SG-V232-I-052018

PHYSICIANS CIRCULAR

Injection

HBvaxPRO®

(hepatitis B vaccine [recombinant] thimerosal-free, MSD)

HBvaxPRO® (hepatitis B vaccine [recombinant] thimerosal-free, MSD) is a non-infectious subunit viral vaccine consisting of surface antigen (HBsAg or Australia antigen) of hepatitis B virus produced in yeast cells. A portion of the hepatitis B virus gene, coding for HBsAg, is cloned into yeast and the vaccine for hepatitis B is produced from cultures of this recombinant yeast strain according to methods developed in the Merck Research Laboratories.

The antigen is harvested and purified from fermentation cultures of a recombinant strain of the yeast *Saccharomyces cerevisiae* containing the gene for the *adw* subtype of HBsAg. The HBsAg protein is released from the yeast cells by cell disruption and purified by a series of physical and chemical methods. Each dose contains less than 1% yeast protein. The purified protein is treated in phosphate buffer with formaldehyde and then coprecipitated with alum (potassium aluminum sulfate) to form bulk vaccine adjuvanted with amorphous aluminum hydroxyphosphate sulfate (previously referred to as aluminum hydroxide). The vaccine produced by the Merck method has been shown to be comparable to the plasma-derived vaccine in terms of protective efficacy (chimpanzee and human).

The vaccine against hepatitis B, prepared from recombinant yeast cultures, is free of association with human blood or blood products.

Each lot of hepatitis B vaccine is tested for sterility.

HBvaxPRO is a sterile suspension for intramuscular injection; however, it may be administered subcutaneously to persons at risk of hemorrhage following intramuscular injections (see DOSAGE AND ADMINISTRATION).

HBvaxPRO (hepatitis B vaccine [recombinant] thimerosal-free, MSD) is supplied in three formulations:

- Pediatric/Adolescent Formulation, 5 mcg of hepatitis B surface antigen in 0.5 mL dose;
- Adult Formulation, 10 mcg of hepatitis B surface antigen in 1.0 mL dose;
- Dialysis Formulation, 40 mcg of hepatitis B surface antigen in 1.0 mL dose.

In each formulation, hepatitis B surface antigen is adsorbed onto approximately 0.5 mg of aluminum (provided as amorphous aluminum hydroxyphosphate sulfate) per mL of vaccine. The vaccine is of the *adw* subtype.

CLINICAL PHARMACOLOGY

Hepatitis B virus is one of several hepatitis viruses that causes a systemic infection, with major pathology in the liver. These include hepatitis A and D plus C and E viruses previously referred to as non-A, non-B hepatitis viruses.

Hepatitis B virus is an important cause of viral hepatitis. There is no specific treatment for this disease. The incubation period for type B hepatitis is relatively long; six weeks to six months may elapse between exposure and the onset of clinical symptoms. The prognosis following infection with hepatitis B virus is variable and dependent on at least three factors: (1) Age - Infants and younger children usually experience milder initial disease than older persons; (2) Dose of virus - The higher the dose, the more likely acute icteric hepatitis B will result; and (3) Severity of associated underlying disease - Underlying malignancy or pre-existing hepatic disease predisposes to increased morbidity and mortality.

Persistence of viral infection (the chronic hepatitis B virus carrier state) occurs in 5-10% of persons following acute hepatitis B, and occurs more frequently after initial anicteric hepatitis B than after initial icteric disease. Consequently, carriers of hepatitis B surface antigen (HBsAg) frequently give no history of recognized acute hepatitis. It has been estimated that more than

170 million people in the world today are persistently infected with hepatitis B virus. There are more than 300 million chronic carriers worldwide. Chronic carriers represent the largest human reservoir of hepatitis B virus.

Serious complications and sequelae of hepatitis B virus infection include massive hepatic necrosis, cirrhosis of the liver and chronic active hepatitis. More than one million people worldwide die each year of hepatitis-B-associated acute and chronic liver disease.

