HEPATITIS B VACCINE RECOMBINANT (Systemic)

Introduction

VA CLASSIFICATION (Primary)¾IM100

Note: This monograph is specific to the recombinant DNA hepatitis B vaccine derived from the surface antigen of hepatitis B virus (HBsAg) and produced in yeast (Saccharomyces cerevisiae) cells 43, 44.

Commonly used brand name(s):Engerix-B; Recombivax HB; Recombivax HB Dialysis Formulation.

Another commonly used name is HB vaccine 5.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

Category

Immunizing agent (active).

Indications

General considerations

Hepatitis B virus (HBV) (previously known as the serum hepatitis virus) infection is a major cause of acute and chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma worldwide 8, 45, 66.

It is estimated that more than 200 million persons are chronically infected with HBV worldwide, and up to 80% of new liver cancer cases each year are attributable to HBV infection 67.

Viral hepatitis is the second most reported disease in the U.S., with hepatitis B accounting for about 45% of cases 46.

HBV infection is a significant cause of morbidity and mortality in the U.S. 47 , and there are approximately 200,000 to 300,000 new cases of hepatitis B infection each year 47, 48.

Among infected persons, approximately 4000 to 5000 die each year of HBV-induced chronic liver disease or hepatocellular carcinoma 48.

It is estimated that more than 1 million Americans have chronic HBV infection 47.

In the U.S., most persons infected with HBV acquire the infection during adolescence or young adulthood 49.

HBV is transmitted primarily through sexual contact, intravenous drug use, regular household contact with a chronically infected person, or occupational exposure 49, 50.

However, for approximately one third of persons who have acute hepatitis B, the source of infection is unknown [49].

Because of lifestyle, occupation, or ethnicity, certain groups have a much higher risk of hepatitis B infection than the general population [46].

These groups include health care workers [46], those undergoing dialysis [73], persons from areas in which HBV infection is endemic, homosexual men, heterosexual persons with multiple sex partners, intravenous drug users, household contacts of HBV carriers, children of carrier mothers, and clients and staff of programs for the developmentally disabled [46].

In pregnancy, HBV is thought to be transmitted primarily at the time of delivery [51, 53].

Vertical transmission is an effective route for neonatal infection, and 10 to 85% of infants born to hepatitis B surface antigen (HBsAg)-positive mothers will become infected, depending on the hepatitis B e antigen (HBeAg) status of the mother [51].

Morbidity and mortality rates are significant higher among infected infants than in the general newborn population, with 90% having chronic infection, and 25% of this population ultimately dying of complications of liver disease [51].

However, 90% of infections can be prevented if HBsAg-positive mothers are identified, and their offspring are treated promptly after delivery with hepatitis B immune globulin and hepatitis B vaccine [51, 52].

The Centers for Disease Control and Prevention (CDC) and the American College of Obstetricians and Gynecologists recommend adding HBsAg to routine early prenatal tests and notifying the pediatrician as soon as possible as to the HBV status of the mother so the newborn can be given HBV vaccination and hepatitis B immune globulin as appropriate [51].

After a person has been exposed to HBV, appropriate immunoprophylactic treatment can effectively prevent infection. The mainstay of postexposure immunoprophylaxis is hepatitis B vaccine, but in some settings the addition of hepatitis B immune globulin will provide some increase in protection [23].

Coinfection with HBV and human immunodeficiency virus (HIV) is common in the U.S [54].

The two viruses are transmitted through similar routes, including sexual contact, sharing of infected needles, and exposure to infected blood products [54].

In one study, the prevalence of HBV markers in patients with acquired immune deficiency syndrome (AIDS) was reported to be as high as 89% [54].

These patients are at high risk of developing a chronic carrier state, viremia, and chronic hepatitis [54].

At present, no medication therapy can reliably treat patients with chronic HBV infection [54].

Theoretically, early identification and vaccination of high-risk groups against HBV before they acquire HIV infection should produce the best response to the vaccine 54.

However, this strategy has not been successful, and coinfection continues to be a significant cause of morbidity and mortality in these patients 54.

Accepted

Hepatitis B virus infection (prophylaxis)¾Hepatitis B recombinant vaccine is indicated for immunization of persons of all ages against infection caused by all subtypes of hepatitis B virus. The dialysis formulation of hepatitis B recombinant vaccine is indicated for immunization of adult predialysis and dialysis patients 1, 4, 6, 7, 10, 23.

Hepatitis B recombinant vaccine is also recommended in conjunction with hepatitis B immune globulin (HBIG) for postexposure prophylaxis 1, 5, 12, 23.

Unless otherwise contraindicated, hepatitis B recombinant vaccine is recommended for all infants (whether at high or low risk), adolescents, and persons of all ages who live in areas of high prevalence of hepatitis B infection or who are, or will be, at increased risk of infection from hepatitis B virus 43, 44.

The Committee on Infectious Diseases of the American Academy of Pediatrics, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention, and the American Academy of Family Physicians recommend that all adolescents who have not previously received three doses of hepatitis B vaccine should initiate or complete the series at the 11- to 12-year-old visit to the physician 55.

Examples of groups identified as being at increased risk of infection include:
· Newborn infants, including those born to HBsAg-positive mothers whether or not the infants are HBeAg-positive 43.

The routine hepatitis B vaccination series should begin at birth for all infants 57.

Infants of HBsAg-positive mothers should receive the first dose of vaccine along with immunoprophylaxis with hepatitis B immune globulin 57.

· Health care personnel 43, 44, 64.

