SUMMARY OF PRODUCT CHARACTERISTICS
1. **NAME OF THE MEDICINAL PRODUCT**

Cytotect® CP Biotest 100 U/ml solution for infusion

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Human cytomegalovirus immunoglobulin

Human plasma protein 50 mg/ml (of which at least 96 % is immunoglobulin G), with a content of antibodies against cytomegalovirus of 100 U*/ml

* Units of the Paul-Ehrlich-Institut reference preparation

The distribution of IgG subclasses is defined around 65 % IgG1, 30 % IgG2, 3 % IgG3, 2 % IgG4.

The immunoglobulin A (IgA) content is limited to ≤ 2 mg/ml.

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Solution for infusion

Solution is clear or slightly opalescent and transparent to pale yellow.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

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

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.

**Method of administration**

Cytotect CP Biotest should be infused intravenously at an initial rate of 0.08 ml/kg BW/hr for 10 minutes. 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 ingredients or to any other components. Hypersensitivity to homologous immunoglobulins, especially in very rare cases of IgA deficiency, when the patient has antibodies against IgA.

### 4.4 Special warnings and precautions for use

Certain severe adverse drug reactions may be related to the rate of infusion. The recommended infusion rate given under "4.2 Posology and method of administration" must be closely followed as the incidence of adverse events tends to increase with the rate of infusion. 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 with hypo- or agammaglobulinemia with or without IgA deficiency,
- 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.

True hypersensitivity reactions are rare. They can occur in the very seldom cases of IgA deficiency with anti-IgA antibodies. Rarely, human immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human immunoglobulin.

Potential complications can often be avoided by ensuring:
- that patients are not sensitive to human immunoglobulin
- that by first injecting the medicinal product will be administered slowly (0.08 ml/kg BW/hour),
- that patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive to human immunoglobulin, patients switched from an alternative intravenous immunoglobulin product, or when there has been a long interval since the previous infusion, should be monitored 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.

There is clinical evidence of an association between intravenous immunoglobulin administration and thromboembolic events such as myocardial infarction, 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 intravenous immunoglobulin 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.

Cases of acute renal failure have been reported in patients receiving intravenous immunoglobulin 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.

In case of renal impairment, intravenous immunoglobulin discontinuation should be considered. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed intravenous immunoglobulin products, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. In patients at risk, the use of intravenous immunoglobulin products that do not contain sucrose may be considered. Cytotect CP Biotest does not contain sucrose.
In patients at risk for acute renal failure or thromboembolic adverse reactions, intravenous immunoglobulin products should be administered at the minimum infusion-rate practicable.

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

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 HIV, HBV and HCV, and for the non-enveloped 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.

It is strongly recommended that every time that Cytotect CP Biotest is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

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 Cytotect CP Biotest, 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.

Interference with serological testing
After injection 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 allo-antibodies (e.g. Coombs test), reticulocyte count and haptoglobin.

4.6 Pregnancy and lactation

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. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected. Immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate.
4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

The following frequency convention is used for description of the following adverse reactions:

Very common: ≥1/10; common: ≥1/100, to <1/10; uncommon: ≥1/1,000, <1/100; rare: ≥1/10,000, <1/1,000; very rare: <1/10,000, not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>MedDRA Standard System Organ Class</th>
<th>Undesirable effects</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Reversible haemolytic anaemia/haemolysis</td>
<td>Not known</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>uncommon</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Vomiting, nausea</td>
<td>uncommon</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Increase in serum creatinine level and/or acute renal failure</td>
<td>not known</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Transient cutaneous reactions</td>
<td>rare</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia, mild low back pain</td>
<td>uncommon</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Reversible aseptic meningitis</td>
<td>not known</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Low blood pressure, Thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism and deep vein thromboses</td>
<td>uncommon very rare</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Chills, fever</td>
<td>uncommon</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Allergic reactions</td>
<td>uncommon</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity reactions with sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hyper-sensitivity to previous administration</td>
<td>rare</td>
</tr>
</tbody>
</table>

For safety with respect to transmissible agents, see 4.4.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Specific immunoglobulins, ATC code: J06BB09.

Cytotect CP Biotest is an immunoglobulin preparation from plasma of donors with a high antibody titer against the cytomegalovirus. It has a distribution of IgG subclasses closely proportional to that in native human plasma.

5.2 Pharmacokinetic properties
Cytotect CP Biotest 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.

Cytotect CP Biotest 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. In animals, single dose toxicity testing is of no relevance since higher doses result in overloading. Repeated dose toxicity testing and embryo-foetal toxicity studies are impracticable due to induction of, and interference with antibodies. Effects of the product on the immune system of the newborn have not been studied.

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.

6.3 Shelf-life

3 years.

The solution should be administered immediately after opening the receptacle. Any unused solution must be discarded because of bacterial contamination risk.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Keep the container in the outer carton in order to protect from light.

Do not freeze.

The product should not be used after the expiry date indicated on the label.

6.5 Nature and contents of container

Ready-for-use solution for intravenous infusion in vials (type II glass) with a stopper (bromobutyl) and a cap (aluminium).
Infusion vial of 10 ml (1000 U)
Infusion vial of 50 ml (5000 U)

6.6 Special precautions for disposal and other handling

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

Dissolved products should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear or slightly opalescent. Do not use solutions which are cloudy or which have deposits.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

Germany: 6a/96

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/01/2000, 04/01/2005, 04/01/2010

10. DATE OF REVISION OF THE TEXT

November 2012