Defense against reinfection post-transplant and post-exposure prophylaxis[1].

A hepatitis B immune globulin (HBIg) approved to prevent hepatitis B virus (HBV) recurrence following liver transplantation in HBsAg-positive patients and for post-exposure prophylaxis[1]

Indications

Prevention of Hepatitis B Recurrence Following Liver Transplantation – prevention of hepatitis B recurrence following liver transplantation in adult patients with hepatitis B who have no or low levels of HBV replication.

Post-exposure Prophylaxis – 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.

HepaGam B indicated for the prevention of hepatitis B recurrence following liver transplantation, has been issued marketing authorization with conditions pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

This product has been approved under the Notice of Compliance with Conditions (NOC/c) policy for one of its indicated uses.*

*An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada. Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment.

Selected Important Risk Information

Individuals known to have severe, potentially life-threatening reaction to human globulin preparations should not receive HepaGam B® or any other immune globulin (human). Individuals who are deficient in IgA may have the potential to develop IgA antibodies and have severe, potentially life-threatening allergic reactions.

Please see Important Risk Information on Page 7 and refer to Product Monograph at Hepagam.ca for full Prescribing Information.

HEPAGAM B®
Hepatitis B Immune Globulin Intravenous (Human)

Contents

Packaging

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 (>1560 IU/5 ml) in a 6 mL glass vial with a plastic flip off seal and a package insert

Storage and Handling

- Store under refrigeration (2 to 8ºC).
- Do not freeze.
- Do not use after expiration date indicated on the label.
- 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.
- Do not shake vial; avoid foaming.

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 collected from healthy, screened donors 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-butylphosphate and Triton X-100®) and a Planova® 20 nm virus filtration. These two processes are designed to increase product safety by reducing the risk of viral transmission.

HEPAGAM B®
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Contraindications

- History of anaphylactic or severe systemic reactions to human globulins.
- IgA deficient individuals may have the potential to develop IgA antibodies and have an anaphylactoid reaction.
- IM injections may be contraindicated in patients with coagulation disorders.

Please see Important Risk Information on Page 7 and refer to Product Monograph at Hepagam.ca for full Prescribing Information

Drug Administration – Liver Tranplant

Recommended Dose and Dosage Adjustment for HBV-Related Liver Transplant Patients

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

Anhepatic Phase	Week 1 Post Transplant	Weeks 2-12 Post Transplant	Month 4 Onwards
First dose	Daily from Day 1-7	Biweekly from Day 14	Monthly

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.

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.

Missed Dose

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.

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).

Intravenous Infusion Rate

Rate of administration should be set at 2 mL per minute. Infusion time approximately 17.5 minutes depending on actual dose.
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. Infusion time will change to approximately 35 minutes depending on actual dose and speed of infusion.

Selected Important Risk Information

HepaGam B [Hepatitis B Immune Globulin Intravenous (Human)] is a sterile solution of gamma globulin (IgG) made from human plasma. Products made from human plasma may carry a risk of transmitting infectious agents, eg, viruses and, theoretically, the Creutzfeldt-Jacob disease (CJD) agent.

Please see Important Risk Information on Page 7 and refer to Product Monograph at Hepagam.ca for full Prescribing Information

Drug Administration – Post-Exposure Prophylaxis

Recommended Dose for Post-Exposure Prophylaxis

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

Indication	Dosage	Instructions
Acute Exposure to Blood Containing HBsAg	0.06 mL/kg	Administer HepaGam B® as soon as possible after exposure. The value after 7 days following exposure is unclear.
		For persons who refuse Hepatitis B vaccine or who are known nonresponders to vaccine, give a second dose of HepaGam B® one month after the first dose.
Perinatal Exposure of Infants Born to HBsAg-Positive Mothers	0.5 mL	Administer after physiologic stabilization of the infant and preferably within twelve hours of birth. Administer concurrently with Hepatitis B vaccine.
Sexual Exposure to HBsAg-Positive Person(s)	0.06 mL/kg	Administer HepaGam B® and Hepatitis B vaccine series within 14 days of sexual contact or if sexual contact with the infected person will continue.
Household Exposure to Person with Acute HBV Infection	0.5 mL	For infants less than 12 months of age, administer concurrently with Hepatitis B Vaccine. Prophylaxis of other household contacts of persons with acute HBV infection is not indicated unless there is an identifiable blood exposure to the index patient, such as by sharing toothbrushes or razors. Treat such exposures like sexual exposures.

