

## PRESCRIBING INFORMATION

# ENGERIX-B<sup>®</sup>

## [Hepatitis B Vaccine (Recombinant)]

### DESCRIPTION

ENGERIX-B [Hepatitis B Vaccine (Recombinant)] is a noninfectious recombinant DNA hepatitis B vaccine developed and manufactured by GlaxoSmithKline Biologicals. It contains purified surface antigen of the virus obtained by culturing genetically engineered *Saccharomyces cerevisiae* cells, which carry the surface antigen gene of the hepatitis B virus. The surface antigen expressed in *Saccharomyces cerevisiae* cells is purified by several physicochemical steps and formulated as a suspension of the antigen adsorbed on aluminum hydroxide. The procedures used to manufacture ENGERIX-B result in a product that contains no more than 5% yeast protein. No substances of human origin are used in its manufacture.

ENGERIX-B is supplied as a sterile suspension for intramuscular administration. The vaccine is ready for use without reconstitution; it must be shaken before administration since a fine white deposit with a clear colorless supernatant may form on storage.

ENGERIX-B is formulated without preservatives.

ENGERIX-B is available in vials and 2 types of prefilled syringes, syringes containing latex and syringes containing no latex. In the latex-containing syringes, the tip cap and the rubber plunger contain dry natural latex rubber. The vial stopper does not contain latex. (See HOW SUPPLIED.)

**Pediatric/Adolescent:** Each 0.5-mL dose contains 10 mcg of hepatitis B surface antigen adsorbed on 0.25 mg aluminum as aluminum hydroxide. The pediatric formulation contains sodium chloride (9 mg/mL) and phosphate buffers (disodium phosphate dihydrate, 0.98 mg/mL; sodium dihydrogen phosphate dihydrate, 0.71 mg/mL).

**Adult:** Each 1-mL adult dose contains 20 mcg of hepatitis B surface antigen adsorbed on 0.5 mg aluminum as aluminum hydroxide. The adult formulation contains sodium chloride (9 mg/mL) and phosphate buffers (disodium phosphate dihydrate, 0.98 mg/mL; sodium dihydrogen phosphate dihydrate, 0.71 mg/mL).

### CLINICAL PHARMACOLOGY

Several hepatitis viruses are known to cause a systemic infection resulting in major pathologic changes in the liver (e.g., A, B, C, D, E, and G). The estimated lifetime risk of HBV infection in the United States varies from almost 100% for the highest-risk groups to less than 20% for the population as a whole.<sup>1</sup> Hepatitis B infection can have serious consequences including acute massive hepatic necrosis, chronic active hepatitis, and cirrhosis of the liver. Up to 90% of neonates and 6% to 10% of adults who are infected in the United States will become hepatitis B virus carriers.<sup>1</sup> It has been estimated that 200 to 300 million people in the world today are persistently infected with hepatitis B virus.<sup>1</sup> The Centers for Disease Control and Prevention (CDC) estimates that there are approximately 1 to 1.25 million chronic carriers of hepatitis B

virus in the United States.<sup>1</sup> Those patients who become chronic carriers can infect others and are at increased risk of developing primary hepatocellular carcinoma. Among other factors, infection with hepatitis B may be the single most important factor for development of this carcinoma.<sup>1,2</sup>

**Reduced Risk of Hepatocellular Carcinoma:** According to the CDC, the hepatitis B vaccine is recognized as the first anti-cancer vaccine because it can prevent primary liver cancer.<sup>3</sup>

A clear link has been demonstrated between chronic hepatitis B infection and the occurrence of hepatocellular carcinoma. In a Taiwanese study, the institution of universal childhood immunization against hepatitis B virus has been shown to decrease the incidence of hepatocellular carcinoma among children.<sup>4</sup> In a Korean study in adult males, vaccination against hepatitis B virus has been shown to decrease the incidence of, and risk of, developing hepatocellular carcinoma in adults.<sup>5</sup>

