PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

HepaGam B®

Hepatitis B Immunoglobulin (Human) Injection

Liquid >312 IU/mL

Standard: World Health Organization (WHO) International Reference Preparation

Passive Immunizing Agent

Immune sera and immunoglobulins

ATC code: J06BB04

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

HepaGam B (Hepatitis B Immunoglobulin (Human) Injection) is indicated for:

Post-exposure Prophylaxis

HepaGam B is indicated for the treatment of acute exposure to blood containing hepatitis B surface antigen (HBsAg), perinatal exposure of infants born to HBsAg-positive mothers, sexual exposure to HBsAg-positive persons and household exposure to persons with acute HBV infection in the following settings:

Acute Exposure to Blood Containing HBsAg

Following either parenteral exposure (needlestick, bite, sharps), direct mucous membrane contact (accidental splash), or oral ingestion (pipetting accident) involving HBsAg-positive materials such as blood, plasma, or serum).

Perinatal Exposure of Infants Born to HBsAg-positive Mothers

Infants born to mothers positive for HBsAg with or without Hepatitis B e antigen (HBeAg).

Sexual Exposure to HBsAg-positive Persons Sexual partners of HBsAg-positive persons.

Household Exposure to Persons with Acute HBV Infection

Infants less than 12 months old whose mother or primary caregiver is positive for HBsAg, or other household contacts with identifiable blood exposure to the index patient.

HepaGam B is administered intramuscularly for post-exposure prophylaxis.

Prevention of Hepatitis B Recurrence Following Liver Transplantation

HepaGam B is indicated for the prevention of hepatitis B recurrence following liver transplantation in adult patients with hepatitis B who have no or low levels of HBV replication. HepaGam B should be administered intravenously for this indication. For more information, see **PART II: 14. SCIENTIFIC INFORMATION, CLINICAL TRIALS**.

Pediatrics

Pediatrics (<18 years of age): HepaGam B was found to be safe and effective in a pediatric population (infants born to mothers who were HBsAg-positive). The protection rate against development of hepatitis B in infants, born to mothers who were HBsAg-positive, was 98%. No safety concerns were identified.

Geriatrics

Geriatrics (>65 years of age): Clinical studies of HepaGam B did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

2 CONTRAINDICATIONS

For post-exposure prophylaxis indications, HepaGam B is administered intramuscularly. In patients who have severe thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections, HepaGam B should be given only if the expected benefits outweigh the potential risks.

HepaGam B is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

Patients who are deficient in IgA: While HepaGam B contains less than 40 µg/mL IgA, individuals who are deficient in IgA may have the potential to develop IgA antibodies and have an anaphylactoid reaction if exposed (or treated) again.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

HepaGam B is prepared from pools of human plasma which may contain the causative agents of hepatitis and other viral diseases. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacturing. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products.

True hypersensitivity reactions are rare. These reactions can occur in very rare cases of IgA deficiency or hypersensitivity to human globulin. In case of allergic or anaphylactic reaction, the infusion should be stopped immediately. In case of shock, the current medical standards for treatment of shock should be observed.

The physician should discuss the risks and benefits of this product with the patient before prescribing or administering to the patient (see **WARNINGS AND PRECAUTIONS, General**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Post-exposure Prophylaxis

For post-exposure prophylaxis indications, HepaGam B is administered intramuscularly as directed in

Section 4.2 RECOMMENDED DOSE AND DOSE ADJUSTMENT.

It is important to use a separate vial, sterile syringe, and needle for each individual patient to prevent transmission of infectious agents from one person to another.

HepaGam B may be administered at the same time (but at different site), or up to one month preceding hepatitis B vaccination without impairing the active immune response to hepatitis B vaccine. Efficacy of live attenuated virus vaccines may be impaired by immunoglobulin administration; revaccination may be necessary.

Prevention of Hepatitis B Recurrence Following Liver Transplantation

For the prevention of hepatitis B recurrence following liver transplantation in adult patients with hepatitis B, HepaGam B (Hepatitis B Immunoglobulin (Human) Injection), should be administered intravenously to attain serum anti-HBs levels greater than 500 mIU/mL as described in Section 4.2 RECOMMENDED DOSE AND DOSE ADJUSTMENT.

These dosing recommendations are based on a systematic review of the clinical trial literature and meta-analysis (see **PART II: SCIENTIFIC INFORMATION, 14. CLINICAL TRIALS**).

This report found that Hepatitis B Immunoglobulin (HBIG) prophylaxis was most effective when administered in high doses to achieve anti-HBs levels of greater than 500 mIU/mL over longer time periods (greater than six months). The recommended dosing schedule described below is designed to achieve persistent anti-HBs levels of greater than 500 mIU/mL.

4.2 Recommended Dose and Dosage Adjustment

Post-exposure Prophylaxis

Acute Exposure to Blood Containing HBsAg

Table 1 below summarizes prophylaxis for percutaneous (needlestick, bite, sharps), ocular, or mucous membrane exposure to blood according to the source of exposure and vaccination status of the exposed person. For greatest effectiveness, passive prophylaxis with HepaGam B should be given as soon as possible after exposure, as its value after seven days following exposure is unclear. An injection of 0.06 mL/kg of body weight should be administered intramuscularly as soon as possible after exposure, preferably within 24 hours. Consult the hepatitis B vaccine package insert for dosage information regarding the vaccine.

For persons who refuse hepatitis B vaccine or who are known non-responders to vaccine, a second dose of HepaGam B should be given one month after the first dose.

Table 1 Recommendations for Hepatitis B Prophylaxis following Percutaneous or Permucosal Exposure

Source	Exposed Person	
	Unvaccinated	**Vaccinated**
HBsAg-positive	. Hepatitis B Immunoglobulin (Human) x 1 immediately[a] . Initiate HB vaccine series[b]	1. Test exposed person for anti-HBs 2. If inadequate antibody[c], Hepatitis B Immunoglobulin (Human) x 1 immediately plus either HB vaccine booster dose, or a second dose of Hepatitis B Immunoglobulin (Human)[a], 1 month later.
Known Source – High Risk for HBsAg-positive	1. Initiate HB vaccine series 2. Test source of HBsAg. If positive, Hepatitis B Immunoglobulin (Human) x 1	1. Test source for HBsAg only if exposed is vaccine nonresponder; if source is HBsAg- positive, give Hepatitis B Immunoglobulin (Human) x 1 immediately plus either HB vaccine booster dose, or a second dose of Hepatitis B Immunoglobulin (Human)*, 1 month later[d]
Known Source – Low Risk for HBsAg-positive	Initiate HB vaccine series	Nothing required
Unknown Source	Initiate HB vaccine series	Nothing required

[a] Hepatitis B Immunoglobulin (Human) dose of 0.06 mL/kg (intramuscular)
[b] See manufacturer's recommendation for appropriate dose.
[c] Less than 10 mIU/mL anti-HBs by radioimmunoassay, negative by enzyme immunoassay.
[d] Two doses of Hepatitis B Immunoglobulin (Human) is preferred if no response after at least four doses of vaccine.

