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Prescribing Information

HyperHEP B[®] S/D **Hepatitis B Immune Globulin (Human)** **Solvent/Detergent Treated**

DESCRIPTION

Hepatitis B Immune Globulin (Human)- HyperHEP B S/D[®] treated with solvent/detergent is a colorless 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 S/D is prepared by cold ethanol fractionation from the plasma of donors with high titers of antibody to the hepatitis B surface antigen (anti-HBs). The immune globulin is isolated from solubilized 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 S/D 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 S/D 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, FDA). The U.S. reference has been tested against the World Health Organization standard Hepatitis B Immune Globulin 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 S/D 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 solubilized 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.²²⁻²⁵

Studies of the HyperHEP B S/D manufacturing process demonstrate that TSE clearance is achieved during the Pooled Plasma to Effluent III Fractionation Process (6.7 log₁₀). These studies provide reasonable assurance that low levels of CJD/vCJD agent infectivity, if present in the starting material, would be removed.

CLINICAL PHARMACOLOGY

Hepatitis B Immune Globulin (Human) provides passive immunization for individuals exposed to the hepatitis B virus (HBV) as evidenced by a reduction in the attack rate of hepatitis B following its use.¹⁻⁶ The administration of the usual recommended dose of this immune globulin 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:⁷

<u>DAY</u>	<u>% OF SUBJECTS</u>
3	38.9%
7	41.7%
14	11.1%
21	8.3%

Mean values for half-life were between 17.5 and 25 days, with the shortest being 5.9 days and the longest 35 days.⁷

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

In a clinical study in eight healthy human adults receiving another hyperimmune immune globulin product treated with solvent/detergent, Rabies Immune Globulin (Human), HyperRab[®] S/D, prepared by the same manufacturing process, detectable passive antibody titers were observed in the serum of all subjects by 24 hours post injection and persisted through the 21 day study period. These results suggest that passive immunization with immune globulin products is not affected by the solvent/detergent treatment.

INDICATIONS AND USAGE

Recommendations on post-exposure prophylaxis are based on available efficacy data and on the likelihood of future HBV exposure for the person requiring treatment. In all exposures, a regimen combining Hepatitis B Immune Globulin (Human) with hepatitis B vaccine will provide both short- and long-term protection, will be less costly than the two-dose Hepatitis B Immune Globulin (Human) treatment alone, and is the treatment of choice^{8†}.

HyperHEP B S/D is indicated for post-exposure prophylaxis in the following situations:

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 Immune Globulin (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.^{5,8-10} This risk is especially great if the mother is HBeAg-positive.¹¹⁻¹³ For an infant with perinatal exposure to an HBsAg-positive and HBeAg-positive mother, a regimen combining one dose of Hepatitis B Immune Globulin (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.^{8,14} Regimens involving either multiple doses of Hepatitis B Immune Globulin (Human) alone or the vaccine series alone have 70%-90% efficacy, while a single dose of Hepatitis B Immune Globulin (Human) alone has only 50% efficacy.^{8,15}

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 Immune Globulin (Human) is 75% effective if administered within 2 weeks of last sexual exposure.¹⁸¹

Household Exposure to Persons with Acute HBV Infection

Since infants have close contact with primary care-givers and 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 Immune Globulin (Human) and hepatitis B vaccine is indicated if the mother or primary care-giver has acute HBV infection.⁸

Administration of Hepatitis B Immune Globulin (Human) either preceding or concomitant with the commencement of active immunization with Hepatitis B Vaccine provides for more rapid achievement of protective levels of hepatitis B antibody, than when the vaccine alone is administered.¹⁶ 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.¹⁶ Administration of Hepatitis B Immune Globulin (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.¹⁶

CONTRAINDICATIONS

None known.

WARNINGS

HyperHEP B S/D 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 possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Therapeutics, Inc. [1-800-520-2807]. The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to the patient.

HyperHEP B S/D should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immune globulin preparations. Epinephrine should be available.

In patients who have severe thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injections, Hepatitis B Immune Globulin (Human) should be given only if the expected benefits outweigh the risks.

PRECAUTIONS

General

HyperHEP B S/D should not be administered intravenously because of the potential for serious reactions. Injections should be made intramuscularly, and care should be taken to draw back on the plunger of the syringe before injection in order to be certain that the needle is not in a blood vessel. Intramuscular injections are preferably administered in the deltoid muscle of the upper arm or lateral thigh muscle. The gluteal region should not be used as an injection site because of the risk of injury to the sciatic nerve.¹⁷ An individual decision as to which muscle is injected must be made for each patient based on the volume of material to be administered.

Laboratory Tests

None required.

Drug Interactions

Although administration of Hepatitis B Immune Globulin (Human) did not interfere with measles vaccination,¹⁸ it is not known whether Hepatitis B Immune Globulin (Human) may interfere with other live virus vaccines. Therefore, use of such vaccines should be deferred until approximately 3 months after Hepatitis B Immune Globulin (Human) administration. Hepatitis B Vaccine may be administered at the same time, but at a different injection site, without interfering with the immune response.¹⁶ No interactions with other products are known.