Reduced Risk of Hepatocellular Carcinoma

Hepatocellular carcinoma is another serious complication of hepatitis B virus infection. Studies have demonstrated the link between chronic hepatitis B infection and hepatocellular carcinoma; 80% of primary liver cancers are caused by hepatitis B virus infection. Hepatitis B vaccine has been recognized as the first anti-cancer vaccine because it can prevent primary liver cancer.

There is also evidence that several diseases other than hepatitis have been associated with hepatitis B virus infection through an immunologic mechanism involving antigen-antibody complexes. Such diseases include a syndrome with rash, urticaria and arthralgia resembling serum sickness; polyarteritis nodosa; membranous glomerulonephritis and infantile papular acrodermatitis.

Although the vehicles for transmission of the virus are predominantly blood and blood products, viral antigen has also been found in tears, saliva, breast milk, urine, semen and vaginal secretions. Hepatitis B virus is capable of surviving at least a month on environmental surfaces exposed to body fluids containing hepatitis B virus. Infection may occur when hepatitis B virus, transmitted by infected body fluids, is implanted via mucous surfaces or introduced percutaneously through accidental or deliberate breaks in the skin. Transmission of hepatitis B virus infection is often associated with close interpersonal contact with an infected individual and with crowded living conditions. In such circumstances, transmission by inoculation via routes other than overt parenteral ones may be quite common. Perinatal transmission of hepatitis B infection from infected mother to child, at, or shortly after birth, can occur if the mother is a hepatitis B surface antigen (HBsAg) carrier or if the mother has an acute hepatitis B infection in the third trimester. Infection in infancy by the hepatitis B virus usually leads to the chronic carrier state. Without prophylaxis, infants born to women whose sera are positive for both the hepatitis

B surface antigen and the e antigen have an 85-90% likelihood of being infected and becoming a chronic carrier.

Well-controlled studies have shown that administration of three 0.5 mL doses of Hepatitis B Immune Globulin (Human) starting at birth can be 75% effective in preventing establishment of the chronic carrier state in these infants during the first year of life. However, the protective effect of Hepatitis B Immune Globulin (Human) is transient.

Hepatitis B is endemic throughout the world and is a serious medical problem (see VACCINATION STRATEGY). The prevalence of HBsAg in the general population varies between less than 0.5% in the U.S. and Western Europe, 1-2% in South America and Southern Europe, 3-5% in North Africa and in many parts of the former USSR region and 9-10% and higher in sub-Saharan Africa and Southeast Asia. The overall prevalence of serologic markers of infection varies between 7-10% in the U.S. and 60% and 80% in Southeast Asia or Africa. Even in countries like those in Northern and Western Europe and other highly developed countries with a relatively low prevalence of hepatitis B, certain populations are at high risk of acquiring the disease and have cumulative infection rates of up to 70% (Refer to VACCINATION STRATEGY). In countries or areas with a high prevalence rate, the entire population is at risk and infection tends to occur during childhood.

Because vaccination has been limited to high-risk individuals, e.g., health care workers and infants of HBV carrier mothers, vaccination has failed to substantially lower the overall incidence of hepatitis B infection. Consequently, the World Health Organization through their Global Advisory Group has recommended that hepatitis B vaccine should be a part of routine infant immunization programs in all countries. They have also recommended that countries with a lower prevalence of hepatitis B should consider immunization of all adolescents.

Numerous epidemiological studies have shown that persons who develop anti-HBs following active infection with the hepatitis B virus are protected against the disease on re-exposure to the virus.

Clinical studies have established that HBvaxPRO* when injected into the deltoid muscle induced protective levels of antibody in 96% of 1213 healthy adults who received the recommended three-dose regimen. Antibody responses varied with age; a protective level of antibody was induced in 98% of 787 young adults 20-29 years of age, in 94% of 249 adults 30-39 years of age, and in 89% of 177 adults ≥ 40 years of age. Studies with hepatitis B vaccine derived from plasma have shown that a lower response rate (81%) to vaccine may be obtained if the vaccine is administered as a buttock injection. Seroconversion rates and geometric mean antibody titers were measured 1 to 2 months after the third dose. A protective antibody (anti-HBs) level has been defined as 10 or more sample ratio units (SRU) as determined by radioimmunoassay or positive by enzyme immunoassay. Note: 10 SRU is comparable to 10 mIU/mL of antibody.

