הודעה על החמרה (מידע בטיחות) בעלון לרופא

תאריך: 14/10/2012

שם תכשיר באנגלית:

Hepatect CP

מספר רישום 127 04 30518 00

שם בעל הרישום Kamada Ltd.

מפתח:
מודגש בצהוב - החמרות ושינויים מהותיים
מודגש באפור – מילים/משפטים ששינו מקום/הנוסח שלהם שונה
~~קו חוצה אדום~~ – מילים/משפטים שנמחקו, הנוסח שלהם שונה או שעברו מקום

פרטים על השינוי/ים המבוקש/ים

פרק בעלון	טקסט נוכחי	טקסט חדש
QUALITATIVE AND QUANTITATIVE COMPOSITION	**Composition** 1 ml of solution for infusion contains: *– Active substance(s):* Human plasma protein 50 mg of which immunoglobulin G ≥ 96 % HBs antibody content 50 IU ~~*– Excipients:*~~ ~~Glycine, water for injections~~ The IgG subclass distribution is approx. 59% (IgG1), 35% (IgG2), 3% (IgG3), 3% (IgG4) The IgA content is ≤ 2 mg/ml	**QUALITATIVE AND QUANTITATIVE COMPOSITION** ~~**Active substance**~~: Human hepatitis B immunoglobulin~~. for intravenous administration~~ ~~**Composition**~~ ~~1 ml of solution for infusion contains:~~ ~~*– Active substance(s):*~~ Human ~~plasma~~ protein 50 ~~mg~~ 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 One vial of 2 ml contains: 100 IU One vial of 10 ml contains: 500 IU One vial of 40 ml contains: 2000 IU Distribution of IgG subclasses:IgG1: 59% IgG2: 35 % IgG3: 3 % IgG4: 3 % ~~The~~ IgA ~~content~~ max ~~is ≤~~ 2 mg/ml. For excipients, see section 6.1.
Pharmaco-therapeutic group	~~**Pharmacotherapeutic group**~~ ~~Human hepatitis B immunoglobulin for intravenous administration~~ ~~**Name and address of the marketing authorisation holder and the manufacturer:**~~ ~~Biotest Pharma GmbH Landsteinerstraß~~ ~~63303 Dreieich Germany~~	

Solution for infusion The solution is clear or slightly opalescent.	~~Solution for infusion~~ ~~Vial with 2 ml (100 IU)~~ ~~Vial with 10 ml (500 IU)~~ ~~Vial with 40 ml (2000 IU)~~	**Pharmaceutical form**
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.	**Dosage and method of administration** Unless otherwise prescribed, the following recommendations apply: After exposure to material containing hepatitis B surface antigen: As soon as possible but not later than within 72 hours, injection of 8–10 IU (0.16 to 0.20 ml) of Hepatect® CP per kg body weight after investigation of the at-risk person for HBsAg and anti-HBs. Unless the anti HBs antibody determination at monthly intervals (which also acts as a control of the success of vaccination following the simultaneous vaccination) indicates that earlier administration is necessary, repetition of the dose at intervals of 2 months. Continuation of the immunisation schedule up to the onset of seroconversion in ongoing risk of infection. Passive administration is no longer necessary once active raising of anti HBs antibodies has commenced. For prophylaxis against re-infection of a transplanted liver in HBsAg-positive patients, 10'000 IU (200 ml) of Hepatect® CP is infused intravenously during surgery in the anhepatic phase and 2'000 IU (40 ml) is infused daily over a period of 7 days after surgery. During the subsequent long-term treatment, a serum level of 100 IU/litre should be maintained with monthly checks of the anti-HBs	**Dosage and method of administration**

