PRODUCT MONOGRAPH

RECOMBIVAX HB®

(hepatitis B vaccine [recombinant])

Suspension for Injection

Vaccine for immunization against infection
caused by hepatitis B virus including
all known subtypes

Merck Canada Inc.
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Kirkland, Quebec H9H 4M7

Date of Revision:
May 15, 2012

Global Trade Identification No.:
Pediatric: 0 67055 04523 3 (1 x 0.5 mL)
Adult: 0 67055 04569 1 (1 x 1 mL); 0 67055 04633 9 (10 x 1 mL)
Adult Dialysis: 0 67055 04560 8 (1 x 1 mL)

Submission Control No: 155287 **Date of Approval: May 22, 2012**

Table of Contents

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(hepatitis B vaccine [recombinant])

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular injection	Suspension for injection Pediatric: single-dose vial containing 5 μg hepatitis B surface antigen (HBsAg)/0.5 mL dose Adult: single-dose vial containing 10 μg HBsAg/1.0 mL dose Adult dialysis: single-dose vial containing 40 μg HBsAg/1.0 mL dose	Aluminum hydroxyphosphate, yeast protein Latex in vial stopper *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

DESCRIPTION

RECOMBIVAX HB® (hepatitis B vaccine [recombinant]) 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.

INDICATIONS AND CLINICAL USE

RECOMBIVAX HB® (hepatitis B vaccine [recombinant]) is indicated for immunization against infection caused by all known subtypes of hepatitis B virus.

RECOMBIVAX HB® will not prevent hepatitis caused by other agents, such as hepatitis A virus, non-A, non-B hepatitis viruses, or other viruses known to infect the liver.

Vaccination with RECOMBIVAX HB® is recommended in persons of all ages, especially those who are or will be at increased risk of infection with hepatitis B virus. In areas with low prevalence like Canada, universal immunization before adolescence is recommended.[1] Special efforts should also target the high-risk populations.[1]

A. Infants Born to HBsAg-Positive Mothers

B. Children < 7 years of age whose families have immigrated to Canada from areas where there is a high prevalence of hepatitis B, and who are exposed to hepatitis B virus carriers through their extended families.

C. Adolescents (see CLINICAL TRIALS)

D. Health-Care Personnel
Dentists and oral surgeons
Physicians and surgeons
Nurses
Paramedical personnel and custodial staff who may be exposed to the virus via blood or other patient specimens (i.e., body fluids and tissues)
Dental hygienists and dental nurses
Laboratory personnel handling blood, blood products and other patient specimens (i.e., body fluids and tissues)
Dental, medical and nursing students, preferably soon after acceptance in the university

E. 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)
Patients (residents) and staff of institutions for the mentally handicapped
Classroom contacts of deinstitutionalized mentally handicapped persons who have persistent hepatitis B antigenemia and who show aggressive behavior
Household and other intimate contacts of persons with persistent hepatitis B antigenemia
Children in child-care settings in which there is a hepatitis B virus-infected child. These children should receive serious consideration for immunization against hepatitis B virus.

F. Travellers to Hepatitis B Endemic Areas

G. Military Personnel Identified as Being at Increased Risk

H. Emergency Service Workers (police, firefighters)

I. Morticians and Embalmers

J. Blood Bank and Plasma Fractionation Workers

K. Persons at Increased Risk of the Disease Due to Their Sexual Practices[2] such as:
Persons who have heterosexual activity with multiple partners
Persons who repeatedly contract sexually transmitted diseases
Homosexually active males
Female prostitutes

L. Prisoners

M. Users of Illicit Injectable Drugs

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section.

WARNINGS AND PRECAUTIONS

Because of the long incubation period for hepatitis B, it is possible for unrecognized infection to be present at the time RECOMBIVAX HB® (hepatitis B vaccine [recombinant]) is given. RECOMBIVAX HB® may not prevent hepatitis B in such patients.

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

Use caution when vaccinating latex-sensitive individuals since the vial stopper contains dry natural latex rubber that may cause allergic reactions.

