

New Zealand Data Sheet

HyperHEP B

Hepatitis B Immunoglobulin (Human)

Qualitative and Quantitative Composition

Quantitative Composition

1 mL contains:

Hepatitis B Immunoglobulin, USP	220 IU
Glycine, USP	19.5 mg
Water for injection, USP	qs

It contains no preservative and is latex-free.

Pharmaceutical Form

Solution for intramuscular injection

Presentation

Hepatitis B Immunoglobulin (Human) - HyperHEP B is supplied in a 0.5 mL neonatal single dose syringe with attached needle, a 1 mL single dose syringe with attached needle and a 5 mL single dose vial.

Uses

Therapeutic Indications

Hepatitis B Immunoglobulin (Human) is indicated for post-exposure prophylaxis in persons who did not receive prior vaccination, or whose prior vaccination regimen is incomplete or when the antibody level is inadequate i.e. <10 IU/mL. A regimen combining Hepatitis B Immunoglobulin (Human) with hepatitis B vaccine will provide both short and long-term protection. This post exposure prophylaxis should be considered following either parenteral exposure, direct mucous membrane contact, oral ingestion, sexual exposure to an HBsAg-positive person and for infants <12 months, if the mother or primary contact person has acute HBV infection. Infants born of HBsAg-positive mothers should receive Hepatitis B Immunoglobulin (Human) in conjunction with the first dose of Hepatitis B Vaccine.

Hepatitis B Immunoglobulin (Human) can also be considered for haemodialysis patients and recipients of certain blood products unable to develop adequate immune protection.

Acute Exposure to Blood Containing HBsAg

After either parenteral exposure, e.g., by accidental 'needlestick' or direct mucous membrane contact (accidental splash), or oral ingestion (pipetting accident) involving HBsAg-positive materials such as blood, plasma or serum. For inadvertent percutaneous exposure, a regimen of two doses of Hepatitis B Immunoglobulin (Human), one given after exposure and one a month later, is about 75% effective in preventing hepatitis B in this setting.

Perinatal Exposure of Infants Born to HBsAg-positive Mothers

Infants born to HBsAg-positive mothers are at risk of being infected with hepatitis B virus and becoming chronic carriers. This risk is especially great if the mother is HBeAg-positive. For an infant with perinatal exposure to an HBsAg-positive and HBeAg-positive mother, a regimen combining one dose of Hepatitis B Immunoglobulin (Human) at birth with the hepatitis B vaccine series started soon after birth is 85% -95% effective in preventing development of the HBV carrier state. Regimens involving either multiple doses of Hepatitis B Immunoglobulin (Human) alone or the vaccine series alone have 70% -90% efficacy, while a single dose of Hepatitis B Immunoglobulin (Human) alone has only 50% efficacy.

Sexual Exposure to an HBsAg-positive Person

Sex partners of HBsAg-positive persons are at increased risk of acquiring HBV infection. For sexual exposure to a person with acute hepatitis B, a single dose of Hepatitis B Immunoglobulin (Human) is 75% effective if administered within 2 weeks of last sexual exposure.

Household Exposure to Persons with Acute HBV Infection

Since infants have close contact with primary care-givers, they have a higher risk of becoming HBV carriers. After acute HBV infection, prophylaxis of an infant less than 12 months of age with Hepatitis B Immunoglobulin (Human) and hepatitis B vaccine is indicated if the mother or primary care-giver has acute HBV infection.

Administration of Hepatitis B Immunoglobulin (Human) either preceding or concomitant with the commencement of active immunisation with Hepatitis B Vaccine provides for more rapid achievement of protective levels of hepatitis B antibody, than when the vaccine alone is administered. Rapid achievement of protective levels of antibody to hepatitis B virus may be desirable in certain clinical situations, as in cases of accidental inoculations with contaminated medical instruments. Administration of Hepatitis B Immunoglobulin (Human) either 1 month preceding or at the time of commencement of a program of active vaccination with Hepatitis B Vaccine has been shown not to interfere with the active immune response to the vaccine.

