October 1, 2007

IMPORTANT INFORMATION – New Product Introduction

HepaGam B™
Hepatitis B Immune Globulin (Human) Injection

Liquid (for Injection) Formulation

Cangene Corporation is pleased to announce that HepaGam B™ (Hepatitis B Immune Globulin [Human] Injection) will be available for distribution through Canadian Blood Services in late October 2007. Cangene’s HepaGam B™ is indicated for the prevention of hepatitis B recurrence following liver transplantation in adult patients with no or low levels of HBV replication. It is the only intravenous HBIG (Hepatitis B Immune Globulin [Human]) licensed in Canada for this indication. HepaGam B™ has been approved by Health Canada under the Notice of Compliance with Conditions (NOC/c) policy. This authorization reflects the promising nature of the clinical evidence, which must be verified with further data. Products approved under Health Canada’s NOC/c policy, have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment.

Detailed information on HepaGam B™, including important safety information, is provided in the attached Health Canada “Dear Health Care Professional” letter and the Product Fact Sheet available to provide to your physician population.

HepaGam B™ is available in following packaging formats:

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

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

Please refer to the Product Monograph for further details. The Product Monograph and/or Package Insert are available at www.cangene.com or by contacting Cangene at 1-877-226-4363.
January 10, 2007

Dear Health Professional(s),

Cangene Corporation is pleased to announce that Health Canada has granted a Notice of Compliance with Conditions (NOC/c) to HepaGam B™ (Hepatitis B Immune Globulin [Human] Injection), for the prevention of hepatitis B recurrence following liver transplantation in adult patients with hepatitis B.

Health Canada has issued a conditional marketing authorization under the Notice of Compliance with Conditions policy to reflect the promising nature of the clinical evidence in patients with this serious disease, and the need for further follow up to verify the clinical benefit.

This NOC/c is based on an interim analysis of an ongoing Phase III clinical study examining the effectiveness of HepaGam B™ in hepatitis B surface antigen positive / hepatitis B ‘e’ antigen negative liver transplant patients. This open-label study compares the efficacy of HepaGam B during the first year following transplant to data from untreated retrospective control patients meeting similar entry criteria. For the HepaGam B treated patients, 1/14 (7.1%) evaluable patients exhibited hepatitis B recurrence (hepatitis B surface antigen positive) compared to 12/14 (85.7%) of historical control patients. These results provide promising clinical evidence that HepaGam B™ is efficacious in preventing hepatitis B recurrence.
A systematic review of the clinical trial literature and meta-analysis supports the efficacy of hepatitis B immune globulin (HBIG) prophylaxis in the prevention of hepatitis B recurrence following liver transplantation.

Patients should be advised about the conditional nature of the marketing authorization for HepaGam B™.

HepaGam B™ is the only intravenous hepatitis B immune globulin (HBIG) in Canada licensed for prevention of re-infection after liver transplantation.

Indications and Clinical use

HepaGam B™ is used in the prevention of hepatitis B recurrence following liver transplantation, in adult patients with Hepatitis B who have no or low levels of HBV replication. The efficacy of HepaGam B™ in conjunction with antivirals such as lamivudine will be assessed in a Phase III confirmatory study. For more information, see PRODUCT MONOGRAPH, PART II: SCIENTIFIC INFORMATION - CLINICAL TRIALS.

Clinical Pharmacology

HBIG products provide passive immunization to HBV and significantly decrease HBV recurrence and increase graft and patient survival following liver transplantation in hepatitis B surface antigen positive patients. The clinical effectiveness of HBIG prophylaxis in the prevention of HBV 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.

Hepatitis B immune globulin is most effective when administered in high doses (to achieve anti-HBs levels greater than 500 mIU/mL), over long time periods (greater than 6 months). A Cangene meta-analysis of the literature data showed that patients treated with long-term high-dose HBIG had a HBV recurrence rate of 15%, compared to a 40% recurrence rate in subjects treated with long-term, low-dose HBIG. Short-term immunoprophylaxis with HBIG may delay HBV recurrence, but the overall rate of reinfection is similar to untreated patients. Therefore, it is important that treatment be continued long-term.

The absence of HBV replication 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.
**Warnings**

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 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.