General

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

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

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

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

Special Populations

Pregnant Women:
Animal reproduction studies have not been conducted with RECOMBIVAX HB®. It is also not known whether RECOMBIVAX HB® can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. RECOMBIVAX HB® should be given to a pregnant woman only if clearly needed.

Nursing Women:
It is not known whether RECOMBIVAX HB® is excreted in human milk. However, studies with RECOMBIVAX HB® in 12 lactating women have failed to reveal evidence of this vaccine being secreted.

Pediatrics:
RECOMBIVAX HB® 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.

Geriatrics:
Clinical studies of RECOMBIVAX HB® 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
RECOMBIVAX HB® (hepatitis B vaccine [recombinant]) is generally well-tolerated. No adverse reactions 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 rare adverse reactions not observed in clinical trials.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another vaccine. Adverse drug reaction information from clinical trials is useful for identifying vaccine-related adverse events and for approximating rates.

In a group of studies, 3258 doses of RECOMBIVAX HB®, 10 μg, were administered to 1252 healthy adults. Vaccine recipients were monitored for 5 days after each dose, and the following adverse reactions were reported:

Incidence Equal to or Greater Than 10% 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).

Incidence Equal to or Greater Than 1% and Less Than 10% of Injections

Body as a Whole
Fatigue/asthenia
Malaise
Fever ≥ 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 μg) with the two-dose regimen (10 μg) of RECOMBIVAX HB® in adolescents, the overall frequency of adverse reactions was generally similar.

Post-Market Adverse Drug Reactions

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

Hematologic
Increased erythrocyte sedimentation rate, thrombocytopenia

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 WARNINGS AND 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

DRUG INTERACTIONS

Use With Other Vaccines

According to the National Advisory Committee on Immunization (NACI), RECOMBIVAX HB® (hepatitis B vaccine [recombinant]) may be administered simultaneously with other vaccines at different sites. A separate needle and syringe should be used for each vaccine.

The safety and immunogenicity of co-administration of RECOMBIVAX HB® with GARDASIL® (quadrivalent human papillomavirus [types 6, 11, 16, 18] recombinant vaccine) (same visit, injections at separate sites) were evaluated in a randomized study of 1,871 women aged 16 to 24 years at enrolment. Immune response and safety profile to both RECOMBIVAX HB® and GARDASIL® were similar whether they were administered at the same visit or at a different visit.

Results from published clinical studies[3,4] indicate that RECOMBIVAX HB® can be administered concomitantly with DTaP-IPV-Hib (diphtheria, tetanus, acellular pertussis, inactivated

poliomyelitis, and *Haemophilus influenzae* type b conjugate vaccine), or M-M-R® II (measles, mumps and rubella virus vaccine, live, attenuated, Merck Std.), using separate syringes and injection sites for each vaccine. No impairment of immune response to individually tested vaccine antigens was seen in these studies.

In addition, an HBsAg-containing product, COMVAX™ (*Haemophilus* b conjugate vaccine [meningococcal protein conjugate] and hepatitis B [recombinant] vaccine) was given concomitantly with M-M-R® II and VARIVAX® III (varicella virus vaccine, live, attenuated [Oka/Merck]), using separate syringes and injection sites for each vaccine[5]. No impairment of immune response to these individually tested vaccine antigens was demonstrated.

Another randomized study conducted in 1993 with COMVAX™, administered concurrently with routine pediatric vaccines (DTP, OPV/IPV, M-M-R® II, booster dose of DTaP) in 94 infants who completed the study, showed an acceptable response rate for most antigens but a lower response than pre-specified to polio antigens type 1 and type 3, pertussis antigens and rubella. However, the assays, endpoints and time points used differ from currently used criteria. The response to polio was assessed on sera at week-12 (instead of week-4) post-dose 2 and not after the third dose.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

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 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 for Infants Born to HBsAg-Positive Mothers**.

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.

The dose of vaccine to be given on each occasion is as follows:

GROUP	REGIMEN
INFANTS*/CHILDREN (birth to 10 years of age)	3 X 2.5 µg
ADOLESCENTS (11 – 19 years of age)	3 X 5 µg
ADULTS (≥ 20 years)	3 X 10 µg

* Infants born of HBsAg-negative mothers.

