Package leaflet: Information for the user

Hepatect CP 50 IU/ml solution for infusion
Human hepatitis B immunoglobulin for intravenous administration

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 Hepatect CP is and what it is used for

Hepatect CP contains the active ingredient human hepatitis B immunoglobulin, which can protect you from hepatitis B. Hepatitis B is an inflammation of the liver caused by the hepatitis B virus. Hepatect CP is a solution for infusion (into a vein) and comes in vials containing 2 ml (100 International Units [IU]), 10 ml (500 IU), 40 ml (2000 IU) and 100 ml (5000 IU).

Hepatect CP is used to give immediate and long-term immunity (protection) to:
- prevent hepatitis B infection in patients who have not been vaccinated or fully vaccinated against hepatitis B and who are at risk of infection with hepatitis B.
- prevent infection of a transplanted liver in patients who test positive for hepatitis B.
- newborn babies whose mothers are infected with the hepatitis B virus.
- protect patients for whom hepatitis B vaccination has not provided adequate protection.

2. What you need to know before you use Hepatect CP

Do not use Hepatect CP:
- if you are allergic to human 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.

Warning and precautions
Talk to your doctor, pharmacist or nurse before using Hepatect CP if you
- have not received this medicine before or if there has been a long interval (e.g. several weeks) since you last received it (you will need to be closely monitored during your infusion and for an hour after your infusion has stopped).
- have been given Hepatect CP recently (you will need to be observed during the infusion and for at least 20 minutes after your infusion).

- have an untreated infection or underlying chronic inflammation.
- have had a reaction to other antibodies (in rare cases you may be at risk of allergic reactions).
- have or have had a kidney disorder.
- have received medicines that may harm your kidneys (if your kidney function worsens, you may need to stop treatment with Hepatect CP).

Your doctor will take special care if you are overweight, elderly, diabetic, or if you suffer from high blood pressure, low blood volume (hypovolaemia), if your blood is thicker than normal (high blood viscosity), if you have been bed-ridden or immobile for some time (immobilisation) or if you have problems with your blood vessels (vascular diseases) or other risks for thrombotic events (blood clots).

Please note - reactions
You will be carefully observed during the infusion period with Hepatect CP to make sure that you do not suffer a reaction (e.g. anaphylaxis). Your doctor will make sure that the rate at which Hepatect CP is infused is suitable for you.

If you notice any of the following signs of a reaction, i.e. headache, flushing, chills, muscle pain, wheezing, rapid heartbeat, lower back pain, nausea, low blood pressure during the infusion of Hepatect CP, tell your doctor immediately. The rate of infusion can be slowed or the infusion can be stopped altogether.

Information on transmission of infectious agents
Hepatect CP is made from human plasma (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. These include:

- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded,
- the testing of each donation and pools of plasma for signs of virus/infections,
- the inclusion of steps in the processing of the blood or plasma that can inactivate or remove viruses.

Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus.

The measures taken may be of limited value against non-enveloped viruses such as hepatitis A virus and parvovirus B19.

Immunoglobulins have not been associated with hepatitis A or parvovirus B19 infections possibly because the antibodies against these infections, which are contained in the product, are protective.

It is strongly recommended that every time you receive a dose of Hepatect CP the name and batch number of the medicine are recorded in order to maintain a record of the batches used.

Other medicines and Hepatect CP
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines.
Hepatect CP can reduce the effectiveness of some vaccines such as:

- measles
- rubella
- mumps
- chicken pox

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 together with Hepatect CP.

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 Hepatect CP may be used during pregnancy and breast-feeding.

Driving and using machines
Hepatect CP has minor influence on the ability to drive and use machines. If you experience adverse reactions during treatment you should wait for these to resolve before driving or operating machines.

3. How to use Hepatect CP

Hepatect CP is intended for intravenous administration (infusion into a vein). It is given to you by a doctor or nurse. The recommended dose will depend on your condition and your body weight. Your doctor will know the right amount to give you.

At the beginning of your infusion you will receive Hepatect CP at a slow rate. Your doctor may then gradually increase the infusion rate.

If you have any further questions on the use of this product, ask your doctor 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 Hepatect CP:
Not known: frequency cannot be estimated from the available data
- severe allergic reactions (anaphylactic shock)
- Hypersensitivity reactions
- Headache
- dizziness
- faster heart beat (tachycardia)
- low blood pressure (hypotension)
- nausea
- skin (cutaneous) reactions such as rash, itching
- fever
- malaise (feeling sick)

Human normal immunoglobulin preparations 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 vain (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).

If a side effect occurs, the infusion rate will be decreased or stopped.

Reporting of side effects
If you get any side effects talk to your doctor, pharmacist or nurse. This includes any side effects not listed in this leaflet. You can also report side effects directly via

HPRA Pharmacovigilance
Website: www.hpra.ie
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Hepatect CP

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 label.

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

The solution should be clear or slightly opalescent and colourless to pale yellow. Do not use solutions that are cloudy or have deposits.

The solution should be administered immediately after opening the receptacle. The product must be brought to room or body temperature before use.

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 protect the environment.

6. Contents of the pack and other information

What Hepatect CP contains:
- The active substance of Hepatect CP is human hepatitis B immunoglobulin for intravenous administration.
  Hepatect CP contains 50 mg/ml of human plasma protein of which at least 96 % is immunoglobulin G (IgG). The content of hepatitis B antibody is 50 IU/ml. The maximum immunoglobulin A (IgA) content is 2,000 micrograms/ml. The IgG subclass distribution is approx. 59% IgG1, 35% IgG2, 3% IgG3 and 3% IgG4.
- The other ingredients are glycine and water for injections.

What Hepatect CP looks like and the contents of the pack
Hepatect CP is a solution for infusion. The solution is clear to faintly opalescent (milky colours like an opal) and colourless to pale yellow.

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

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The following information is intended for healthcare professionals only:

Method of administration
Intravenous use
Hepatect CP should be infused intravenously at an initial rate of 0.1 ml/kg body weight/hour 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 1 ml/kg body weight/hour.

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.

Special Precautions
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 dosage).

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.

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.

Hypersensitivity
Hypersensitivity reactions are rare.
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.

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 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 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.

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.

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.

Dosage
Unless otherwise prescribed, the following recommendations apply:

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.