HBV infection is a major infectious occupational hazard for healthcare and public safety workers. The risk of acquiring HBV infection from occupational exposure is dependent on the frequency of percutaneous and permucosal exposures to blood or blood products. Risk is often the highest during the professional training period of medical personnel. Therefore, immunization should be completed during training in the schools of medicine, dentistry, nursing, laboratory technology, and other allied health professions before workers have their first occupational contact with human 39 blood 1, 5, 6, 23, 31.

· Employees in medical facilities, such as paramedical personnel and custodial staff, who may be exposed to the virus via blood, blood products, or other patient specimens 1, 6, 23, 31.

· Patients and staff of institutions or residential settings for the developmentally disabled. Staff who work closely with patients, and the patients themselves, should be immunized. The risk in institutional environments is associated not only with blood exposure, but also with bites and contact with skin lesions and other infective secretions 1, 5, 6, 23, 31.

· Staff of nonresidential day-care programs for the developmentally disabled, such as schools and sheltered workshops. Staff who have clients who are HBV carriers are at a risk of HBV infection comparable to that of health care workers 39.

Although the risk of HBV infection to other clients appears to be lower than the risk to staff, immunization of clients is recommended if a client who is an HBV carrier is aggressive or has special medical problems that increase the risk of others exposure to his or her blood or serous secretions 1, 5, 6, 23, 31.

· Sexually active homosexual and bisexual males, including those with human immunodeficiency virus (HIV) infection. Sexually active homosexual and bisexual males should be immunized regardless of their age or the duration of their homosexual practices. Males should be immunized as soon as possible after their homosexual activity begins or if they anticipate initiating homosexual activity 1, 5, 6, 23, 31.

· Sexually active heterosexual persons with multiple sexual partners. Heterosexual persons with multiple sexual partners are at increased risk of HBV infection; the risk increases with the number of sexual partners. Immunization is recommended for prostitutes, persons with a history of multiple sexual partners in the last 6 months, and persons who have recently or repeatedly acquired other sexually transmitted diseases 1, 5, 6, 23, 31.

· Hemodialysis patients. Although seroconversion rates and antibody to hepatitis B surface antigen (anti-HBs) titers are lower after vaccination in hemodialysis patients than in healthy persons, for the patients who do respond, hepatitis B recombinant vaccine will protect them from HBV infection and reduce the need for frequent serologic screening 5, 6, 23, 37.

· Patients with renal disease. Some studies have shown higher seroconversion rates and antibody titers after vaccination for patients with uremia who were immunized before they required dialysis. Therefore, it is recommended that patients be immunized early in the course of renal disease 5.

· Users of illicit injection drugs. Injection drug abusers should be immunized as soon as possible after drug abuse begins 1, 5, 6, 23, 31.

· Patients with clotting disorders who receive clotting factor concentrates. These patients are at increased risk of HBV infection and should be immunized at the time that their specific clotting disorder is identified 39.

Preimmunization testing for HBsAg 39 may be cost-effective in patients who have already received multiple infusions of these blood products 5, 6, 12.

· Household and sexual contacts of HBV carriers. Household contacts of HBV carriers are at high risk, and their sexual contacts appear to be at the greatest risk, of HBV infection 1, 5, 6, 23, 31.

· Persons accepting orphans or adoptees from countries of high or intermediate HBV endemicity. The children should be tested for HBsAg. If the children are found to be positive, the adopting family members should be immunized 5, 23.

· Populations with high endemicity of HBV infection, such as Alaskan Eskimos, Pacific Islanders, Haitian and Indochinese immigrants 43 , and refugees from HBV-endemic areas 1, 5, 6, 12, 17, 31.

· Inmates of long-term correctional facilities 1, 5, 23, 31.

· International travelers. Immunization should be considered for travelers who plan to reside abroad 39 for more than 6 months and will have close contact with the local population in areas with high levels of endemic HBV. Immunization also should be considered for short-term travelers who are likely to have sexual contact with, or contact with blood from, members of the local population in endemic areas 5, 6, 23.

· Military personnel identified as being at increased risk 1, 6, 31.

· Morticians and embalmers 1, 31.

· Police and fire department personnel. Paramedical or other personnel who render first aid or medical assistance may be exposed to the hepatitis B virus 6, 31.

Hepatitis D virus infection (prophylaxis)¾Since hepatitis D infection (caused by the delta hepatitis virus) can occur only in the presence of hepatitis B infection, it can be expected that hepatitis D infection will be prevented by immunization with hepatitis B recombinant vaccine 1, 2, 5, 6, 23.

Unaccepted

Because this vaccine protects only against infection with subtypes of hepatitis B virus (and indirectly against infection with hepatitis D virus), immunization with hepatitis B recombinant vaccine is not an indication for, and will not provide protection against, hepatitis caused by other hepatitis viruses or by other viruses known to infect the liver 1, 4, 6, 7, 12, 39.

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Hepatitis B recombinant vaccines are produced from Saccharomyces cerevisiae74 , into which a plasmid containing the gene for the hepatitis B surface antigen (HBsAg) has been inserted. Purified HBsAg is obtained by lysis of the yeast cells and separation of the HBsAg from the yeast components. These vaccines contain more than 95% HBsAg protein. Yeast-derived protein constitutes no more than 5% of the final product. Hepatitis B recombinant vaccines are adsorbed with aluminum hydroxide (0.5 mg per mL). No substances of human origin are used in their manufacture 1, 4, 5, 6, 7, 23, 31.

Protective effect

Well-designed clinical trials have demonstrated the efficacy of hepatitis B recombinant vaccines 69, 73.

Immunization reduced the incidence of hepatitis B by 90 to 95% in cohorts of homosexual men and of health care workers frequently exposed to blood 69.

Protection is evident within weeks after the first two doses of vaccine in adults and, in large prospective studies, is correlated with anti-HBs titers above 10 milliInternational Units per milliliter (mIU/mL) 69.