Two-Dose Regimen - Adolescents (11 to 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 µg) given according to the following schedule:

1st dose: at elected date
2nd dose: 4 to 6 months after the first dose

GROUP	INITIAL	4-6 MONTHS
ADOLESCENTS** (11 - 15 years of age)	10 µg	10 µg

** Adolescents (11 to 15 years of age) may receive either regimen, the 3 X 5 µg or the 2 X 10 µg (see DOSAGE AND ADMINISTRATION, Three-Dose and Two-Dose Regimens).

RECOMBIVAX HB® Dialysis 40 µg/mL Formulation
RECOMBIVAX HB® DIALYSIS FORMULATION (40 µg/mL) IS INTENDED ONLY FOR ADULT PREDIALYSIS/DIALYSIS PATIENTS.

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

GROUP	INITIAL	1 MONTH	6 MONTHS
PREDIALYSIS/DIALYSIS Adult dialysis presentation 40 µg/1.0 mL	40 µg	40 µg	40 µg

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.[6,7] 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.

Dosage 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.[8] 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 µg (0.5 mL) doses of RECOMBIVAX HB®, 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- 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
RECOMBIVAX HB®	5 µg***	5 µg	5 µg
Hepatitis B immune globulin	0.5 mL		

***The first dose of RECOMBIVAX HB® (5 µg) may be given at birth at the same time as hepatitis B immune globulin, but should be administered in the opposite anterolateral thigh. This procedure may be preferable to ensure absorption of the vaccine.

Acute Exposure to Blood Containing HBsAg

There are no prospective studies directly testing the efficacy of a combination of hepatitis B immune globulin and RECOMBIVAX HB® in preventing clinical hepatitis B following percutaneous, ocular or mucous membrane exposure to hepatitis B virus. However, recent studies have established the relative efficacies of immune globulins and/or hepatitis B vaccine in various exposure situations. 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 should be given intramuscularly within 7

days of exposure and second and third doses given one and six months, respectively, after the first dose.

Administration

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 children. Data suggest that injections given in the buttocks are given frequently into fatty tissue instead of into muscle. Such injections may result in a lower seroconversion rate than is expected[9].

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

It is recommended to record lot numbers when the vaccine is administered to a recipient.

FOR INTRAMUSCULAR USE

Do not inject intravenously or intradermally.

RECOMBIVAX HB® (hepatitis B vaccine [recombinant]) is for intramuscular injection. It may, however, 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. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. After thorough agitation, RECOMBIVAX HB® is a slightly opaque, white suspension.

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

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.

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.

OVERDOSAGE

There are no data with regard to overdose.

For management of a suspected overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Hepatitis B virus is one of at least five hepatitis viruses that cause a systemic infection, with major pathology in the liver. The others are hepatitis A, hepatitis C, hepatitis D, and hepatitis E 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;[10] (2) Dose of Virus - The higher the dose, the more likely acute icteric hepatitis B will result;[10] and, (3) Severity of associated underlying disease - Underlying malignancy or pre-existing hepatic disease predisposes to increased morbidity and mortality.[10]

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. The World Health Organization estimated that more than 2 billion people worldwide have evidence of post or current hepatitis B virus infection, and 350 million are chronic carriers of the virus.[11] The Centers for Disease Control (CDC) estimate that there are approximately 0.5 to 1.0 million chronic carriers of hepatitis B virus in the USA and that this pool of carriers grows by 2-3% (8000 to 16,000 individuals) annually.[12] Chronic carriers represent the largest human reservoir of hepatitis B virus.

