פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר על ידו

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Omri-Hep-B™ 5% IV

Hepatitis B Human Immunoglobulin – 50 IU/ml

Nanofiltered and Solvent /Detergent virus inactivated

The method of preparation includes a step to remove detectable thrombosis-generating agents

Composition

Omri-Hep-B™ 5% IV is a sterile solution containing 5% protein (50 mg in 1 ml solution) of which at least 95% is Human Immunoglobulin G, at least 50 IU/ml of antibodies to the Hepatitis B Surface Antigen (HBsAg) as the active ingredient, 10% Maltose and Water for Injection. The Immunoglobulin A content is ≤0.15 mg/ml. **Omri-Hep-B™ 5% IV** does not contain sucrose. No preservatives are added.

Description

Omri-Hep-B™ 5% IV provides passive immunization for the prevention of Hepatitis B virus re-infection after liver transplantation. Re-infection may originate from either the recipient or the donor transplant in case any of them was exposed to Hepatitis B Virus.

Omri-Hep-B™ 5% IV obtained by Cohn-cold ethanol fractionation of human plasma collected from donors with high titer of antibodies to the Hepatitis B Surface Antigen (anti HBsAg). This step has also been shown in literature to be a

primary virus inactivation step. **Omri-Hep-B™ 5% IV** undergoes a second virus inactivation step by the solvent/detergent (SD) method with Tri-n-Butyl Phosphate (TnBP) and Triton X-100 and a third inactivation step by nanofiltration at pH 4.

Manufacturing process includes a specific step to remove detectable thrombosis-generating agents (see Warnings and Special Precautions).

Pharmaceutical Form

Omri-Hep-B™ 5% IV is a clear to slightly opalescent, colorless to pale yellow solution for intravenous infusion.

Pharmacological Properties

Pharmacodynamic properties

Omri-Hep-B™ 5% IV provides passive immunization that is particularly effective against hepatitis B virus (HBV).

The mechanisms by which hepatitis B immunoglobulin immunoprophylaxis protects the new liver from HBV reinfection are based on the rationale that administered anti-HBsAg will bind to and neutralize circulating virions as well as virions within the reticulo-endothelial tissue, thereby preventing graft infection.

Binding and avidity of **Omri-Hep-B™ 5% IV** to the HBsAg have been documented to be equal or better than those of the relevant WHO standards. **Omri-Hep-B™ 5% IV** also showed specificity for the HBsAg through dose dependent competition with a reference human ^{125}I-anti-HBsAg. The product has a distribution of IgG subclasses that is closely proportional to that of normal human plasma.

Pharmacokinetic properties

Omri-Hep-B™ 5% IV, as all immunoglobulins**,** is immediately and completely bioavailable in the recipient's circulation after intravenous administration. It is distributed rapidly between plasma and extravascular fluid. After approximately 3-5 days equilibrium is reached between the intra- and extravascular compartments.

Administration of **Omri-Hep-B™ 5% IV** was shown to induce high and long lasting levels of circulating anti-HBsAg antibodies which have a half life of 22± 1.3 days. Mean time to reach threshold levels of 150 mIU/ml anti-HBsAg is 79 days. These results suggest that intervals between injections after orthotopic liver transplantation (OLT) may be more than 2.5 months for most patients. These values may vary from patient to patient.

Preclinical safety data

Immunoglobulins are normal constituents of the human body. In animals, single dose toxicity testing is of no relevance and higher doses result in overloading. Repeated dose toxicity testing and embryo-fetal toxicity studies are impractical due to induction of, and interference with antibodies. Effects of the product on the immune system of the newborn have not been studied. Since clinical experience with normal immunoglobulins provides no indication of tumorigenic or mutagenic effects, experimental studies, particularly in heterologous species, are not considered necessary.

Virus inactivation of **Omri-Hep-B™ 5% IV** is carried out using a solvent/detergent (SD) method with TnBP and Triton X-100. These SD reagents are removed during the

purification process. At the doses at which **Omri-Hep-B™ 5% IV** is administered, no toxic effects have occurred with these reagents in animal studies of single or repeated dose toxicity, and in studies of reproduction toxicity.

Viral safety

Omri-Hep-B™ 5% IV is obtained by Cohn-cold ethanol fractionation (this step has also been validated as a primary virus inactivation/removal step). The product then undergoes a second virus inactivation step by the solvent /detergent method using TnBP and Triton X-100, and a third inactivation/removal step by nanofiltration at pH 4.