Pre-exposure vaccination produces protective levels of antibody in 95 to 100% of infants after three doses, in 80 to 95% after two doses, and in 20 to 50% after one dose 61.

For infants born to HBsAg-positive mothers, the average efficacy of postexposure prophylaxis with hepatitis B recombinant vaccine and hepatitis B immune globulin to prevent chronic infection is 95%; vaccination alone and the combined regimen have similar efficacy 61.

Studies have revealed that the percentage of infants who develop protective levels (³ 10 mIU/mL) of antibody to HBsAg (anti-HBs) and the final anti-HBs concentrations may be lower in premature infants given the hepatitis B recombinant vaccines beginning at birth than if the initial dose is delayed until they are older or weigh more than 2000 grams 71.

In one study, the response rates for premature infants who received their first doses of hepatitis B recombinant vaccine at a weight of either 1000 to 1999 grams or 2000 grams or more were 79% and 91% respectively; the response rate was 100% for full-term infants 71.

The second dose was given 1 month later, and the third dose was given approximately 5 months after the first dose 71.

In a study of premature Thai infants with gestational ages of 28 to 32 weeks, 11 of 14 (78%) developed protective levels of anti-HBs after receiving three 10-mcg doses of hepatitis B recombinant vaccine; doses were given at birth, 1 month of age, and 6 months of age. Eleven of 11 infants with gestational ages of 33 to 37 weeks developed protective levels. The overall response rate for premature infants was 22 of 25 (88%) 71.

A third study in Italy revealed that 37 of 37 premature infants (< 37 weeks' gestation) developed anti-HBs levels of 10 mIU/mL or greater after receiving 10-mcg doses of hepatitis B recombinant vaccine at birth, 1 month of age, and 3 months of age; or at birth, 1 month of age, and 6 months of age 71.

Lower gestational age but not lower birth weight was associated with lower final antibody concentrations 71.

As is seen with other vaccines, serologic response of human immunodeficiency virus (HIV)-infected patients to both plasma-derived and recombinant HBV vaccines have been suboptimal 54.

Protective antibody responses after three doses of hepatitis B recombinant vaccine were achieved in 28% of 32 HIV-infected patients, as compared with 88% of 75 HIV-negative individuals 54.

An additional dose given 9 months after the last of three doses led to only one additional HIV-infected patient achieving protective level 54.

The CD4+ cell count was significantly higher in responders than in nonresponders 54.

In addition, nonresponders were significantly more likely to progress to HIV-related diseases within 24 months than were responders 54.

In one study, hepatitis B recombinant vaccine was administered to 16 HIV-positive and 68 HIV-negative patients 54.

One month after the last vaccine of the series, low or no antibody response had occurred in 44% of the HIV-positive group as compared with only 9% in the HIV-negative group 54.

Duration of protective effect

Long-term protection (6 to 13 years) from hepatitis B virus (HBV) infection has been shown in approximately 3700 immunized persons from populations that continue to be exposed to HBV 61.

Vaccine-induced antibody levels may decline with age 60.

Loss of antibody has occurred in one third of adults and 15% of infants and children. Asymptomatic infections have been identified in approximately 3% of these individuals, and HBsAg-positive infections in less than 0.5%, but not all infections were chronic 61.

Protection against HBV infection persists even when antibody titers subsequently decline; therefore, booster doses are not necessary 68.

In contrast, a lower proportion (50 to 60%) of vaccinated hemodialysis patients develops a protective antibody response 68.

Booster doses are necessary to maintain protection against hepatitis B infection when antibody titers decline below protective levels 68.

However, more than 50% of hemodialysis patients can be protected from hepatitis B infection by vaccination, and maintaining immunity among these patients will reduce the frequency and cost of serologic screening 68.

Precautions to Consider

Cross-sensitivity and/or related problems

Patients sensitive to the plasma-derived hepatitis B vaccine may be sensitive to the recombinant hepatitis B vaccine also.

Pregnancy/Reproduction

Pregnancy¾Adequate and well-controlled studies have not been done in humans 39.

However, risk from vaccination is largely theoretical; there is no convincing evidence of risk from vaccinating pregnant women 56.

Hepatitis B recombinant vaccine is recommended for pregnant women at risk of hepatitis B infection. All pregnant women should be tested for the presence of hepatitis B virus surface antigen (HBsAg), and those infected with hepatitis B virus (HBV) should be monitored carefully to ensure that the infant receives hepatitis B immune globulin and begins the hepatitis B vaccine series shortly after birth 56.

Studies have not been done in animals.

FDA Pregnancy Category C 1, 6.

Breast-feeding

It is not known whether the vaccine is distributed into breast milk 1, 6.

However, the vaccine does not affect the safety of breast-feeding for mothers or infants. Breast-feeding does not adversely affect immunization, and is not a contraindication for vaccination. Breast-fed infants should be vaccinated according to the routine, recommended schedule 56.

Pediatrics

Note: Because infants born to HBsAg-negative women are not at immediate risk of exposure to HBV, the first dose of vaccine can be deferred 71.

Infants born to HBsAg-positive women, however, are at immediate risk of contracting HBV infection 71.

Immunization, together with a dose of hepatitis B immune globulin, should be given at birth and these infants should be tested for anti-HBs antibody 71.

Infants born to mothers who have not been screened should receive the first dose of hepatitis B vaccine at birth using the dose of vaccine recommended for infants born to HBsAg-positive mothers 71.

Subsequent management of these infants is dependent on the results of the serologic screening of the mother 71.

Hepatitis B recombinant vaccine has been shown to be well tolerated and highly immunogenic in infants and children of all ages. Neonates also respond well, and maternally transferred antibodies do not interfere with the active immune response to the vaccine 1, 6.

