SUMMARY OF BASIS FOR APPROVAL

Reference Numbers: ***98-0889 and 98-0883***

Applicant: Nabi
5800 Park of Commerce Boulevard N.W.
Boca Raton, FL 33487

Licensed Name: Hepatitis B Immune Globulin (Human)

Trade Name: ***Nabi-HB***™

I. Indications for Use

- Acute Exposure to Blood Containing HBsAg
  Following either parenteral exposure (needlestick, bite, sharps), direct mucous membrane contact (accidental splash), or oral ingestion (pipetting accident), involving HBsAg-positive materials such as blood, plasma or serum.

- Perinatal Exposure of Infants Born to HBsAg-positive Mothers
  Infants born to mothers positive for HBsAg with or without HBeAg.

- Sexual Exposure to HBsAg-positive Persons
  Sexual partners of HBsAg-positive persons.

- Household Exposure to Persons with Acute HBV Infection
  Infants less than 12 months old whose mother or primary caregiver is positive for HBsAg. Other household contacts with an identifiable blood exposure to the index patient.

II. Dosage and Route of Administration

The product is supplied as a sterile solution in single-use 1 and 5 mL vials. The product potency is expressed in international units (IU) by comparison to the World Health Organization (WHO) standard. Each vial contains greater than 312 IU/mL anti-HBs. The potency of each vial exceeds the potency of anti-HBs in an U.S. reference hepatitis B immune globulin (FDA). The U.S. reference has been tested by Nabi against the WHO standard and found it to be equal to 208 IU/mL.

For post-exposure prophylaxis, the product must be administered intramuscularly.

- Acute Exposure to Blood Containing HBsAg

  Table 1 summarizes prophylaxis for percutaneous (needlestick, bite, sharps), 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, as its value after seven days following exposure is unclear. An injection of 0.06 mL/kg of body weight

should be administered intramuscularly as soon as possible after exposure and within 24 hours, if possible. Consult the Hepatitis B Vaccine package insert for dosage information regarding the vaccine.

For persons who refuse Hepatitis B Vaccine or are known non-responders to vaccine, a second dose of Hepatitis B Immune Globulin (Human) should be given one month after the first dose.

Table 1 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) X 1 immediately plus HB vaccine booster dose.
Known Source - High Risk for HBsAg-positive	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) X 1 immediately plus HB vaccine booster dose.
Known Source - Low Risk for HBsAg-positive	Initiate HB vaccine series	Nothing required.
Unknown Source	Initiate HB vaccine series	Nothing required.

* Hepatitis B Immune Globulin (Human) dose of 0.06 mL/kg IM.
† See manufacturers' recommendation for appropriate dose.
‡ Less than 10 mIU/mL by radioimmunoassay, negative by enzyme immunoassay.

- Prophylaxis of Infants born to Mothers who are positive for HBsAg with or without HBeAg

Table 2 contains the recommended schedule of hepatitis B prophylaxis for infants born to mothers that are either known to be positive for HBsAg or have not been screened. Infants born to mothers known to be HBsAg-positive should receive 0.5 mL Hepatitis B Immune Globulin (Human) after physiologic stabilization of the infant and preferably within 12 hours of birth. The Hepatitis B Vaccine series should be initiated simultaneously, if not contraindicated, with the first dose of the vaccine given concurrently with the Hepatitis B Immune Globulin (Human), but at a different site. Subsequent doses of the vaccine should be administered in accordance with the recommendations of the manufacturer.

Women admitted for delivery, who were not screened for HBsAg during the prenatal period, should be tested. While test results are pending, the infant should receive hepatitis B vaccine within 12 hours of birth (see manufacturers' recommendations for dose). If the mother is later found to be HBsAg positive, the infant should receive 0.5 mL Hepatitis B Immune Globulin (Human) soon as possible and within seven days of birth; the efficacy of Hepatitis B Immune Globulin (Human) administered after 48 hours of age is not known. Testing for HBsAg and anti-HBs is recommended at 12-15 months of age. If HBsAg is not detectable and anti-HBs is present, the child has been protected.

