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Hepatitis B Immune Globulin (Human)

Hyper**HEP B**®

DESCRIPTION

Hepatitis B Immune Globulin (Human) — Hyper**HEP B**® is a clear or slightly opalescent, and colorless or pale yellow sterile solution of human hepatitis B immune globulin for intramuscular administration. Hyper**HEP B** contains no preservative. Hyper**HEP B** is prepared from pools of human plasma collected from healthy donors by a combination of cold ethanol fractionation, caprylate precipitation and filtration, caprylate incubation, anion exchange chromatography, nanofiltration and low pH incubation. Hyper**HEP B** consists of a 15% to 18% protein solution at a pH of 4.1 to 4.8 in 0.16 M to 0.26 M glycine. The product 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.

When medicinal biological products are administered, the risk of infectious diseases due to transmission of pathogens cannot be totally excluded. However, in the case of products prepared from human plasma, the risk of transmission of pathogens is reduced by epidemiological surveillance of the donor population and selection of individual donors by medical interview; testing of individual donations and plasma pools; and the presence in the manufacturing processes of steps with demonstrated capacity to inactivate/remove pathogen.

In the manufacturing process of Hyper**HEP B,** there are several steps with the capacity for viral inactivation or removal.(1) The main steps of the manufacturing process that contribute to the virus clearance capacity are as follows:

- Caprylate precipitation/depth filtration
- Caprylate incubation
- Depth filtration
- Column chromatography
- Nanofiltration
- Low pH final container incubation

To provide additional assurance of the pathogen safety of the final product, the capacity of the Hyper**HEP B** manufacturing process to remove and/or inactivate viruses has been demonstrated by laboratory spiking studies on a scaled down process model using a wide range of viruses with diverse physicochemical properties.

The combination of all of the above mentioned measures provides the final product with a high margin of safety from the potential risk of transmission of infectious viruses.

The caprylate/chromatography manufacturing process was also investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the variant Creutzfeldt-Jakob disease (vCJD), and Creutzfeldt-Jakob disease (CJD) agents.(1) These studies provide reasonable assurance that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be removed by the caprylate/chromatography manufacturing process.

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.(2-7) 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: (8)

DAY	% OF SUBJECTS
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.(8)

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.

In a clinical study, 12 healthy human adults receiving another hyperimmune immune globulin product, Rabies Immune Globulin (Human), Hyper**RAB**®, 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.

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.(9)

Hyper**HEP B** 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.(6,9-11) This risk is especially great if the mother is HBeAg-positive.(13-15) 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.(9,15) 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.(9,16)

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.(9)

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.(9)

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.(17) 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.(17) 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.(17)

CONTRAINDICATIONS

None known.

WARNINGS

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 possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Therapeutics LLC [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.

Hyper**HEP B** 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

Hyper**HEP B** 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.(18) 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,(19) 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.(17) No interactions with other products are known.

Pregnancy

Animal reproduction studies have not been conducted with Hyper**HEP B**. It is also not known whether Hyper**HEP B** can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Hyper**HEP B** 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.(20)

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 HBsAg(16)

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), 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 (21)) Recommendations for Hepatitis B Prophylaxis Following Percutaneous or Permucosal Exposure

	Exposed Person	
Source	Unvaccinated	Vaccinated
HBsAg-Positive	1. Hepatitis B Immune Globulin (Human) x 1 immediately* 2. Initiate HB Vaccine Series†	1. Test exposed person for anti-HBs. 2. 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)	1. Initiate HB Vaccine Series 2. Test source for HBsAg. If positive, Hepatitis B Immune Globulin (Human)x 1	1. Test Source for HBsAg only if exposed is vaccine nonresponder; if source is HBsAg-positive, give 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.
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.(16)

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 protection.(9)

Table 2. (adapted from (22)) 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 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 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.(9)

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.(17)

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) —Hyper**HEP 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 needle shield secured on the syringe tip, push the plunger rod forward a few millimeters to break any friction seal between the stopper and the glass syringe barrel.
4. Remove the needle shield and expel air bubbles. [Do not remove the 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

Hyper**HEP 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 1 mL and a 5 mL single dose vial. Hyper**HEP B** contains no preservative and is not made with natural rubber latex.

NDC Number	Size
13533-636-03	0.5 mL syringe
13533-636-02	1 mL syringe
13533-636-01	1 mL vial
13533-636-05	5 mL vial

STORAGE

Store at 2–8°C (36–46°F). Do not freeze. Do not use after expiration date. Discard unused portion.

CAUTION

℞ only

U.S. federal law prohibits dispensing without prescription.

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