Considering the serious consequences of infection, immunization should be considered for all persons at potential risk of exposure to the hepatitis B virus. Mothers infected with hepatitis B virus can infect their infants at, or shortly after, birth if they are carriers of the hepatitis B surface antigen (HBsAg) or develop an active infection during the third trimester of pregnancy. Infected infants usually become chronic carriers. Therefore, screening of pregnant women for hepatitis B is recommended.<sup>1</sup> Because a vaccination strategy limited to high-risk individuals has failed to substantially lower the overall incidence of hepatitis B infection, the Advisory Committee on Immunization Practices (ACIP) recommends vaccination of all persons from birth to age 18.<sup>6</sup> The Committee on Infectious Diseases of the American Academy of Pediatrics (AAP) has also endorsed universal infant immunization as part of a comprehensive strategy for the control of hepatitis B infection.<sup>7</sup> The AAP, American Academy of Family Physicians (AAFP), and American Medical Association (AMA) also recommend routine vaccination of adolescents 11 to 12 years of age who have not been vaccinated previously.<sup>8</sup> The AAP further recommends that providers administer hepatitis B vaccine to all previously unvaccinated adolescents.<sup>9</sup> (See INDICATIONS AND USAGE.) There is no specific treatment for acute hepatitis B infection. However, those who develop anti-HBs antibodies after active infection are usually protected against subsequent infection. Antibody titers  $\geq 10$  mIU/mL against HBsAg are recognized as conferring protection against hepatitis B.<sup>1</sup> Seroconversion is defined as antibody titers  $\geq 1$  mIU/mL.

**Protective Efficacy:** Protective efficacy with ENGERIX-B has been demonstrated in a clinical trial in neonates at high risk of hepatitis B infection.<sup>10,11</sup> Fifty-eight neonates born of mothers who were both HBsAg and HBeAg positive were given ENGERIX-B (10 mcg at 0, 1, and 2 months) without concomitant hepatitis B immune globulin. Two infants became chronic carriers in the 12-month follow-up period after initial inoculation. Assuming an expected carrier rate of 70%, the protective efficacy rate against the chronic carrier state during the first 12 months of life was 95%.

**Immunogenicity in Neonates:** Immunization with 10 mcg at 0, 1, and 6 months of age produced seroconversion in 100% of infants by month 7, with a geometric mean antibody titer (GMT) of 713 mIU/mL (N = 52), and the seroprotection rate was 97%.

Clinical trials indicate that administration of hepatitis B immune globulin at birth does not alter the response to ENGERIX-B.

Immunization with 10 mcg at 0, 1, and 2 months of age produced a seroprotection rate of 96% in infants by month 4, with a GMT among seroconverters of 210 mIU/mL (N = 311); an additional dose at month 12 produced a GMT among seroconverters of 2,941 mIU/mL at month 13 (N = 126).

**Immunogenicity in Pediatric Patients:** In clinical trials with 242 children aged 6 months to 10 years given 10 mcg at months 0, 1, and 6, the seroprotection rate was 98% 1 to 2 months after the third dose; the GMT of seroconverters was 4,023 mIU/mL.

In a separate clinical trial including both children and adolescents aged 5 to 16 years, 10 mcg of ENGERIX-B was administered at 0, 1, and 6 months (N = 181) or 0, 12, and 24 months (N = 161). Immediately before the third dose of vaccine, seroprotection was achieved in 92.3% of subjects vaccinated on the 0-, 1-, and 6-month schedule and 88.8% of subjects on the 0-, 12-, and 24-month schedule (117.9 mIU/mL versus 162.1 mIU/mL, respectively,  $P = 0.18$ ). One month following the third dose, seroprotection was achieved in 99.5% of children vaccinated on the 0-, 1-, and 6-month schedule compared to 98.1% of those on the 0-, 12-, and 24-month schedule. GMTs were higher ( $P = 0.02$ ) for children receiving vaccine on the 0-, 1-, and 6-month schedule compared to those on the 0-, 12-, and 24-month schedule (5,687.4 mIU/mL versus 3,158.7 mIU/mL, respectively). The clinical relevance of this finding is unknown.