No published pediatrics-specific information is available for the dialysis formulation of hepatitis B recombinant vaccine. Safety and efficacy have not been established [1, 39].

Although long-term carriage of HBV in children is usually asymptomatic, it may lead to chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma in later life [60].

Many studies have demonstrated the efficacy of hepatitis B vaccine in reducing long-term carriage in neonates at high risk [60].

The World Health Organization (WHO) has endorsed the inclusion of hepatitis B vaccine in routine childhood immunization programs, especially in areas where hepatitis B is endemic [69].

Studies suggest that universal hepatitis B vaccination of infants in the first year of life is effective in the improvement of the endemic status of the infection [63].

Premature infants born to HBsAg-positive mothers should receive immunoprophylaxis with hepatitis B recombinant vaccine and hepatitis B immune globulin, beginning at birth [56, 73].

For premature infants of HBsAg-negative mothers, the optimal timing of hepatitis B vaccination has not been determined [56].

Some studies suggest that decreased seroconversion rates may occur in some premature infants with low birthweight (i.e., less than 2000 grams) following administration of hepatitis B recombinant vaccine at birth [56].

Such low-birthweight premature infants born to HBsAg-negative mothers should receive the hepatitis B vaccine series at discharge from the nursery, if the infant weighs at least 2000 grams, or at 2 months of age along with diphtheria, tetanus, and pertussis vaccine; oral poliovirus vaccine; and haemophilus b conjugate vaccine [56].

Adolescents

Studies have shown that hepatitis B recombinant vaccine is highly immunogenic in adolescents and young adults when administered in varying three-dose schedules [49, 65].

Routine vaccination of adolescents 11 to 12 years of age who have not been vaccinated previously is an effective strategy for rapidly lowering the incidence of HBV infection and its transmission in the U.S. 49 Studies performed in Canada [62], and Italy [63] indicated that universal vaccination of this age group can be highly acceptable and efficient [62, 63].

An adolescent's visit to a physician at 11 to 12 years of age gives the provider an opportunity to initiate protection against HBV before the adolescent begins high-risk behaviors [49].

Unvaccinated adolescents older than 12 years of age who are at increased risk for HBV infection also should be vaccinated [49].

Geriatrics

Studies have shown that the adult response to hepatitis B recombinant vaccine is inversely related to age: more than 90% response in young adults, 70% in persons 50 to 59 years of age, and 50 to 70% in persons 60 years of age and over 12, 17, 18, 23, 26, 31.

Other geriatrics-specific problems that would limit the usefulness of this medication in the elderly are not expected 39.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Immunosuppressive agents or

Radiation therapy

(because normal defense mechanisms are suppressed, the patient's antibody response to hepatitis B recombinant vaccine may be decreased. Larger vaccine doses [2 to 4 times the normal adult dose] or an increased number of doses [4 doses] may be required to induce protective levels of antibody in immunocompromised persons 5)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

With physiology/laboratory test values

Erythrocyte sedimentation (SED) rate 11

(may be increased)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).

Except under special circumstances, this medication should not be used when the following medical problem exists

>> Previous hypersensitivity reaction to hepatitis B recombinant vaccine

(rare cases of anaphylaxis [1 per 600,000 vaccine doses administered] among vaccine recipients has been reported to the Vaccine Adverse Events Reporting System [VAERS] 58 ; although none of the persons who developed anaphylaxis died, this adverse event can be fatal; in addition, hepatitis B vaccine can, in rare instances, cause a life-threatening hypersensitivity reaction in some persons 58 ; therefore, subsequent vaccination with hepatitis B vaccine is contraindicated for persons who previously had anaphylactic responses to a dose of this vaccine 58)

Risk-benefit should be considered when the following medical problems exist

Allergy to yeast

(hepatitis B recombinant vaccine is produced using yeast 39, 74 ; a maximum of 1 or 5%, depending on the manufacturer, of yeast-derived protein may be present in the final vaccine; although there have not been any proven allergic reactions to the yeast, the possibility exists that they may occur 1, 9, 31, 39)

Cardiopulmonary status, severely compromised

(a febrile or systemic reaction to the vaccine could pose a significant risk to persons with this condition 1)

Illness, moderate or severe, with or without fever 36

(administration of the vaccine should be delayed, except when withholding the vaccine entails a greater risk to the patient than a possible superimposed reaction to the vaccine 1, 6, 36)

Immune deficiency conditions

(antibody response to hepatitis B recombinant vaccine may be decreased; larger vaccine doses [2 to 4 times the normal adult dose] or an increased number of doses [4 doses] may be required to induce protective levels of antibody in immunocompromised persons 5)

Side/Adverse Effects

Note: In the U.S., an estimated 2.5 million adults received one or more doses of hepatitis B recombinant vaccine between 1986 and 1990, and available data concerning these vaccinees do not indicate an association between receipt of hepatitis B recombinant vaccine and Guillain-Barre syndrome (GBS) 58.

Moreover, large-scale hepatitis B immunization programs for infants in Alaska, New Zealand, and Taiwan have not established an association between vaccination and the occurrence of GBS 58.

However, systematic surveillance for adverse reactions in these populations has been limited, and only a minimal number of children have received the recombinant vaccine 58.

Any presumed risk for adverse events that could be causally associated with hepatitis B vaccination must be balanced against the expected risk for hepatitis B virus (HBV)-related liver disease 58.

Currently, an estimated 2000 to 5000 persons in each U.S. birth cohort will die as a result of HBV-related liver disease because of the 5% lifetime risk for HBV infection 58.