For complete dosing information please refer to the Product Monograph on Hepagam.ca

Selected Important Risk Information

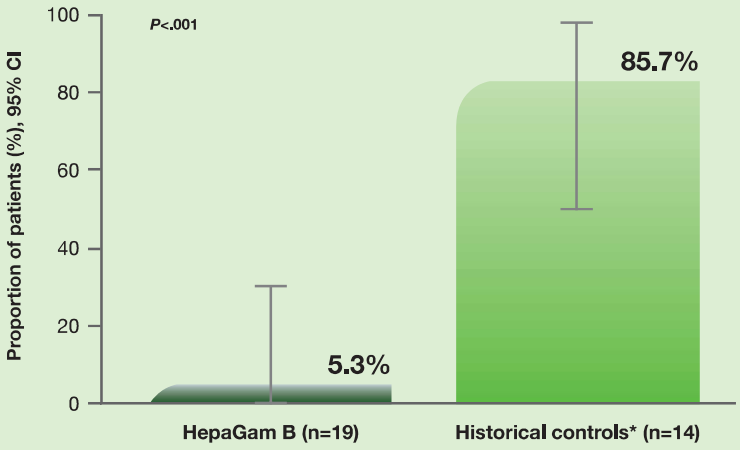
For post-exposure prophylaxis indications, HepaGam B® must be administered intramuscularly only. In patients who have severe thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections, HepaGam B® should be given only if the expected benefits outweigh the potential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

Please see Important Risk Information on Page 7 and refer to Product Monograph at Hepagam.ca for full Prescribing Information

Clinical Trial in Liver Transplant[2]
An important component of a regimen to prevent HBV recurrence

- A significantly lower rate of HBV recurrence following liver transplantation (5.3% vs 85.7% for historical controls)[2]
  - Recurrence was defined as the development of detectable serum HBsAg between Days 28 and 365 following liver transplant (LT)[2]

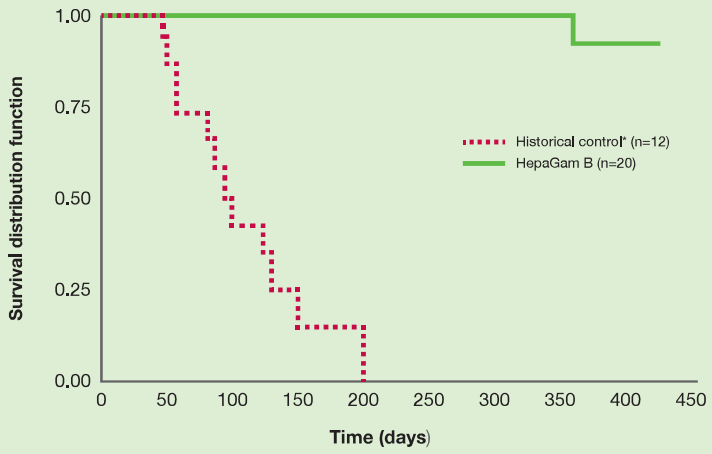
Proportion of Patients With HBV Recurrence[a]



CI = confidence interval
[a]Adapted from Terrault et al.[2] Used with permission.
*Retrospective untreated control group of historical patients with data gathered by chart review.

- Median time to re-infection in the 12 historical control patients was 88 days post-LT, while only 1 patient in the active treatment group became HBsAg-positive (Day 365) and another became HBeAg-positive (Day 257)[2]
  - Time to recurrence of HBV infection was defined as the first detectable serum HBsAg finding after LT[2]

Time to Recurrence of Hepatitis B Virus Infection[a]



[a]Adapted from Terrault et al.[2] Used with permission.
*Retrospective untreated control group of historical patients with data gathered by chart review.

Of the 177 adverse events reported in this study, only three (tremor, hypotension, and fever) were determined to be related to study drug and resolved without sequelae.