Actions

Pharmacodynamic Properties

Hepatitis B Immunoglobulin (Human) contains specific neutralising antibodies (mainly IgG) that provide passive immunisation for individuals exposed to the hepatitis B virus (HBV) as evidenced by a reduction in the attack rate of hepatitis B following its use.

Pharmacokinetic Properties

The administration of the usual recommended dose of this immunoglobulin generally results in a detectable level of circulating anti-HBs, which persists for approximately 2 months or longer. The highest antibody (IgG) serum levels were seen in the following distribution of subjects studied:

<u>DAY</u>	<u>% OF SUBJECTS</u>
3	38.9%
7	41.7%
14	11.1%

Mean value for half-life were between 17.5 and 25 days, with the shortest being 5.9 days and the longest 35 days.

Cases of type B hepatitis are rarely seen following exposure to HBV in persons with preexisting anti-HBs. No confirmed instance of transmission of hepatitis B has been associated with this product.

Dosage and Administration

Acute Exposure to Blood Containing HBsAg

Table 1 summarises prophylaxis for percutaneous (needlestick or bite), 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 Hepatitis B Immunoglobulin (Human) should be given as soon as possible after exposure (its value beyond 7 days of exposure is unclear). If Hepatitis B Immunoglobulin (Human) is indicated (see Table 1), an injection of 0.06 mL/kg of body weight should be administered intramuscularly (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE) as soon as possible after exposure and within 24 hours, if possible. Consult Hepatitis B Vaccine Data Sheet (New Zealand) for dosage information regarding that product.

Table 1. Recommendations for Hepatitis B Prophylaxis Following Percutaneous or Permucosal Exposure

Exposed Person		
Source	Unvaccinated	Vaccinated
HBsAg-Positive	<ol style="list-style-type: none"> 1. Hepatitis B Immunoglobulin (Human) x1 immediately * 2. Initiate HB Vaccine Series † 	<ol style="list-style-type: none"> 1. Test exposed person for anti-HB's. 2. If inadequate antibody, ‡ Hepatitis B Immunoglobulin (Human) (x1) immediately plus HB Vaccine booster dose, or 2 doses of HBIG*, one as soon as possible after exposure and the second 1 month later
Known Source (High Risk)	<ol style="list-style-type: none"> 1. Initiate HB Vaccine Series 2. Test source for HBsAg. If positive, Hepatitis B Immunoglobulin (Human) x1 	<ol style="list-style-type: none"> 1. Test source for HbsAg only if exposed is vaccine nonresponder; if source is HBsAg-positive, give Hepatitis B Immunoglobulin (Human) x1 immediately plus HB Vaccine booster dose, or 2 doses of HBIG*, one as soon as possible after exposure and the second 1 month later
Low Risk HBsAg-positive	Initiate HB Vaccine series	Nothing required
Unknown source	Initiate HB Vaccine series within 7 days of exposure.	Nothing required

* Hepatitis B Immunoglobulin (Human), dose 0.06 mL/kg IM

† HB Vaccine dose 20 µg IM for adults; 10 µg IM for infants or children under 10 years of age. First dose within 1 week; second and third doses, 1 and 6 months later.

‡ Less than 10 sample ratio units (SRU) by radioimmunoassay (RIA), negative by enzyme immunoassay (EIA).

For persons who refuse Hepatitis B Vaccine, a second dose of Hepatitis B Immunoglobulin (Human) should be given 1 month after the first dose.

Perinatal Exposure of Infants Born to HBsAg-positive Mothers

Efficacy of prophylactic Hepatitis B Immunoglobulin (Human) in infants at risk depends on administering Hepatitis B Immunoglobulin (Human) on the day of birth. It is therefore vital that HBsAg-positive mothers be identified before delivery.