Prophylaxis of Infants Born to Mothers who are Positive for HBsAg with or without HBeAg

Table 2 contains the recommended schedule of hepatitis B prophylaxis for infants born to mothers that are either known to be positive for HBsAg or have not been screened. Infants born to mothers known to be HBsAg-positive should receive 0.5 mL HepaGam B after physiologic stabilization of the infant and preferably within 12 hours of birth. The hepatitis B vaccine series should be initiated simultaneously, if not contraindicated, with the first dose of the vaccine given concurrently with the HepaGam B, but at a different site. Subsequent doses of the vaccine should be administered in accordance with the recommendations of the manufacturer. Women admitted for delivery, who were not screened for HBsAg during the prenatal period, should be tested.

While test results are pending, the newborn infant should receive hepatitis B vaccine within 12 hours of birth (see manufacturer's recommendations for dose). If the mother is later found to be HBsAg-positive, the infant should receive 0.5 mL HepaGam B as soon as possible and within seven days of birth; however, the efficacy of HepaGam B administered after 48 hours of age is not known. Testing for HBsAg and anti-HBs is recommended at 12 to 15 months of age. If HBsAg is not detectable and anti-HBs is present, the child has been protected.

Table 2 Recommended Schedule of Hepatitis B Immunoprophylaxis to Prevent Perinatal Transmission of Hepatitis B Virus Infection

Age of Infant		
Administer	**Infant Born to Mother Known to be HBsAg-positive**	**Infant Born to Mother Not Screened for HBsAg**
First Vaccination[a]	Birth (within 12 hours)	Birth (within 12 hours)
Hepatitis B Immunoglobulin (Human) [b]	Birth (within 12 hours)	If mother is found to be HBsAg-positive, administer dose to infant as soon as possible, not later than 1 week after birth
Second Vaccination[a]	1 month	1–2 months
Third Vaccination[a]	6 months[c]	6 months[c]

[a] See manufacturer's recommendation for appropriate dose
[b] 0.5 mL administered intramuscularly at a site different from that used for the vaccine
[c] Advisory Committee on Immunization Practices (ACIP) recommendation

Sexual Exposure to HBsAg-positive Persons

All susceptible persons whose sexual partners have acute hepatitis B infection should receive a single dose of HepaGam B (0.06 mL/kg) and should begin the hepatitis B vaccine series, if not contraindicated, within 14 days of the last sexual contact or if sexual contact with the infected person will continue. Administering the vaccine with HepaGam B may improve the efficacy of post-exposure treatment. The vaccine has the added advantage of conferring long-lasting protection.

Household Exposure to Persons with Acute HBV Infection

Prophylaxis of an infant less than 12 months of age with 0.5 mL HepaGam B and hepatitis B vaccine is indicated if the mother or primary caregiver has acute HBV infection. Prophylaxis of other household contacts of persons with acute HBV infection is not indicated unless they had an identifiable blood exposure to the index patient, such as by sharing toothbrushes or razors. Such exposures should be treated like sexual exposures. If the index patient becomes an HBV carrier, all household contacts should receive hepatitis B vaccine.

Prevention of Hepatitis B Recurrence Following Liver Transplantation

Each dose of HepaGam B should be administered as an intravenous dose of 35 mL (10,920 IU anti-HBs). The first dose should be administered concurrently with the grafting of the transplanted liver (the anhepatic phase) with subsequent dosing as recommended in Table 3.

Anti-HBs levels should be measured after the first week of treatment to allow for initial adjustment of dosage.

Table 3 HepaGam B Dosing Regimen

Anhepatic Phase*	Week 1 Post-operative[a]	Months 1-3 Post-operative	Month 4 Onwards
First dose	Daily from Day 1–7	Every two weeks from Day 14	Monthly

[a] Anti-HBs levels should be measured after the first week of treatment, to allow for initial adjustment of dosage.

HepaGam B dose adjustments may be required in patients who fail to reach anti-HBs levels of 500 mIU/mL within the first week post-liver transplantation. Patients who have surgical bleeding or abdominal fluid drainage (>500 mL) or patients who undergo plasmapheresis are particularly susceptible to extensive loss of circulated anti-HBs. The following dose adjustment is recommended:

- the dosing regimen should be increased to 5460 IU (17.5 mL intravenous) every six hours until the target anti-HBs is reached.

Regular monitoring of serum HBsAg, HBV-DNA and HBeAg as well as anti-HBs antibody levels should be performed to decide on the continuation of HepaGam B treatment and/or treatment adjustment.

In patients who develop treatment-related adverse events, especially during early the post- operative period when immune complexes may develop, such as from the large amounts of hepatitis B immunoglobulin immunoprecipitating with HBsAg, the HepaGam B infusion rate should be decreased. Symptoms related to immune complex formation should be treated with antihistamines or analgesic agents.

4.4 Administration

Post-exposure Prophylaxis (Intramuscular Administration)

HepaGam B should be prepared for intramuscular administration under aseptic conditions. **DO NOT SHAKE VIAL; AVOID FOAMING**. Parenteral drugs should be visually assessed for particulate matter and discolouration prior to administration. HepaGam B should be administered intramuscularly within 12

hours of birth in infants, or within 48 hours of exposure for adults.

Injection should be given into the deltoid muscle or into the anteriolateral thigh in term infants. If administered in combination with hepatitis B vaccine, HepaGam B must be injected into a separate site to prevent vaccine neutralization.

Prevention of Hepatitis B Recurrence Following Liver Transplantation (IV Administration)

HepaGam B should be prepared for IV administration under aseptic conditions. **DO NOT SHAKE VIAL; AVOID FOAMING.** Parenteral drugs should be visually assessed for particulate matter and discolouration prior to administration.

- HepaGam B should be administered as provided through a separate intravenous line using an administration set containing an in-line filter and a constant infusion pump.
- Use normal saline as the diluent if dilution of HepaGam B is preferred prior to intravenous administration.
- Do not use dextrose (5%) in water (D5W) as the diluent.
- Rate of administration should be set at 2 mL per minute.
- The rate of infusion should be decreased to 1 mL per minute or slower if the patient develops discomfort or there is concern about the speed of infusion.

4.5 Missed Dose

Post-exposure Prophylaxis (Intramuscular Administration) & Prevention of Hepatitis B Recurrence Following Liver Transplantation (IV Administration)

If a scheduled dose is missed, HepaGam B should be administered as soon as possible after the missed dose(s). Scheduling of subsequent doses should be determined by the treating physician and the HepaGam B dosing regimen (see **4.2 Recommended Dose and Dosage Adjustment**).

5 OVERDOSAGE

Consequences of an overdose with HepaGam B are not known.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

HepaGam B (Hepatitis B Immunoglobulin (Human) Injection), is a sterile solution of purified gamma globulin (5% or 50 mg/mL) fraction (human plasma protein (≥96% Human IgG)) containing antibodies to hepatitis B surface antigen (anti-HBs).

Table 4 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous, intramuscular	Solution/ Liquid >312 IU/mL/ contains no preservative and is stabilized with 10% maltose and 0.03% polysorbate 80.	Maltose, Polysorbate 80; may contain trace amounts of tri-n-butyl phosphate and Triton X-100®

HepaGam B, Hepatitis B Immunoglobulin (Human), is supplied as:

A carton containing a 1 mL single dose (>312 IU/mL) in a 3 mL glass vial with a plastic flip off seal and a package insert

A carton containing a 5 mL single dose (>312 IU/mL) in a 6 mL glass vial with a plastic flip off seal and a package insert

To help ensure the traceability of biologic products, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

This product is prepared from large pools of human plasma. Thus, there is a possibility it may contain causative agents of viral or other undetermined diseases.