The following viruses have been included in the viral safety assessment:

• Type 1 human immunodeficiency virus (HIV-1) (RNA enveloped) (AIDS)
• Pseudorabies virus (PRV) (DNA enveloped, model for Herpes)
• Bovine viral diarrhoeal virus (BVDV) (RNA enveloped, model for HCV)
• Hepatitis A virus (HAV) (RNA-naked).
• Encephalomyocarditis Virus (EMCV) (RNA-naked, model for HAV)
• Theiler's Mouse Encephalomyelitis Virus (TMEV) (RNA-naked, model for HAV)
• Minute Virus of Mice (MVM) (DNA-Naked, model for Parvo virus B-19).

Log reduction of infective agents during the **Omri-Hep-B™ 5% IV** manufacturing process:

Virus	**HIV-1**	**PRV**	**BVDV**	**HAV**	**EMCV**	**TMEV**	**MVM**
Cohn	not done	not done	>4.55	not done	4.19	not done	4.14
S/D step	>4.01	>4.0	>5.74	1.76	not done	not done	not done
Nanofiltration	>5.18	>5.03	>5.49	>7.31	not done	1.73	1.51

Therapeutic Indications

Passive immunization for the prevention of Hepatitis B virus re-infection after liver transplantation.

Contraindications

Omri-Hep-B™ 5% IV is contra-indicated for individuals who are known to have anaphylactic or severe systemic response to intramuscular or intravenous immunoglobulin preparations or to any of the excipients. As with other immunoglobulin preparations **Omri-Hep-B™ 5% IV** should not be given to patients with antibodies to IgA or selective IgA deficiency.

Warnings and Special Precautions

***Any vial that has been penetrated should be used promptly. Partially used vials should be discarded. Do not use if turbid. Solutions that have been frozen should not be used*.**

General

Adequate hydration prior to the initiation of IVIG infusion is required.

Potential complications can often be avoided by ensuring that patients:

- Are not sensitive to human immunoglobulin by initially injecting the product slowly.
- Are carefully monitored for any symptoms throughout the infusion period. In particular, patient's naive to human immunoglobulin, patients switched from an alternative IVIG product or when there has been a long interval since the previous infusion should be monitored during the first infusion, and for the first hour after the first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration.

Certain severe adverse drug reactions may be related to the rate of infusion, therefore the recommended infusion rate given under "Dosage and Administration" section must be closely followed.

In all patients, IVIg administration requires:

- adequate hydration prior to initiation of infusion;
- monitoring of urine output;
- monitoring of serum creatinine levels;
- avoidance of concomitant use of loop diuretics

Patients naive to immunoglobulin G (IgG)

Patients naive to immunoglobulin G or to **Omri-Hep-B™ 5% IV** usually experience a higher frequency of minor events than those well maintained on regular therapy. The recommended infusion rate given under “Dosage and Administration” section must be closely followed and patients carefully observed for any symptoms throughout the infusion period, for 1 hour after the first infusion and for at least 20 minutes after subsequent administrations. In case of adverse reactions either the rate of administration must be reduced or the infusion stopped until symptoms disappear. If severity of reactions persists after discontinuation of the infusion, appropriate treatment is recommended. In case of anaphylactic reaction or shock, treatment should follow the guidelines for shock therapy. Epinephrine should be available for the treatment of any acute anaphylactoid reactions.

Patients with agammaglobulinemia or extreme hypogammaglobulinemia

Patients with agammaglobulinemia or extreme hypogammaglobulinemia who have not received immunoglobulin therapy within the preceding 8 weeks may be at risk of developing inflammatory reactions upon the infusion of human immunoglobulins. These reactions are manifested by a rise in temperature, chills, nausea and vomiting, and appear to be related to the rate of infusion.

Hypersensitivity

True hypersensitivity reactions are rare. They can occur in patients with anti-IgA antibodies.

IVIG is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern.

Rarely, human normal immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin.

Acute Renal Failure

Cases of acute renal failure have been reported in patients receiving IVIG therapy. In most cases risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, age over 65, hypovolemia, overweight or concomitant nephrotoxic medical products.