**Immunogenicity in Adolescents:** In clinical trials with healthy adolescent subjects 11 through 19 years of age, immunization with 10 mcg using a 0-, 1-, and 6-month schedule produced a seroprotection rate of 97% at month 8 (N = 119) with a GMT of 1,989 mIU/mL (N = 118, 95% confidence intervals = 1,318-3,020). Immunization with 20 mcg using a 0-, 1-, and 6-month schedule produced a seroprotection rate of 99% at month 8 (N = 122) with a GMT of 7,672 mIU/mL (N = 122, 95% confidence intervals = 5,248-10,965).

**Immunogenicity in Healthy Adults and Adolescents:** Clinical trials in healthy adult and adolescent subjects have shown that following a course of 3 doses of 20 mcg ENGERIX-B given according to the ACIP-recommended schedule of injections at months 0, 1, and 6, the seroprotection (antibody titers  $\geq 10$  mIU/mL) rate for all individuals was 79% at month 6 and 96% at month 7; the GMT for seroconverters at month 7 was 2,204 mIU/mL. On an alternate schedule (injections at months 0, 1, and 2) designed for certain populations (e.g., neonates born of hepatitis B-infected mothers, individuals who have or might have been recently exposed to the virus, and certain travelers to high-risk areas. See INDICATIONS AND USAGE), 99% of all individuals were seroprotected at month 3 and remained protected through month 12. On the alternate schedule, an additional dose at 12 months produced a GMT for seroconverters at month 13 of 9,163 mIU/mL.

**Immunogenicity in Older Subjects:** Among older subjects given 20 mcg at months 0, 1, and 6, the seroprotection rate 1 month after the third dose was 88%. However, as with other hepatitis B vaccines, in adults over 40 years of age, ENGERIX-B vaccine produced anti-HBs titers that were lower than those in younger adults (GMT among seroconverters 1 month after the third 20-mcg dose with a 0-, 1-, and 6-month schedule: 610 mIU/mL for individuals over 40 years of age, N = 50).

**Immunogenicity in Subjects With Chronic Hepatitis C:** In a clinical trial of subjects with chronic hepatitis C, 31 subjects received ENGERIX-B on the usual 0-, 1-, and 6-month schedule. All subjects responded with seroprotective titers. The GMT of anti-HBs was 1,260 mIU/mL (95% CI: 709-2,237).

**Immunogenicity in Hemodialysis Patients:** Hemodialysis patients given hepatitis B vaccines respond with lower titers,<sup>12</sup> which remain at protective levels for shorter durations than in normal subjects. In a study in which patients on chronic hemodialysis (mean time on dialysis was 24 months; N = 562) received 40 mcg of the plasma-derived vaccine at months 0, 1, and 6, approximately 50% of patients achieved antibody titers  $\geq 10$  mIU/mL.<sup>12</sup> Since a fourth dose of ENGERIX-B given to healthy adults at month 12 following the 0-, 1-, and 2-month schedule resulted in a substantial increase in the GMT (see above), a 4-dose regimen was studied in hemodialysis patients. In a clinical trial of adults who had been on hemodialysis for a mean of 56 months (N = 43), 67% of patients were seroprotected 2 months after the last dose of 40 mcg of ENGERIX-B (2  $\times$  20 mcg) given on a 0-, 1-, 2-, and 6-month schedule; the GMT among seroconverters was 93 mIU/mL.

**Thimerosal Free Formulation:** In 3 comparative clinical trials with 1,339 adults and 587 children, the thimerosal free formulation performed as well as the preservative free formulation that contained trace amounts of thimerosal.

**Interchangeability With Other Hepatitis B Vaccines:** Recombinant DNA vaccines are produced in yeast by expression of a hepatitis B virus gene sequence that codes for the hepatitis B surface antigen. Like plasma-derived vaccine, the yeast-derived vaccines are protein particles visible by electron microscopy and have hepatitis B surface antigen epitopes as determined by monoclonal antibody analyses. Yeast-derived vaccines have been shown by in vitro analyses to induce antibodies (anti-HBs) which are immunologically comparable by epitope specificity and binding affinity to antibodies induced by plasma-derived vaccine.<sup>13</sup> In cross-absorption studies, no differences were detected in the spectra of antibodies induced in man to plasma-derived or to yeast-derived hepatitis B vaccines.<sup>13</sup>