General

Although HepaGam B is formulated for intravenous or intramuscular administration, HepaGam B should only be administered intravenously for the prevention of hepatitis B recurrence following liver transplantation. Intravenous administration is required due to the large volume required per dose (35 mL) and because many liver transplant patients will have thrombocytopenia or coagulation disorders following transplantation, which may contraindicate intramuscular administration.

For intravenous administration, following liver transplant, certain adverse drug reactions may be

related to the rate of infusion. The recommended infusion rate given under DOSAGE AND ADMINISTRATION, Administration must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period and immediately following an infusion.

If patients develop treatment-related adverse events due to immune complex formation between HBIG and circulating HBsAg, dose adjustments may be required. Symptoms related to immune complexes should be treated with antihistamines or analgesic agents and the HepaGam B infusion rate should be decreased (see Administration).

HepaGam B is made from human plasma. Products made from human plasma may contain infectious agents such as viruses and, theoretically, the Creutzfeldt-Jakob disease agent. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. The manufacturing process includes both a Planova® 20 nm virus filter that effectively removes lipid-enveloped and non- enveloped viruses based on size, and a solvent/detergent treatment step (using tri-n-butyl phosphate and Triton X-100®) that effectively inactivates lipid-enveloped viruses by irreversibly destroying the lipid coat. These two processes are designed to increase product safety by reducing the risk of viral transmission of several viruses including human immunodeficiency virus (HIV), hepatitis B and hepatitis C. However, despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections. All infections thought to have been possibly transmitted by this product should be reported by the physician or other health care provider to KI BioPharma LLC at 1-866-916-0077.

Cardiovascular

For the post-exposure prophylaxis indications, HepaGam B is administered intramuscularly. In patients who have severe thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections, HepaGam B should be given only if the expected benefits outweigh the potential risks.

Rare thrombotic events have been reported in association with immunoglobulin intravenous (Human) (IGIV). Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, and/or known or suspected hyperviscosity.

Although the risk of thrombotic adverse events following HepaGam B is extremely low, care should be taken in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests). For patients who are at risk of developing thrombotic events, administer HepaGam B at the minimum rate of infusion practicable.

Hematologic

IGIV products can contain blood group antibodies which may act as haemolysins and induce in vivo coating of red blood cells (RBC) with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs' test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IGIV therapy

due to enhanced RBC sequestration. IGIV recipients should be monitored for clinical signs and symptoms of haemolysis (see **WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests**).

Monitoring and Laboratory Tests

Liver transplant patients should be monitored regularly for serum anti-HBs antibody levels.

Assessment and Monitoring for Thrombotic Risk Factors

Because of the potentially increased risk of thrombosis, baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.

Blood Glucose Testing

The maltose contained in HepaGam B can interfere with some types of blood glucose monitoring systems, i.e., those based on the glucose dehydrogenase pyrroloquinequinone (GDH-PQQ) method. This can result in falsely elevated glucose readings and, consequently, in the inappropriate administration of insulin resulting in life-threatening hypoglycemia. Cases of true hypoglycemia may go untreated if the hypoglycemic state is masked by falsely elevated results.

Neurologic

Neurologic Aseptic Meningitis Syndrome (AMS) has been reported to occur in association with IGIV treatment. The syndrome usually begins within several hours to 2 days following IGIV treatment. Cerebrospinal fluid (CSF) 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) IGIV 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 IGIV treatment has resulted in remission of AMS within several days without sequelae.

Renal

Intravenous immunoglobulin (human) products have been reported to produce renal dysfunction in patients that are predisposed to acute renal failure or those who have renal insufficiency. In such patients, it has been recommended that intravenous immunoglobulin (human) products be administered at a minimum practical concentration and infusion rate. While renal dysfunction has been reported with various intravenous immunoglobulin (human) products, the vast majority of these reports have involved products that utilize sucrose as a stabilizer.

HepaGam B does not contain sucrose as a stabilizer. Regardless, it is recommended that renal function be assessed prior to administration of HepaGam B and at appropriate intervals following administration, especially for patients at risk of developing acute renal failure. If renal dysfunction occurs, clinical judgment should be used to determine whether the infusion rate of HepaGam B should be decreased or the product should be discontinued.

Respiratory

In patients receiving IGIV, there have been some reports of acute non-cardiogenic pulmonary oedema [Transfusion-related acute lung injury (TRALI)]. TRALI is characterised by severe hypoxia, dyspnoea, tachypnoea, cyanosis, fever and hypotension. Symptoms of TRALI typically develop during or within 6 hours after a transfusion, often within 1–2 hours. Therefore, IGIV recipients must be monitored for and IGIV infusion must be immediately stopped in case of pulmonary adverse reactions. TRALI is a potentially life-threatening condition requiring immediate intensive-care-unit management.

Sensitivity/Resistance

Although only single mild allergic reaction had been reported following HepaGam B administration during clinical studies (see **Adverse Reaction Overview**), epinephrine and diphenhydramine should be available for the treatment of any allergic reactions.

HepaGam B contains trace amounts of IgA (<40 µg/mL). Patients with known antibodies to IgA may have a greater risk of severe hypersensitivity and anaphylactic reactions if exposed to blood products again. HepaGam B is contraindicated in IgA deficient patients with antibodies against IgA and a history of hypersensitivity reactions (see **CONTRAINDICATIONS**).

Special Populations

7.1.1 Pregnant Women

Animal reproduction studies have not been conducted with HepaGam B. It is also not known whether HepaGam B can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. However, immunoglobulins have been widely used during pregnancy for many years without any apparent negative reproductive effects. The risk/benefit of HepaGam B administration should be assessed for each individual case.

Extent of exposure in pregnancy during clinical trials: No experience.

7.1.2 Breast-feeding

It is not known whether HepaGam B is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HepaGam B is administered to a nursing mother.

7.1.3 Pediatrics

Pediatrics (<18 years of age): HepaGam B was found to be safe and effective for prevention of vertical transmission of the hepatitis B virus. Infants born to mothers who were HBsAg-positive had a protection rate against developing the hepatitis B virus of 98%. No safety concerns were identified during the trial.

7.1.4 Geriatrics

Geriatrics (>65 years of age): Clinical studies of HepaGam B did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common expected adverse drug reactions for intravenous immunoglobulins like HepaGam B are chills, fever, headaches, vomiting, allergic reactions, nausea, arthralgia and moderate low back pain.

Although anaphylactic reactions to HepaGam B are very rare they have been reported following the administration of other forms of intravenous immunoglobulin (human) products (see **WARNINGS AND PRECAUTIONS, General**).

Post-exposure Prophylaxis

In clinical trial HB-004, 253 infants born to HBsAg-positive mothers received a single dose of HepaGam B and hepatitis B vaccine intramuscularly within 12 hours of birth. A total of 531 adverse events were reported for 159 of the infants (63%). The most common adverse events were diarrhea (57 events) and pyrexia (52 events). The majority of adverse events were mild in intensity. Only one adverse event, indurations of the right and left thighs, was reported as possibly treatment-related. A total of 43 serious adverse event terms were captured on Case Report Forms (CRFs) for 38 infants during the study. None of the serious adverse events were related to HepaGam B administration.

In addition, 42 adult males and females were administered a single dose of HepaGam B along with hepatitis B vaccine within 48 hours of possible exposure to hepatitis B virus (needle stick, bite, sharps, etc). A total of 69 adverse events were reported for 25 of the patients (60%). The most frequent adverse event was headache (12 events). The majority of events were reported as mild. Nineteen adverse events were reported as possibly related to HepaGam B administration. The most common related adverse events were nausea, pyrexia, arthralgia, myalgia and headache.