Agitation, conjunctivitis, constipation, erythrocyte sedimentation rate increase, hepatic enzyme elevation, herpes zoster, hypesthesia, irritability, keratitis, migraine, myelitis, petechiae, radiculopathy, somnolence, Stevens-Johnson syndrome, syncope, tachycardia, thrombocytopenia, tinnitus, and visual disturbances also have been reported in temporal association with administration of hepatitis B recombinant vaccine, but their relationship to the vaccine is unclear 1, 6, 31, 39.

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:

Those indicating need for medical attention

Incidence rare

Anaphylactic reaction (difficulty in breathing or swallowing; hives; itching, especially of feet or hands; reddening of skin, especially around ears; swelling of eyes, face, or inside of nose; unusual tiredness or weakness, sudden and severe) 1, 6; neuropathy (muscle weakness or numbness or tingling of limbs) 1, 6; optic neuritis (blurred vision or other vision changes 39) 1, 6; serum sickness-like reaction (aches or pain in joints, fever, or skin rash or welts)¾may occur days or weeks following administration of the vaccine 1

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Soreness at injection site¾20 to 30% 1, 5, 6, 9, 23, 24

Incidence less frequent (1 to 10% frequency)

Fatigue (unusual tiredness or weakness); fever of 37.7 °C (100 °F) or over 1, 6, 9, 23; headache 1, 6, 9; induration 6, 9 (hard lump); erythema 1, 6, 9 (redness); swelling 1, 6, 9; pain 1, 6; pruritus 1, 6 (itching); ecchymosis 1, 6 (purple spot); tenderness 1; or warmth at injection site 1; vertigo (dizziness) 1, 6, 9

Incidence rare (less than 1% frequency)

Anorexia (lack of appetite); or decreased appetite 1, 6; arthralgia, arthritis, or myalgia (aches or pain in joints or muscles) 1, 6; back pain 1, 6; chills 1, 6; diarrhea or abdominal cramps or pain 1, 6 (stomach cramps or pain); flushing (sudden redness of skin) 1, 6; hypotension (unusual tiredness or weakness) 1, 6; increased sweating 1, 6; influenza-like symptoms or upper respiratory tract illness (headache, sore throat, runny nose, or fever) 1, 6; insomnia or sleep disturbance (trouble in sleeping) 1, 6; lymphadenopathy (swelling of glands in armpit or neck) 1, 6; malaise (general feeling of discomfort or illness) 1, 6; nausea or vomiting 1, 6; nodule at injection site 1 (lump at place of

injection)¾probably from the aluminum content of the vaccine and may persist for a few weeks; pruritus (itching); skin rash; or urticaria (welts) 1, 6; stiffness or pain in neck or shoulder 1, 6

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Hepatitis B Vaccine Recombinant (Systemic).

In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):

Before receiving this vaccine

>> Conditions affecting use, especially:

Hypersensitivity to plasma-derived hepatitis B vaccine or recombinant hepatitis B vaccine or allergy to yeast

Use in the elderly¾Compared with younger adults, persons over 50 years of age may be less likely to develop a protective antibody level following immunization with hepatitis B recombinant vaccine 39

Proper use of this vaccine

>> Proper dosing

Side/adverse effects

Signs of potential side effects, especially anaphylactic reaction, neuropathy, optic neuritis, or serum sickness-like reaction

General Dosing Information

Although systemic reactions to hepatitis B recombinant vaccine are rare, anaphylaxis among vaccine recipients has been reported to the Vaccine Adverse Events Reporting System (VAERS) 58.

Therefore, appropriate precautions should be taken prior to hepatitis B recombinant vaccine injection to prevent allergic or any other unwanted reactions. Precautions should include review of the patient's history regarding possible sensitivity and the ready availability of 1:1000 epinephrine injection and other appropriate agents used for control of immediate allergic reactions 43.

Only persons who have not been infected with hepatitis B virus (HBV) previously need to be immunized with hepatitis B recombinant vaccine. Therefore, as a cost-effective measure, testing for prior HBV infection should be considered for adults in groups having a high prevalence of HBV infection (e.g., users of injection drugs, homosexual men, and household contacts of HBV carriers). If the group to be tested is also expected to have a high prevalence of carriers, it may be preferable to test for antibody to hepatitis B core antigen (anti-HBc), since this test identifies previously infected persons, both carriers and noncarriers. If the group to be tested is not expected to have a high rate

of carriers, the test for antibody to hepatitis B surface antigen (anti-HBs) will be adequate, since this test identifies previously infected persons, except for carriers 23, 39, 40, 41, 42.

There is no harm but also no proven benefit in immunizing those already infected with HBV 69.

Recent claims of a therapeutic response in carriers of hepatitis B surface antigen (HBsAg) have not been confirmed 69.

Although the dosages are different for the products of different manufacturers, the resulting immunogenicity of each is comparable 39.

An immunization schedule started with one manufacturer's vaccine and dose may be completed with the other manufacturer's vaccine and dose 5, 6, 13, 39.

However, in the dialysis setting, the two vaccines should not be used interchangeably 70.

Because of the long incubation period of HBV 39 , unrecognized infection may be present at the time of immunization; the vaccine may not prevent hepatitis B in already-infected patients 1, 6.

Passively acquired antibody, whether acquired by administration of immune globulins or via the transplacental route, will not interfere with active immunization with hepatitis B recombinant vaccine. In addition, there is no interference with the induction of protective antibodies elicited by hepatitis B recombinant vaccine when hepatitis B immune globulin (HBIG) is administered at the same time at different body sites 1, 5, 6.

The Committee on Infectious Diseases of the American Academy of Pediatrics, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention, and the American Academy of Family Physicians offer the following recommendations for the use of hepatitis B recombinant vaccine among infants, children, and adolescents:

· Infants born to HBsAg-negative mothers should receive 2.5 mcg Recombivax HB or 10 mcg Engerix-B. A second dose should be administered 1 or more months after the first dose 55.