Hepatitis B Immunoglobulin (Human) (0.5 mL) should be administered intramuscularly (IM) to the new-born infant after physiologic stabilisation of the infant and preferably within 12 hours of birth. Hepatitis B Immunoglobulin (Human) efficacy decreases markedly if treatment is delayed beyond 48 hours. Hepatitis B Vaccine should be administered IM in three doses of 0.5 mL of vaccine (10 µg) each. The first dose should be given within 7 days of birth and may be given concurrently with Hepatitis B Immunoglobulin (Human) but at a separate site. The second and third doses of vaccine should be given 1 month and 6 months, respectively, after the first. If administration of the first dose of Hepatitis B Vaccine is delayed for as long as 3 months, then a 0.5 mL dose of Hepatitis B Immunoglobulin (Human) should be repeated at 3 months. If Hepatitis B Vaccine is refused, the 0.5 mL dose of Hepatitis B Immunoglobulin (Human) should be repeated at 3 and 6 months. Hepatitis B Immunoglobulin (Human) administered at birth should not interfere with oral polio and diphtheria-tetanus-pertussis vaccines administered at 2 months of age.

Sexual Exposure to an HBsAg-positive Person

All susceptible persons, whose sex partners have acute hepatitis B infection, should receive a single dose of HBIG (0.06 mL/kg) and initiate Hepatitis B Vaccine series. If prophylaxis can not be started within 14 days of the last sexual contact or if sexual contact with the infected person will continue, see Table 2 below. Administering the vaccine with HBIG may improve the efficacy of post-exposure treatment. The vaccine has the added advantage of conferring long-lasting protection.

Table 2 Recommendations for Post-exposure Prophylaxis for Sexual Exposure to Hepatitis B

HBIG*		Vaccine	
Dose	Recommended timing	Dose	Recommended timing
0.06 mL/kg IM†	Single dose within 14 days of last sexual contact.	1.0 mL IM†	First dose at a time of HBIG* treatment‡

* HBIG = Hepatitis B Immunoglobulin (Human)

† IM = Intramuscularly

‡ The first dose can be administered the same time as the HBIG dose but at a different site; subsequent doses should be administered as recommended for specific vaccine

Household Exposure to Persons with Acute HBV Infection

Prophylactic treatment with a 0.5 mL dose of Hepatitis B Immunoglobulin (Human) and hepatitis B vaccine is indicated for infants < 12 months of age, who have been exposed to a primary care-giver who has acute hepatitis B. Prophylaxis for other household contacts of persons with acute HBV infection is not indicated unless they have had 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.

Hepatitis B Immunoglobulin (Human) may be administered at the same time (but at a different site), or up to 1 month preceding Hepatitis B Vaccination without impairing the active immune response from Hepatitis B Vaccination.

Method of administration

Administer intramuscularly. Do not inject intravenously. Use only clear, particle free solution.

Contraindications

Intolerance to homologous immunoglobulins.

Hepatitis B Immunoglobulin (Human) should not be given to patients suffering from severe thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections.

Special Warnings and Precautions for Use

HyperHEP B should **not** be administered intravenously because of the potential for serious reactions. Injections should be administered intramuscularly and care should be taken to draw back the plunger of the syringe before injection in order to be certain that the needle is not in a blood vessel. Patients should be observed for at least 20 minutes after administration. Intramuscular injections are preferably administered in the anterolateral aspects of the upper thigh and the deltoid muscle of the upper arm. The gluteal region should not be used as an injection site because of the risk of injury to the sciatic nerve. An individual decision as to which muscle is injected must be made for each patient based on the volume of material to be administered.

True allergic response to Hepatitis-B IgG given intramuscularly is rare. In the case of shock, treatment should follow guidelines for shock therapy. Intolerance to immunoglobulins is likely to develop in the very rare cases of IgA deficiency when the patient has antibodies against IgA. Suspicion of allergic or anaphylactic type reaction requires immediate discontinuation of the injection.

HyperHEP B is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, and, theoretically, the Creutzfeldt-Jakob Disease (CJD) agent that can cause disease. 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. 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, particularly hepatitis C. All infections, thought by a physician, to possibly have been transmitted by this product should be reported by the physician or other healthcare provider to Medica Limited (Phone (09) 526-1944).

The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to the patient.