Additionally, patients immunized approximately 3 years previously with plasma-derived vaccine and whose antibody titers were  $< 100$  mIU/mL (GMT: 35 mIU/mL; range: 9-94) were given a 20-mcg dose of ENGERIX-B. All patients, including 2 who had not responded to the plasma-derived vaccine, showed a response to ENGERIX-B (GMT: 5,069 mIU/mL; range: 624-15,019). There have been no clinical studies in which a 3-dose vaccine series was initiated with a plasma-derived hepatitis B vaccine and completed with ENGERIX-B, or vice versa. However, because the in vitro and in vivo studies described above indicate the comparability of

the antibody produced in response to plasma-derived vaccine and ENGERIX-B, it should be possible to interchange the use of ENGERIX-B and plasma-derived vaccines (but see CONTRAINDICATIONS).

A controlled study (N = 48) demonstrated that completion of a course of immunization with 1 dose of ENGERIX-B (20 mcg, month 6) following 2 doses of RECOMBIVAX HB<sup>®\*</sup> (10 mcg, months 0 and 1) produced a similar GMT (4,077 mIU/mL) to immunization with 3 doses of RECOMBIVAX HB (10 mcg, months 0, 1, and 6; 2,654 mIU/mL). Thus, ENGERIX-B can be used to complete a vaccination course initiated with RECOMBIVAX HB.<sup>14</sup>

**Other Clinical Studies:** In 1 study, 4 of 244 (1.6%) adults (homosexual men) at high risk of contracting hepatitis B virus became infected during the period prior to completion of 3 doses of ENGERIX-B (20 mcg at 0, 1, and 6 months).<sup>15</sup> No additional patients became infected during the 18-month follow-up period after completion of the immunization course.

## INDICATIONS AND USAGE

ENGERIX-B is indicated for immunization against infection caused by all known subtypes of hepatitis B virus. As hepatitis D (caused by the delta virus) does not occur in the absence of hepatitis B infection, it can be expected that hepatitis D will also be prevented by ENGERIX-B vaccination.

ENGERIX-B will not prevent hepatitis caused by other agents, such as hepatitis A, C, and E viruses, or other pathogens known to infect the liver.

Immunization is recommended in persons of all ages, especially those who are, or will be, at increased risk of exposure to hepatitis B virus,<sup>1</sup> for example:

- Infants, Including Those Born of HBsAg-Positive Mothers (*See DOSAGE AND ADMINISTRATION.*)
- Adolescents (*See CLINICAL PHARMACOLOGY.*)
- Healthcare Personnel: *Dentists and oral surgeons. Dental, medical, and nursing students. Physicians, surgeons, and podiatrists. Nurses. Paramedical and ambulance personnel and custodial staff who may be exposed to the virus via blood or other patient specimens. Dental hygienists and dental nurses. Laboratory and blood bank personnel handling blood, blood products, and other patient specimens. Hospital cleaning staff who handle waste.*
- Selected Patients and Patient Contacts: *Patients and staff in hemodialysis units and hematology/oncology units. Patients requiring frequent and/or large volume blood transfusions or clotting factor concentrates (e.g., persons with hemophilia, thalassemia, sickle cell anemia, cirrhosis). Clients (residents) and staff of institutions for the mentally handicapped. Classroom contacts of deinstitutionalized mentally handicapped persons who have persistent hepatitis B surface antigenemia and who show aggressive behavior. Household and other intimate contacts of persons with persistent hepatitis B surface antigenemia.*

- Subpopulations With a Known High Incidence of the Disease, such as: *Alaskan Eskimos. Pacific Islanders. Indochinese immigrants. Haitian immigrants. Refugees from other HBV-endemic areas. All infants of women born in areas where the infection is highly endemic.*
- Individuals With Chronic Hepatitis C: *Risk factors for hepatitis C are similar to those for hepatitis B. Consequently, immunization with hepatitis B vaccine is recommended for individuals with chronic hepatitis C.*
- Persons Who May Be Exposed to the Hepatitis B Virus by Travel to High-Risk Areas (*See ACIP Guidelines, 1990.*)
- Military Personnel Identified as Being at Increased Risk
- Morticians and Embalmers
- Persons at Increased Risk of the Disease Due to Their Sexual Practices,<sup>1,16</sup> such as: *Persons with more than 1 sexual partner in a 6-month period. Persons who have contracted a sexually transmitted disease. Homosexually active males. Female prostitutes.*
- Prisoners
- Users of Illicit Injectable Drugs
- Others: *Police and fire department personnel who render first aid or medical assistance, and any others who, through their work or personal life-style, may be exposed to the hepatitis B virus. Adoptees from countries of high HBV endemicity.*