**Drug Interactions**

Immune globulin administration may impair the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. Persons requiring vaccination with these vaccines while receiving HepaGam B should be tested for titers of antibodies against the said vaccine 3 months after vaccination and if titers are insufficient to afford protection should be revaccinated. 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 PRODUCT MONOGRAPH, Drug-Laboratory Interactions).

**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 pyrroloquinonequinone (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.

**Adverse Events**

The most common expected adverse drug reactions for intravenous immune globulins like HepaGam B™ are chills, fever, headaches, vomiting, allergic reactions, nausea,
arthralgia and moderate low back pain\textsuperscript{1,2,6}. 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\textsuperscript{TM}\textsuperscript{2}. In studies with healthy volunteers, only 1 adverse drug reaction of nausea was been reported in the 70 adult subjects who received an intramuscular administration of HepaGam B\textsuperscript{TM}\textsuperscript{2}.

Although no anaphylactic reactions have been reported following HepaGam B\textsuperscript{TM} administration, anaphylactic reactions have been reported following the administration of intravenous immune globulin (human) products on rare occasions\textsuperscript{16}.

**Dosage and Administration**

**Dosing Considerations**

For the prevention of hepatitis B recurrence following liver transplantation in adult patients with hepatitis B, HepaGam B\textsuperscript{TM}, should be administered intravenously to attain serum anti-HBs levels greater than 500 mIU/mL as described below\textsuperscript{1,2}.

These dosing recommendations are based on a systematic review of the clinical trial literature and meta-analysis undertaken by Cangene Corporation (see PRODUCT MONOGRAPH, PART II: SCIENTIFIC INFORMATION - CLINICAL TRIALS). This report found that hepatitis B Immune globulin (HBIG) prophylaxis was most effective when administered in high doses (to achieve anti-HBs levels of greater than 500 mIU/mL) over longer time periods (greater than 6 months). The recommended dosing schedule described below is designed to achieve anti-HBs levels of greater than 500 mIU/mL. This regimen is based on that published in Terrault et al., 1996\textsuperscript{3} and reviewed by Shouval & Samuel, 2000\textsuperscript{3}. This regimen is currently being evaluated in a Phase III clinical trial. Recommendations for dose adjustments are based on McGory et al., 1996\textsuperscript{11}, using a similar dosing regimen.

**Recommended Dose and Dosage Adjustment**\textsuperscript{2}

Each dose of HepaGam B\textsuperscript{TM} 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 daily dosing from Day 1 through Day 7 post-operatively, followed by biweekly dosing from Day 14 up to 3 months, and thereafter from Month 4 onwards once every month.

**HepaGam B\textsuperscript{TM} Dosing Regimen**

<table>
<thead>
<tr>
<th>Anhepatic Phase*</th>
<th>Week 1 Post-Operative*</th>
<th>Months 1-3 Post-Operative</th>
<th>Month 4 onwards</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Dose</td>
<td>Daily from Day 1 - 7</td>
<td>Biweekly from Day 14</td>
<td>Monthly</td>
</tr>
</tbody>
</table>

* Anti-HBs levels should be measured after the first week of treatment, to allow for initial adjustment of dosage.
Anti-HBs levels should be measured after the first week of treatment, to allow for initial adjustment of dosage (see PRODUCT MONOGRAPH, PART I: HEALTH PROFESSIONAL INFORMATION – DOSAGE AND ADMINISTRATION).

**Administration**

HepaGam BTM should be prepared for IV administration under aseptic conditions. **DO NOT SHAKE VIAL; AVOID FOAMING** (see PRODUCT MONOGRAPH, Administration).

**HepaGam BTM is available in following packaging formats:**

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

A carton containing a 5 mL single dose (> 312 IU/mL) filled in a 6 mL glass vial with a plastic flip off seal and a package insert. Please refer to the product monograph for further details.

For medical inquiries regarding HepaGam BTM, please contact Cangene Corporation, at: 1-877-CANGENE (226-4363).