Selected Important Risk Information

The maltose contained in HepaGam B® can interfere with some types of blood glucose monitoring systems. Only testing systems that are glucose-specific should be used in patients receiving HepaGam B®. This interference can result in falsely elevated glucose readings that can lead to untreated hypoglycemia or to inappropriate insulin administration, resulting in life-threatening hypoglycemia.

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

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Guidelines for Use in Liver Transplant

SASLT Practice Guidelines[3]

Patients with Chronic Hepatitis B (CHB) and end-stage liver disease who are awaiting liver transplant should be treated with Nucleotide Analogues (NA), regardless of alanine aminotransferase (ALT) and HBV DNA levels, to maintain an undetectable viral load at the time of transplantation.

After transplantation, long-term combination treatment with NAs and Hepatitis B Immune Globulin (HBIG) reduces the risk of HBV re-infection of the graft. Recent evidence suggests the safety of early cessation of HBIG post-liver transplant in the era of new potent antiviral agents.

AST Transplant Guidelines[4]

Post transplant Recommendation:

- Administration of antivirals (ETV, TDF, or TAF), with or without short-term HBIg, is recommended after liver transplant (LT) for prevention of HBV recurrence in recipients who are HBsAg positive, regardless of HBV DNA level or HBeAg status at time of LT (strong recommendation, moderate evidence).
- Recipients who are co-infected with HIV or Hepatitis D Virus (HDV) may warrant longer-term HBIg (one year or longer) in addition to indefinite NA therapy to prevent HBV recurrence (moderate recommendation, low evidence).
- HBsAg-negative recipients who receive livers from HBcAb-positive donors are at risk for HBV transmission and should receive long-term NA prophylaxis (strong recommendation, moderate evidence).
- While immediate post-LT HBIG use is a common practice amongst LT centers, the dose and duration of use vary greatly beyond the first week of LT.
- Organs from HBsAg-positive donors may be considered with use of HBIg/antiviral prophylaxis on individual case basis, weighing the risks and benefits, and informed consent (weak recommendation, low evidence).

Selected Important Risk Information

Thrombotic events have been reported in association with immune globulin 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.

HEPAGAM B®
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Please see Important Risk Information on Page 7 and refer to Product Monograph at Hepagam.ca for full Prescribing Information

Summary of HepaGam B® [Hepatitis B Immune Globulin Intravenous (Human)]

- Hepagam B provides defense against reinfection post-transplant and post-exposure prophylaxis.
- An important component of a regimen to prevent HBV recurrence post-liver transplant.
- An established choice for HBV post-exposure prophylaxis.
- HepaGam B is well tolerated and adverse events are as expected in this patient population.
- Dosing with high levels of anti-HBs.

Important Risk Information for HepaGam B® [Hepatitis B Immune Globulin Intravenous (Human)]

Individuals with a history of anaphylactic or severe system reaction to any component of the product should not receive HepaGam B or any other immune globulin (human). Individuals who are deficient in IgA may have the potential to develop IgA antibodies and have an anaphylactoid reaction.

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 [Hepatitis B Immune Globulin Intravenous (Human)] is a sterile solution of gamma globulin (IgG) made from human plasma. Products made from human plasma may carry a risk of transmitting infectious agents, eg, viruses and, theoretically, the Creutzfeldt-Jacob disease (CJD) agent.

Thrombotic events have been reported in association with immune globulin 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.

The maltose contained in HepaGam B can interfere with some types of blood glucose monitoring systems. 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. 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.

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

For product inquiries about HepaGam B call 001(833) 644-4216.

References

1. HepaGam B Product Monograph, Saol Therapeutics Research Limited, Dublin, Ireland; September 2018.
2. Terrault NA, Kilic M, Karademir S, et al. HepaGam B after liver transplant in patients with hepatitis B virus. *US Gastroenterol Rev.* 2007;2:39-45.
3. SASLT Practice Guidelines, Saudi J Gastroenterol. 2014 Jan-Feb; 20(1): 5–25.
4. AST Transplant Guidelines, Te H, Doucette K. Viral hepatitis: Guidelines by the American Society of Transplantation Infectious Disease Community of Practice. *Clin Transplant.* 2019;e13514. https://doi.org/10.1111/ctr.13514.

Please see Important Risk Information on Page 7 and refer to Product Monograph at Hepagam.ca for full Prescribing Information