Interactions with Other Medicaments and Other Forms of Interaction

Live Attenuated Virus Vaccine

Although administration of Hepatitis B Immunoglobulin (Human) did not interfere with measles vaccination, it is not known whether Hepatitis B Immunoglobulin (Human) may impair, for a period of 5 weeks and up to 3 months, the efficacy of live attenuated virus vaccine. Therefore, use of such vaccines should be deferred until approximately 3 months after Hepatitis B Immunoglobulin (Human) administration. Hepatitis B Vaccine may be administered at the same time, but at a different injection site, without interfering with the immune response. No interactions with other products are known.

Interference with Serological Testing

After injection of immunoglobulins, the transitory rise of various passively transferred antibodies in the patient's blood may result in misreading positive results in serological testing.

Pregnancy and Lactation

Animal reproduction studies have not been conducted with HyperHEP B. The safety of this medicinal product for use in human pregnancy has not been established in a controlled clinical trial, therefore, it should be administered with caution to pregnant or breast feeding women. Long lasting clinical experience with immunoglobulin (Ig), in particular the application of anti-D-Ig, does indicate that no harmful effects on the course of pregnancy, on the foetus and the neonate are to be expected. Immunoglobulins are excreted into the milk and may contribute to transfer of protective antibodies to the neonates.

Paediatric Use

Safety and effectiveness in the paediatric population have not been established.

Effects on Ability to Drive and Use Machines

There is no indication that Hepatitis B Immunoglobulin (Human) may impair the ability to drive and use machines.

Adverse Effects

Local pain and tenderness at the injection site, urticaria and angioedema may occur. This can be prevented by dividing larger doses over several sites. Occasionally fever, cutaneous reactions and chills occur. In rare cases the following symptoms are reported: nausea, vomiting, hypotension, tachycardia, allergic or anaphylactic type reactions including shock.

When medicinal products prepared for human blood or plasma are administered, infectious diseases due to transmission of infective agents cannot be totally excluded. This also applies to pathogens of hitherto unknown nature.

Overdose

Although no data are available, clinical experience with other immunoglobulin preparations suggests that the only manifestations would be pain and tenderness at the injection site.

Pharmaceutical Precautions

Incompatibilities

Hepatitis B Immunoglobulin (Human) should not be mixed with other medicinal products.

Shelf-Life

36 months when stored at 2 -8°C.

Special Precautions for Storage

Store at 2-8°C (36-46°F). Do not freeze. Do not use after expiration date.

Instructions for Use and Handling

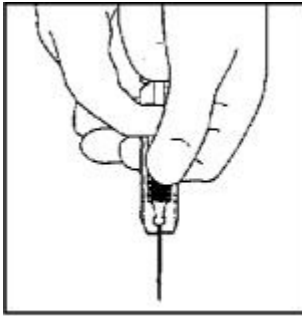
Do not use if the solution is cloudy or has particles.

Hepatitis B Immune Globulin (Human) — HyperHEP B is supplied in a syringe with an attached UltraSafe® Needle Guard for your protection and convenience, as well as in vials. Please follow instructions below for proper use of syringe and UltraSafe® Needle Guard.

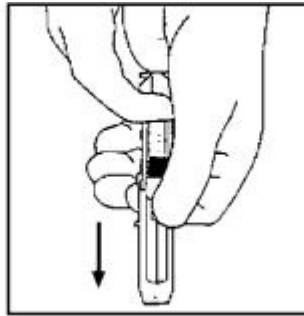
Directions for Syringe Usage

1. Remove the prefilled syringe from the package. Lift syringe by barrel, not by plunger
2. Twist the plunger rod clockwise until the threads are seated.
3. With the rubber needle shield secured on the syringe tip, push the plunger rod forward a few millimeters to break any friction seal between the rubber stopper and the glass syringe barrel.
4. Remove the needle shield and expel air bubbles. Do not remove the rubber needle shield to prepare the product for administration until immediately prior to the anticipated injection time.
5. Proceed with hypodermic needle puncture.
6. Aspirate prior to injection to confirm that the needle is not in a vein or artery.
7. Inject the medication