The serious complications and sequelae of hepatitis B virus infection include massive hepatic necrosis, cirrhosis of the liver, chronic active hepatitis, and hepatocellular carcinoma.[13] Chronic carriers of HBsAg appear to be at increased risk of developing hepatocellular carcinoma, which accounts for 80 to 90% of primary liver carcinomas.[14] Although a number of etiologic factors are associated with development of hepatocellular carcinoma, the single most important etiologic factor appears to be active infection with the hepatitis B virus.[11] Globally, approximately one million individuals die each year as a direct result of HBV-induced cirrhosis or liver cancer.[15] Based on death certificates, about 100 Canadians died in 1995 due to hepatitis B associated acute or chronic liver disease.[16]

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.[11]

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 for days on environmental surfaces. Infection may occur when hepatitis B virus, transmitted by infected body fluids, is implanted via mucous surfaces or percutaneously introduced 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.[17] Perinatal transmission of hepatitis B infection from infected mother to child, at, or shortly after birth, can occur if the mother is an HBsAg carrier or if the mother has an acute hepatitis B infection in the third trimester.[18] Infection in infancy by the hepatitis B virus usually leads to the chronic carrier state. Among infants born to women whose sera are positive for both the hepatitis B surface antigen and the e antigen, 85-90% are infected and become chronic carriers.[18,19]

Hepatitis B is endemic throughout the world, and is a serious medical problem in population groups at increased risk (see INDICATIONS AND CLINICAL USE). The prevalence of HBsAg in the general population varies between less than 0.5% in the U.S., Canada and Western Europe, 1 to 2% in South America and Southern Europe, 3 to 5% in North Africa and in many parts of the Federation of Russia (formally known as USSR) and 9 to 10% and higher in sub-Saharan Africa, Southeast Asia and Alaska.[20,21] The overall prevalence of serologic markers of infection varies between 7 and 10% in the U.S. and 60 and 80% in Southeast Asia or Africa.[20] 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% (see INDICATIONS AND CLINICAL USE).[20] In countries or areas with a high prevalence rate, the entire population is at risk and infection tends to occur during childhood.

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.

Reports in the literature describe a more virulent form of hepatitis B associated with superinfections or coinfections 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.[8,22]

STORAGE AND STABILITY

Store vaccine refrigerated at 2°C to 8°C. Storage above and below the recommended temperature may reduce potency. **Do not freeze (below 0°C) since freezing destroys potency.**

RECOMBIVAX HB® 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.

Do not use vaccine after the expiration date.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

RECOMBIVAX HB® (hepatitis B vaccine [recombinant]) is supplied as a sterile, slightly opaque, white suspension for injection in a single-dose vial.

The vaccine is used directly as supplied. No dilution or reconstitution is necessary.

Composition

RECOMBIVAX HB® is available in three presentations, summarized below. Each single dose contains:

	Pediatric Presentation	**Adult Presentation**	**Adult Dialysis Presentation**
Dose volume	0.5 mL	1.0 mL	1.0 mL
Active Ingredient Hepatitis B surface antigen	5 µg	10 µg	40 µg
Other Ingredients: *Excipients:* Aluminum (as amorphous aluminum hydroxyphosphate) Sodium chloride Sodium borate Water for injection	0.25 mg 4.5 mg 35.0 µg to volume	0.5 mg 9.0 mg 70.0 µg to volume	0.5 mg 9.0 mg 70.0 µg to volume

All presentations are preservative-free (thimerosal-free).

Manufacturing Process Residuals

Each dose contains less than 1% yeast protein. The vaccine also contains < 15 µg/mL formaldehyde as all preparations have been treated with formaldehyde prior to adsorption onto amorphous aluminum hydroxyphosphate.

Packaging

Pediatric Presentation: RECOMBIVAX HB® is supplied in 3 mL, single-dose Type I glass vials containing one 0.5 mL dose (5 μg HBsAg). The vial stopper contains latex. It is available in packages of 1 single-dose vial.

Adult Presentation: RECOMBIVAX HB® is supplied in 3 mL, single-dose Type I glass vials containing one 1.0 mL dose (10 μg HBsAg). The vial stopper contains latex. It is available in packages of 1 and 10 single-dose vials.

Adult Dialysis Presentation: RECOMBIVAX HB® is supplied in 3 mL, single-dose Type I glass vials containing one 1.0 mL dose (40 μg HBsAg). The vial stopper contains latex. It is available in packages of 1 single-dose vial.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: hepatitis B vaccine [recombinant]

Physicochemical properties:

RECOMBIVAX HB® (hepatitis B vaccine [recombinant]) 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 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.

