1. NAME OF THE MEDICINAL PRODUCT
Hepatect® 50 IU/ml
Solution for intravenous administration

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Human hepatitis B immunoglobulin (IVIg)

1 ml Hepatect® contains:
- human plasma protein 100 mg
- thereof immunoglobulin G (IgG) ≥ 95 %
- with antibodies to HBs-antigen 50 I.U.

The IgG subclass distribution is approx. 62% IgG1, 34% IgG2, 0.5% IgG3, 3.5% IgG4.
The IgA content is ≤ 5 mg

For excipients, see 6.1.

3. PHARMACEUTICAL FORM
Solution for intravenous infusion.

4. CLINICAL PARTICULARS
4.1 Therapeutic Indications

Postexposure prophylaxis following either parenteral exposure (e.g., accidental "needle-stick"), direct mucous membrane contact (e.g., accidental splash) or oral ingestion (e.g., pipetting accident) involving HBsAg-positive materials such as blood, plasma or serum.

Prophylaxis of graft reinfection in HBsAg-positive patients undergoing liver transplantation.

Prophylaxis of infants born to HBsAg-positive mothers.

Individuals who are at increased risk of infection with hepatitis B virus should receive hepatitis B immunoglobulin i.v. either preceding or concomitant with the commencement of active immunisation with hepatitis B vaccine.

Prophylaxis in persons who are unable to develop adequate protection and who are exposed to a continual risk of infection, e.g. dialysis patients, those receiving multiple transfusion or blood components.

Hepatect® is also indicated in persons who require an acute hepatitis-B prophylaxis and who have a hemorrhagic diathesis at the same time.

4.2 Posology and Method of Administration

Posology
The dose and the dosage regimen is dependent on the indication.
After inoculation of HBsAg containing material, 6 IU to 10 IU (0.12 to 0.2 ml) Hepatect® per kg body weight
should be administered as soon as possible.

Prophylaxis in persons at high risk of hepatitis B infection (e.g. in dialysis units): Screen for HBsAg and for antibodies against HBsAg and inject 7 IU (0.14 ml) Hepatect® per kg body weight. The administration should be repeated at intervals of two months, provided the monthly antibodies against HBsAg testing does not reveal the necessity of an earlier administration. The immunisation program should be continued until the onset of a seroconversion, if the risk lasts on.

Prophylaxis of reinfection of a transplanted liver in HBsAg-positive patients: 10,000 IU (200 ml) of Hepatect® are infused perioperatively during the anhepatic phase followed by daily infusions of 2,000 IU (40 ml) for the first seven postoperative days. In the subsequent long-term therapy an anti-HBs serum level of ≥ 100 I.U./l has to be maintained over at least 6 months by monthly monitoring for anti-HBs serum titre.

Prophylaxis in neonates: 20 IU (0.4 ml) Hepatect® per kg body weight should be injected immediately after birth.

The given dosage instruction is based on the clinical experience.

Method of administration

Hepatect® 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.

4.3 Contraindications

Hypersensitivity to any of the 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 Special 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. 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 administration

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 by first injecting the product slowly (0.1 mg/kg/h)
- that patients are carefully monitored for any symptoms throughout the administration period. In particular, patients naive to human immunoglobulin, patients switched from an alternative product or when there has been a long interval since the previous administration should be monitored during the first administration and for the first hour after the first administration in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after the first administration.

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.
In all patients, IVIg administration requires:
- adequate hydration prior to the initiation of the administration of IVIg
- monitoring of urine output
- monitoring of serum creatinine levels
- avoidance of concomitant use of loop diuretics.
In case of renal impairment IVIg 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 IVIg products, 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. Hepatect does not contain sucrose. In addition, the product should be administered at the minimum infusion rate practicable.

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, the current medical standards for shock treatment should be observed.

When medicinal products prepared from human blood or plasma are administered, infectious diseases due to transmission of infective agents cannot be totally excluded. This also applies to pathogens of unknown nature. The risk of transmission of infective agents is however reduced by:
- selection of donors by a medical interview
- screening of individual donations and plasma pool for HBsAg and antibodies to HIV and HCV.
- testing of plasma pools for HCV genomic material.
- inactivation/removal procedures included in the production process that have been validated using model viruses. These procedures are considered effective for HIV, HCV, and HBV.

The viral inactivation/removal procedures may be of limited value against non-enveloped viruses such as HAV and/or Parvovirus B19.

In the interest of patients, it is recommended that, whenever possible, every time that Hepatect® is administered to them, the name and batch number of the product is registered.
4.5 Interactions with other Medicinal Products and other forms of Interactions

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 the administration of this product, 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 patients 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 test.

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 or 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
There are no indications that Hepatect® may impair the ability to drive and use machines.

4.8 Undesirable Effects

Adverse reactions such as chills, headache, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally. Rarely, human immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Cases of reversible aseptic meningitis, isolated cases of reversible haemolytic anaemia/haemolysis and rare cases of transient cutaneous reactions, have been observed with human immunoglobulin.

Increase in serum creatinine level and/or acute renal failure have been observed.

Thrombotic events have been reported in the elderly, in patients with signs of cerebral or cardiac ischemia and in overweight and severely hypovolaemic patients.

For information on risk of infection see 4.4.
4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Immune sera and immunoglobulins: Hepatitis B immunoglobulin for intravascular administration, ATC code: J06B B04

Hepatect® contains specific antibodies against HBs-antigen, mainly IgG.

It has a distribution of IgG subclasses closely proportional to that in native human plasma.

5.2 Pharmacokinetic Properties

Human Hepatitis B immunoglobulin 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.

Hepatect® has a half-life of 21.6 ± 1.8 days. This half-life may vary from patient to patient in particular in primary immunodeficiency.

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 embryofetal 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 tumourigenic or mutagenic effects of immunoglobulins, experimental studies, particularly in heterologous species, are not considered necessary.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium chloride, water for injections.

6.2 Incompatibilities

Hepatect® is miscible with isotonic saline solution. However, no other preparations may be added to the Hepatect® solution.

6.3 Shelf Life

The shelf-life is 2 years.
6.4 Special Precautions for Storage

Keep Container in the outer carton
Hepatect® should be stored at +2 °C to +8 °C.
Do not freeze.
Hepatect® should not be used after the expiry date indicated on the label.
Any unused solution must be discarded because of bacterial risk.

6.5 Nature and Contents of Containers

Hepatect® is a ready-for-use solution for infusion provided in glass containers:
Ampoule with 2 ml solution (100 IU)
Ampoule with 10 ml solution (500 IU)
Vial with 40 ml solution (2000 IU)

6.6 Instructions for Use/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 which are cloudy or which have a deposit.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

Biotest Pharma GmbH
Landsteinerstraße 5
D-63303 Dreieich
Germany

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT

December 2001