Table 2 Recommended Schedule of Hepatitis B Immunoprophylaxis to Prevent Perinatal Transmission of Hepatitis B Virus Infection

	Age of Infant	
Administer	Infant Born to mother known to be HBsAg positive	Infant born to mother not screened for HBsAg
First Vaccination*	Birth (within 12 hours)	Birth (within 12 hours)
Hepatitis B Immune Globulin (Human)†	Birth (within 12 hours)	If mother is found to be HBsAg positive, administer dose to infant as soon as possible, not later than 1 week after birth
Second Vaccination*	1 month	1-2 months
Third Vaccination*	6 months‡	6 months‡

* See manufacturers' recommendations for appropriate dose.
†0.5 mL administered IM at a site different from that used for the vaccine.
‡See ACIP recommendation.

- Sexual Exposure to HBsAg-positive Persons

  All susceptible persons whose sexual partners have acute hepatitis B infection should receive a single dose of Hepatitis B Immune Globulin (Human) (0.06 mL/kg) and should begin the Hepatitis B Vaccine series, if not contraindicated, within 14 days of the last sexual contact or if sexual contact with the infected person will continue. Administering the vaccine with Hepatitis B Immune Globulin (Human) may improve the efficacy of post exposure treatment. The vaccine has the added advantage of conferring long-lasting protection.

- Household Exposure to Persons with Acute HBV Infection

  Prophylaxis of an infant less than 12 months of age with 0.5 mL Hepatitis B Immune Globulin (Human) and Hepatitis B Vaccine is indicated if the mother or primary caregiver has acute HBV infection. Prophylaxis of other household contacts of persons with acute HBV infection is not indicated unless they had an 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.

III. Manufacturing and Controls

PRODUCTION: The product is manufactured from pooled source plasma selected for high titers of antibodies to hepatitis B surface antigen (anti-HBs) collected at Nabi's FDA licensed plasmapheresis centers. The plasma units are tested and found nonreactive for HBsAg, anti-hepatitis C virus (HCV) and anti-HIV-1/2, HIV-1 p24 antigen, and to have an alanine aminotransferase level less than twice the upper limit of normal. The IgG is separated by ——— ——————— and anion-exchange chromatography, and concentrated by ultrafiltration. The product is filtered using a Planova 35 nm Virus Filter that is effective in reducing some known enveloped and non-enveloped viruses. Inactivation of enveloped viruses is accomplished by the addition of a solvent-detergent (SD) mixture of —— tri-(n-butyl)-phosphate (TNBP) and —— Triton X-100. The SD mixture is then removed by ——————————— The immune globulin fraction is formulated in 0.075 M sodium chloride, 0.15 M glycine, and 0.1% polysorbate 80, pH 6.25. Following sterile filtration, it is filled into vials. The product is tested for:

Potency	Glycine	Total Protein
pH	Sodium Chloride	Total Monomer & Dimer
IgG/Protein Ratio	Aggregation & Fragmentation	Anti-Complementary Activity
TNBP	Triton X-100	Immunoglobulins A, G, M
Identity ELISA	Identity (Human)	Agarose Gel Electrophoresis
Safety	Sterility	Polysorbate 80
Bacterial Endotoxin	Heat Stability	Appearance

STABILITY STUDIES: Studies were performed to support a dating period of 12 months under recommended storage condition (2 to 8 °C). The date of manufacture is defined as the date that the first ___ filtration is performed. Data from studies to monitor product stability

LOT RELEASE: Samples from product lots have been analyzed by the FDA and found to be satisfactory. The product will be subject to lot-by-lot release.

LABELING: The label, carton, and package insert have been reviewed and found to comply with applicable regulations.

ESTABLISHMENT INSPECTION: The prelicensing inspections were performed at Nabi-Miami on October 26-30, 1998

ENVIRONMENTAL IMPACT ANALYSIS: Nabi claimed an exemption from the requirement for preparing an environmental assessment based on 21 CFR 25.31(a), (b), and (i). The PLA/ ELA for ***Nabi-HB*** complied with one or more of the above categorical exclusion criteria and no extraordinary circumstances exist.

IV. Pharmacology

PHARMACOLOGICAL PROFILE: The product is prepared by purification of a human plasma protein fraction, consisting primarily of IgG, by means of anion-exchange chromatography and ultrafiltration. This process causes very little change in the physical and chemical properties of the IgG molecules. Consequently, the preparation has a metabolic half-life similar to that of native IgG. Potency of the preparation has been demonstrated both by laboratory tests and by clinical studies. Thus, the purified IgG in the product appears to be pharmacologically similar to IgG that normally circulates in human plasma.

INVESTIGATION IN ANIMALS: No animal toxicity studies were performed for this product, as there is broad experience in humans with immunoglobulin products containing similar formulations and manufactured by the same process.

