VI.2 Elements for a Public Summary

Overview of disease epidemiology

From Source: WHO Hepatitis B (2015) the following overview is provided:

The hepatitis B virus is an ubiquitous virus with a global distribution. Hepatitis B is one of the world's most common and serious infectious diseases. It is estimated that more than one third of the world's population has been infected with the hepatitis B virus. About 5% of the population are chronic carriers of HBV, and nearly 25% of all carriers develop serious liver diseases such as chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma. HBV infection causes more than one million deaths every year. The HBsAg carrier rate varies from 0.1 to 20% in different populations around the world. The incidence of the HBsAg carrier state in populations is related most importantly to the incidence and age of primary infection. In low-risk areas of the world, the highest incidence of the disease is seen in teenagers and young adults. Despite the low incidence of disease seen in the general population, certain groups who are sexually promiscuous or who have frequent contact with blood or blood products have a high rate of HBV infection. Nevertheless, the availability of an effective vaccine, optimized blood donor screening, and better sterilization procedures for blood derivatives have lowered substantially the infection risk. In endemic areas of Africa and Asia, the epidemiological patterns differ from those seen in north America and western Europe. In these regions, most infections occur in infants and children as a result of maternal-neonatal transmission or close childhood contact, although percutaneous exposure with contaminated needles or following unsafe injections is always a possibility in these countries. The chronic liver disease and HCC associated with HBV infections are among the most important human health problems in high-prevalence regions. There is no seasonal trend. Epidemics are unusual unless associated with contaminated blood or blood products, or the use of nonsterile injection equipment. Evaluations of infant vaccination programs need to compare vaccination coverage data with population-based serological analyses, since most HBV infection in young children are asymptomatic and are therefore not detected in surveillance studies of acute disease. A decline in the prevalence of chronic disease is on the other hand a major indicator of program success and infection reduction. A reduction in the prevalence of chronic HBV infection after implementation of infant immunization programmes has been demonstrated in high endemicity areas like Alaska, Taiwan, Indonesia, Polynesia, and the Gambia. The implementation of routine infant immunization will eventually achieve broad-population-based immunity to HBV infection and prevent HBV transmission among all age groups. However, it is only in the longer term that infant immunization in countries that have adopted the HBV vaccination programme will affect the incidence of hepatitis B and the severe consequences of chronic infections.

Hepatitis B is a significant health problem and vaccination saves both money and lives. Consideration of epidemiological and economic data shows that universal vaccination strategies are cost-effective even in countries with a low prevalence of hepatitis B. Hepatitis B prevention programmes incorporating universal immunization of newborns and/or adolescents have been highly successful in Spain and Italy, and their success offers an exemplary model for other countries. Even in low HBV endemicity areas of the world it is more cost-saving for the society to follow prevention programmes against HBV infection for the younger age groups than to face an increase in chronic liver disease among adults.

All pregnant women should be routinely tested for HBsAg before delivery, so that newborns of positive mothers can be appropriately immunized after birth. In developing countries, where funds and infrastructure to screen pregnant women may not be available, routine vaccination of infants at birth may be appropriate. Post exposure immunization should especially be considered for neonates born of HBsAg-positive mothers. Such infants are infected commonly, especially when mothers are HBeAg-positive, and the risk of becoming chronic carriers is extremely high (90%). When HBIG is given within the first hours after birth, the risk of infection can be reduced to 20%. Following sexual exposure to an infected person, it is currently recommended to use both HBIG and hepatitis B vaccine. For no reason should an HBIG be delayed until the results of HBV tests become available. There is no precedent for recommending HBIG prophylaxis if HBV exposure has occurred more than 7 days earlier. If a significant delay is anticipated in obtaining or dispensing the HBIG, conventional IG containing anti-HBs should be substituted for the HBIG until HBIG can be dispensed.

Summary of treatment benefits

Benefit (sufficient anti HBS trough levels and prevention of HBV re-infection) has been demonstrated in controlled clinical trials and the non-interventional PASS for Zutectra, Fovepta and Hepatect CP and proven during registration of the products. In study 987 Zutectra demonstrated sufficient anti HBS trough levels and prevention of HBV re-infection when given at least 1 week post OLT.

Pharmacokinetic evaluation of HBIg level after OLT at the end of i.v. administration (before start of s.c. administration) show plasma levels of HBIg below the expected range assuming i.v. pharmacokinetic parameter derived from i.v. PK data from patient 6 months after OLT. This could be explained by increased metabolism in patients close to experienced OLT. Dosing based upon pharmacokinetic parameters from metabolic stabilized patients could led to less protective level and increase the risk for HBIg re-infection. Subcutaneous administration of HBIg starting early after OLT based upon the trough level provide more secure plasma level to prevent Hepatitis B re-infection. In addition, patients are trained for s.c. home treatment under well controlled clinical conditions at a time point the patient stays at the hospital already. The early switch from i.v. to s.c. reduces the number of intravenous administration and the general risk associated with intravenous administration.