Predialysis and hemodialysis patients responded less well to HBvaxPRO than do healthy individuals; however, vaccination of adult patients early in the course of their renal disease produces higher seroconversion rates than revaccination after dialysis has been initiated. In two studies, where 40 mcg doses of vaccine were administered in the deltoid muscle, 89% of 28 participants developed anti-HBs with 86% achieving levels ≥ 10 mIU/mL. However, in two other studies, in which vaccine was inappropriately administered either in the buttock or a combination of buttock and deltoid, 62% of 47 participants developed anti-HBs with 55% achieving levels of ≥ 10 mIU/mL.

HBvaxPRO is highly immunogenic in younger individuals. In clinical studies, 99% of 94 infants under 1 year of age born of non-carrier mothers, 96% of 46 children 1-10 years of age, and 99% of 112 adolescents 11-19 years of age developed a protective level of antibody following the recommended three-dose regimen of vaccine.

The protective efficacy of three 5-mcg doses of HBvaxPRO has been demonstrated in neonates born of mothers positive for both HBsAg and HBeAg (a core-associated antigenic complex which correlates with high infectivity). In a clinical study of infants who received one dose of Hepatitis B Immune Globulin at birth followed by the recommended three-dose regimen of

* HBvaxPRO is the preservative containing version of the vaccine (hepatitis B vaccine [recombinant] thimerosal-containing, MSD).

HBvaxPRO, chronic infection had not occurred in 96% of 130 infants after nine months of follow-up. The estimated efficacy in prevention of chronic hepatitis B infection was 95% as compared to the infection rate in untreated historical controls. Significantly fewer neonates became chronically infected when given one dose of Hepatitis B Immune Globulin at birth followed by the recommended three-dose regimen of HBvaxPRO when compared to historical controls who received only a single dose of Hepatitis B Immune Globulin. 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.

As demonstrated in the above study, hepatitis B immune globulin, when administered simultaneously with HBvaxPRO at separate body sites, did not interfere with the induction of protective antibodies against hepatitis B virus elicited by the three-dose vaccine.

For adolescents (11 to 15 years of age), the immunogenicity of a two-dose regimen (10 mcg at 0 and 4-6 months) was compared with that of the standard three-dose regimen (5 mcg at 0, 1 and 6 months) in an open, randomized, multicenter study. The proportion of adolescents receiving the two-dose regimen who developed a protective level of antibody one month after the last dose (99% of 255 subjects) appears similar to that among adolescents who received the three-dose regimen (98% of 121 subjects). After adolescents (11 to 15 years of age) received the first 10-mcg dose of the two-dose regimen, the proportion who developed a protective level of antibody was approximately 72%.

The duration of the protective effect of HBvaxPRO in healthy vaccinees is unknown at present, and the need for booster doses is not yet defined. However, long-term follow-up (5 to 9 years) of approximately 3000 high-risk vaccinees (infants of carrier mothers, male homosexuals, Alaskan Natives) who developed an anti-HBs titer of ≥ 10 mIU/mL when given a similar plasma-derived vaccine at intervals of 0, 1, and 6 months showed that no subjects developed clinically apparent hepatitis B infection and that 5 subjects developed antigenemia, even though up to half of the subjects failed to maintain a titer at this level. Persistence of vaccine-induced immunologic memory among healthy vaccinees who responded to a primary course of plasma-derived or recombinant hepatitis B vaccine has been demonstrated by an anamnestic antibody response to a booster dose of HBvaxPRO given 5-12 years later. Data from a follow-up study showed that a group of adolescents and adults immunized 13 years earlier with a primary series of

HBvaxPRO, including several individuals whose antibody level had subsequently fallen below 10 mIU/mL, retained immunologic memory and were able to mount a vigorous secondary antibody response to a booster dose of HBvaxPRO. A booster dose or revaccination with the dialysis formulation may be considered in predialysis/dialysis patients if the anti-HBs level is less than 10 mIU/mL 1 to 2 months after the third dose.