Prevention of Hepatitis B Recurrence Following Liver Transplantation

In clinical trial HB-005 with 27 liver transplant patients who received intravenous infusions of HepaGam B , one adverse drug reaction of hypotension was reported. In studies with healthy volunteers, only one adverse drug reaction of nausea had been reported in the 70 adult subjects who received an intramuscular administration of HepaGam B.

In an open-label extension study (HB-006), four HBsAg-negative post-transplant patients who participated in HB-005 received 47 infusions of HepaGam B in total. Seventeen adverse events were reported. None considered as related to study drug.

In clinical trial HB-009, with 11 liver transplant patients who received total of 194 infusions of HepaGam B, 212 adverse events were reported. Only five adverse events were deemed related to study drug, all affecting a single participant. These five AEs were hypertension, dyspnea, pyrexia, infusion related

reaction, and increased respiratory rate. All were deemed mild in intensity and consistent with a faster than usual infusion rate. A total of 25 serious adverse events were reported by six participants. None of the serious adverse events were deemed related to study drug.

Healthy Volunteer Studies

Seventy healthy male and female volunteers received a single dose of HepaGam B, Hepatitis B Immunoglobulin (Human), intramuscularly in clinical trials. Seventeen subjects reported 30 adverse events following administration of HepaGam B. The most frequently reported adverse events included four subjects (6%) who experienced headache, seven subjects (10%) who had cold symptoms or flu and two subjects (3%) who experienced lightheadedness/fainted. The majority of events were reported as mild. One adverse event, an episode of nausea, was considered to be drug related. There were no serious adverse events reported. A similar number of subjects in the comparator groups reported adverse events.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Hepatitis B-Related Liver Transplantation

A single adverse drug reaction of hypotension occurred following a total of 578 (<1%) HepaGam B infusions administered to 27 subjects in a Phase III clinical trial examining HepaGam B for the prevention of hepatitis B recurrence following liver transplantation. This study utilized the recommended dosing regimen outlined in Table 3 (see **DOSAGE AND ADMINISTRATION**). The reaction was recorded during the first week post-transplant and resolved on the same day and did not recur with subsequent HepaGam B infusions.

In clinical trial HB-009, with 11 liver transplant patients who received total of 194 infusions of HepaGam B, 212 adverse events were reported. Five adverse events were deemed related to study drug, all affecting a single patient. These five adverse events were hypertension, dyspnea, pyrexia, infusion related reaction, and increased respiratory rate.

Healthy Volunteer Studies

Seventy healthy male and female volunteers received a single dose of Hepatitis B Immunoglobulin (Human), intramuscularly, in clinical trials. One adverse event, an episode of nausea, was considered to be drug related.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Please refer to 8.1 Adverse Reaction Overview, Post-exposure Prophylaxis

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

There have been no abnormal hematology or clinical chemistry values reported to be related to HepaGam B administration.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of HepaGam B. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The system organ classification of reported adverse reactions is provided below:

Table 6: Adverse Reactions identified during post-approval use of HepaGam B.

Organ system/Disorder	**Adverse Reaction**
Cardiac Disorders:	Sinus tachycardia
Gastrointestinal Disorders:	Abdominal pain
	Nausea
General Disorders and Administration Site Conditions:	Asthenia
	Chest pain
	Chills
	Feeling cold
	Feeling hot
	Influenza like illness
	Malaise
	Pain
	Pyrexia
Immune System Disorders:	Anaphylactoid reaction

	Anaphylactic shock
	Hypersensitivity
Investigations:	Lipase increased
	Transaminases increased
Musculoskeletal and Connective Tissue Disorders:	Back pain
	Groin pain
Nervous System Disorders:	Dizziness
	Headache
Respiratory, Thoracic and Mediastinal Disorders:	Dyspnoea
Skin and Subcutaneous Tissue Disorders:	Cold sweat
	Rash erythematous
Vascular Disorders:	Flushing

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
Live attenuated virus vaccines: immunoglobulin administration may impair the efficacy of live attenuated virus vaccines for a period of three months or more (see **DRUG INTERACTIONS, Overview**).

9.2 Drug Interactions Overview

Immunoglobulin administration may impair the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. Vaccination with live virus vaccines should be deferred until approximately three months after administration of HepaGam B (Hepatitis B Immunoglobulin (Human) Injection). Persons who received HepaGam B less than 14 days after live virus vaccination should be revaccinated three months after the administration of the immunoglobulin, unless serologic test results indicate that antibodies were produced.

There are no available data on concomitant use of HepaGam B and other medications.

Antibodies present in HepaGam B may interfere with some serological tests (see **Drug- Laboratory Interactions**).

9.3 Drug-behaviours interactions

Interactions with behaviour have not been established.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 7 - Established or Potential Drug-Drug Interactions

Hepatitis B Immunoglobulin (Human)	Source of Evidence	Effect	Clinical comment
Live attenuated virus vaccines (e.g. measles, rubella, mumps, varicella)	T	Immunoglobulin may impair efficacy	If Hepatitis B Immunoglobulin is given less than 14 days after live virus vaccination, revaccination should be considered.

T = Theoretical

The use of live virus vaccination before or after HepaGam B administration should follow the recommendations by the Canadian National Advisory Committee on Immunization.

Interactions with other drugs have not been established

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

After administration of Hepatitis B Immunoglobulin (Human), a transitory increase of passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing (e.g. 'Coombs' test).

HepaGam B contains maltose, which can interfere with certain types of blood glucose testing and monitoring systems, i.e., those based on the GDH-PQQ (see **WARNINGS AND PRECAUTIONS, Blood Glucose Testing**). Even though HepaGam B is administered intravenously, due to the potential for falsely elevated glucose readings only testing systems that are glucose-specific should be used to test or monitor blood glucose levels in patients receiving maltose-containing parenteral products, including

HepaGam B.

The product information of the blood glucose testing system, including that of the test strips, should be carefully reviewed to determine if the system is appropriate for use with maltose- containing parenteral products. If any uncertainty exists, contact the manufacturer of the testing system to determine if the system is appropriate for use with maltose-containing parenteral products.

10 CLINICAL PHARMACOLOGY

Mechanism of Action

Post-exposure Prophylaxis

Clinical studies conducted prior to 1983 with hepatitis B immunoglobulins similar to HepaGam B demonstrated the advantage of simultaneous administration of hepatitis B vaccine and Hepatitis B Immunoglobulin (Human) by the intramuscular route. The Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) advises that the combination prophylaxis be provided following certain instances of hepatitis B exposure. Recommendations on post-exposure prophylaxis are based on available efficacy data, primarily from studies in neonates. Cases of hepatitis B are rarely seen following exposure to HBV in persons with pre-existing anti-HBs antibodies.

Prevention of Hepatitis B Recurrence following Liver Transplantation

Hepatitis B virus re-infection is the consequence of an immediate re-infection of the graft due to circulating HBV particles, a re-infection of the graft from HBV particles coming from extra hepatic sites, or both.