~~**Dosage and method of administration**~~ ~~Unless otherwise prescribed, the following recommendations apply:~~ ~~After exposure to material containing hepatitis B surface antigen: As soon as possible but not later than within 72 hours, injection of 8–10 IU (0.16 to 0.20 ml) of Hepatect® CP per kg body weight after investigation of the at-risk person for HBsAg and anti-HBs.~~ ~~Unless the anti HBs antibody determination at monthly intervals (which also acts as a control of the success of vaccination following the simultaneous vaccination) indicates that earlier administration is necessary, repetition of the dose at intervals of 2 months.~~ ~~Continuation of the immunisation schedule up to the onset of seroconversion in ongoing risk of infection. Passive administration is no longer necessary once active raising of anti HBs antibodies has commenced.~~ ~~For prophylaxis against re-infection of a transplanted liver in HBsAg-positive patients, 10'000 IU (200 ml) of Hepatect® CP is infused intravenously during surgery in the anhepatic phase and 2'000 IU (40 ml) is infused daily over a period of 7 days after surgery.~~ ~~During the subsequent long-term treatment, a serum level of 100 IU/litre should be maintained with monthly checks of the anti-HBs serum level. The duration of treatment should be at least 6 months.~~ ~~Immunoprophylaxis for the prevention of hepatitis B in the newborn, of a hepatitis B virus carrier-mother: 20–50 IU per kg bodyweight (at least 100 IU) from birth-onward, until active immunity has developed. Vaccination against hepatitis B virus is highly recommended.~~ ~~The first vaccine dose can be injected on the same day as Hepatect® CP, however in different sites.~~ **Method of administration** ~~The product should be inspected visually for particulate matter and discoloration prior to administration. Do not use solutions which are cloudy or have deposits.~~ 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.	serum level. The duration of treatment should be at least 6 months. Immunoprophylaxis for the prevention of hepatitis B in the newborn, of a hepatitis B virus carrier-mother: 20–50 IU per kg bodyweight (at least 100 IU) from birth-onward, until active immunity has developed. Vaccination against hepatitis B virus is highly recommended. The first vaccine dose can be injected on the same day as Hepatect® CP, however in different sites. Mode of administration The product should be inspected visually for particulate matter and discoloration prior to administration. Do not use solutions which are cloudy or have deposits. The product should be brought to room or body temperature before use. 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 infusion 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.	

Hypersensitivity to any of the components. Hypersensitivity to ~~homologous~~ human immunoglobulins. ~~especially in very rare cases of IgA deficiency, when the patient has antibodies against immunoglobulin A (IgA).~~ ~~Treatment with Hepatect® CP in the prophylaxis against hepatitis B is not indicated if the person at risk has been fully vaccinated against hepatitis B and his immune response has been adequate.~~	Hypersensitivity to any of the compounds. Hypersensitivity to homologous immunoglobulins, especially in very rare cases of IgA deficiency, when the patient has antibodies against immunoglobulin A (IgA). Treatment with Hepatect® CP in the prophylaxis against hepatitis B is not indicated if the person at	**Contraindications**
Special warnings and ~~Appropriate~~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 ~~„Route of administration“~~ "4.2 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. ~~Patients should be observed for at least 20 minutes after administration.~~ 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~~ Specific allergic reactions are rare. ~~They can occur in the very seldom cases of IgA deficiency with anti IgA antibodies.~~ 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. ~~Potential complications can often be avoided by ensuring:~~ ~~– that patients are not sensitive to human immunoglobulin by first injecting the product slowly (0.1 ml/kg/hr)~~ ~~– that patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients who have never been treated with 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~~	**Appropriate precautions for use** Certain severe side effects may be related to the rate of infusion. The recommended infusion rate given under ‚Route 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. Patients should be observed for at least 20 minutes after administration. Certain adverse effects may occur more frequently – in case of high rate of infusion – in patients with hypo- or agammaglobulinaemia 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 by first injecting the product slowly (0.1 ml/kg/hr)	**Appropriate precautions for use**

~~order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration.~~ 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. 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. 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. ~~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, hypovolaemia, overweight, concomitant nephrotoxic medicinal products or age over 65 years.~~ ~~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 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. In addition, the product should be administered at the minimum concentration and infusion rate practicable. 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~~	– that patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients who have never been treated with 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. 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, hypovolaemia, overweight, concomitant nephrotoxic medicinal products or age over 65 years. 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 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. In addition, the product should be administered at the minimum concentration and infusion rate practicable. When medicinal products prepared from human blood or plasma are administered, infectious diseases due to	