**Use With Other Vaccines:** The ACIP states that, in general, simultaneous administration of certain live and inactivated pediatric vaccines has not resulted in impaired antibody responses or increased rates of adverse reactions.<sup>17</sup> Separate sites and syringes should be used for simultaneous administration of injectable vaccines.

## CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including yeast, is a contraindication (see DESCRIPTION). This vaccine is contraindicated in patients with previous hypersensitivity to any hepatitis B-containing vaccine.

## WARNINGS

ENGERIX-B is available in vials and 2 types of prefilled syringes, syringes containing latex and syringes containing no latex. In the latex-containing syringes, the tip cap and the rubber plunger contain dry natural latex rubber; use of the latex-containing syringes may cause allergic reactions in latex sensitive persons. The vial stopper does not contain latex. (See HOW SUPPLIED.)

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including ENGERIX-B, to infants born prematurely should be based on consideration of the individual infant's medical status, and the potential benefits and possible risks of vaccination. For

ENGERIX-B, this assessment should include consideration of the mother's hepatitis B antigen status and the high probability of maternal transmission of hepatitis B virus to infants born of mothers who are HBsAg positive if vaccination is delayed.

Hepatitis B has a long incubation period. Hepatitis B vaccination may not prevent hepatitis B infection in individuals who had an unrecognized hepatitis B infection at the time of vaccine administration. Additionally, it may not prevent infection in individuals who do not achieve protective antibody titers.

## **PRECAUTIONS**

**General:** As with other vaccines, although a moderate or severe febrile illness is sufficient reason to postpone vaccination, minor illnesses such as mild upper respiratory infections with or without low-grade fever are not contraindications.<sup>17</sup>

Prior to immunization, the patient's medical history should be reviewed. The physician should review the patient's immunization history for possible vaccine sensitivity, previous vaccination-related adverse reactions, and occurrence of any adverse event-related symptoms and/or signs in order to determine the existence of any contraindication to immunization with ENGERIX-B and to allow an assessment of benefits and risks. Epinephrine injection (1:1,000) and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

A separate sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another. Needles should be disposed of properly and should not be recapped.

Special care should be taken to prevent injection into a blood vessel.

As with any vaccine administered to immunosuppressed persons or persons receiving immunosuppressive therapy, the expected immune response may not be obtained. For individuals receiving immunosuppressive therapy, deferral of vaccination for at least 3 months after therapy may be considered.<sup>17</sup>

**Multiple Sclerosis:** Although no causal relationship has been established, rare instances of exacerbation of multiple sclerosis have been reported following administration of hepatitis B vaccines and other vaccines. In persons with multiple sclerosis, the benefit of immunization for prevention of hepatitis B infection and sequelae must be weighed against the risk of exacerbation of the disease.

**Information for the Patient:** Patients, parents, or guardians should be informed of the potential benefits and risks of the vaccine, and of the importance of completing the immunization series. As with any vaccine, it is important when a subject returns for the next dose in a series that he or she be questioned concerning occurrence of any symptoms and/or signs of an adverse reaction after a previous dose of the same vaccine. Patients, parents, or guardians should be told to report severe or unusual adverse reactions to their healthcare provider.

The parent or guardian should be given the Vaccine Information Materials, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization.

**Drug Interactions:** For information regarding simultaneous administration with other vaccines, refer to INDICATIONS AND USAGE.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** ENGERIX-B has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

**Pregnancy:** Pregnancy Category C. Animal reproduction studies have not been conducted with ENGERIX-B. It is also not known whether ENGERIX-B can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ENGERIX-B should be given to a pregnant woman only if clearly needed.