The mechanism whereby Hepatitis B Immunoglobulin (HBIG) protects the transplanted liver against HBV re-infection is not well understood. One hypothesis is that HBIG protects naïve hepatocytes against HBV release from extra hepatic sites through blockage of a putative HBV receptor. Alternatively, HBIG may neutralize circulating virions through immune precipitation and immune complex formation or trigger an antibody-dependent cell-mediated cytotoxicity response resulting in target cell lysis. In addition, HBIG has been reported to bind to hepatocytes and interact with HBsAg within cells.

Regardless of the mechanism, there is evidence of a dose-dependent response to HBIG treatment.

Pharmacodynamics

Hepatitis B immunoglobulin products provide passive immunization to the hepatitis B virus and significantly decrease hepatitis B recurrence and increase graft and patient survival following liver transplantation in hepatitis B surface antigen (HBsAg) positive patients.

The clinical effectiveness of HBIG prophylaxis in the prevention of hepatitis B recurrence following liver transplantation is dependent on the dose, length of administration and the viral replication status of the patient at the time of transplant.

HBIG is most effective when administered in high doses to achieve anti-HBs levels greater than 500

mIU/mL over long time periods (greater than six months). A meta-analysis of the literature data showed that patients treated with long-term high-dose HBIG had a hepatitis B recurrence rate of 15.2%, compared to a 40.4% recurrence rate in subjects treated with long- term, low-dose HBIG. Short-term immunoprophylaxis with HBIG may delay hepatitis B recurrence, but the overall rate of re-infection is similar to untreated patients. Therefore, it is important that treatment be continued long-term.

The absence of viral replication (absence of HBeAg and/or HBV DNA in serum) at the time of liver transplant is associated with an increase in the effectiveness of HBIG (see **PART II: SCIENTIFIC INFORMATION, Table 16**). As a result, HepaGam B is recommended in patients who have no or low levels of viral replication at the time of liver transplantation.

Animal Studies

Nonclinical pharmacology studies have not been performed with Hepatitis B Immunoglobulin (Human) as there is broad experience in humans with intravenous and intramuscular administration of immunoglobulin products. Since the product is of human origin, immunogenicity is expected when administered to animals.

Pharmacokinetics

Currently there is no pharmacokinetic data available for HepaGam B intravenous administration in liver transplant patients. The ability of the described dosing regimen (see Table 3 in **DOSAGE AND ADMINISTRATION**) to maintain anti-HBs levels was examined in an analysis of 24 hepatitis B-related liver transplant patients from a Phase III clinical trial. Anti-HBs levels taken before and after each dose showed that the target trough of 500 mIU/mL was achieved after the first few HepaGam B doses and maintained in the first year post-transplant in 22 of the 24 patients. As described above under Dosing Considerations, these levels have been associated with efficacy.

The pharmacokinetic profile of HepaGam B in healthy volunteers after intramuscular injection of 0.06 mL/kg is summarized in Table 8.

Table 8: Pharmacokinetic profile of HepaGam B in healthy volunteers after intramuscular injection of 0.06 mL/kg

	Cmax	**T ½ (h)**	**AUC0-4**	**Volume of Distribution**
Single dose mean	211.6 mIU/mL	24.5 days	8253.9 mIU*day/mL	7.0 ±1.5 L

Absorption

A pharmacokinetic trial of HepaGam B (Hepatitis B Immunoglobulin (Human) Injection), given intramuscularly to 30 healthy male and female volunteers demonstrated pharmacokinetic parameters similar to those reported in the literature. The volume of distribution was 7.0 ±1.5 L. Maximum concentration of HepaGam B was 215.6 mIU/mL, which was reached 5.4 ±2.4 days following

administration. The maximum concentration of anti-HBs achieved by HepaGam B was consistent with that of a commercially available HBIG when compared in the same comparative pharmacokinetics trial. There is an immediate time to the onset of HepaGam B action, and the time to steady state between intravascular and extravascular spaces is approximately five days.

Distribution:

The bioavailability of Hepatitis B Immunoglobulin (Human) for intravenous use is complete and immediate. IgG is quickly distributed between plasma and extravascular fluid. Immunoglobulin products have been demonstrated to poorly penetrate across an intact blood brain barrier.

Metabolism:

Immunoglobulins and immune complexes are broken down in the reticuloendothelial system.

Elimination

The elimination half-life of HepaGam B is 24.5 days following intramuscular administration. Based on studies with other immunoglobulin products, a slightly decreased half-life is expected following intravenous administration.

Duration of effect

Immunoglobulin administration may impair the efficacy of live attenuated virus vaccines for a period of three months or more (see 9.1 Serious Drug Interactions).

11 STORAGE, STABILITY AND DISPOSAL

Store under refrigeration (2 to 8ºC). Do not freeze. Do not use after expiration date indicated on the label.

12 SPECIAL HANDLING INSTRUCTIONS

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.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

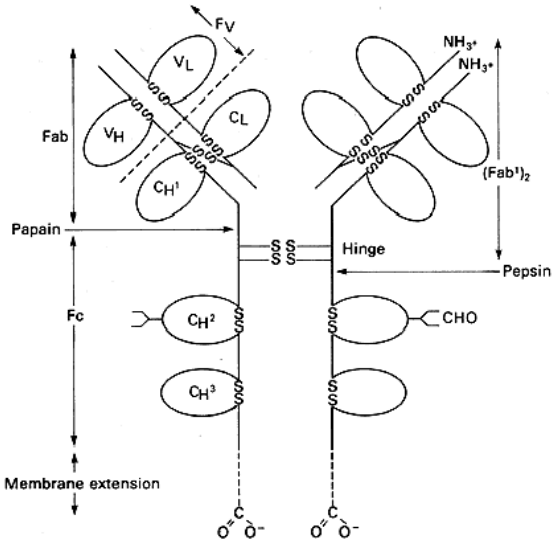
Drug Substance

Proper name: Hepatitis B Immunoglobulin (Human)

Chemical name: Hepatitis B Immunoglobulin (Human)

Molecular formula and molecular mass: Glycoprotein of approximately 160,000 Da

Structural formula: Gamma Globulin (IgG)



Structure of an IgG molecules. Each chain is made up of a series of homology units of approximately 110 amino acids. The sites of proteolytic cleavage usually lie between the homology units. Membrane forms possess a hydrophobic C-terminal extension, but are otherwise identical in sequence to the secretory forms.

Physicochemical properties: IgG is a monomeric protein with a sedimentation coefficient of 7S and a molecular weight ranging from 146,000 to 170,000 Da. Carbohydrate content of IgG is approximately 2 to 3%.

Product Characteristics:

HepaGam B (Hepatitis B Immunoglobulin (Human) Injection) is a sterile solution of purified gamma globulin (5% or 50 mg/mL) fraction containing polyclonal antibodies to hepatitis B surface antigen (anti-HBs). It is prepared from plasma donated by individuals with high titres of anti-HBs. The plasma is purified by an anion-exchange column chromatography method. The manufacturing process includes two viral inactivation/removal steps including a solvent detergent treatment step (using tri-n-butyl phosphate and Triton X-100®) and a Planova® 20 nm virus filtration (see Viral Inactivation).

The product potency is expressed in international units (IU) by comparison to the World Health Organization (WHO) international Hepatitis B Immunoglobulin reference preparation. Each vial contains greater than 312 IU/mL.