In patients with diabetes at risk of renal failure or those with systemic lupus erythematosus and renal involvement, creatinine levels should be measured for 3 days after intravenous immunoglobulin infusion. In patients at risk of acute renal failure, IVIG products should be administered at the minimum rate of infusion and dose practicable.

In case of renal impairment, IVIG discontinuation should be considered. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIG products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. In patients at risk, the use **of Omri-Hep-B™**, which does not contain sucrose, is advantageous.

See 'Drug interactions and other forms of interactions' for information regarding blood glucose testing.

Hemolysis

Heightened awareness of the potential for hemolysis is recommended in individuals receiving immune globulin products, particularly those who are determined to be at increased risk.

Patients at increased risk for hemolysis following treatment with immune globulins include those with non-O blood group types, those who have underlying associated inflammatory conditions, and those receiving high cumulative doses of immune globulins over the course of several days.

Patients receiving immune globulin products should be monitored for hemolysis, particularly those at increased risk.

Clinical symptoms and signs of hemolysis include fever, chills and dark urine. If these occur, appropriate laboratory testing should be obtained.

Thrombolytic Events

Despite the new step to remove detectable thrombosis-generating agents, there is clinical evidence of an association between IVIG administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (including stroke), pulmonary embolism and deep vein thrombosis, which is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin in at-risk patients. Care should be used when immune globulin products are given to individuals determined to be at increased risk of thrombosis.

Caution should be exercised in prescribing and infusing IVIG in obese patients and in patients with pre-existing risk factors for thrombotic events (such as acquired or hereditary hypercoagulable states, prolonged immobilization, in dwelling vascular catheters, advanced age, estrogen use, a history of venous or arterial thrombosis, cardiovascular risk factors (including history of atherosclerosis and/or impaired cardiac output) and hyperviscosity (including cryoglobulins, fasting chylomicronemia and/or high triglyceride levels, and monoclonal gammopathies), patients with advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, or patients with severe hypovolemia, or with diseases which increase blood viscosity).
Patients at risk for thrombosis should receive immune globulin products at the slowest infusion rate practicable, and these individuals should be monitored for thrombotic complications. Consideration should also be given to measurement of baseline blood viscosity in individuals at risk for hyperviscosity.

An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with intravenous human immunoglobulin treatment. The syndrome usually begins within several hours to two days following administration.
Symptoms including severe headaches, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea and vomiting. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm^3, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL.
Patients exhibiting such symptoms should receive a thorough neurological examination, including CSF studies, to rule out other possible causes for meningitis. AMS may occur more frequently in association with high dose (2 g/kg) human immunoglobulin

intravenous treatment. Discontinuation of this treatment has resulted in remission of AMS within several days without sequelae.

Products made from plasma may contain infectious agents, such as viruses, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by effective donor screening, testing for the presence of certain current virus infections and by inactivating and/or removing certain viruses. In addition, three virus inactivation procedures are included in the production process **Omri-Hep-B™ 5% IV** (See *viral safety* above). Despite these measures, such products can still potentially transmit diseases. Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g. viruses, and theoretically the Creutzfeldt-Jakob disease (CJD) agent.

It is strongly recommended that every time that **Omri-Hep-B™ 5% IV** is administered to a patient, the name and batch number of the product be recorded in order to maintain a link between the patient and the batch of the product. For this purpose a sticker with the batch identification will be added to each **Omri-Hep-B™ 5% IV** vial.

Drug interactions and other forms of interactions

• Live attenuated vaccines: Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps, and varicella. After administration of this medicinal product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore patients receiving measles vaccine should have their antibody status checked.

- Interference with serological testing: Passive transmission of antibodies to erythrocyte antigen, e.g. A, B or D may interfere with some serological tests (Coombs test, haptoglobin, reticulocyte count).
- Incompatibilities: **Omri-Hep-B™ 5% IV** should not be mixed with other medicinal products. A separate intravenous line should be used for the infusion.

Omri-Hep B™ 5% IV contains maltose which can be misinterpreted as glucose by certain types of blood glucose testing systems (for example, by systems based on GDH-

PQQ or glucose-dye-oxidoreductase methods). 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 **Omri-Hep B™ IV**.

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. The interference of maltose in blood glucose assays may result in falsely elevated glucose readings and, consequently, in the inappropriate administration of insulin, resulting in life threatening hypoglycaemia and death.