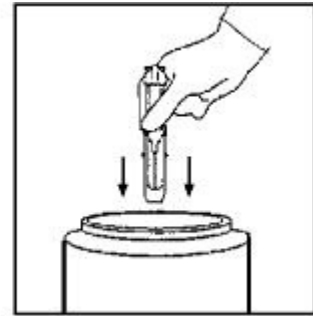
8. Keeping your hands behind the needle, grasp the guard with free hand and slide forward toward needle until it is completely covered and guard clicks into place. If audible click is not heard, guard may not be completely activated. (See Diagrams A and B)
9. Place entire prefilled glass syringe with guard activated into an approved sharps container for proper disposal. (See Diagram C)



A



B



C

A number of factors could reduce the efficacy of this product or even result in an ill effect following its use. These include improper storage and handling of the product after it leaves our hands, diagnosis, dosage, method of administration and biological differences in individual patients. Because of these factors, it is important that this product be stored properly and that the directions be followed carefully during use.

Medicine Classification

Prescription Medicine

Package Quantities

1 X 0.5 mL neonatal single dose syringe with attached needle;

1 X 1.0 mL single dose syringe with attached needle

1 X 5.0 mL single dose vial

Further Information

Preclinical Safety Data

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

List of Excipients

Glycine.

Consent

Provisional consent for distribution under section 23 of the Medicines Act 1981

Description

Hepatitis B Immune Globulin (Human) — HyperHEP B treated with solvent/detergent is a colourless to pale yellow or pink sterile solution of hepatitis B hyperimmune immune globulin for intramuscular administration; it is preservative-free and latex-free. HyperHEP B is prepared by cold ethanol fractionation from the plasma of donors with high titres of antibody to the hepatitis B surface antigen (anti-HBs). The immune globulin is isolated from solubilised Cohn Fraction II. The Fraction II solution is adjusted to a final concentration of 0.3% tri-n-butyl phosphate (TNBP) and 0.2% sodium cholate. After the addition of solvent (TNBP) and detergent (sodium cholate), the solution is heated to 30°C and maintained at that temperature for not less than 6 hours. After the viral inactivation step, the reactants are removed by precipitation, filtration and finally ultrafiltration and diafiltration. HyperHEP B is formulated as a 15–18% protein solution at a pH of 6.4–7.2 in 0.21–0.32 M glycine. HyperHEP B is then incubated in the final container for 21–28 days at 20–27°C. Each vial or syringe contains anti-HBs antibody equivalent to or exceeding the potency of anti-HBs in a U.S. reference hepatitis B immune globulin (Center for Biologics Evaluation and Research, United States Food and Drug Administration). The U.S. reference has been tested against the World Health Organisation standard Hepatitis B Immunoglobulin and found to be equal to 220 international units (IU) per mL.

The removal and inactivation of spiked model enveloped and non-enveloped viruses during the manufacturing process for HyperHEP B has been validated in laboratory studies. Human Immunodeficiency Virus, Type 1 (HIV-1), was chosen as the relevant virus for blood products; Bovine Viral Diarrhea Virus (BVDV) was chosen to model Hepatitis C virus; Pseudorabies virus (PRV) was chosen to model Human Herpes viruses and other large enveloped DNA viruses; and Reo virus type 3 (Reo) was chosen to model non-enveloped viruses and for its resistance to physical and chemical inactivation. Significant removal of model enveloped and non-enveloped viruses is achieved at two steps in the Cohn fractionation process leading to the collection of Cohn Fraction II: the precipitation and removal of Fraction III in the processing of Fraction II + IIIW suspension to Effluent III and the filtration step in the processing of Effluent III to Filtrate III.

Significant inactivation of enveloped viruses is achieved at the time of treatment of solubilised Cohn Fraction II with TNBP/sodium cholate.

Additionally, the manufacturing process was investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents.

Studies of the HyperHEP B manufacturing process demonstrate that TSE clearance is achieved during the Pooled Plasma to Effluent III Fractionation Process ($6.7 \log_{10}$). These studies provide

reasonable assurance that low levels of CJD/vCJD agent infectivity, if present in the starting material, would be removed.

Name and Address

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04 October 2011