Viral Inactivation

Anti-HBs plasma is collected from donors at US FDA-licensed collection facilities. Plasma donors are carefully screened for eligibility by physical exam and through questionnaires and interviews to assess

risk of exposure to certain viruses. Each plasma donation is tested for HIV-1/2 and HCV antibodies and HBsAg. PCR tests for enveloped (HCV, HIV-1 and HBV) and non-enveloped (HAV and Parvovirus B-19) viruses are also performed on plasma mini- pools representing each of the individual donations used in HepaGam B manufacturing. As an additional precaution, the manufacturing plasma pools are also tested for the presence of hepatitis B (HBsAg).

To further increase product safety by reducing the risk of virus transmission, two virus removal and inactivation steps are included in the HepaGam B manufacturing process. The solvent detergent treatment step (using tri-n-butyl phosphate and Triton X-100®) inactivates lipid enveloped viruses such as hepatitis C and HIV by irreversibly destroying the lipid coat. The Planova® 20 nm virus filter removes both lipid-enveloped and non-enveloped viruses based on virus size. These two processes are designed to increase product safety by effectively clearing several viruses including human immunodeficiency virus (HIV), herpes viruses, hepatitis B (HBV) and hepatitis C (HCV) if they were to be present and reducing the risk of viral transmission. The inactivation and reduction of known enveloped and non-enveloped model viruses were validated in laboratory studies as summarized in Table 9.

Table 9 Virus Reduction Values Obtained Through Validation Studies

	Enveloped			**Non-Enveloped**			
Genome	**RNA**		**DNA**	**RNA**		**DNA**	
Virus	HIV-1	BVDV	PRV	HAV	EMC	MMV	PPV
Family	Retro	Flavi	Herpes	Picorna		Parvo	
Size (nm)	80–100	50–70	120–200	25–30	30	20–25	18–24
Anion-Exchange Chromatography (Partitioning)	Not Evaluated			2.3	NE	3.4	NE
20N Filtration (Size Exclusion)	≥4.7	≥3.5	≥5.6[a]	NE	4.4	NE	3.5[b]
Solvent/Detergent	>4.7	≥7.1	≥5.4	Not Evaluated			
Total Reduction (log10)	**≥9.4**	**≥10.6**	**≥11.0**	**2.3**	**4.4**	**3.4**	**3.5**

Abbreviations:
HIV-1: human immunodeficiency virus-1; relevant virus for human immunodeficiency virus-1 and model for HIV-2
BVDV: bovine viral diarrhea virus; model virus for hepatitis C virus (HCV) and West Nile virus (WNV) PRV: pseudorabies virus; model for large enveloped DNA viruses, including herpes
HAV: human hepatitis A virus; relevant virus for HAV and model for small non-enveloped viruses in general EMC: encephalomyocarditis virus; model for HAV and for small non-enveloped viruses in general
MMV: murine minute virus; model for human B19 parvovirus and for small non-enveloped viruses in general PPV: porcine parvovirus; model for human B19 parvovirus and for small non-enveloped viruses in general NE.: not evaluated
a The PRV was retained by the 0.1µm pre-filter during the virus validation. Since manufacturing employs a 0.1µm pre-filter before the 20N filter, the claim of ≥ 5.6 reduction is considered applicable.
b One of the five PPV runs for the 20N filter yielded a 1.25 log clearance over the 0.1 µm pre-filter. Since

production employs a 0.1 µm pre-filter before the 20N filter, the 1.25 logs were added to the 2.2 log clearance obtained over the 20N filter, and the value of 3.5 was used for determination of the mean reduction factor.

14 CLINICAL TRIALS

17.0 Trial Design and Study Demographics

Clinical Trials in Post-exposure Populations

In a clinical study, the efficacy and safety of HepaGam B were evaluated in post-exposure prophylaxis in two different populations: infants born to HBsAg-positive mothers (vertical arm) and adults possibly exposed to HBV (horizontal arm). A summary of patient demographic information for this study is presented in Table 10.

Table 10 Summary of Patient Demographics for Post-exposure Prophylaxis Study

Study Number	Design	Dosage, Route of Administration, Duration	Study Subjects	Gender	Age
HB-004	phase 3, multi-centre, open-label, non-randomized, historically controlled study	0.5 mL intramuscular administered once, within 12 hours of birth	253 infants born to HbsAg-positive mothers; 178 in efficacy analysis population	M: 137 (54.2%); F: 116 (45.8%)	less than 12 hours
		0.06 mL/kg intramuscular once, within 48 hours of exposure to hepatitis B virus	42 adults dosed, 23 completed the study	M: 17 (40.5%) F: 25 (59.5%)	37.8 (10.3) yr; range 20.5–57.4

Infants and adults in study HB-004 also received the hepatitis B vaccine on Day 0, concurrent with HepaGam B, and on Days 30 and 180, as per the manufacturer's recommendation. All infants were followed up for safety for up to one year and adults for six months following HepaGam B administration.

Clinical Trials for the Prevention of Hepatitis B Recurrence Following Liver Transplantation (HB-005)

A clinical trial examined the effectiveness of HepaGam B in the prevention of hepatitis B recurrence following liver transplantation. This-was a multi-center, open-labeled, superiority study involving HbsAg- positive/HbeAg-negative liver transplant patients. The study included two arms; an active treatment group of patients enrolled to receive the described dosing regimen of HepaGam B starting during transplant and continuing over the course of a year, and a retrospective untreated control group of historical patients with data gathered by chart review.

Table 11 Summary of Patient Demographics for Clinical Trials in Hepatitis B-related Liver Transplant Patients

Study No.	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n=number)	Mean Age (Range)	Gender
HB-005	Multi-center, open-labeled, historically controlled, superiority study in HbsAg-positive/HbeAg-negative liver transplant patients	HepaGam B was administered by intravenous infusion of >10 000 IU/dose. The dosing regimen consisted of 24 doses over a 1-year period, beginning during transplant, followed by daily for 7 days, biweekly for 3 months and then monthly.	N=41 (n=27 for HepaGam B and n=14 for retrospective untreated control group)	48.8 years (31–68 years)	34 Males, 7 Females
HB-006	multi-centre, historically controlled, open-label extension study (of HB-005)	HepaGam B was administered as an intravenous infusion of > 10 000 IU. The dosing regimen consisted of one dosed ate baseline and at monthly intervals thereafter for approximately one year.	N=13	46 (33 – 63)	10 Males 3 females

There were 27 liver transplant patients who received HepaGam B and 14 retrospective untreated control patients in clinical trial HB-005. The patients in both groups were HbsAg-positive/HbeAg-negative liver transplant patients who met similar entry criteria, had similar medical history and had similar status at transplant based on MELD and/or ChildPugh-Turcotte scores.

Clinical Trials in preventing HBV recurrence in Liver Transplant Patients (HB-009)

A Phase III clinical trial assessed the pharmacokinetics (PK), safety, and efficacy of HepaGam B in combination with antiviral therapy in hepatitis B-related liver transplant study participants. The primary objective was to assess the efficacy of HepaGam B in combination with antivirals in preventing HBV recurrence in the study population compared to a reference rate for antiviral therapy alone.

Table 12 Summary of Patient Demographics for Clinical Trials in Hepatitis B-related Liver Transplant Patients

Study Number	Design	Dosage, Route of Administration, Duration	Study Subjects	Gender	Age

HB-009	multi-center, open-label, non-randomized study	~10,000 IU daily for 7 days, followed by every 2 weeks from day 14 to 84, and monthly from day 120 to 360	n=11	M: 10 F: 1	52.5 (± 13.1) years

A Systematic Review of the Clinical Trial Literature and Meta-Analysis of Hepatitis B Immuno globulin (HBIG) prophylaxis in the prevention of hepatitis B recurrence following liver transplantation

A systematic review of the clinical trial literature and meta-analysis, supporting the efficacy of Hepatitis B Immuno globulin (HBIG) prophylaxis in the prevention of hepatitis B recurrence following liver transplantation was completed. The meta-analysis examined clinical literature reports from studies of HBIG monotherapy and/or no prophylaxis following liver transplantation in subjects with hepatitis B. A total of 37 studies in 1922 patients were analyzed.