V. Medical

INTRODUCTION: Estimates from the U. S. Centers for Disease Control suggest that the incidence of acute viral hepatitis has been rising slowly over the last 25 years. Approximately

300,000 cases annually are due to hepatitis B. The true incidence of viral hepatitis in the U.S. may be five to eight times that actually reported each year, and may be as high as 1-2 per 1,000 population. The lifetime risk of hepatitis B virus (HBV) infection for all U.S. residents has been estimated at 5%, but certain groups may have significantly higher risk. After acute hepatitis B infection, 6-10% of patients develops chronic infection. Of these, most have relatively benign chronic persistent hepatitis, but one quarter develop chronic active hepatitis. A substantial proportion of these patients goes on to develop cirrhosis. In the U.S., approximately 5,000 persons per year die of complications of HBV infection, including fulminant hepatitis with hepatic failure, cirrhosis, or hepatocellular carcinoma. Perinatal transmission of the hepatitis B virus has serious consequences for the infant, because most become chronic carriers and are at risk for eventual development of cirrhosis and hepatocellular carcinoma.

——— ***Nabi-HB*** is a 5% immunoglobulin containing only anti-HBs-rich material, and thus reducing the number of plasma donors contributing to the final product. In addition, ***Nabi-HB*** is solvent/detergent treated to inactivate enveloped viruses and nanofiltered to reduce the levels of some enveloped and non-enveloped viruses.

Neonatal studies demonstrated the combined use of hepatitis B vaccine and Hepatitis B Immune Globulin (Human) to be more effective in the maintenance of protective antibody levels than prophylactic administration of hepatitis B vaccine or Hepatitis B Immune Globulin (Human) alone. No prospective studies have been performed on the efficacy of concurrent hepatitis B vaccine and Hepatitis B Immune Globulin (Human) administration following parenteral exposure, mucous membrane contact or oral ingestion in adults; however, the Centers for Disease and Prevention Advisory Committee on Immunization Practices (ACIP) advises that the combination prophylaxis be provided based upon the increased efficacy found with that regimen in neonates. Cases of type B hepatitis are rarely seen following exposure to HBV in persons with preexisting anti-HBs.

PHARMACOKINETICS AND BIOEQUIVALENCE: Nabi conducted two pharmacokinetic trials to evaluate the pharmacokinetics of ***Nabi-HB*** administered intramuscularly. The first study was designed to characterize secondary pharmacokinetic parameters. The second study was designed to test pharmacokinetic equivalence between ***Nabi-HB*** and ————

Nabi —— was conducted over 84 days to allow collection of data on at least three half-lives. Eighteen healthy volunteers were randomized to receive one of two lots of ***Nabi-HB*** as a single intramuscular injection at 0.06 mL/kg. Serum samples were drawn for anti-HBs levels and for safety laboratory tests. Noncompartmental and compartmental pharmacokinetic analyses on the anti-HBs levels were performed using descriptive statistics.

This study demonstrated that ***Nabi-HB*** administered as a single intramuscular dose to healthy people was safe, well tolerated, and was pharmacokinetically similar to other immune globulins with a $t_{½}$ of 26.9 days and elimination constant of 0.0287 day^{-1}. The C_{max} of 94.1 mIU/mL (range 49.6-176.5 mIU/mL) was lower than anticipated. Therefore, the specifications for the potency range for ***Nabi-HB*** were raised by —— to allow for possible pharmacokinetic

differences between the investigational product and ——— Other pharmacokinetic parameters revealed an average T_{max} of 6.6 days (median 5.1 days; range 2.9-14.3 days) and AUC_{0-84} 3282 mIU x day/mL (median 2922 mIU x day/ mL; range 2148-5598 mIU x day/mL).

In clinical trial Nabi —— the pharmacokinetic profile of ***Nabi-HB*** and ——— were each evaluated in a parallel design study in 30 subjects (15 male and 15 female) to establish their comparability. Each subject received, in blinded fashion, a single intramuscular injection of 0.06 mL/kg in accordance with the label rather than a dose based on test article potency. To correct for this feature in the analysis of plasma levels of anti-HBs, the data were normalized by the ratio of the potency of ***Nabi-HB*** to ——— Potency was determined using the ——— assay. When dosage was based on mL/kg rather than potency, the two products were not pharmacokinetically equivalent with regard to C_{max} or AUC. The geometric mean for AUC_{0-28} of ***Nabi-HB*** was 4573 mIU x day/mL (range 2155-8297 mIU x day/mL) and that for ——— ——— Similarly, geometric mean for C_{max} of ***Nabi-HB*** was 232.9 mIU/mL (range 108.8-471.4 mIU/mL) and that for ——— ——— Since a parallel study design was used, statistical differences for AUC and Cmax were assessed using a t-test with alpha 0.05. When adjusted for potency, no statistically significant differences in AUC ($p = 0.27$, power = 0.8) or C_{max} ($p = 0.50$; power = 0.6) were observed. The time to C_{max} or T_{max} was comparable between the two products with a arithmetic mean for ***Nabi-HB*** of 5.73 days (median 5 days; range 3-21 days) and that of ———