· Infants born to HBsAg-positive mothers should receive 0.5 mL HBIG within 12 hours of birth, and either 5 mcg Recombivax HB or 10 mcg Engerix-B at a separate injection site. A second dose should be administered at 1 to 2 months of age and a third dose at 6 months of age 55.

· Infants born to mothers whose HBsAg status is unknown should receive either 5 mcg Recombivax HB or 10 mcg Engerix-B within 12 hours of birth. A second dose should be administered at 1 month of age and a third dose at 6 months of age 55.

· Adolescents who have not previously received three doses of hepatitis B vaccine should initiate or complete the series at the 11- to 12-year-old visit to the physician 55.

A second dose should be administered at least 1 month after the first dose, and a third dose should be administered at least 4 months after the first dose, and at least 2 months after the second dose 55.

If within 7 days after delivery, a mother of unknown HBsAg status is found to be HBsAg positive, the infant should receive HBIG immediately. In addition, immunization with the appropriate dosage of hepatitis B recombinant vaccine should be initiated or continued 39.

If hepatitis B recombinant vaccine and HBIG are administered at the same time, they should be administered in the anterolateralaspects of opposite thighs. If a mother of unknown HBsAg status is found not to be HBsAg-positive, the infant should complete the immunization series with 39 the appropriate dosage of hepatitis B recombinant vaccine 31.

For known or presumed exposure to the hepatitis B virus, HBIG should be administered according to its directions as soon as possible after exposure and within 24 hours if possible. (HBIG's value if given later than 39 7 days after exposure is unclear; in addition, the period after sexual exposure to HBV during which HBIG is effective is unknown, but extrapolation from other data suggests that this period does not exceed 14 days.) In addition, hepatitis B recombinant vaccine should be administered at a separate body site, using one of the following dosage schedules and the dosage that applies to it: 1, 5, 23

· If using Recombivax HB¾At the same time as HBIG or within 7 days after exposure, then 1 month and 6 months after the first dose, for a total of three doses 1, 5.

· If using Engerix-B¾
¾At the same time as HBIG or within 7 days after exposure, then 1 month and 6 months after the first dose, for a total of three doses 5, 12, 26.

¾Alternatively, at the same time as HBIG or within 7 days after exposure, then 1 month, 2 months, and 12 months after the first dose, for a total of four doses 5, 6, 26, 39.

If the exposed person has begun, but not completed, immunization with hepatitis B recombinant vaccine, HBIG should be given as usual, and immunization with the vaccine should be completed as scheduled 5.

For travelers: Ideally, immunization with hepatitis B recombinant vaccine should begin at least 6 months before travel to allow completion of the full three-dose vaccine series (given at 0, 1, and 6 months). However, if there is less time available before travel than a full 6 months, the first three doses of an alternative four-dose schedule (given at 0, 1, 2, and 12 months) may provide earlier 38 protection during travel if the doses can be administered before travel begins 1, 5, 6.

Although the alternative four-dose schedule (given at 0, 1, 2, and 12 months)(Engerix-B) provides a more rapid induction of immunity, there is no clear evidence that this schedule provides greater long-term protection than the standard three-dose schedule (given at 0, 1, and 6 months) 4, 5, 6, 33, 39.

Vaccine doses administered at longer-than-recommended intervals (recommended intervals being 0, 1, and 6 months) provide equally satisfactory protection. However, optimal protection is not conferred until after the third dose. If the vaccine series is interrupted after the first dose, the second dose should be given as soon as possible, followed by the third dose 3 to 5 months later. Persons who receive the third dose later than 6 months after the initial dose should be given the third dose as soon as is practical. In healthy persons it is not considered necessary to perform

postvaccination testing to ensure an adequate antibody response, in either of the above situations 5, 12, 19.

When sterilizing syringes and skin before vaccination, care should be taken to avoid contact of the vaccine with preservatives, antiseptics, detergents, and disinfectants, since the vaccine virus particles may be easily denatured by these substances 1, 12, 38, 39.

The hepatitis B recombinant vaccine should be administered by intramuscular (IM) injection. The needle should be of sufficient length and bore to reach the muscle mass itself and to prevent vaccine from seeping into subcutaneous tissue. For adults, the suggested needle length is 11/2 inches. For children, a 20- or 22-gauge needle 1 to 11/4 inches long is recommended. For small infants, a 25-gauge needle 5/8 inch long may be adequate 31.

However, for persons at risk of hemorrhage following IM injections, the vaccine may be administered subcutaneously, although the subsequent antibody titer may be lower and there may be an increased risk of local reactions. The vaccine should not be administered intravenously or intradermally 1, 6, 12, 20, 22, 29, 31.

The deltoid muscle (outer aspect of the upper arm) is the recommended site for the immunization of adults and older children. For infants and young children, the anterolateral aspect of the thigh muscle is the recommended site. The vaccine should not be administered in the gluteal region (buttock), because the immunogenicity of the vaccine is substantially lowered 1, 5, 6, 12, 23, 31.

The 40 mcg/mL strength (Recombivax HB Dialysis Formulation) is given in a three-dose regimen, with a total of three doses required. The 20 mcg/mL strength (Engerix-B) requires either one 2-mL injection or two separate 1-mL injections during a four-dose regimen for a total of either four or eight injections 70.

Larger vaccine doses (2 to 4 times the normal adult dose) or an increased number of doses (4 doses) may be necessary for immunocompromised persons (such as those on immunosuppressive medications or with human immunodeficiency virus [HIV] infection). However, although persons with HIV infection have an impaired response to hepatitis B recombinant vaccine, the immunogenicity of higher doses of the vaccine in these persons is unknown, and specific recommendations on dosage are not available 5.