Reports in the literature describe a more virulent form of hepatitis B associated with superinfections or co-infections by delta virus, an incomplete RNA virus. Delta virus can only infect and cause illness in persons infected with hepatitis B virus since the delta agent requires a coat of HBsAg in order to become infectious. Therefore, persons immune to hepatitis B virus infection should also be immune to delta virus infection.

INDICATIONS

All formulations of HBvaxPRO are indicated for immunization against infection caused by all known subtypes of hepatitis B virus.

HBvaxPRO should also prevent hepatitis D (caused by the delta virus), since hepatitis D does not occur in the absence of hepatitis B infection.

DOSAGE AND ADMINISTRATION

DO NOT INJECT INTRAVENOUSLY OR INTRADERMALLY.

HBvaxPRO (hepatitis B vaccine [recombinant], MSD), [40 mcg/1.0 mL] IS INTENDED ONLY FOR ADULT PREDIALYSIS/DIALYSIS PATIENTS.

HBvaxPRO (hepatitis B vaccine [recombinant], MSD), [5 mcg/0.5 mL and 10 mcg/1.0 mL ARE NOT INTENDED FOR USE IN PREDIALYSIS/DIALYSIS PATIENTS.

This formulation is intended for single use only (no preservative).

HBvaxPRO is for intramuscular injection. The deltoid muscle is the preferred site for intramuscular injection in adults. The anterolateral thigh is the recommended site for intramuscular injection in infants and young children. Data suggest that injections given in the buttocks are given frequently into fatty tissue instead of into muscle. Such injections have resulted in a lower seroconversion rate than is expected.

HBvaxPRO may be administered subcutaneously to persons at risk of hemorrhage following intramuscular injections. However, 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 (e.g., hemophiliacs) at risk of hemorrhage following intramuscular injections.

Shake well before withdrawal and use. Thorough agitation at the time of administration is necessary to maintain suspension of the vaccine.

The vaccine should be used as supplied; no dilution or reconstitution is necessary. The full recommended dose of the vaccine should be used.

NOTE: For All Formulations: Since none of the formulations contain a preservative, once the single-dose vial has been penetrated, the withdrawn vaccine should be used promptly, and the vial must be discarded.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis and other infectious agents from one person to another.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. After thorough agitation, HBvaxPRO is a slightly opaque, white suspension.

Three-Dose Regimen

The vaccination regimen consists of three doses of vaccine given according to the following schedule:

First injection: at elected date
Second injection: ≥ 1 month after first injection
Third injection: ≥ 1 month after second injection

Within limits, the timing of successive injections may be adjusted to accommodate a variety of needs, such as coadministration with other EPI vaccines.

For infants born of mothers who are HBsAg positive or mothers of unknown HBsAg status, treatment recommendations are described in the subsections titled: **Dosage Regimen for Infants Born to HBsAg-Positive Mothers and Dosage Regimen for Infants Born to Mothers of Unknown HBsAg Status.**

A minimum of one month should separate successive injections of vaccine. Accelerated three-dose regimens (e.g. 0, 1, 2 months; 0, 2, 4 months) may induce protective antibody earlier in a slightly larger proportion of vaccinees. However, regimens that extend the time interval between the second and third injections (e.g. 0, 1, 6 months; 0, 1, 12 months) will ultimately seroconvert a similar proportion of vaccinees while inducing substantially higher antibody titers than accelerated regimens.

Two-Dose Regimen – Adolescents (11 – 15 years of age)

An alternate two-dose regimen is available for routine vaccination of adolescents (11 to 15 years of age). The regimen consists of two doses of vaccine (10 mcg) given according to the following schedule:

First injection: at elected date
Second injection: 4-6 months later

The dosing regimens of HBvaxPRO for specific populations other than predialysis/dialysis patients, regardless of the risk of infection with hepatitis B virus, are as follows:

GROUP	REGIMEN

Infants**/Children/Adolescents‡ (0-19 years of age)	3 X 5 mcg
Adolescents‡ 11-15 years of age	2 X 10 mcg†
Adults (≥ 20 years)	3 X 10 mcg†

** Infants born of HBsAg-negative mothers.

† The appropriate dosage can be achieved from another formulation provided that the total volume of vaccine administered does not exceed 1.0 mL. (Excess vaccine must be discarded.) However the 40 mcg/1.0 mL formulation can be used only for adult predialysis/dialysis patients.