**Nursing Mothers:** It is not known whether ENGERIX-B is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ENGERIX-B is administered to a nursing woman.

**Pediatric Use:** ENGERIX-B has been shown to be well tolerated and highly immunogenic in infants and children of all ages. Newborns also respond well; maternally transferred antibodies do not interfere with the active immune response to the vaccine. (See CLINICAL PHARMACOLOGY for seroconversion rates and titers in neonates and children. See DOSAGE AND ADMINISTRATION for recommended pediatric dosage and for recommended dosage for infants born of HBsAg-positive mothers.)

**Geriatric Use:** Clinical studies of ENGERIX-B did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects. Other reports from the clinical literature indicate that hepatitis B vaccines are less immunogenic in adults 65 years of age and older than in younger individuals. Other reported clinical experience has not identified differences in overall safety between these subjects and younger adult subjects.

## ADVERSE REACTIONS

ENGERIX-B is generally well tolerated. As with any vaccine, however, it is possible that expanded commercial use of the vaccine could reveal rare adverse reactions.

Ten double-blind studies involving 2,252 subjects showed no significant difference in the frequency or severity of adverse experiences between ENGERIX-B and plasma-derived vaccines. In 36 clinical studies, a total of 13,495 doses of ENGERIX-B were administered to 5,071 healthy adults and children who were initially seronegative for hepatitis B markers, and healthy neonates. All subjects were monitored for 4 days post-administration. Frequency of adverse experiences tended to decrease with successive doses of ENGERIX-B. Using a symptom checklist,<sup>†</sup> the most frequently reported adverse reactions were injection site soreness (22%) and fatigue<sup>†</sup> (14%). Other reactions are listed below.

### Incidence 1% to 10% of Injections:

**Nervous System Disorders:** Dizziness<sup>†</sup>, headache.<sup>†</sup>

**General Disorders and Administration Site Conditions:** Fever (>37.5°C), injection site erythema, injection site induration, injection site swelling.

†Parent or guardian completed forms for children and neonates. Neonatal checklist did not include headache, fatigue, or dizziness.

**Incidence <1% of Injections:**

**Infections and Infestations:** Upper respiratory tract illnesses.

**Blood and Lymphatic System Disorders:** Lymphadenopathy.

**Metabolism and Nutrition Disorders:** Anorexia.

**Psychiatric Disorders:** Agitation, insomnia.

**Nervous System Disorders:** Somnolence, tingling.

**Vascular Disorders:** Flushing, hypotension.

**Gastrointestinal Disorders:** Abdominal pain/cramps, constipation, diarrhea, nausea, vomiting.

**Skin and Subcutaneous Tissue Disorders:** Erythema, petechiae, pruritus, rash, sweating, urticaria.

**Musculoskeletal and Connective Tissue Disorders:** Arthralgia, back pain, myalgia, pain/stiffness in arm, shoulder, or neck.

**General Disorders and Administration Site Conditions:** Chills, influenza-like symptoms, injection site ecchymosis, injection site pain, injection site pruritus, irritability, malaise, weakness.

**Postmarketing Reports: Additional adverse experiences have been reported with the commercial use of ENGERIX-B. Those listed below are to serve as alerting information to physicians.**

**Infections and Infestations:** Herpes zoster, meningitis.

**Blood and Lymphatic System Disorders:** Thrombocytopenia.

**Immune System Disorders:** Allergic reaction, anaphylactoid reaction, anaphylaxis. An apparent hypersensitivity syndrome (serum sickness-like) of delayed onset has been reported days to weeks after vaccination, including: arthralgia/arthritis (usually transient), fever, and dermatologic reactions such as urticaria, erythema multiforme, ecchymoses, and erythema nodosum (see CONTRAINDICATIONS).

**Nervous System Disorders:** Encephalitis, encephalopathy, migraine, multiple sclerosis, neuritis, neuropathy including hypoesthesia, paresthesia, Guillain-Barré syndrome and Bell's palsy, optic neuritis, paralysis, paresis, seizures, syncope, transverse myelitis.