Although postimmunization testing for serologic response and immunity is not routinely recommended, it is recommended for the following: 5, 23

· Persons whose subsequent management depends on knowledge of their immune status, such as dialysis patients, medical staff, and infants born to HBsAg-positive mothers 5, 23, 39.

· Persons in whom a less-than-optimal response may be anticipated, such as those who were administered the vaccine in the buttock or subcutaneously, persons over 50 years of age, and persons with HIV infection or other immune deficiencies 5, 6, 23.

· Persons at occupational risk who may have HBV exposures necessitating postexposure prophylaxis 5, 23.

Postimmunization testing should be done 1 to 6 months after completion of the immunization series to provide definitive information on the response to the vaccine 5.

Reimmunization of persons who did not originally respond to the primary series produces adequate antibody response in 15 to 25% after 1 additional dose and in 30 to 50% after 3 additional doses, when the original immunization was administered in the deltoid muscle 5.

Data suggest that in more than 75% of persons who did not adequately respond to a primary vaccine series given in the buttock, reimmunization in the arm induces adequate antibody response 5.

In adult predialysis and dialysis patients, hepatitis B recombinant vaccine-induced protection is less complete and may persist only as long as antibody levels remain at or above 10 milliInternational Units (mIU) per mL. The need for additional doses of the vaccine should be assessed by annual antibody testing. It is recommended that additional doses of 40 mcg of hepatitis B recombinant vaccine be given when antibody levels decline to below 10 mIU per mL 1, 6, 23, 24, 26, 31, 39.

Hepatitis B recombinant vaccine, an inactivated product, can be administered concurrently with the following, using separate body sites (in infants, selecting separate sites in the same anterolateral aspect of the thigh muscle is preferable to administering hepatitis B recombinant vaccine in the buttock or deltoid muscle) 23 , separate syringes (for parenterals), and the precautions that apply to each immunizing agent: 35

· Polysaccharide vaccines, such as haemophilus b conjugate vaccine, haemophilus b polysaccharide vaccine, meningococcal polysaccharide vaccine, or pneumococcal polyvalent vaccine.
· Influenza virus vaccine, whole or split virus.
· Diphtheria toxoid, tetanus toxoid, and/or pertussis (whole cell or acellular) vaccine.
· Live virus vaccines, such as measles, mumps, and/or rubella vaccines.
· Poliovirus vaccines (oral [OPV], inactivated [IPV], or enhanced-potency inactivated [enhanced-potency IPV]).
· Immune globulin and disease-specific immune globulins.
· Inactivated vaccines, other, except cholera, typhoid (parenteral), and plague. It is recommended that cholera, typhoid (parenteral), and plague vaccines be administered on separate occasions because of these vaccines' propensity to cause side/adverse effects.

For treatment of adverse effects

Recommended treatment includes:
· For mild hypersensitivity reaction¾Administering antihistamines, and, if necessary, corticosteroids 59.

In mild anaphylaxis, antihistamines or subcutaneous epinephrine may be all that is necessary if the condition is progressing slowly and is not life-threatening, regardless of the organ or system affected 59.

Under these circumstances the risks associated with intravenous epinephrine administration outweigh the benefits 59.

· For severe hypersensitivity or anaphylactic reaction¾Administering epinephrine. Antihistamines or corticosteroids may also be administered as required 33, 59.

Epinephrine is the treatment of choice for severe hypersensitivity or anaphylactic reaction 59.

If the patient's condition is not stable, epinephrine should be infused. Norepinephrine may be preferable if there is no bronchospasm 59.

For bronchospasm, epinephrine should be given with corticosteroids. Other bronchodilators, such as intravenous aminophylline or albuterol by nebulization, also should be considered 59.

Parenteral Dosage Forms

STERILE HEPATITIS B VACCINE RECOMBINANT SUSPENSION

Usual adult and adolescent dose

Immunizing agent (active)¾Adolescents 11 to 19 72, 74 years of age: Intramuscular, into the deltoid muscle, 5 mcg (Recombivax HB¾U.S. and Canada), or 10 mcg (Recombivax HB¾Canada), or 20 mcg (Engerix-B¾U.S. and Canada), at initial visit, then one month and six months after the first dose, for a total of three doses 23, 26, 31, 32, 33.

Adults 19 72, 74 years of age and older: Intramuscular, into the deltoid muscle, 10 mcg (Recombivax HB¾U.S. and Canada) or 20 mcg (Engerix-B¾U.S. and Canada), at initial visit, then one month and six months after the first dose, for a total of three doses 1, 4, 6, 7, 23, 26, 31, 32, 33.

Adult predialysis and dialysis patients¾Intramuscular, into the deltoid muscle, 40 mcg (Recombivax HB Dialysis Formulation¾U.S. and Canada), at initial visit, then one month and six months after the first dose, for a total of three doses 1, 23, 31, 32 ;

or

40 mcg (Engerix-B¾U.S. and Canada), at initial visit, then one month, two months, and six months after the first dose, for a total of four doses 4, 6, 26, 33.

The 20 mcg/mL strength (Engerix-B) requires either one 2-mL injection or two separate 1-mL injections during a four-dose regimen for a total of either four or eight injections 70.

Usual pediatric dose

Immunizing agent (active)¾Neonates born to hepatitis B surface antigen (HBsAg)-positive mothers: Intramuscular, into the anterolateral aspect of the thigh¾5 mcg (Recombivax HB¾U.S. and Canada), 10 mcg (Engerix-B¾U.S. and Canada 72), within twelve hours after birth (preferably) or within seven days after birth, then one month and six months after the first dose, for a total of three doses 1, 5, 7, 23, 26, 31, 32, 33 ;

10 mcg (Engerix-B¾U.S. and Canada 72), within twelve hours after birth (preferably) or within seven days after birth, then one month, two months, and twelve months after the first dose, for a total of four doses 4, 5, 6, 26, 33.