Pregnancy Category C

Animal reproduction studies have not been conducted with HyperHEP B S/D. It is also not known whether HyperHEP B S/D can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HyperHEP B S/D should be given to a pregnant woman only if clearly needed.

Pediatric Use

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

ADVERSE REACTIONS

Local pain and tenderness at the injection site, urticaria and angioedema may occur; anaphylactic reactions, although rare, have been reported following the injection of human immune globulin preparations.¹⁹

OVERDOSAGE

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.

DOSAGE AND ADMINISTRATION

Acute Exposure to Blood Containing HBsAg¹⁵

Table 1 summarizes 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 Immune Globulin (Human) should be given as soon as possible after exposure (its value beyond 7 days of exposure is unclear). If Hepatitis B Immune Globulin (Human) is indicated (see Table 1 below), an injection of 0.06 mL/kg of body weight should be administered intramuscularly (see PRECAUTIONS) as soon as possible after exposure and within 24 hours, if possible. Consult Hepatitis B Vaccine package insert for dosage information regarding that product.

Table 1. (adapted from ²⁰)

Recommendations for Hepatitis B Prophylaxis Following Percutaneous or Permucosal Exposure

Source	Exposed Person	
	Unvaccinated	Vaccinated
HBsAg-Positive	<ol style="list-style-type: none"> Hepatitis B Immune Globulin (Human) x 1 immediately* Initiate HB Vaccine Series† 	<ol style="list-style-type: none"> Test exposed person for anti-HBs If inadequate antibody,‡ Hepatitis B Immune Globulin (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"> Initiate HB Vaccine Series Test source of HbsAg. If positive, Hepatitis B Immune Globulin (Human) x 1 	<ol style="list-style-type: none"> Test Source for HbsAg only if exposed is vaccine nonresponder; if source is HbsAg-positive, give Hepatitis B Immune Globulin (Human) x 1 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 Immune Globulin (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 Immune Globulin (Human) should be given 1 month after the first dose.

Prophylaxis of Infants Born to HBsAg and HBeAg Positive Mothers

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

Hepatitis B Immune Globulin (Human) (0.5 mL) should be administered intramuscularly (IM) to the newborn infant after physiologic stabilization of the infant and preferably within 12 hours of birth. Hepatitis B Immune Globulin (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 Immune Globulin (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 Immune Globulin (Human)-- should be repeated at 3 months. If Hepatitis B Vaccine is refused, the 0.5 mL dose of Hepatitis B Immune Globulin (Human) should be repeated at 3 and 6 months. Hepatitis B Immune Globulin (Human) administered at birth should not interfere with oral polio and diphtheria-tetanus-pertussis vaccines administered at 2 months of age. ^[15]

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 should begin the hepatitis B vaccine series if prophylaxis can 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 postexposure treatment. The vaccine has the added advantage of conferring long-lasting protection⁸.

Table 2.

(adapted from [21]) Recommendations for Postexposure 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 time of HBIG* treatment¶

*HBIG = Hepatitis B Immune Globulin (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 the specific vaccine.

Household Exposure to Persons with Acute HBV Infection

Prophylactic treatment with a 0.5 mL dose of Hepatitis B Immune Globulin (Human) and hepatitis B vaccine is indicated for infants < 12 months of age who have been exposed to a primary caregiver 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.⁸

Hepatitis B Immune Globulin (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.¹⁶

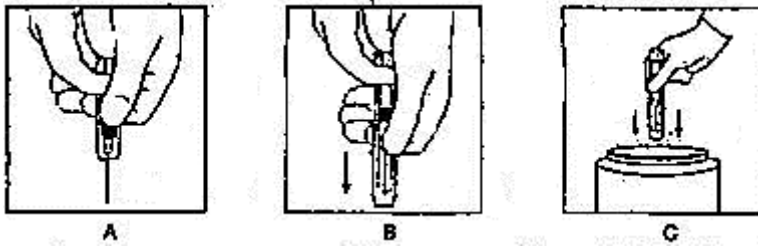
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Administer intramuscularly. Do not inject intravenously.

Hepatitis B Immune Globulin (Human) – HyperHEP B S/D[®] 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 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.

HOW SUPPLIED

HyperHEP B S/D 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 1 mL and a 5 mL single dose vial. HyperHEP B S/D is preservative-free and latex-free.

<u>NDC Number</u>	<u>Size</u>
13533-636-03	0.5 mL syringe
13533-636-02	1 mL syringe
13533-636-01	1 mL vial
13533636-05	5 mL vial

STORAGE

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

CAUTION

Rx only

U.S. federal law prohibits dispensing without prescription.

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Manufacturer: Grifols Therapeutics, Inc. USA

Registration Holder and Importer: Perrigo Israel Agencies Ltd.