~~however reduced by:~~ ~~– selection of donors by a medical interview and screening of individual donations and plasma pools for Hepatitis B surface antigen (HBsAg) and antibodies to human immunodeficiency virus (HIV) and hepatitis C virus (HCV)~~ ~~– testing of plasma pools for Hepatitis C virus genomic material~~ ~~– inactivation/removal procedures included in the production process that have been validated using model viruses. These procedures are considered effective for human immunodeficiency virus, hepatitis C and hepatitis B virus. The viral removal/inactivation procedures may be of limited value against non-enveloped viruses such as hepatitis A virus and/or parvovirus B 19.~~ ~~In the interest of patients, it is recommended that whenever possible, every time that Hepatect® CP is administered to them, the name and the batch number of the product is registered.~~	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 and screening of individual donations and plasma pools for Hepatitis B surface antigen (HBsAg) and antibodies to human immunodeficiency virus (HIV) and hepatitis C virus (HCV) – testing of plasma pools for Hepatitis C virus genomic material – inactivation/removal procedures included in the production process that have been validated using model viruses. These procedures are considered effective for human immunodeficiency virus, hepatitis C and hepatitis B virus. The viral removal/inactivation procedures may be of limited value against non-enveloped viruses such as hepatitis A virus and/or parvovirus B 19. In the interest of patients, it is recommended that whenever possible, every time that Hepatect® CP is administered to them, the name and the batch number of the product is registered.	
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 administrated 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. Interference with 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 antiglobulin test	**Interactions with other medicinal products** Live attenuated 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 this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. Interference with 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.	**Interactions with other medicinal products**

The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials. ~~It should therefore 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.~~	The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials. It should therefore 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.	**Pregnancy and lactation**
Effects on ability to drive and use machines No effects on ability to drive and use machines have been observed.	**Effects on the ability to drive or use machines** No effects on the ability to drive and use machines have been observed.	**Effects on the ability to drive or use machines**
Consequences of an overdose are not known	~~Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients and patients with renal~~	**Overdose**

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

~~Adverse effects such as chills, headache, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and mild 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. Particular cases and especially after intravenous administration of high immunoglobulin dose symptoms of aseptic meningitis such as severe headache, nausea, vomiting, fever, nuchal rigidity, photosensitivity and clouding of conciousness have been observed. Such symptoms may occur several hours or even days after infusion and have been reversible after the discontinuation of the immunoglobulin treatment. Special caution is advised in patients with anamnestic known history of migraine. 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. See „Precautions“ for information regarding anaphylaxis, aseptic meningitis syndrome (AMS), renal dysfunction and haemolysis. The following adverse reactions were reported spontaneously to be possible or probably related to Hepatect® CP administration with an incidence of less than 0.1% each: Skin and subcutaneous tissue: Cutaneous reactions, exanthema, itching, pruritus, rash, sweating, urticaria.~~

~~In case of adverse reaction, either the rate of infusion must be reduced or the infusion stopped. The treatment required depends on the nature and severity of side effect. In the case of renal impairment, discontinuation of administration of~~

Undesirable effects

	~~intravenous immunoglobulin should be considered. In the case of shock, the current medical standards for shock therapy should be observed.~~ ~~The patient is invited to communicate any undesirable effect not mentioned above to the doctor or pharmacist.~~	

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.**	*Composition* *– Excipients:* Glycine, water for injections	**Excipients**
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 denaturisation of the proteins.	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.	**Incompatibilities**

Shelf-life ~~and special precautions for storage~~ 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 container in the outer carton. The solution should be administered immediately after opening the ~~container~~ receptacle. ~~Any unused product or waste material should be disposed in accordance with local requirements.~~	**Shelf-life and 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 container in the outer carton. The solution should be administered immediately after opening the container. Any unused product or waste material should be disposed in accordance with local requirements.	**Shelf-life and special precautions for storage**
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	**Pharmaceutical form and presentations** Solution for infusion Vial with 2 ml (100 IU) Vial with 10 ml (500 IU) Vial with 40 ml (2000 IU)	
6.6 Instructions for use and handling and disposal 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.	**Mode of administration** The product should be inspected visually for particulate matter and discoloration prior to administration. Do not use solutions which are cloudy or have deposits. The product should be brought to room or body temperature before use.	
LICENSE HOLDER	**Registration holder**	**Registration holder**
LICENSE NUMBER 127-04-30518-00		

העלון, שבו מסומנים השינויים המבוקשים: על רקע צהוב , מודגש באפור – מילים/משפטים ששינו מקום/הנוסח שלהם שונה;