‡ Adolescents (11 to 15 years of age) may receive either the 3 X 5 mcg or the 2 X 10 mcg regimen.

Dosage Regimen for Infants Born to HBsAg-Positive Mothers

Infants born to HBsAg-positive mothers are at high risk of becoming chronic carriers of hepatitis B virus and of developing the chronic sequelae of hepatitis B virus infection. Well-controlled studies have shown that administration of three 0.5 mL doses of hepatitis B immune globulin starting at birth is 75% effective in preventing establishment of the chronic carrier state in these infants during the first year of life. Protection is transient under these circumstances, and the effectiveness of the passively administered hepatitis B immune globulin declines thereafter. Results from clinical studies indicate that administration of one 0.5 mL dose of hepatitis B immune globulin at birth and three 5-mcg (0.5 mL) doses of HBvaxPRO, the first dose given within one week after birth, was 96% effective in preventing establishment of the chronic carrier state in infants born to HBsAg-positive and HBeAg-positive mothers. Testing for HBsAg and anti-HBs is recommended at 12-15 months to monitor the final success or failure of therapy. If HBsAg is not detectable, and anti-HBs is present, the child has been protected.

The recommended dosage for infants born to HBsAg-positive mothers is as follows:

TREATMENT	BIRTH	1 MONTH	6 MONTHS
HBvaxPRO	5 mcg‡	5 mcg	5 mcg
Hepatitis B immune globulin	0.5 mL	--	--

‡ The first dose of HBvaxPRO may be given at birth at the same time as hepatitis B immune globulin, but it should be administered in the opposite anterolateral thigh.

Dosage Regimen for Infants of Mothers of Unknown HBsAg Status

In the event that a mother's HBsAg status is unknown, vaccination should be initiated as soon as possible with a 5 mcg dose of vaccine. If within 7 days of delivery, the mother is determined to be HBsAg-positive, the infant also should be given a dose of Hepatitis B Immune Globulin immediately; the vaccination series should then be completed with 5 mcg dosages. If the mother's HBsAg antigen test is negative, then complete the vaccination series with the 5 mcg dosages.

Predialysis/Dialysis Regimen

The recommended three-dose vaccination regimen for predialysis/dialysis patients is as follows:

GROUP	INITIAL	1 MONTH	6 MONTHS
Adult Predialysis and Dialysis Patients	40 mcg	40 mcg	40 mcg

A booster dose or revaccination with HBvaxPRO may be considered in predialysis/dialysis patients if the anti-HB level is less than 10 mIU/mL 1 to 2 months after the third dose.

The need for booster doses of vaccine should be assessed by annual antibody testing, and a booster dose given when antibody levels decline to less than 10 mIU/mL.

Use with Other Vaccines

Results from clinical studies indicate that HBvaxPRO can be administered concomitantly with DTP (Diphtheria, Tetanus and whole cell Pertussis), OPV (oral Poliomyelitis vaccine), M-M-R II (Measles, Mumps, and Rubella Virus Vaccine Live), Liquid PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] or a booster dose of DTaP [Diphtheria, Tetanus, acellular Pertussis], using separate sites and syringes for injectable vaccines. No impairment of immune response to individually tested vaccine antigens was demonstrated.

In addition, an HBsAg-containing product, COMVAX [Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine], was given concomitantly with eIPV (enhanced inactivated Poliovirus vaccine) or VARIVAX [Varicella Virus Vaccine Live (Oka/Merck)], using separate sites and syringes for injectable vaccines. No impairment of immune response to these individually tested vaccine antigens was demonstrated.

Revaccination of Nonresponders

When persons who do not respond (anti-HBs < 10 IU/l) to the primary vaccine series are revaccinated, 15-25% produce an adequate antibody response after one additional dose and 30-50% after three additional doses. However, because data are insufficient concerning the safety of hepatitis B vaccine when additional doses in excess of the recommended two or three-dose series are administered, revaccination following completion of the primary series is not routinely recommended. Revaccination should only be considered for high-risk individuals, after weighing the benefits of vaccination against the potential risk of experiencing increased local or systemic adverse reactions.

