Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Hepatect CP 50 IU/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human hepatitis B immunoglobulin.

Human protein 50 g/l of which at least 96 % is IgG, with a content of antibodies to Hepatitis B virus surface antigen (HBs) of at least 50 IU/ml

Each vial of 2 ml contains: 100 IU
Each vial of 10 ml contains: 500 IU
Each vial of 40 ml contains: 2000 IU
Each vial of 100 ml contains: 5000 IU

Distribution of IgG subclasses (approx. values):
IgG1: 59%
IgG2: 35 %
IgG3: 3 %
IgG4: 3 %

The maximum IgA content is 2,000 micrograms/ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion

The solution is clear or slightly opalescent and colourless to pale yellow.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of hepatitis B virus re-infection after liver transplantation for hepatitis B induced liver failure.

Immunoprophylaxis of hepatitis B

- In case of accidental exposure in non-immunised subjects (including persons whose vaccination is incomplete or status unknown).
- In haemodialysed patients, until vaccination has become effective.
- In the newborn of a hepatitis B virus carrier-mother.
- In subjects who did not show an immune response (no measurable hepatitis B antibodies) after vaccination and for whom a continuous prevention is necessary due to the continuous risk of being infected with hepatitis B.

4.2 Posology and method of administration

Posology

Prevention of hepatitis B re-infection after liver transplantation for hepatitis B induced liver failure:

In adults:
10 000 IU on the day of transplantation, peri-operatively
then 2000-10 000 IU (40-200 ml)/day for 7 days,
and as necessary to maintain antibody levels above 100-150 IU/l in HBV-DNA negative patients and above 500 IU/l in HBV-DNA positive patients.

In children:
Posology should be adjusted according to body surface area, on the basis of 10 000 IU/1.73 m^2.

Immunoprophylaxis of hepatitis B:

- Prevention of hepatitis B in case of accidental exposure in non-immunised subjects:

At least 500 IU (10 ml), depending on the intensity of exposure, as soon as possible after exposure, and preferably within 24 - 72 hours.

- Immunoprophylaxis of hepatitis B in haemodialysed patients:

8-12 IU (0.16-0.24 ml)/kg with a maximum of 500 IU (10 ml), every 2 months until seroconversion following vaccination.

- Prevention of hepatitis B in the newborn, of a hepatitis B virus carrier-mother, at birth or as soon as possible after birth:

30-100 IU (0.6-2 ml)/kg. The hepatitis B immunoglobulin administration may be repeated until seroconversion following vaccination.

In all these situations, vaccination against hepatitis B virus is highly recommended. The first vaccine dose can be injected on the same day as human hepatitis B immunoglobulin, however in different sites.

In subjects who did not show an immune response (no measurable hepatitis B antibodies) after vaccination, and for whom continuous prevention is necessary, administration of 500 IU (10 ml) to adults and 8 IU (0.16 ml)/kg to children every 2 months can be considered; a minimum protective antibody titre is considered to be 10 mIU/mL.

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

Hepatect CP should be infused intravenously at an initial rate of 0.1 ml/kg/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 1 ml/kg/hr.

Clinical experience in newborns of hepatitis B virus carrier mothers has shown, that Hepatect CP intravenously used at an infusion rate of 2 ml in-between 5 to 15 minutes has been well tolerated.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to human immunoglobulin.
- 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

Monitoring of anti-HBs antibody level:
Patients should be monitored for serum anti-HBs antibody levels regularly. The dosage shall be adjusted to maintain the therapeutic antibody levels and to avoid underdosing (see section 4.2).

Potential complications can often be avoided by ensuring that patients:

- are not sensitive to human immunoglobulins by initially injecting Hepatect CP slowly (0.1 ml/kg/hr).
- are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive to human immunoglobulin products, patients switched from other immunoglobulins or when there has been a long interval since the previous infusion. These patients 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.

Especially if applied at higher doses, intravenous human immunoglobulin administration requires:

- adequate hydration prior to the initiation of the infusion of human immunoglobulins
- 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 "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 case of high rate of infusion,
- in patients with hypo- or agammaglobulinemia with or without IgA deficiency
- in patients who receive human immunoglobulins 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.

Hepatect CP contains a small quantity of IgA. Individuals who are deficient in IgA have the potential for developing IgA antibodies and may have anaphylactic reactions after administration of blood components containing IgA. The physician must therefore weigh the benefit of treatment with Hepatect CP against the potential risk of hypersensitivity reactions.

Rarely, human hepatitis B immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with immunoglobulin.

Suspicion of allergic or anaphylactic type reactions requires immediate discontinuation of the injection. In case of shock, standard medical treatment for shock should be implemented.

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

The following adverse reactions have been associated with the use of human normal immunoglobulin for intravenous administration (IVIg):

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 hypovolaemic 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, hypovolaemia, 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 human immunoglobulin products that do not contain these excipients may be considered.
Hepatect CP does not contain sucrose, maltose or glucose.

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 IVIgs. 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 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.

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 rubella, mumps, measles and varicella. After administration of this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In case of measles vaccination, 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
The listed interactions apply to adults and children.

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. Intravenous immunoglobulin G 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.

Breastfeeding
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

Hepatect CP has 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).

Tabulated list of adverse reactions:

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term 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).

Adverse reactions from clinical trials:
In four clinical trials no adverse reactions with Hepatect CP were identified.

Adverse reactions from post-marketing experience and non-interventional studies (frequencies not known - cannot be estimated from the available data):

MedDRA Standard System Organ Class	**Adverse reactions**
Immune system disorders	Anaphylactic shock, hypersensitivity
Nervous system disorders	Headache, dizziness
Cardiac disorders	Tachycardia
Vascular disorders	Hypotension
Gastrointestinal disorders	Nausea
Skin and subcutaneous tissue disorders	Skin reaction, rash, pruritus
General disorders and administration site conditions	Pyrexia, malaise

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

Paediatric population

Adverse reactions in children are expected to be the same as in adults.

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 of immunoglobulins 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/Hepatitis B immunoglobulin
ATC code: J06BB04

Human hepatitis B immunoglobulin contains mainly immunoglobulin G (IgG) with a specifically high content of antibodies against hepatitis B virus surface antigen (HBs).

5.2 Pharmacokinetic properties

The bioavailability of human hepatitis B immunoglobulin for intravenous use is complete and immediate. IgG is quickly distributed between plasma and extravascular fluid.

Hepatect CP has a half-life of about 22 days. This half-life may vary from patient to patient.

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. Effects of the product on the immune system of the new-born 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, nor with any other IVIg products.
No other preparations may be added to the Hepatect CP solution as any change in the electrolyte concentration or the pH may result in precipitation or denaturisation of the proteins.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Hepatect CP is a ready-for-use solution for infusion provided in vials (Type II glass) with a stopper (bromobutyl) and a cap (aluminium):

Pack size of 1 vial with 2ml, 10ml, 40 ml or 100 ml solution.

6.6 Special precautions for disposal and other handling

The product must be brought to room or body temperature before use.
The solution should be administered immediately after opening the receptacle.
The solution should be clear or slightly opalescent and colourless to pale yellow.
Do not use solutions that are cloudy or 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
Dreieich
63303
Germany

8 MARKETING AUTHORISATION NUMBER

PA0592/005/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 August 2008 Date of last renewal: 12 April 2015

10 DATE OF REVISION OF THE TEXT

October 2025