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 surface antigen (anti-HBs).

For a full list of excipients, see section 6.1.

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 containing polyclonal antibodies to hepatitis B surface antigen (anti-HBs).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

4.1.1 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.

4.1.2 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.

4.2 Posology and method of 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.

4.2.1 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 1.

Table 1 - 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.

4.2.2 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 2 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 2 - 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 3 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 3 - 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.

4.3 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 with a history of anaphylactic or severe system reaction to any component of the product.
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.

4.4 Special warnings and precautions of use
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 Special warnings and precautions of use, General (4.4.1)].

4.4.1 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 "Posology and method of administration" section.

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 can 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 Planova 20 nm 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 lipid coat. These two processes are designed to increase product safety by redusing the risk of viral transmission of several viruses including human immunodeficiency virus (HIV), hepatitis B, 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 a physician or other healthcare provider.

4.4.2 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 Special warnings and precautions of use, Monitoring and Laboratory Tests (4.4.5)]. For patients who are at risk of developing thrombotic events, administer HepaGam B™ at the minimum rate of infusion practicable.

4.4.3 Renal

Intravenous Immunoglobulin (human) products have been reported to produce renal dysfunction in patients that are predisposed to acute renal failure or those that have renal insufficiency. It has been recommended that intravenous Immunoglobulin (human) products be administered at a minimum practical concentration and infusion rate at such patients 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.

4.4.4 Sensitivity

Although allergic reactions have not been reported following HepaGam B™ administration [See Undesirable effects (4.7)], 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. HepaGam B™ is contraindicated in IgA

deficient patients with antibodies against IgA and a history of hypersensitivity reactions [See Contraindications (4.3)].

4.4.5 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.

4.4.6 Specific populations

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 (>65 years of age):

Safety and effectiveness in the geriatric population have not been established for HepaGam B™.

4.5 Interactions with other medicinal products and other forms of interactions

4.5.1 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 3 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™ with other medications. Antibodies present in HepaGam B™ may interfere with some serological tests (See Drug Laboratory Interactions).

Table 4-Established or Potential Drug-Drug Interactions

Hepatitis B Immunoglobulin (Human	Reference	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 Canadian National Advisory Committee on Immunization. Interactions with other drugs have not been established.

4.5.2 Drug-Food Interactions

Interactions with food have not been established.

4.5.3 Drug-Herb Interactions

Interactions with herbal products have not been established.

4.5.4 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 Special warnings and precautions of use, Blood Glucose Testing (4.4.5)].
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.

4.6 Pregnancy and Lactation

Pregnancy

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

Nursing Mothers

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.

4.7 Undesirable effects

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

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. In a clinical trial in liver transplant patients, 2 adverse drug reactions of tremor and hypotension were reported in 2 of 14 patients who received intravenous infusions of HepaGam B™. In studies with healthy volunteers, only 1 adverse drug reaction of nausea has been reported in the 70 adult subjects who received an intramuscular administration of HepaGam B™.

Although no anaphylactic reactions have been reported following HepaGam B™ administration, anaphylactic reactions have been reported following the administration of other immunoglobulin (human) products on rare occasions [See Special warnings and precautions of use (4.4)].

Clinical trials adverse drug reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Hepatitis B-Related Liver Transplantation:

In an ongoing clinical trial, only 2 adverse drug reactions occurred following the 313 (<1%) HepaGam B™ infusions in 14 liver transplant patients. These adverse events were reported in an interim analysis from Phase 3 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 1 [See Posology and method of administration (4.2)]. The 2 adverse drug reactions of tremor and hypotension were reported in 2 patients. All reactions were associated with a single HepaGam B™ infusion during the first week post-transplant. All reactions resolved on the same day and did not recur with subsequent HepaGam B™ infusions.

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 4 subjects (6%) who experienced headache, 7 subjects (10%) who had cold symptoms or flu and 2 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.

Abnormal Hematologic and Clinical Chemistry Findings

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

Post-market Adverse Drug 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:

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

4.8 Overdose
Consequences of an overdose are not known.

5. PHARMACOLOGICAL PROPORTIES
ATC: SPECIFIC IMMUNOGLOBULINS

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.

5.1 Pharmacodynamic properties

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.

5.2 Pharmacokinetics properties

Currently there is no pharmacokinetic data available for HepaGam B™ intravenous administration in liver transplant patients. The ability of the described dosing regimen to maintain anti-HBs levels was examined in an interim analysis of 14 hepatitis B-related liver transplant patients from an ongoing 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 12 of the 14 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 5.

Table 5 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

5.3 Nonclinical toxicology

Toxicology studies have not been performed with Hepatitis B Immunoglobulin Intravenous (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.

5.4 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.

5.5 Human Studies

A single-centre, randomized, single-blind, comparative, parallel arm study was conducted to assess the safety and comparative pharmacokinetics of HepaGam B™ and a reference product when administered intramuscularly

to healthy male and female subjects under fasting conditions Seventy subjects were enrolled in the study, and 61 subjects received a single dose of 0.06 mL/kg of either HepaGam B™ or the reference product. Sixty subjects completed the study (thirty subjects in each treatment arm). Safety and pharmacokinetic data as assessed by anti-HBs plasma levels of all subjects who completed the study was collected for 84 days (3 half-lives of the product). The half-life of HepaGam B™ was 24.5 ±4.6 days and the volume of distribution was 7.0 ±1.5 L. Maximum concentration of HepaGam B™ was 215.6 mIU/mL and was reached in 5.4 ±2.4 days. As the test: reference ratios and 90% confidence intervals for the parameters AUC_{0-T}, AUC_{0-inf} and C_{max} (log-transformed data) met the 0.8 to 1.25 criteria, HepaGam B™ was concluded to be bioequivalent to the reference product.

6. PHARMACEUTICAL PARTICULARS

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

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

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

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

6.5 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.

7. MANUFACTURER
Emergent Biosolution Canada Inc., Winnipeg, Manitoba, Canada.

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

Revised in September 2023, according to MOHs guidelines.