KNOWN or PRESUMED EXPOSURE TO HBsAg

There are no prospective studies directly testing the efficacy of a combination of hepatitis B immune globulin and HBvaxPRO in preventing clinical hepatitis B following percutaneous, ocular or mucous membrane exposure to hepatitis B virus. Since most persons with such exposures (e.g. health care workers) are candidates for the hepatitis B vaccine and since combined hepatitis B immune globulin plus vaccine is more efficacious than hepatitis B immune globulin alone in perinatal exposures, the following guidelines are recommended for persons who have been exposed to hepatitis B virus such as through (1) percutaneous (needlestick),

ocular, mucous membrane exposure to blood known or presumed to contain HBsAg, (2) human bites by known or presumed HBsAg carriers, that penetrate the skin, or (3) following intimate sexual contact with known or presumed HBsAg carriers.

Hepatitis B immune globulin (0.06 mL/kg) should be given as soon as possible after exposure and within 24 hours if possible. Hepatitis B vaccine**,** with the age-appropriate dose, (10 mcg for adults) should be given intramuscularly within 7 days of exposure and second and third doses given one and six months, respectively, after the first dose.

Revaccination

The duration of the protective effect of HBvaxPRO in healthy vaccinees is unknown at present and the need for booster doses is not yet defined.

For Syringe Use Only: Withdraw the recommended dose from the vial using a sterile needle and syringe free of preservatives, antiseptics and detergents.

Storage

Store vials at 2 - 8°C (35.6 - 46.4°F). *Do not freeze since freezing destroys potency*. Protect from light. When stored at 2 - 8°C, the pediatric, adult and dialysis formulations have a shelf life of 36 months. Storage above or below the recommended temperature may reduce potency.

HBvaxPRO should be administered as soon as possible after being removed from refrigeration. HBvaxPRO can be administered provided total (cumulative multiple excursion) time out of refrigeration (at temperatures between 8°C and 25°C) does not exceed 72 hours. Cumulative multiple excursions between 0°C and 2°C are also permitted as long as the total time between 0°C and 2°C does not exceed 72 hours. These are not, however, recommendations for storage.

CONTRAINDICATIONS

Hypersensitivity to yeast or any other component of the vaccine.

PRECAUTIONS

General

Persons with immunodeficiency or those receiving immunosuppressive therapy require larger vaccine doses and respond less well than healthy individuals.

Because of the long incubation period for hepatitis B, it is possible for unrecognized infection to be present at the time HBvaxPRO is given. HBvaxPRO may not prevent hepatitis B in such patients.

Patients who develop symptoms suggestive of hypersensitivity after an injection should not receive further injections of HBvaxPRO (see CONTRAINDICATIONS).

Use caution when vaccinating latex-sensitive individuals since the vial stopper and the syringe plunger stopper and tip cap contain dry natural latex rubber that may cause allergic reactions.

As with any parenteral vaccine, epinephrine (adrenaline) should be available for immediate use should an anaphylactoid reaction occur.

Any serious active infection is reason for delaying use of HBvaxPRO except when in the opinion of the physician, withholding the vaccine entails a greater risk.

Caution and appropriate care should be exercised in administering HBvaxPRO to individuals with severely compromised cardiopulmonary status or to others in whom a febrile or systemic reaction could pose a significant risk.

PREGNANCY

There are no well-controlled studies in pregnant women. HBvaxPRO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal reproduction studies have not been conducted with HBvaxPRO.

NURSING MOTHERS

It is not known whether HBvaxPRO is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when the vaccine is administered to nursing mothers. However, studies with H-B-VAX in 12 lactating women have failed to reveal evidence of this vaccine being excreted.

PEDIATRIC USE

HBvaxPRO has been shown to be generally well-tolerated and highly immunogenic in infants and children of all ages. Newborns have responded well; maternally transferred antibodies did not interfere with the active immune response to the vaccine. See DOSAGE AND ADMINISTRATION for recommended pediatric dosage and recommended dosage for infants born to HBsAg-positive mothers. The safety profile and effectiveness of the dialysis formulation in children have not been established.