**Eye Disorders:** Conjunctivitis, keratitis, visual disturbances.

**Ear and Labyrinth Disorders:** Earache, tinnitus, vertigo.

**Cardiac Disorders:** Palpitations, tachycardia.

**Vascular Disorders:** Vasculitis.

**Respiratory, Thoracic and Mediastinal Disorders:** Apnea, bronchospasm including asthma-like symptoms.

**Gastrointestinal Disorders:** Dyspepsia.

**Skin and Subcutaneous Tissue Disorders:** Alopecia, angioedema, eczema, erythema multiforme including Stevens-Johnson syndrome, erythema nodosum, lichen planus, purpura.

**Musculoskeletal and Connective Tissue Disorders:** Arthritis, muscular weakness.

**General Disorders and Administration Site Conditions:** Injection site reaction.

**Investigations:** Abnormal liver function tests.

**Reporting Adverse Events:** The National Childhood Vaccine Injury Act requires that the manufacturer and lot number of the vaccine administered be recorded by the healthcare provider in the vaccine recipient's permanent medical record, along with the date of administration of the vaccine and the name, address, and title of the person administering the vaccine.<sup>18</sup> The Act further requires the healthcare provider to report to the US Department of Health and Human Services via VAERS the occurrence following immunization of any event set forth in the Vaccine Injury Table including: Anaphylaxis or anaphylactic shock within 4 hours, encephalopathy or encephalitis within 72 hours, or any sequelae thereof (including death).<sup>18,19</sup> In addition, any event considered a contraindication to further doses should be reported. The VAERS toll-free number is 1-800-822-7967.

## DOSAGE AND ADMINISTRATION

**Injection:** ENGERIX-B should be administered by intramuscular injection. *Do not inject intravenously or intradermally.* In adults, the injection should be given in the deltoid region but it may be preferable to inject in the anterolateral thigh in neonates and infants, who have smaller deltoid muscles. ENGERIX-B should not be administered in the gluteal region; such injections may result in suboptimal response. The attending physician should determine final selection of the injection site and needle size, depending upon the patient's age and the size of the target muscle. A 1-inch, 23-gauge needle is sufficient to penetrate the anterolateral thigh in infants younger than 12 months of age. A 5/8-inch, 25-gauge needle may be used to administer the vaccine in the deltoid region of toddlers and children up to, and including, 10 years of age. The 1-inch, 23-gauge needle is appropriate for use in older children and adults.<sup>17</sup>

ENGERIX-B may be administered subcutaneously to persons at risk of hemorrhage (e.g., hemophiliacs). However, hepatitis B vaccines administered subcutaneously are known to result in lower GMTs. Additionally, when other aluminum-adsorbed vaccines have been administered subcutaneously, an increased incidence of local reactions including subcutaneous nodules has been observed. Therefore, subcutaneous administration should be used only in persons who are at risk of hemorrhage with intramuscular injections.

**Preparation for Administration:** *Shake well before withdrawal and use.* Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered. With thorough agitation, ENGERIX-B is a slightly turbid white suspension. Discard if it appears otherwise. The vaccine should be used as supplied; no dilution is necessary. The full recommended dose of the vaccine should be used. Any vaccine remaining in a single-dose vial should be discarded.

**Dosing Schedules:** The usual immunization regimen (see Table 1) consists of 3 doses of vaccine given according to the following schedule: first dose: at elected date; second dose: 1 month later; third dose: 6 months after first dose.

**Table 1. Recommended Dosage and Administration Schedules**

Group	Dose	Schedules
Infants born of:		
HBsAg-negative mothers	10 mcg/0.5 mL	0, 1, 6 months
HBsAg-positive mothers	10 mcg/0.5 mL	0, 1, 6 months
Children:		
Birth through 10 years of age	10 mcg/0.5 mL	0, 1, 6 months
Adolescents:		
11 through 19 years of age	10 mcg/0.5 mL	0, 1, 6 months
Adults (>19 years)	20 mcg/1.0 mL	0, 1, 6 months
Adult hemodialysis	40 mcg/2.0 mL <sup>a</sup>	0, 1, 2, 6 months

<sup>a</sup> Two × 20 mcg in 1 or 2 injections.