SAFETY: Expected reactions that may occur following intramuscular injection of human immunoglobulin preparations include local pain and tenderness at the injection site, urticaria and angioedema. Anaphylactic reactions, although rare, have been reported.

Nabi conducted three pharmacokinetic trials to evaluate the safety of ***Nabi-HB*** administered intramuscularly. Seventy-six healthy volunteers received ***Nabi-HB*** compared to ——— ——— Forty-six ***Nabi-HB*** subjects and ——— subjects were followed for 84 days; 30 subjects in each group were followed for 28 days. There were no statistically significant differences between treatment groups for frequency of adverse events in any body system. There were no deaths and no serious adverse events. The spectrum and severity of adverse events observed with ***Nabi-HB*** were similar to those seen with ———

RELATED ADVERSE EVENTS: The number of patients with reactions related to the administration of ***Nabi-HB*** included local reactions such as pain 9 (12%), ache 2 (3%), erythema 2 (3%), heat 1 (1%), and burning 2 (3%) at the injection site, as well as systemic reactions such as headache 20 (26%), malaise 4 (5%), nausea 4 (5%), diarrhea 2 (3%) and myalgia 4 (5%). The majority of reactions were reported as mild. The following adverse events were reported once each in pharmacokinetics trials and were probably related to ***Nabi-HB***: chills, fatigue, lightheadedness, abdominal cramping, and retching. No anaphylactic reactions with ***Nabi-HB*** have been reported.

Hematology and Chemistry Laboratory Tests: The majority of subjects remained within normal limits for hematologic parameters over the course of the study. A shift analysis did not reveal any abnormal hematologic response associated with either product. Mean values for clinical chemistry parameters were within normal limits and did not differ significantly between groups at each time interval or over time within each group.

VIRAL MARKERS: HBsAg and anti-HIV-1 were negative for all subjects at Screening and Termination. In Nabi —— anti-HCV was positive at Screening and Termination for two subjects with normal liver function tests. No subjects seroconverted to HCV between Screening and Termination.

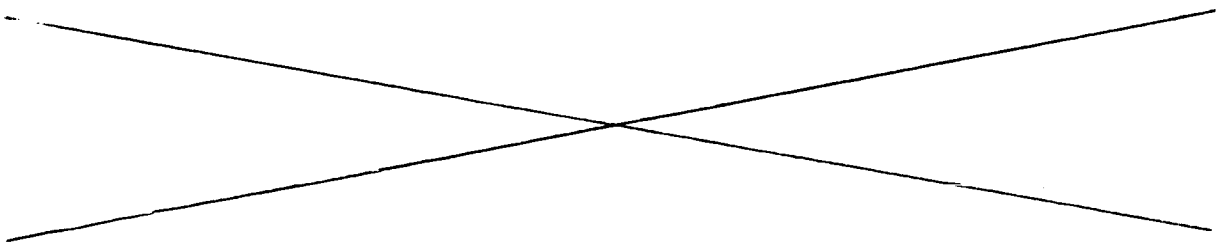
VITAL SIGNS: Although several statistically significant differences were noted between the two treatment groups, none of these differences was clinically relevant.

CONCLUSION: Overall, ***Nabi-HB*** was safe and well tolerated and had no adverse effects on vital signs or laboratory measurements of hematologic, renal, or hepatic function. There was no seroconversion to HIV-1 or HBsAg. Reactogenicity and adverse events were similar between ***Nabi-HB*** and ———— The most common reactions were headache and local pain, ——

VI. Adequacy of Labeling

The labeling of the product is adequate; the product pharmacology, recommended uses, dosing and administration procedures, and possible adverse reactions are sufficiently described. Claims for bioequivalence are supported by adequate and well-controlled clinical studies.

VII. Phase IV Commitment



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