

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 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:

- IgG1: 59%
- IgG2: 35 %
- IgG3: 3 %
- IgG4: 3 %

IgA max 2000 micrograms/ml.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion

The solution is clear or slightly opalescent.

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 m².

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.

Method of administration

Hepatect CP should be infused intravenously at an initial rate of 0.1 ml/kg/hr for 10 minutes. 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 any of the components.

Hypersensitivity to human immunoglobulins.

4.4 Special warnings and precautions for use

Thromboembolic complications have been associated with the use of normal IVIg. Therefore, caution is recommended especially for patients with thrombotic risk factors.

Patients should be monitored for serum anti-HBs antibody levels regularly.

Certain severe adverse drug reactions may be related to the rate of infusion.

The recommended infusion rate given under "4.2 Method of administration" must be closely followed. 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.

Specific allergic reactions are rare.

Hepatect CP contains 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 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 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 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.

It is strongly recommended that every time that Hepatect CP 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 interfere with the development of an immune response to live attenuated virus vaccines such as rubella, mumps, measles and varicella for a period of up to 3 months. After administration of this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines.

Human hepatitis B immunoglobulin should be administered three to four weeks after vaccination with such a live attenuated vaccine; in case administration of human hepatitis B immunoglobulin is essential within three to four weeks after vaccination, then revaccination should be performed three months after the administration of human hepatitis B immunoglobulin.

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 have been shown to cross the placenta, increasingly in 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 to be expected.

Breast-feeding

Immunoglobulins are excreted into the milk and may contribute to protecting the neonate from pathogens which have a mucosal portal of entry.

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

The ability to drive and operate machines may be impaired by some adverse reactions associated with intravenous immunoglobulins. Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines.

4.8 Undesirable effects

There are no robust data on the frequency of undesirable effects from clinical trials. The following undesirable effects have been reported according to the following frequency:

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).

MedDRA Standard System Organ Class	Undesirable effects	Frequency
Immune system disorders	Hypersensitivity	Rare
	anaphylactic shock	Very rare
Nervous system disorders	Headache	Rare
Cardiac disorders	Tachycardia	Rare
Vascular disorders	Hypotension	Rare
Gastrointestinal disorders	Nausea, vomiting	Rare
Skin and subcutaneous tissue disorders	Skin reaction, erythema, itching, pruritus	Rare
Musculoskeletal, connective tissue and bone disorders	Arthralgia	Very rare
General disorders and administration site conditions	Fever, malaise, chill	Rare

During graft re-infection preventive therapy very rare cases of intolerance reactions may be linked to an interval increase between administrations.

With human normal immunoglobulin, cases of reversible aseptic meningitis, reversible haemolytic anaemia/haemolysis, increase in serum creatinine level and/or acute renal failure have been observed. Thromboembolic events have been reported in the elderly, in patients with signs of cerebral or cardiac ischemia, and in overweight and severely hypovolaemic patients.

For further information and for safety with respect to transmissible agents see section 4.4.

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Consequences of an overdose are not known

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and 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. 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 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.

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 denaturation of the proteins.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

The product should not be used after the expiry date indicated on the label.
Hepatect CP should be stored at + 2°C to + 8°C. Do not freeze.
Keep the vial in the outer carton in order to protect from light.
The solution should be administered immediately after opening the receptacle.

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):

Vial with 100 IU in 2 ml solution
Vial with 500 IU in 10 ml solution
Vial with 2000 IU in 40 ml solution
Vial with 5000 IU in 100 ml solution

Pack size of one vial. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The product should be brought to room or body temperature before use.
The solution should be clear or slightly opalescent.
Do not use solutions that are cloudy or have deposits.
Any unused 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

PA0592/005/004

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

January 2015