14.2 Study Results

Clinical Trials in Post-exposure Populations

Four infants tested positive for HbsAg during the study, representing a 0.98 (174/178) protection rate (Table 13).

Table 13 Protection Rate against Hepatitis B Infection in Infants Born to HbsAg-positive Mothers, who were Administered HepaGam B within 12 Hours of Birth and Hepatitis B Vaccine

N	Protection Rate	95% Confidence Interval
178	0.978	(0.944, 0.994)

Exact confidence interval limits for the binomial proportion using the F distribution method

HepaGam B was not inferior to the historical reference protection rate of 0.97 (lower 95% confidence bound for the calculated protection rate was greater than 0.92). Of note, each of the four infants who became HbsAg positive during the study subsequently became HbsAg-negative. Two of them seroconverted and became anti- HBs positive during the study. The other two infants remained anti-HBs negative (anti-HBs <10 mIU/mL) after one year follow-up. Anti-HBc (IgM), indicating a new HBV infection, was detected in one of these four infants.

A total of 42 adults received HepaGam B and hepatitis B vaccine. Among them, 23 completed the study. None of the 23 adults became HbsAg positive during the study. The efficacy results from the remaining 19 adults are unknown.

HepaGam B is effective in combination with the hepatitis B vaccine in post-exposure prophylaxis against hepatitis B infection.

Clinical Trials for the Prevention of Hepatitis B Recurrence Following Liver Transplantation (HB-005)

For the efficacy endpoint of the proportion of patients with HBV recurrence (HbsAg positive and/or HbeAg positive after 4 weeks post-orthotopic Liver Transplantation [OLT]), a significant treatment effect was observed. As summarized in Table 14, HBV recurrence was seen in 2/24 or 8.3% of HepaGam B patients compared to 12/14 or 86% of retrospective untreated control patients. Two of the HepaGam B patients who died within 28 days post-transplant were excluded from all efficacy analyses, but included for safety analyses. The deaths were not HBV, nor study drug related.

Table 14 – Results of Study HB-005 for the Prevention of Hepatitis B Recurrence Following Liver Transplantation

Primary Endpoint	HepaGam B	Retrospective Untreated Control	P-value (Fischer's Exact Test)
HBV Recurrence Proportion, % (95% confidence interval)	8.3 (1.0-27.0)	85.7 (57.2–98.2)	<0.001

The conclusion that HepaGam B monotherapy post-OLT is effective at preventing HBV recurrence post-OLT is further supported by the secondary endpoints of time to recurrence, survival, anti-HBs levels, biochemical markers of liver inflammation, and liver biopsy. Time to recurrence for the HepaGam B treatment group was 365 days for the HbsAg positive patient and 257 days for the HbeAg positive patient. In comparison, the retrospective untreated control patients had a median time to recurrence of 88 days with a 95% confidence interval of 47 to 125 days. Survival calculations showed that 96% (23/24) of patients in the active treatment group survived for at least 1 year post-OLT compared to 43% (6/14) retrospective control patients. The endpoints for HBV recurrence were supported by an observed drop in anti-HBs levels, elevated liver function tests, and abnormal liver biopsy result at the time of recurrence.

In the open-label extension (HB-006), a significant treatment effect was observed for the primary efficacy endpoint, the proportion of patients with HBV recurrence (HbsAg positive between 4 weeks and 2 years post-OLT). As summarized in the table below, HBV recurrence was seen in 1/11 or 9.1% of active patients compared to 12/14 or 86% of retrospective untreated control patients.

Table 15 – Results of Study HB-006 Extension Study for the Prevention of Hepatitis B Recurrence Following Liver Transplantation

Primary Endpoint	HepaGam B	Retrospective Untreated Control	P-value (Fischer's Exact Test)

HBV Recurrence Proportion, % (95% confidence interval)	9.1 (0.2, 41.3)	85.7 (57.2, 98.2)	<0.0001

Clinical Trials in preventing HBV recurrence in Liver Transplant Patients (HB-009)
The primary endpoint of the study was recurrence of HBV, as shown by 2 successive positive HbsAg tests. Eight of 11 participants were HbsAg positive at baseline and day 0 (anhepatic phase). By day 4, all participants were negative except for one, and all were negative by day 6 post-OLT. The last participant to clear was the one with the highest viral load at screening and baseline. All participants remained negative for HbsAg at all time points thereafter and consequently, none of the participants had a recurrence of HBV. There was no HBV recurrence observed over the 1-year observation period.

A Systematic Review of the Clinical Trial Literature and Meta-Analysis

A large number of literature reports have shown that treatment with Hepatitis B Immunoglobulin, or HBIG, has been effective in decreasing hepatitis B recurrence and increasing graft and patient survival following liver transplantation in HbsAg positive patients. In particular, a landmark European study examining 372 consecutive HbsAg-positive patients from 17 centres established the efficacy of long-term immunoprophylaxis with high- dose HBIG in the prevention of hepatitis B recurrence after liver transplantation and changed the clinical practice for this indication. A systematic review and meta-analysis of this literature data was conducted to assess the efficacy of HBIG in the prevention of HBV recurrence following liver transplantation.

The meta-analysis examined clinical literature reports from studies of HBIG monotherapy and/or no prophylaxis following liver transplantation in subjects with hepatitis B. A total of 37 studies in 1922 patients were analyzed. The main finding was that HBIG prophylaxis is effective in the prevention of HBV recurrence following liver transplantation as compared to no prophylaxis. The meta-analysis results indicated that HBIG prophylaxis significantly decreases hepatitis B recurrence following liver transplantation, with hepatitis B recurrence rates of 37.5% in patients receiving HBIG compared to 80.3% for patients receiving no prophylaxis. The meta-analysis also showed a correlation between the reduced hepatitis B recurrence rate in patients treated with HBIG and a decreased incidence of hepatitis B virus (HBV)-related deaths following liver transplantation: from 14% in patients receiving no prophylaxis to 5% in patients treated with HBIG.

HBIG prophylaxis was most effective when administered in high doses to achieve anti-HBs concentrations greater than 500 mIU/mL over long time periods (greater than six months) to patients that had no or low levels of HBV replication immediately prior to liver transplantation. These results are demonstrated in Table 16.

Table 16 Results from a Meta-analysis of Literature Data Showing Efficacy of Long-term High-dose HBIG

Treatment Group	HBV Recurrence Rate % (n)
No prophylaxis	80.3% (n=362)
HBIG prophylaxis (all durations and doses)	37.5 % (n=1496)
Short-term HBIG	72.7 % (n=166)
Long-term HBIG	23.0% (n=1028)
Long-term Low- dose HBIG	40.4% (n=289)
Long-term High- dose HBIG	15.2 % (n=254)
Long-term High-dose Replicators	49.6% (n=27)
Long-term High-dose Non-replicators	5.4% (n=175)

Short-term <6 months treatment
Long-term ≥6 months treatment
Low-dose = anti-HBs targets 100–200 IU/L High-dose = anti-HBs targets ≥500 IU/L
Replicators = HBV-DNA positive or HbeAg positive at the time of transplantation Non-replicators = HBV-DNA negative and HbeAg negative at the time of transplant

14.3 Comparative Bioavailability Studies

The comparative pharmacokinetics of HepaGam B and a commercially available HBIG product following intramuscular administration was assessed in healthy male and female subjects. The study was a single-centre, randomized, single blind, comparative, parallel study. The pharmacokinetic data was assessed by measurement of plasma levels of anti-HBs over a period of 84 days (~3 half-lives of immunoglobulin products).