Neonates born to mothers of unknown HBsAg status: Intramuscular, into the anterolateral aspect of the thigh: 5 mcg (Recombivax HB¾U.S.), 10 mcg (Engerix-B¾U.S. and Canada 72), within twelve hours after birth (preferably) or within seven days after birth, then:

Infants of mothers subsequently determined to be HBsAg-positive¾
5 mcg (Recombivax HB¾U.S.), 10 mcg (Engerix-B¾U.S. and Canada 72), one month and six months after the first dose, for a total of three doses 26, 31, 33 ;
10 mcg (Engerix-B¾U.S. and Canada 72), one month, two months, and twelve months after the first dose, for a total of four doses 26, 33.

Infants of mothers subsequently determined to be HBsAg-negative¾
2.5 mcg (Recombivax HB¾U.S.), 10 mcg (Engerix-B¾U.S. and Canada 72), one month and six months after the first dose, for a total of three doses 26, 31, 33.

Neonates born to HBsAg-negative mothers or

Infants and children up to 11 years of age: Intramuscular, into the anterolateral aspect of the thigh for neonates, infants, and young children and into the deltoid muscle for older children, 2.5 mcg (Recombivax HB¾U.S. and Canada), 10 mcg (Engerix-B¾U.S. and Canada 72), at initial visit, then one month and six months after the first dose, for a total of three doses 23, 26, 31, 32, 33.

Note: Physicians have a great deal of flexibility in scheduling the three-dose immunization series for full-term infants born to HBsAg-negative mothers 71.

The recommended schedule is to give the first dose during the neonatal period or by two months of age, the second dose one to two months later, and the third dose at six to eighteen months of age 71.

The vaccines, however, are highly immunogenic when given according to other schedules 71.

Although the highest titers of anti-HBs are achieved when the last two doses of vaccine are spaced four months apart or longer, schedules with two-month intervals between doses have been shown to produce high rates of seroconversion 71.

Some pediatricians have adopted other three-dose schedules in order to minimize the number of simultaneous injections 71.

Schedules with intervals of up to ten months between the second and the third doses have been shown to be highly effective 71.

Intervals longer than two months between the first two doses or more than one year between the second and the third dose have not been evaluated in controlled trials 71.

The American Academy of Pediatrics currently recommends that children of all ages for whom a longer time than recommended has elapsed between doses of hepatitis B vaccine can complete the series without repeating a dose or starting the series over [71].

Strength(s) usually available

U.S.¾2.5 mcg (0.0025 mg) of hepatitis B surface antigen (HBsAg) protein per 0.5 mL (Rx)[Recombivax HB (0.25 mg aluminum as aluminum hydroxide) (thimerosal 1:20,000)] [25, 31]

5 mcg (0.005 mg) of HBsAg protein per 0.5 mL (Rx)[Recombivax HB (0.25 mg aluminum as aluminum hydroxide) (thimerosal 1:20,000)] [31]

10 mcg (0.01 mg) of HBsAg protein per mL (Rx)[Recombivax HB (0.5 mg aluminum as aluminum hydroxide) (thimerosal 1:20,000)] [1, 5, 25, 31]

10 mcg (0.01 mg) of HBsAg protein per 0.5 mL (Rx)[Engerix-B (0.25 mg aluminum as aluminum hydroxide) (thimerosal 1:20,000)] [6, 26]

20 mcg (0.02 mg) of HBsAg protein per mL (Rx)[Engerix-B (0.5 mg aluminum as aluminum hydroxide) (thimerosal 1:20,000)] [6, 26]

40 mcg (0.04 mg) of HBsAg protein per mL (Rx)[Recombivax HB Dialysis Formulation (0.5 mg aluminum as aluminum hydroxide) (thimerosal 1:20,000)] [1, 25, 31]

Canada¾5 mcg (0.005 mg) of HBsAg protein per 0.5 mL (Rx)[Recombivax HB (alum adjuvant) (thimerosal 1:20,000)] [7, 27, 32]

10 mcg (0.01 mg) of HBsAg protein per mL (Rx)[Recombivax HB (alum adjuvant) (thimerosal 1:20,000)] [7, 27, 32]

10 mcg (0.01 mg) of HBsAg protein per mL (Rx)[Engerix-B (0.25 mg aluminum as aluminum hydroxide) (thimerosal 1:20,000)] [72]

20 mcg (0.02 mg) of HBsAg protein per mL (Rx)[Engerix-B (0.5 mg aluminum as aluminum hydroxide) (thimerosal 1:20,000)] [4, 28, 33]

40 mcg (0.04 mg) of HBsAg protein per mL (Rx)[Recombivax HB Dialysis Formulation (thimerosal 1:20,000)] [27, 32]

Packaging and storage:

Store between 2 and 8 °C (36 and 46 °F), unless otherwise specified by manufacturer. Protect from freezing [1, 4, 5, 6, 7, 26, 31, 33].

Preparation of dosage form:

The vaccine should be used as supplied, and should not be diluted. The vial should be shaken well immediately before withdrawal of the dose. In addition, thorough agitation at the time of

administration is necessary to maintain suspension of the vaccine. After agitation, the vaccine is a slightly opaque, white suspension [1, 6, 26].

Stability:

Storage above or below the recommended temperature may reduce potency. Freezing destroys potency, and the vaccine should be discarded if freezing occurs [1, 4, 5, 6, 7, 25, 26, 31, 33].

Auxiliary labeling:

- Do not freeze; discard if freezing occurs [1, 4, 6, 7, 25, 31, 33].
- Shake well [1, 6, 25].