

Omri-Hep-B™ 5% IV

Hepatitis B Human Immunoglobulin – 50 IU/ml

Solvent /Detergent virus inactivated

DRUGS-ABOUT.COM

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 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 incubation at pH 4.

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, 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 anti-HBsAg /ml 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 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 step by incubation at pH 4.

Seven types of viruses have been included in the viral safety studies:

- Type 1 human immunodeficiency virus, HIV-1, (RNA enveloped) (AIDS)
- Sindbis virus (RNA enveloped, model for HCV)
- Pseudorabies virus (PRV, DNA enveloped, model for Herpes)
- Type 1 poliovirus (RNA naked, model for HAV)
- Vesicular stomatitis virus (VSV, RNA enveloped, model for HCV)
- Coxsackie virus B6 (RNA naked)
- Polyomavirus maccacae SV40 (DNA naked)

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

Virus/ Inactivation step	HIV-1	Sindbis	PRV	Poliovirus	VSV	SV40	Coxsackie B6
Cohn fractionation	≥ 5.50	≥ 6.36	≥ 7.28	≥ 3.80	ND*	≥ 5.51	2.7
SD step	≥ 5.25	≥ 5.20	≥ 7.23	ND*	≥ 5.30	ND*	ND*
pH4	≥ 7.05	≥ 8.38	≥ 5.42	ND*	ND*	1.15	2.72

* Not determined

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. 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.

Certain severe adverse drug reactions may be related to the rate of infusion. 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" should be closely followed. Patients must be closely monitored 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 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.

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 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

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.

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.

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 mm³, 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.

When medical products are prepared from human plasma, the transmission of infectious agents cannot be totally excluded. To reduce this risk, stringent controls are applied to the selection of blood donors and donations. In addition, three virus inactivation procedures are included in the production process **Omri-Hep-B™ 5% IV** (See viral safety above).

Drug interactions and other forms of interactions

- Live attenuated vaccines: Immunoglobulin administration may impair the efficacy of live attenuated virus vaccines such as measles, rubella, mumps, and varicella for a period of at least 3 months.
- 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.

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. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the fetus or neonate are to be expected.

Immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate. FDA Pregnancy Category C.

Effects on ability to drive and use machines

There is no indication that immunoglobulins may impair the ability to drive and use machines.

Adverse reactions

Patients naive to Omri-Hep-B™ 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, fever, allergic reactions, nausea, arthralgia, and mild back pain may occur occasionally. Dyspnea and tachycardia may occur more frequently and require medical attention. Cases of reversible meningitis, 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 creatinemia 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 IV (100-500 mg prednisolone)
Dyspnea Shock	Dopamine continuous infusion (2-4 µg/kg/min) high doses of glucocorticoids IV (up to 1 g prednisone [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 doses up to a maximum of 10 µg/kg/min in combination with noradrenaline.
Cardiac or respiratory arrest	Resuscitation

Dosage and Administration

10,000 IU **Omri-Hep-B™ 5% IV** should be administered in the anhepatic stage of OLT followed by 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.

Omri-Hep-B™ 5% IV should be administered by intravenous infusion at an initial rate of 0.01-0.02 ml/kg/min for 15 minutes, increasing gradually to a maximum of 0.08 ml/kg/min. However, it is recommended not to exceed a rate of 3 ml/min.

Overdosage

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

Packaging: 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!

Manufacturer: Omrix Biopharmaceuticals Ltd, Weizmann Science Park, Bldg. 14 Nes-Ziona, ISRAEL. Manufacturing site: Plasma Fractionation Institute, MDA- Tel-Hashomer, ISRAEL.