Unknowns relating to treatment benefits

None

Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Injection site reactions (1)	Injection site reactions are common as type of unspecific sensitivity. The reactions are non-serious, mild to moderate and patients recover within short time.	Potential complications can often be avoided by ensuring that patients are not sensitive to human immunoglobulin or had previous experiences of injection site reactions.

Risk	What is known	Preventability
Hypersensitivity (2)	Zutectra, Fovepta and Hepatect CP must not be used if a patient is allergic (hypersensitive) to human plasma protein (a specific protein) or any of the other ingredients of Hepatect CP or if a patient is hypersensitive to human immunoglobulin, especially in very rare cases in which immunoglobulin A (IgA) is missing and antibodies against IgA are present in the patient's blood; in extremely rare cases, true hypersensitivity reactions may occur. Special care with Hepatect CP should be taken when the infusion rate is high, in patients with complete or incomplete immunoglobulin deficiency 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, in people without IgA in their blood and who have formed antibodies against IgA, in patients who have already shown hypersensitivity reactions in the past.	Potential complications can often be avoided by ensuring that patients are not sensitive to human immunoglobulin that the product first injected slowly that patients are carefully monitored for any symptoms of undesired effects throughout the infusion period. In particular, patients naive to 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. Pre-medicating patients with NSAIDs or corticosteroids may prevent hypersensitivity reactions.
Anaphylactic reactions including anaphylactic shock (3)	Anaphylactic shock is a serious, potentially life-threatening side effect with rapid onset after (start of) infusion. Anaphylactic reactions have rarely occurred in patients receiving IVIg therapy. Zutectra, Fovepta and Hepatect CP must not be used if a patient is allergic (hypersensitive) to human plasma protein (a specific protein) or any of the other ingredients of Hepatect CP or if a patient is hypersensitive to human immunoglobulin, especially in very rare cases in which immunoglobulin A (IgA) is missing and antibodies against IgA are present in the patient's blood; in	Patients should be screened for IgA deficiency before starting IVIg treatment, as IVIgs in general are not indicated in these patients.

Risk	What is known	Preventability
	extremely rare cases, true hypersensitivity reactions may occur. In patients who have already shown hypersensitivity reactions in the past, even in patients who have not shown hypersensitivity reactions previously, a drop in blood pressure with an anaphylactic reaction (immediate type hypersensitivity reaction) may occur as a result of administering immunoglobulin.	
Aseptic meningitis *(4)	Only for Hepatect CP (intravenously administered) Aseptic meningitis clinically presents with symptoms such as headache, nausea, vomiting, fever and nuchal rigidity. This type of meningitis is of non-infectious nature and usually of moderate severity. Symptoms caused by inflammation of the meninges typically begin within 6 to 48 hours after the infusion was administered. Recovery time is approximately 5 days. Aseptic meningitis has been reported in patients receiving IVIg therapy. A history of migraine headaches and high IVIg doses (2 g/kg/cycle) are known risk factors for the development of the disease.	Reducing the infusion rate and pre-medicating with acetaminophen or antihistamines may lessen the risk in migraineurs. Pre-treatment with steroids has not been proven to be effective.
Haemolytic anaemia *(5)	Only for Hepatect CP (intravenously administered) Reversible haemolytic reactions (breakdown of red blood cells) have been observed under IVIg treatment. Haemolytic reactions may be particularly associated with high-dose IVIg therapy, especially in patients with blood group A, B and AB and in patients who are rhD-positive. IVIg is prepared by fractionation of	It is difficult to predict the occurrence of haemolytic reactions associated with IVIg infusion. Haemolytic reactions are related to the content of antibodies against red blood cell surface antigens (isoagglutinins) in the IVIg. The content of such isoagglutinins should be low: e.g. below 1:64 in protein solutions

