'SUMMARY OF BASIS FOR APPROVAL

Reference: **STN: 103945 (99-1442)**

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 Exnosure 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 Exuosure of Infants Born to **HBsAg-positive Mothers**
  Infants born to mothers positive for HBsAg with or without **HBeAg.**

- Sexual Exnosure 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 three dosage forms: 1 **mL** in a 2mL vial, 5 **mL** in a 6 **mL** vial, and 0.5 **mL** in a 1 **mL** syringe. The product potency is expressed in international units **(IU)** by comparison to the World Health Organization (WHO) standard. Each vial contains greater than 3 12 **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 Exnosure 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 Pennucosal Exposure

Source	Exposed Person	
	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 hi& titers of antibodies to hepatitis B surface antigen (anti-HE&) collected at. FDA licensed plasmapheresis centers. The plasma units are tested and found nonreactive for HBsAg, anti-hepatitis C virus (HCV) and anti-HIV-l/2, HIV-1 p24 antigen, and to have an alanine aminotransferase level less than twice the upper limit of normal. The plasma is processed using process. 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 0.3% tri-(n-butyl)-phosphate (TNBP) and 1 .O% Triton X-100. The SD mixture is then removed by The immune globulin fraction is further purified by an anion exchange chromatography and formulated in 0.075 M sodium chloride, 0.15 M glycine, and 0.01% polysorbate 80, pH 6.2. Following sterile filtration, it is filled into vials. The product is tested for:

APPEARANCE	GENERAL SAFETY
Glycine	Sterility
Protein Content	
PH	Polysorbate 80
Purity	
Stability	
Potency	Purity
Identity	

STABILITY STUDIES: Studies were performed to support a dating-period of 24 months under recommended storage conditions (5± 3). The date of manufacture is defined as the date of the strile of the formulated bulk product. Data from studies to monitor product stability have been submitted and routine stability monitoring is ongoing in an effort to extend the dating period to -months.

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 Plasma Manufacturing Facility located in . on June 19-28 , 2000.

ENVIRONMENTAL IMPACT ANALYSIS: Nabi claimed an exemption from the requirement for preparing an environmental assessment based on 21 CFR 25.3 l(a), (b), and (i). The BLA 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, using a ' alcohol precipitation process followed by an anion exchange chromatography. 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.

INVESTIGATIONS 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 l-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 develop chronic infection. Of these, most have relatively benign chronic persistent hepatitis, but one quarter develop chronic active hepatitis. A substantial proportion of these patients go 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.

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.

Licensed Nabi-HB, a formulation of Hepatitis B Immune Globulin currently marketed by Nabi, is a 5% anti-H&-rich immunoglobulin solution that is solvent/detergent treated to remove enveloped viruses and nanofiltered to reduce the levels of some enveloped, and non-enveloped viruses. ***Nabi-HB (BocaHB VIg)*** is a 5% immunoglobulin containing only anti-HBs-rich material, that is solvent/detergent treated to inactivate enveloped viruses and nanofiltered to reduce the levels of some enveloped and non-enveloped viruses.

PHARMACOIUNETICS AND BIOEQUIVALENCE: Nabi conducted two pharmacokinetic trials to evaluate the pharmacokinetics of ***Nabi-HB (Boca HBVIg)*** administered intramuscularly. The first study was designed to characterize pharmacokinetic parameters. The second study was designed to test bioequivalence between ***Nabi-HB (Boca HBVIg)*** and licensed Nabi-HB manufactured .

Nabi-4201 was conducted over 84 days to allow collection of data on at least three half-lives. Twenty healthy volunteers were randomized to receive one of two lots of ***Nabi-HB (Boca HBVIg)*** 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 (Boca HBVIg)*** 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 23.1±5.5 days, 1.7±3.1 days for ka, 0.032±.007 days for kel, 0.35±0.12 L/day for clearance and 11.2±3.4 L for volume distribution. The average AUC to day 84 was 4236±13 13 IU-day/L; AUC to infinity was 4654±1529 IU-day/L. The geometric mean for Cmax was 121.3 IU/L and the average t_{max} was 6.5±4.3 days.

In Nabi- 4202 safety and the pharmacokinetics of *Nabi-HB (Boca HBVIg) were* compared to licensed Nabi-HB in 60 healthy volunteers, over 28 days (approximately one half-life). Thirty subjects (fifteen males and fifteen females) were randomized to each of the two study drugs. Each subject received, in a blinded fashion, a single intramuscular injection of 0.06 mL/kg. Serum samples were drawn for anti-HBs levels and for safety laboratory tests. The primary endpoints were observed C_{max}, t_{max}, and AUC. For equivalence to be infii the 90% confidence interval for the ratio of group means had to be within the-interval 0.80, 1.25 for AUC. *Nabi-HB (Boca HB VIg)* and Licensed Nabi-HB were pharmacokinetically equivalent on the basis of AUC with the 90% confidence interval of 0.85 and 1.22. Cmax was also found to be within acceptable limits of pharmacokinetic equivalence with 90% confidence limits of 0.89 and 1.22. Pharmacokinetic differences between male and female subjects were observed. NAB1 study 4202 was analyzed by a t-test for differences in AUC and Cmax between males and females were found to be significantly different. The AUC for males (N=28) was 2007 IU-hr/ml whereas for females (N=30) it was 1447 IU-hr/ml. Similarly, Cmax for males was 105 IU/ml whereas for females it was 69 IU/ml. These differences were significant at P<0.001.

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.

Related Adverse Events: For Nabi 4201, 20 adult male and female subjects were studied for 84 days. Six female subjects experienced 11 reactions and two males experienced 3 reactions. The reactions experienced included localized ache, headache, vomiting, myalgia, and generalized discomfort. All occurred within the first 7 days after injection. No severe adverse reactions occurred.

For Nabi 4202, 30 adult male and female subjects received -material and 30 subjects received Nabi HB (' material) and were studied for 28 days. The spectrum and severity of adverse events observed with the material were similar to those seen with licensed Nabi-HB. There were no statistically significant differences between treatment groups with respect to frequency of adverse events in any body system. There were no deaths and no serious adverse events. Among females, adverse events observed with the material consisted of chills, sore throat, nasal congestion, pain in various locations, emesis, rash, and one instance of ecchymosis near the injection site. Among males, adverse events consisted of upper respiratory symptoms, headache, musculoskeletal changes, upper gastrointestinal symptoms, and elevation in serum creatinine levels.

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-l were negative for all subjects at Screening and Termination. 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 (Boca HBVIg)*** *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 (BocaHBVIg)*** and licensed Nabi-HB . The most common reactions were headache and local pain, both of which also occurred with licensed Nabi-HB.

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.

Mahmood Farshid, Ph.D. 10-17-01
Chair, Review Committee Date

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