This study was conducted in 60 healthy volunteer subjects. The HepaGam B treatment group (n=30) consisted of 16 male and 14 female subjects with a mean age of 35 ±10 years (range 22 to 55 years) and a mean weight of 71.8 ±13.3 kg (range 46.5 to 93.0 kg). The comparator treatment group (n=30) consisted of 17 male and 13 female subjects with a mean age of 35 ±8 years (range 22 to 54 years) and a mean weight of 69.0 ±10.1 kg (range 51.0 to
91.0 kg).

Table 17 Summary of Patient Demographics for Pharmacokinetics Study

Study No.	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n=number)	Mean Age (Range)	Gender

HB-00142	Single centre, randomized, single-blind, parallel arm study in healthy volunteers.	Single dose of 0.06 mL/kg by intramuscular injection	n=60 (30 in each treatment arm)	35 years (22–55 years)	33 Males, 27 Females

Table 18 Measured Pharmacokinetic Parameters from Subjects Administered Either HepaGam B or the Reference HBIG Product at a Dose of 0.06 mL/kg Intramuscular

HepaGam B and a commercially available HBIG product From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Hepagam B**	**Reference HBIG**	**% Ratio of Geometric Means**	**Confidence Interval**
AUC_T (mIU*day/mL)	7356.7 7521.3 (20.6)	5267.7 5418.4 (23.2)	139.7	126.3–154.5
AUC_I (units)	8253.9 8477.4 (22.9)	6051.5 6208.6 (22.8)	136.4	123.2–151.0
C_{MAX} (mIU/mL)	211.6 215.6 (19.1)	153.5 157.2 (22.5)	137.9	125.9–151.1
T_{MAX}[a] (days)	5.4 (43.9)	6.6 (38.9)	Not applicable	Not applicable
$T_{½}$ [a] (days)	24.5 (18.9)	24.4 (21.1)	Not applicable	Not applicable

[a] Expressed as the arithmetic mean (CV%) only.

When the ratios of the geometric means and the 90% confidence intervals were corrected for measured potency, the AUC and Cmax ratios met the standard bioequivalence criteria.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Toxicology studies have not been performed with Hepatitis B Immunoglobulin (Human) because the product has been formulated with ingredients that are known to be non-toxic at the levels at which they are present in the final product.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

HEPAGAM B®

Hepatitis B Immunoglobulin (Human) Injection

Read this carefully before you start taking **HepaGam B®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **HepaGam B®**.

Serious Warnings and Precautions

- HepaGam B is made from human plasma which may contain the causative agents of viral diseases. The risk of getting a disease from this product has been reduced by screening plasma donors, testing for the presence of certain viruses and by inactivating and removing certain viruses during manufacturing. However, there is still a possibility that plasma products could transmit disease.
- Allergic or anaphylactic reactions are rare. These reactions can occur in patients with a history of allergy to blood products or in patients lacking the IgA blood protein.
- Before using HepaGam B, discuss the risk and benefits with your doctor.

What is HepaGam B® used for?

- Prevention of hepatitis B infection following exposure to the hepatitis B virus (post-exposure prophylaxis)
- Prevention of hepatitis B recurrence following liver transplantation in patients with hepatitis B.

How does HepaGam B® work?

HepaGam B binds to the hepatitis B virus and helps to remove the virus from circulation.

HepaGam B also prevents development of a hepatitis B infection after exposure to the hepatitis B virus. HepaGam B should be administered within 12 hours of birth or 48 hours of exposure to the hepatitis B virus.

HepaGam B protects the newly transplanted liver from re- infection with the hepatitis B virus. For HepaGam B to be effective in preventing hepatitis B recurrence, treatment should be started during liver transplantation and continued regularly after transplant. Laboratory tests will determine if HepaGam B is working by measuring levels of HepaGam B in serum (the liquid portion of blood) and by

looking for signs of hepatitis B infection.

What are the ingredients in HepaGam B®?

Medicinal ingredients: Hepatitis B Immunoglobulin (Human)

Non-medicinal ingredients: Human plasma protein, Maltose, Polysorbate 80. HepaGam B may also contain trace amounts of tri-n-butyl phosphate and Triton X-100®.

HepaGam B® comes in the following dosage forms:

HepaGam B is a sterile liquid supplied in 1 mL and 5 mL vials containing >312 IU/mL.

Do not use HepaGam B® if:

- you have a history of allergic reactions to blood products, or to any of the ingredients in HepaGam B
- you have a bleeding disorder and are unable to receive intramuscular injections

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take HepaGam B®. Talk about any health conditions or problems you may have, including if you:

- have experienced allergic reactions to blood products in the past
- have a known IgA deficiency
- are pregnant or nursing
- use any device to measure blood or urine glucose
- have a bleeding disorder that prevents you from receiving intramuscular injections.

While being treated with HepaGam B, regular blood tests will be conducted to check for adequate drug levels.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with HepaGam B®:

- Drugs that may interact with HepaGam B have not been established.
- Immunoglobulins like HepaGam B may impair the effectiveness of certain live virus vaccines such as measles, rubella (German measles), mumps and varicella (chicken pox). Talk to your doctor if you have been recently vaccinated
- Certain devices used to measure blood or urine glucose

How to take HepaGam B®:

- HepaGam B® will be given to you by a healthcare professional in a healthcare setting.

Usual dose:

For Post-exposure prophylaxis:

Each neonatal dose of HepaGam B® is 0.5 mL, administered once intramuscularly. An adult dose of HepaGam B® is 0.06 mL/kg, administered once intramuscularly.

Following liver transplant:

Each dose of 35 mL (10,920 international units) HepaGam B® will be given by an intravenous injection taking approximately 20 minutes.

The typical dose schedule is as follows:

- first dose during liver transplantation operation
- daily doses for the first week post-operative
- once every two weeks for the first three months post- operative
- once a month thereafter

Overdose:

The consequences of an overdose with HepaGam B® are not known.

If you think you, or a person you are caring for, have taken too much HepaGam B®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If a scheduled dose is missed, it should be given as soon as possible after the missed dose. Your doctor will adjust your dosing schedule if required

What are possible side effects from using HepaGam B®?

These are not all the possible side effects you may have when taking HepaGam B®. If you experience any side effects not listed here, tell your healthcare professional.

The most common side effects are chills, fever, headaches, vomiting, allergic reactions, nausea, arthralgia (pain in joints) and moderate low back pain. These side effects are usually mild, but if they require treatment ask your health care professional.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Allergic Reaction		✓	✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store HepaGam B under refrigeration. Do not freeze. Do not use after expiration date.

Keep out of reach and sight of children.

If you want more information about HepaGam B®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; or by calling 1-866-916-0077.

This leaflet was prepared by KI BioPharma LLC at 1-866-916-0077

Last Revised