Sincerely,
CANGENE CORPORATION

Maurice Genereux B.Sc., M.D.
Medical Director
References:


Any suspected adverse drug reactions can also be reported to:
Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Health Product Safety Information Division
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0701C
OTTAWA, Ontario, K1A 1B9
Tel: (613) 957-0337 or Fax: (613) 957-0335
Toll free for consumers and health professionals:
Tel: 866 234-2345, Fax: 866 678-6789
cadrmp@hc-sc.gc.ca

The ADR Reporting Form can be found in The Canadian Compendium of Pharmaceuticals and Specialties, or on the Health Canada web site, along with the ADR Guidelines at:
CONDITIONAL APPROVAL OF HEPAGAM B™ LIQUID > 312 IU/mL FOR USE IN PREVENTION OF HEPATITIS B RECURRENCE FOLLOWING LIVER TRANSPLANTATION

FACT SHEET

What is HepaGam B™?
HepaGam B™ (Hepatitis B Immune Globulin [Human] Injection), is a sterile solution of purified gamma globulin (IgG) fraction of human plasma containing antibodies to hepatitis B surface antigen (anti-HBs).

HepaGam B™, indicated for the prevention of hepatitis B recurrence following liver transplantation, has been approved by Health Canada under the Notice of Compliance with Conditions (NOC/c) policy. This authorization reflects the promising nature of the clinical evidence, which must be verified with further data. Products approved under Health Canada's NOC/c policy, have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment.

What is HepaGam B™ used for?
HepaGam B™ is used in the prevention of hepatitis B recurrence following liver transplantation in adult patients with hepatitis B who have no or low levels of HBV replication.

What is Hepatitis B recurrence?
Hepatitis B recurrence can occur after liver transplantation in patients who are hepatitis B surface antigen (HBsAg) positive at the time of transplant. Recurrence results from the infection of the liver graft with hepatitis B virus (HBV) remaining in circulation and/or coming from extrahepatic sites.

How does HepaGam B™ work?
The mechanism whereby hepatitis B immune globulin (HBIG) protects the transplanted liver against HBV infection is not well defined. HBIG may block HBV binding to liver cells, neutralize circulating HBV, target infected cells through an antibody-mediated immune response and/or interact with HBsAg within cells.

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

For HepaGam B™ to be effective in preventing hepatitis B recurrence, treatment should be started during liver transplantation and continued regularly after transplant. Laboratory tests will determine if HepaGam B™ is working, by measuring levels of
HepaGam BTM in serum (the liquid portion of blood) and by looking for signs of hepatitis B infection.

What other treatments have been used to prevent Hepatitis B recurrence?
There are currently no other products licensed to prevent Hepatitis B recurrence following liver transplantation, although antiviral therapy has been used to prevent the recurrence in some patients.

What do patients need to know about using HepaGam BTM?
Patients should talk to their doctor or pharmacist BEFORE using HepaGam BTM if:
- They have experienced allergic reactions to blood products in the past
- They have a known IgA deficiency
- They are pregnant or nursing
- If they use any device to measure blood glucose

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

Drugs that may interact with HepaGam BTM have not been established.

Immune globulins like HepaGam BTM may impair the effectiveness of certain live virus vaccines such as measles, rubella (German measles), mumps and varicella (chicken pox). Patients should talk to their doctor if they have been recently vaccinated or require vaccination.

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

Certain side effects may be related to the rate of infusion and may resolve if the infusion rate is slowed. Slower infusion rates should be considered for patients with renal dysfunction.

Who can be treated with HepaGam BTM?
HepaGam BTM is most effective in HBsAg positive patients with no or low levels of HBV replication at the time of liver transplantation.

How is HepaGam BTM taken?
Usual dose:
Each dose of 35 mL (10,920 international units) HepaGam BTM will be given by an intravenous injection taking approximately 20 minutes. See Product Monograph HepaGam BTM pharmacokinetic data for administration intramuscularly.
The typical dose schedule is as follows:
- first dose during liver transplantation operation
- daily doses for the first week post-operative
- once every two weeks for the first 3 months post-operative
- once a month thereafter

**Overdose:**
The consequences of an overdose are not known. In case of an overdose, patients should consult their doctor.

**Missed Dose:**
If a scheduled dose is missed, it should be given as soon as possible after the missed dose. The doctor will adjust the patient’s dosing schedule if required.

**What else should patients know about taking HepaGam B™?**
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 manufacturing process includes both a Planova 35 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. 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.

Allergic or anaphylactic reactions are rare. These reactions can occur in patients with a history of allergy to blood products or in patients lacking the IgA blood protein.

**Where can I learn more about HepaGam B™?**
Contact the sponsor, Cangene Corporation, at: 1-877-CANGENE (226-4363).

**References:**