CLINICAL TRIALS

Clinical studies have established that RECOMBIVAX HB® (hepatitis B vaccine [recombinant]), when injected into the deltoid muscle, induced protective levels of antibody in greater than 90% of healthy individuals who received the recommended 3-dose regimen. 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.[9] A protective antibody (anti-HBs) level has been defined as 10 or more sample ratio units (SRU) as determined by radioimmunoassay or a positive by enzyme immunoassay.[23]

Responsiveness to the vaccine was age dependent. The seroprotection rate for children 1-10 years of age and adolescents 11-15 years of age were 100% and 99%, respectively. In contrast, the seroprotection rate for adults ranged from 95 to 98% for those from 20 to 39 years of age and 91% for those of 40 years of age or older.

The protective efficacy of three 5 μg doses of RECOMBIVAX HB® has been demonstrated in neonates born of mothers positive for both HBsAg and HBeAg. 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 RECOMBIVAX HB®, efficacy in prevention of chronic hepatitis B infection was 96% in 47 infants at six months and 100% in 19 infants at nine months.

For adolescents (11 to 15 years of age), the immunogenicity of a two-dose regimen (10 μg at 0 and 4-6 months) was compared with that of the standard three-dose regimen (5 μg 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 μg dose of the two-dose regimen, the proportion who developed a protective level of antibody was approximately 72%.

Predialysis and Dialysis Patients
Immunocompromised persons respond less well to RECOMBIVAX HB® than do healthy individuals. Vaccine-induced levels of anti-HBs are lower in pre-dialysis and hemodialysis patients than are the levels in healthy individuals. Eighty-six percent (86%) of pre-dialysis and hemodialysis patients who received three 40 μg doses of RECOMBIVAX HB® developed protective levels of anti-HBs.

Duration of Protection
As with other hepatitis B vaccines, the duration of protective effect of RECOMBIVAX HB® is unknown at present, and the need for booster doses not 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 ≥10mIU/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.[24-27] 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 RECOMBIVAX HB® given 5-12 years later.[28]

Routine booster vaccinations in immunocompetent persons are not recommended since protection has been shown to last for at least 15 years. Studies of long-term protective efficacy, however, will determine whether booster doses of vaccine are ever needed. It is important to recognize that absence of detectable anti-HBs in a person who has been previously demonstrated to have anti-HBs does not mean lack of protection, because immune memory persists. Booster doses in this situation are not indicated.[1]

Immunocompromised persons often respond suboptimally to the vaccine. Subsequent HBV exposures in these individuals can result in disease or the carrier state. Therefore, boosters may be necessary in this population. The optimal timing of booster doses for immunocompromised individuals who are at continued risk of HBV exposure is not known and should be based on the severity of the compromised state and annual monitoring for the presence of anti-HBs.[1]

Post-Exposure
Studies have established the relative efficacies of immune globulin and/or hepatitis B vaccine in accidental percutaneous or permucosal exposure to HBsAg-positive blood; or sexual exposure to HBsAg-positive persons (see DOSAGE AND ADMINISTRATION).

It has been demonstrated that doses of up to 5 mL of Hepatitis B Immune Globulin, when administered simultaneously with the first dose of RECOMBIVAX HB® at separate body sites, did not interfere with the induction of protective antibodies against hepatitis B virus elicited by the three-dose vaccine regimen.

Interchangeability
Hepatitis B vaccines produced by different manufacturers can be used interchangeably despite different doses and schedules. The dose used should be that recommended by the manufacturer.[1]

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PART III: CONSUMER INFORMATION

RECOMBIVAX HB®
(hepatitis B vaccine [recombinant])

This leaflet is part III of a three-part "Product Monograph" published when RECOMBIVAX HB® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about RECOMBIVAX HB®. Contact your doctor or pharmacist if you have any questions about the vaccine.

ABOUT THIS VACCINE

What the vaccine is used for:
RECOMBIVAX HB® [hepatitis B vaccine (recombinant)] is an injectable vaccine that helps prevent infection of the liver caused by hepatitis B virus.

The vaccine can be administered to infants, children, adolescents, and adults.