Risk	What is known	Preventability
	the pooled plasma from thousands of donors and therefore contains IgG antibodies directed against red blood cell antigens. Haemolytic reactions are caused by such antibodies against red blood cell surface antigens finally resulting in destruction of the erythrocytes. Haemolytic anaemia and haemolytic reactions are usually mild to moderate ADRs. Symptoms of haemolytic reactions develop within days following infusion. Haemolytic anaemia requiring transfusion is a rare and serious ADR.	<30 g/l.
Acute renal failure *(6)	Only for Hepatect CP (intravenously administered) Special care should be taken in patients with impaired renal function or patients with risk factors, such as diabetes, reduced volume of circulating blood, obesity, co-treatment with medications that damage the kidneys, or age over 65 years. Cases of acute renal failure have been reported in this patient group. 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. Too much Hepatect CP can cause fluid overload and hyperviscosity (over-thickening) of the blood in case of impaired renal function.	In case of renal impairment, the administration of immunoglobulin should be discontinued. In patients at risk for acute renal failure immunoglobulins should be administered at the lowest infusion rate possible and at the lowest dosage possible. In patients at risk, the use of intravenous immunoglobulin products that do not contain sucrose may be considered. Hepatect CP does not contain sucrose. 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 (an indicator of renal function) avoidance of concomitant use of loop diuretics
Thromboembolic events *(7)	Only for Hepatect CP (intravenously administered)	Caution should be exercised in overweight patients, as well as patients with pre-existing risk

Risk	What is known	Preventability
	Special care should be taken in patients at risk, as high-dose administration of immunoglobulins is assumed to cause a relative increase in blood viscosity (blood thickening). There is a risk of thromboembolic events (e.g. caused by blood clots), such as heart attack, stroke, lung embolism and deep vein thrombosis.	factors for such events, such as advanced age, high blood pressure, diabetes, known vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, prolonged physical immobilisation, patients with severe hypovolaemia (reduced volume of circulating blood) and patients with disorders that increase viscosity of the blood. In patients at risk for thromboembolic side effects immunoglobulins should be administered at the lowest infusion rate possible and at the lowest dosage possible.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
High infusion rate *(1)	Only for Hepatect CP (intravenously administered) Certain severe undesired side effects may by associated with the rate of infusion. As increasing infusion rates are associated with a tendency for increased adverse events, the infusion rate recommended must be observed. Patients must be monitored throughout the entire duration of infusion and observed for symptoms of undesired effects. Potential complications can often be avoided by ensuring that the product first injected slowly. If well tolerated during the first 10 minutes, the rate of administration may gradually be increased for the remainder of the infusion.
Interference with serological testing (2)	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 allo-antibodies (e.g. Coombs test), reticulocyte count and haptoglobin.
Transmission of infective agents (3)	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, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include 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

Risk	What is known (Including reason why it is considered a potential risk)
	or emerging viruses or other types of infections. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19 virus. 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.

* Only for Hepatect CP (intravenously administered)

Important potential interaction

Risk	What is known (Including reason why it is considered a potential interaction)
Interaction with 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 administration of Hepatect CP, 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.

Missing information*

Risk	What is known
Patients co-infected with HIV and/or HCV)	Patients co-infected with HIV and/or hepatitis C virus(HCV) are not included in study 987.

* Only for Zutectra

Summary of risk minimisation measures by safety concern

For the following safety concerns only routine risk minimisation measures, including special warnings in the SmPC, CCDS or PIL, are applied:

- Important identified risk: Injection site reactions include effects like pain, urticaria at injection site, haematoma and erythema
- Important identified risk: Hypersensitivity with its potentially related symptoms headache, chills, dizziness, pyrexia, vomiting and nausea, allergic reactions, transient cutaneous reactions, arthralgia, etc
- Important identified risk: Anaphylactic reactions including anaphylactic shock
- Important identified risk: Aseptic meningitis (only Hepatect CP)
- Important identified risk: Haemolytic anaemia (only Hepatect CP)
- Important identified risk: Acute renal failure (only Hepatect CP)

- Important identified risk: Thromboembolic events (only Hepatect CP)
- Important potential risk: High infusion rate (only Hepatect CP)
- Important potential risk: Interference with serological testing
- Important potential risk: Transmission of infective agents
- Important potential interaction: Interaction with live attenuated virus vaccines
- Missing information: Patients co-infected with HIV and/or hepatitis C virus (HCV) are not included in study 987 (only Zutectra)

This medicinal product has no additional risk minimisation measures.

Planned post authorisation development plan

After DLP of this RMP, in March 2015, a retrospective data collection started to increase the knowledge base of post transplant treatment with the human hepatitis B immunoglobulin Zutectra or Hepatect CP in liver transplanted patients. The first patient is included in this retrospective data collection.

Studies which are a condition of the marketing authorisation

Not applicable

Summary of changes to the Risk Management Plan over time

This is the 1st RMP on Hepatitis B immunoglobulin (HBIG) combined for Zutectra, Fovepta and Hepatect CP in the new EU format and appropriate changes have been performed.