GERIATRIC USE

Clinical studies of HBvaxPRO used for licensure did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects. However, in later studies of hepatitis B vaccines, it has been shown that a diminished antibody response and seroprotective levels can be expected in persons older than 60 years of age.

SIDE EFFECTS

HBvaxPRO is generally well-tolerated. No adverse experiences were reported during clinical trials which could be related to changes in the titers of antibodies to yeast. As with any vaccine, there is the possibility that broad use of the vaccine could reveal adverse reactions not observed in clinical trials.

In a group of studies, 3258 doses of HBvaxPRO, 10 mcg, were administered to 1252 healthy adults. Vaccine recipients were monitored for 5 days after each dose, and the following side effects were reported:

Incidence Equal to or Greater Than 1% of Injections

Local Reactions at injection site

Injection site reactions, consisting principally of local pain, soreness and tenderness and including pruritus, erythema, ecchymoses, swelling, warmth and nodule formation.

Body as a Whole

Fatigue/asthenia

Malaise

Fever (≥ 100°F or ≥ 38°C)

Digestive System

Nausea

Diarrhea

Nervous System

Headache

Respiratory System

Pharyngitis

Upper respiratory infection (NOS)

Incidence Less Than 1% of Injections

Body as a Whole

Sweating

Chills

Flushing

Aching

Sensation of warmth

Integumentary System

Pruritus

Rash

Urticaria

Angioedema

Digestive System

Vomiting

Abdominal pains/cramps

Dyspepsia

Diminished appetite

Musculoskeletal System

Myalgia

Arthralgia

Back pain

Neck pain

Shoulder pain

Neck stiffness

Nervous System

Lightheadedness

Vertigo/dizziness

Paresthesia

Respiratory System

Rhinitis

Cough

Influenza

Special Senses

Earache

Hemic/Lymphatic System
Lymphadenopathy

Psychiatric/Behavioral
Insomnia/Disturbed sleep

Urogenital System
Dysuria

Cardiovascular System
Hypotension

In a study that compared the three-dose regimen (5 mcg) with the two-dose regimen (10 mcg) of HBvaxPRO in adolescents, the overall frequency of adverse reactions was generally similar.

In a group of studies, 1636 doses of HBvaxPRO were administered to 653 healthy infants and children (up to 10 years of age) who were monitored for 5 days after each dose. Injection site reactions (including erythema and swelling) and systemic complaints were reported following 8% and 17% of the injections, respectively. The most frequently reported systemic adverse reactions (>1% injections), in decreasing order of frequency, were irritability, tiredness, fever (>101°F or >38°C oral equivalent), crying, diarrhea, vomiting, diminished appetite, and insomnia.

ADDITIONAL SIDE EFFECTS

The following additional side effects have been reported with use of the marketed vaccine; however, in many instances a causal relationship to the vaccine has not been established.

Hypersensitivity

Anaphylaxis and symptoms of immediate hypersensitivity reactions including edema, dyspnea, chest discomfort, bronchial spasm, or palpitation have been reported within the first few hours after vaccination. An apparent hypersensitivity syndrome (serum-sickness-like) of delayed onset has been reported days to weeks after vaccination, including: arthritis (usually transient), and dermatologic reactions such as erythema multiforme, ecchymoses and erythema nodosum (see PRECAUTIONS).

Immune System

Vasculitis

Polyarteritis nodosa

Integumentary System

Alopecia

Eczema

Musculoskeletal System

Arthritis

Pain in extremity

Nervous System

Peripheral neuropathy including Bell's Palsy; Guillain-Barré syndrome, exacerbation of multiple sclerosis, multiple sclerosis, optic neuritis, seizure, febrile seizure, encephalitis, vasovagal syncope

Special Senses

Tinnitus

Uveitis

Hematologic

Increased erythrocyte sedimentation rate, thrombocytopenia

AVAILABILITY

HBvaxPRO is available as 5 mcg in 0.5 mL (without preservative).
HBvaxPRO is available as 10 mcg in 1.0 mL (without preservative).
HBvaxPRO is available as 40 mcg in 1.0 mL. [This formulation is intended for predialysis/dialysis patients only (without preservative).]

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