Pregnancy and lactation

The safety of this medical product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women and breast feeding mothers. IVIG products have been shown to cross the placenta, increasingly after the third trimester. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the fetus or neonate are to be expected.

Breast-feeding Immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate from pathogens which have a mucosal portal of entry.

Effects on ability to drive and use machines

The ability to drive and operate machines may be impaired by some adverse reactions associated with **Omri-Hep B™ 5% IV**. Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines.

Adverse reactions

Patients naive to **Omri-Hep-B™ 5% IV** might experience a higher frequency of minor events than those well maintained on regular therapy. These might include inflammatory reactions, manifested by a rise in temperature, chills, nausea and vomiting and appear to be related to the rate of infusion.

During or shortly after the application of intravenous immunoglobulins minor side effects such as headache, chills, dizziness, fever, vomiting, allergic reactions, nausea, athralgia, low blood pressure and moderate back pain may occur occasionally. Dyspnea and tachycardia may occur more frequently and require medical attention. Cases of reversible meningitis, nephrotoxicity isolated cases of reversible haemolytic anemia/haemolysis and rare cases of regressive cutaneous reactions, often eczema-like, have been observed with human immunoglobulin. Increase in creatininemia and/or acute renal failure have been observed.

Thrombotic events have been reported in the elderly, in patients with signs of cerebral or cardiac ischemia, and in overweight and overly volume depleted patients.

Rarely immunoglobulins may cause a fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no sensitivity to previous administrations. Slowing or stopping the infusion should allow the symptoms to disappear promptly. Thereafter the infusion may be started again using a lower infusion rate. Allergic and anaphylactic reactions necessitate immediate cessation of the infusion. Less severe reactions may be controlled with glucocorticoids and/or antihistamines.

Patients previously sensitized to certain antigens, most commonly IgA, may be at risk of immediate anaphylactoid and hypersensitivity reactions. Epinephrine should be available for the treatment of any acute anaphylactoid reaction (see Warnings and Contraindications). When severe reactions occur, treatment for shock must be initiated according to current guidelines. For this purpose see the recommendations given in the following table.

Immediate measures to be taken in case of intolerable reaction:

Clinical symptoms	**Measures**
Subjective complaints (backache, nausea, etc.)	Stop infusion
Skin symptoms (flush, urticaria, etc.)	Antihistamines
Tachycardia, moderate drop in blood pressure (below 90 mm Hg systolic)	Glucocorticoids i.v. (100-500 mg prednisolone)
Dyspnea Shock	Dopamine continuous infusion (2-4 μg/kg/min) high doses of glucocorticoids i.v. (up to 1 g prednisolone [water soluble]), oxygen, volume expander, possibly increased diuresis using furosemide in case of normovolaemia, control of acid base balance and electrolytes (if necessary, correct).
Persistent normovolaemic shock	Dopamine dosage up to a maximum of 10 μg/kg/min in combination with noradrenalin.
Cardiac or respiratory arrest	Resuscitation

Dosage

10,000 IU **Omri-Hep-B™ 5% IV** should be administered in the unhepatic stage of Liver Transplantation followed by maximum dose of 10,000 IU administered daily for the first 5-7 days after transplantation.

It is recommended that patients be tested periodically for Hepatitis B antibody levels in order to determine individual bioavailability.

It is accepted by convention that in order to prevent reinfection of graft, anti-HBsAg levels should be maintained above 100-150 mIU/ml. After an initial period of acclimation to **Omri-Hep-B™ 5% IV**, the interval between injections is usually
6-8 weeks but might vary from patient to patient. Prophylactic treatment and dosage should be adapted to the anti-HBsAg levels of the patient.

Administration

- Omri-Hep-B ™ 5% IV should be infused intravenously at an initial rate of 0.01-0.02 mL/kg/min for 15 minutes.
- Infusion rate may increase gradually to a maximum of 0.08 mL/kg/min.
- It is recommended not to exceed a rate of 2 mL/min.

Overdosage

Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients or patients with renal impairment.

How Supplied

Omri-Hep-B™ 5% IV is available in 100 ml vials containing at least 50 IU/ml anti HBsAg.

Storage Conditions: Omri-Hep-B™ 5% IV should be stored refrigerated at 2-8°C, protected from light. Do not freeze!
Keep out of reach of children.

Registration No.: 122-31-30076

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02/2014

ART. No. 80HZ60C5-0