1. NAME OF THE MEDICINAL PRODUCT

HepaGam B™

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains greater than 312 IU/mL of antibodies to Hepatitis B Immunoglobulin.

For the full list of excipients, see section 12, PHARMACEUTICAL PARTICULARS.

3. PHARMACEUTICAL FORM

HepaGam B™, Hepatitis B Immunoglobulin (Human), solution for injection IM/IV, 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 1 – 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®

4. INDICATIONS

Prevention of Hepatitis B recurrence following Liver Transplantation

HepaGam B™is indicated for the prevention of hepatitis B recurrence following liver transplantation, in HBsAg-positive liver transplant patients.

HepaGam B™ should be administered intravenously for this indication.

Postexposure Prophylaxis

HepaGam B™ is indicated for the treatment of acute exposure to blood containing 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 HBsAg.
Perinatal exposure of infants born to HBsAg-positive persons

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. Other household contacts with an identifiable blood exposure to the index patient.
HepaGam B™ is indicated for intramuscular use only for these post-exposure prophylaxis indications.

5. DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration; if these are seen, vials should not be used. During preparation, do not shake vials; avoid foaming. The HepaGam B™ vial is for single use only. Any vial of HepaGam B™ that has been entered should be used promptly. Do not reuse or save for future use. This product contains no preservative; therefore, partially used vials should be discarded immediately.
For intravenous administration, administer HepaGam B™ through a separate intravenous line using an 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).
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.

Prevention of Hepatitis B recurrence following liver transplantation
For the prevention of hepatitis B recurrence following liver transplantation in HBsAg positive liver transplant patients, in adults: 10,000 IU on the day of transplantation, peri-operatively then 2,000-10,000 IU/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.
The first dose should be administered concurrently with the grafting of the transplanted liver (the anhepatic phase) with subsequent dosing as recommended in Table 2.

Table 2 - HepaGam B™ Dosing Regimen

Anhepatic Phase	**Week 1 Post-Operative**	**HBV-DNA negative patients****	**HBV-DNA positive patients ****
First dose	Daily 2000 to 10000 IU for the first 7 days	Maintain anti-HBs titers >100 to 150 mIU/mL	Maintain anti-HBs titers >500 mIU/mL

**Regular monitoring of serum HBsAg and levels of anti-HBs antibody should be performed pre-infusion to track treatment response and allow for treatment adjustment.

HepaGam B™ dose adjustments may be required in patients who fail to reach anti-HBs levels of 100-150 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. In these cases, the dosing regimen should be increased to a half-dose (≥ 5,000 IU) intravenously every 6 hours until the target anti-HBs is reached.
Hepatitis B Immunoglobulin (HBIG) products are most effective in patients with no or low levels of HBV replication at the time of transplantation.
HepaGam B™ should be prepared for intravenous administration under aseptic conditions. HepaGam B™ should be administered through a separate intravenous line using an intravenous administration set via infusion pump. The 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, infusion-related adverse events or there is concern about the speed of infusion.

Postexposure Prophlyaxis

For postexposure prophylaxis indications, HepaGam B™ must be administered intramuscularly only as directed below.

HepaGam B™ may be administered at the same time (but at a different site), or up to one month preceding hepatitis B vaccination without impairing the active immune response to Hepatitis B Vaccine.

Acute Exposure to Blood Containing HBsAg:

Table 3 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, and within 24 hours if possible. Consult the Hepatitis B Vaccine package insert for dosage information regarding the vaccine.

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

Table 3 - Recommendations for Hepatitis B Prophylaxis Following Percutaneous or Permucosal Exposure

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

* Hepatitis B Immunoglobulin Intravenous (Human) dose of 0.06 mL/kg I.M.

† See manufacturers' recommendation for appropriate dose.

‡ Less than 10 mIU/mL anti-HBs by radioimmunoassay, negative by enzyme immunoassay.

§ Two doses of Hepatitis B Immunoglobulin Intravenous (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 4 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 manufacturers' 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 12-15 months of age. If HBsAg is not detectable and anti-HBs is present, the child has been protected.

Table 4 - 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* Hepatitis B Immunoglobulin Intravenous (Human)†	Birth (within 12 hours) Birth (within 12 hours)	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*	1 month	1-2 months
Third Vaccination*	6 months	6 months

* See manufacturers' recommendations for appropriate dose.
† 0.5 mL administered I.M. at a site different from that used for the vaccine.

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.

6. CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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.
- 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.

7. WARNINGS AND PRECAUTIONS

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].

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. Please see SERIOUS WARNINGS AND PRECAUTIONS BOX above.

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 .

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 healthcare provider.

Traceability

In order to improve the traceability of biological medicinal products, the name of the administered product should be clearly recorded. It is recommended to record the batch number as well.

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 pyrroloquine-quinone (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 mm3, 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 REACTIONS], epinephrine and diphenhydramine should be available for the treatment of any allergic reactions.
HepaGam B™ contains trace amounts of IgA (<40μg/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].

Specific populations

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

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.

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.

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

Adverse reactions 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.

Clinical trials 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. Adversereaction 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 reactions 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 2 [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.

Clinical Trial Adverse Reactions – Pediatrics
Please refer to Adverse Reaction Overview, Post-exposure Prophylaxis

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.

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 5: 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

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

9. DRUG INTERACTIONS

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).

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 Intravenous (Human) solution for 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).

Drug-behaviours interactions
Interactions with behaviour have not been established.

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 6 - 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.

*Theoretical

The use of live virus vaccination before or after HepaGam B™ administration should follow the recommendations by the Ministry of health.

Interactions with other drugs have not been established.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory 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. OVERDOSE

Consequences of an overdose are not known.

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

11. 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 naive 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. 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 2 in DOSAGE AND ADMINISTRATION) to maintain anti-HBs levels was examined in an analysis of 24 hepatitis B-related liver transplant patients from aPhase 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 7.

Table 7 Summary of HepaGam B™ Pharmacokinetic Parameters in Healthy Volunteers when Given via Intramuscular Injection

	Cmax	T1/2 (h)	AUC 0-4	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 Serious Drug Interactions).

12. PHARMACEUTICAL PARTICULARS

List of excipients
Maltose, Polysorbate 80, water for injection. The product contains no preservatives.

Incompatibilities
This medicinal product must not be mixed with other medicinal products.

Shelf life
The expiry date of the product is indicated on the packaging materials.

Special precautions for storage
Store at 2 to 8°C.
Do not freeze.
Use within 6 hours after the vial has been entered.
Do not use after expiration date indicated on the packaging materials.

Nature and contents of container
A carton containing a 1.0 mL single dose vial (>312 IU/mL) and a package insert.
A carton containing a 5.0 mL single dose vial (>312 IU/mL) and a package insert.

The solution should be clear or slightly opalescent.

13. MANUFACTURER
KI BioPharma LLC, Wilmington, New Castle County, Delaware, USA.

14. MARKETING AUTHORISATION HOLDER
Tzamal Bio-Pharma**,** 20 Hamagshimim St., Kiryat Matalon, Petah Tikva

Revised in June 2024, according to MoH's guidelines.