Cytotect CP Biotest than you should
Too much Cytotect CP Biotest can cause fluid overload and hyperviscosity (thickening) of the blood, especially if you are over 65 years of age and/or have impaired cardiac or renal function.
If you think that you have received more Cytotect CP Biotest than you should, talk to your doctor as soon as possible.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects have been reported spontaneously with Cytotect CP Biotest:
Not known: frequency cannot be estimated from the available data
- Anaemia (haemolytic anaemia)
- Severe allergic reaction such as anaphylactic shock, anaphylactic reactions, anaphylactoid reactions, hypersensitivity
- Headache, dizziness

- Vomiting
- Skin reactions including rash, abnormal redness of the skin, itching
- Joint pain
- Results of blood tests that indicate that renal function is impaired (an increase in the serum creatinine level) and/or acute renal failure
- Chills, fever, tiredness

Human normal immunoglobulin preparations in general may cause the following side effects (in decreasing frequency):

- chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, joint pain, low blood pressure and moderate low back pain
- decrease in the number of red blood cells due to a breakdown of these cells in the blood vessels ((reversible) haemolytic reactions) and (rarely) haemolytic anaemia requiring transfusion
- (rarely) a sudden fall in blood pressure and, in isolated cases, anaphylactic shock
- (rarely) transient cutaneous reactions (including cutaneous lupus erythematosus - frequency unknown)
- (very rarely) thromboembolic reactions such as heart attack (myocardial infarction), stroke, blood clots in blood vessels in the lung (pulmonary embolism), blood clots in a vein (deep vein thromboses)
- cases of temporary acute inflammation of the protective membranes covering the brain and spinal cord (reversible aseptic meningitis)
- cases of blood tests results which indicate that the renal function is impaired and/or sudden kidney failure
- cases of Transfusion Related Acute Lung Injury (TRALI). This will lead to non-heart related accumulation of fluid in the air spaces of the lungs (non-cardiogenic pulmonary oedema).You will experience severe difficulty in breathing (respiratory distress), rapid breathing (tachypnoe), abnormally low level of oxygen in the blood (hypoxia) and increased body temperature (fever).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.You can also report side effects directly via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cytotect CP Biotest

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and vial after EXP.
Store in a refrigerator (2° C – 8°C). Store in the original package in order to protect from light.
Do not freeze.

The product should be visually inspected before use: The solution must be clear or slightly opalescent (with a milky sheen) and colourless or pale yellow. Cytotect CP Biotest must not be used if the solution is cloudy or has formed a sediment.

The medicinal product should be used immediately after first opening.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Cytotect CP Biotest contains
The active substance is human cytomegalovirus immunoglobulin (CMVIG).
1 ml solution contains:
50 mg human plasma protein of which at least 96% is immunoglobulin G (IgG), with a content of antibodies against cytomegalovirus (CMV) of 100 U*.

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*.

The IgG subclass distribution is approx. 65% IgG1, 30% IgG2, 3% IgG3, 2% IgG4.
The maximum immunoglobulin A (IgA) content is 2,000 micrograms/ml.
** units of the reference preparation of the Paul-Ehrlich-Institut*

The other ingredients are glycine and water for injections.

What Cytotect CP Biotest looks like and contents of the pack
Cytotect CP Biotest is a clear or slightly opalescent (with a milky sheen), colourless or slightly yellowish solution in vials made from colourless glass.

Cytotect CP Biotest is available in the following pack sizes:
One box containing 1 vial with 10 ml (1,000 U) solution for infusion.
One box containing 1vial with 50 ml (5,000 U) solution for infusion.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Biotest Pharma GmbH
Landsteinerstraße 5
63303 Dreieich
Germany

Tel.: + 49 6103 801-0
Fax: + 49 6103 801-150
Email: mail@biotest.com

PL 04500/0015

This medicinal product is authorised in the Member States of the EEA under the following names:

Croatia, Germany, Hungary, United Kingdom:	Cytotect CP Biotest
Austria:	Cytotect CP Biotest 100 E/ml Infusionslösung
Italy:	Cytomegatect
Spain	Megalotect
Greece, Poland, Portugal:	Megalotect CP
Belgium, Netherlands:	Megalotect 100 E/ml
Slovenia:	Megalotect 100 e./ml raztopina za infundiranje

This leaflet was last revised in 12/2019.

The following information is intended for healthcare professionals only:

Posology and method of administration

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.

Method of administration
Intravenous use.
Cytotect CP Biotest should be infused intravenously at an initial rate of 0.08 ml/kg BW/hr for 10 minutes. 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.

Warnings and precautions
Certain severe drug reactions may be related to the rate of infusion. The recommended infusion rate must be followed closely. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Certain adverse reactions may occur more frequently
- in case of high rate of infusion,
- in patients who receive human immunoglobulin for the first time or, in rare cases, when the immunoglobulin product is being changed or after a long break in treatment.

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 side effects. All other patients should be observed for at least 20 minutes after administration.

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

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

In all patients immunoglobulin treatment requires
- adequate hydration prior to the initiation of the immunoglobulin infusion,
- monitoring of urine output,
- monitoring of serum creatinine levels,
- avoidance of concomitant use of loop diuretics.

Hypersensitivity
Hypersensitivity reactions are rare. They can occur in patients with anti-IgA antibodies.

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 intravenous immunoglobulin (IVIg) administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (stroke), pulmonary embolism and deep vein thrombosis 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 immunoglobulins 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 intravenous immunoglobulin (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 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 discontinuation of the immunoglobulin product 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 immunoglobulin products that do not contain these excipients may be considered. Cytotect CP Biotest does not contain sucrose, glucose or maltose.

Aseptic meningitis syndrome (AMS)

AMS has been reported to occur in association with intravenous immunoglobulin (IVIg products) treatment. The syndrome usually begins within several hours to 2 days following the start of IVIg treatment. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm^3, 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 and without sequelae.

Haemolytic anaemia

Intravenous immunoglobulins (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.

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 administrationof 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 and D may interfere with some serological tests for red cell antibodies for example the direct antiglobulin test (DAT, direct Coombs' test).

Incompatibilities and special precautions for handling
This medicinal product must not be mixed with other medicinal products, nor with any other IVIg products.

The medicinal product should be used immediately after first opening.

The medicinal product should be brought to room or body temperature before use.

Products should be inspected visually 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.