For hemodialysis patients, in whom vaccine-induced protection is less complete and may persist only as long as antibody levels remain above 10 mIU/mL, the need for booster doses should be assessed by annual antibody testing. 40 mcg (2 × 20 mcg) booster doses with ENGERIX-B should be given when antibody levels decline below 10 mIU/mL.<sup>1</sup> Data show individuals given a booster with ENGERIX-B achieve high antibody titers. (See CLINICAL PHARMACOLOGY.)

There are alternate dosing and administration schedules which may be used for specific populations (see Table 2 and accompanying explanations).

**Table 2. Alternate Dosage and Administration Schedules**

Group	Dose	Schedules
Infants born of:		
HBsAg-positive mothers	10 mcg/0.5 mL	0, 1, 2, 12 months <sup>a</sup>
Children:		
Birth through 10 years of age	10 mcg/0.5 mL	0, 1, 2, 12 months <sup>a</sup>
5 through 10 years of age	10 mcg/0.5 mL	0, 12, 24 months <sup>b</sup>
Adolescents:		
11 through 16 years of age	10 mcg/0.5 mL	0, 12, 24 months <sup>b</sup>
11 through 19 years of age	20 mcg/1.0 mL	0, 1, 6 months
11 through 19 years of age	20 mcg/1.0 mL	0, 1, 2, 12 months <sup>a</sup>
Adults (>19 years)	20 mcg/1.0 mL	0, 1, 2, 12 months <sup>a</sup>

<sup>a</sup> This schedule is designed for certain populations (e.g., neonates born of hepatitis B–infected mothers, others who have or might have been recently exposed to the virus,

certain travelers to high-risk areas. See INDICATIONS AND USAGE). On this alternate schedule, an additional dose at 12 months is recommended for prolonged maintenance of protective titers.

<sup>b</sup> For children and adolescents for whom an extended administration schedule is acceptable based on risk of exposure.

**Booster Vaccinations:** Whenever administration of a booster dose is appropriate, the dose of ENGERIX-B is 10 mcg for children 10 years of age and younger, 20 mcg for adolescents 11 through 19 years of age, and 20 mcg for adults. Studies have demonstrated a substantial increase in antibody titers after ENGERIX-B booster vaccination following an initial course with both plasma- and yeast-derived vaccines. (See CLINICAL PHARMACOLOGY.)

See previous section for discussion on booster vaccination for adult hemodialysis patients.

**Known or Presumed Exposure to Hepatitis B Virus:** Unprotected individuals with known or presumed exposure to the hepatitis B virus (e.g., neonates born of infected mothers, others experiencing percutaneous or permucosal exposure) should be given hepatitis B immune globulin (HBIG) in addition to ENGERIX-B in accordance with ACIP recommendations<sup>1</sup> and with the package insert for HBIG. ENGERIX-B can be given on either dosing schedule (see above).

## STORAGE

Store refrigerated between 2° and 8°C (36° and 46°F). *Do not freeze*; discard if product has been frozen. Do not dilute to administer.

## HOW SUPPLIED

ENGERIX-B is available in single-dose vials and prefilled disposable TIP-LOK<sup>®</sup> syringes (packaged without needles) (Preservative Free Formulation):

### **10 mcg/0.5 mL Pediatric/Adolescent Dose**

NDC 58160-820-01 Vial (contains no latex) in Package of 10: NDC 58160-820-11

NDC 58160-820-43 Syringe (contains no latex) in Package of 10: NDC 58160-820-52

NDC 58160-820-32 Syringe (tip cap and plunger contain latex) in Package of 5: NDC 58160-820-46

NDC 58160-820-32 Syringe (tip cap and plunger contain latex) in Package of 10: NDC 58160-820-51

### **20 mcg/mL Adult Dose**

NDC 58160-821-01 Vial (contains no latex) in Package of 10: NDC 58160-821-11

NDC 58160-821-43 Syringe (contains no latex) in Package of 5: NDC 58160-821-48

NDC 58160-821-32 Syringe (tip cap and plunger contain latex) in Package of 1: NDC 58160-821-32

NDC 58160-821-31 Syringe (tip cap and plunger contain latex) in Package of 5: NDC 58160-821-46

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\* Yeast-derived, Hepatitis B Vaccine, MSD.

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