What it does:
Your doctor has recommended or administered RECOMBIVAX HB® to help protect you or your child against hepatitis B, an infection of the liver caused by the hepatitis B virus (HBV).

You could catch this disease by coming into contact with an infected person's blood, semen, vaginal secretions, or other body fluids. For example, if these infected fluids enter your blood stream through a cut, you could become infected. Other circumstances that could lead to infection include:

• being born to a mother who carries the HBV
• living in the same household as someone who carries the HBV
• sexual/close contact with someone who is infected
• having a job that involves exposure to human blood or body fluids
• sharing needles for injecting drugs
• traveling to areas of high frequency of HBV disease

Individuals who have hepatitis B may not look or feel sick when infected. In fact, a person could be infected by the virus six weeks to six months before symptoms occur. Some individuals develop mild, flu-like symptoms. Others may become very ill and extremely tired, develop jaundice (yellow appearance of the skin, eyes, etc.), dark urine and other symptoms that require hospitalization.

Most people recover completely from HBV infection. However, there are some individuals, particularly children, who may not have symptoms but continue to carry the virus in their blood. They are called chronic carriers. These chronic carriers are infectious and can spread the disease to others throughout their lives. All chronic carriers run the risk of developing life threatening liver disease, cirrhosis, or liver cancer.

When it should not be used:
RECOMBIVAX HB® should not be used by anyone who is hypersensitive to this drug or to any ingredient in the formulation or component of the container.

What the medicinal ingredient is:
Pediatric presentation: Each 0.5 mL dose contains 5 μg of hepatitis B surface antigen as the active ingredient.
Adult presentation: Each 1 mL dose contains 10 μg of hepatitis B surface antigen as the active ingredient.
Adult dialysis presentation: Each 1 mL dose contains 40 μg of hepatitis B surface antigen as the active ingredient.

What the important nonmedicinal ingredients are:
Aluminum (as amorphous aluminum hydroxyphosphate), sodium chloride and sodium borate. Each dose contains less than 1% yeast protein.

The vial stopper contains latex.

What dosage forms it comes in:
RECOMBIVAX HB® is supplied as a slightly cloudy, white suspension for injection in glass vials. Three formats are available:

- Pediatric: single-dose vial containing 5 μg hepatitis B surface antigen in 0.5 mL (thimerosal-free)
- Adult: single-dose vial containing 10 μg hepatitis B surface antigen in 1.0 mL (thimerosal-free)
- Adult dialysis: single-dose vial containing 40 μg hepatitis B surface antigen in 1 mL (thimerosal-free).

WARNINGS AND PRECAUTIONS

Before you or your child receive RECOMBIVAX HB®, it is very important to tell your healthcare provider:

- if you or your child are allergic to any component of the vaccine
- if you or your child are allergic to latex
- about any medical problem you or your child have or have had, including any allergies
- if you are pregnant or intend to become pregnant

Use in children
RECOMBIVAX HB® can be used in newborns, infants, and children of all ages.

Use in elderly
Hepatitis B vaccines may not be as effective in individuals 65 years of age and older, as they are with younger subjects.

Use in pregnancy and breast-feeding
It is not known whether the vaccine is harmful to an unborn baby when administered to a pregnant woman. If you are pregnant, you should be vaccinated with RECOMBIVAX HB® only if your doctor decides it is clearly needed.

Tell your doctor if you are breast feeding.

Can I drive or operate machinery after vaccination with RECOMBIVAX HB®?
RECOMBIVAX HB® should not ordinarily interfere with your ability to drive or operate machinery. However, as with any vaccination, it is advisable to wait in your doctor's

office about 20 minutes after vaccination in case an immediate allergic reaction develops.

Other Considerations
Because hepatitis B infection can go undetected for a long period of time, it is possible that an individual may already be infected at the time the vaccine is given. The vaccine may not prevent hepatitis B in these individuals.

INTERACTIONS WITH THIS VACCINE

In general, simultaneous administration of certain childhood vaccines has not decreased their effectiveness or increased their side effects.

PROPER USE OF THIS VACCINE

Usual dose:
RECOMBIVAX HB® is given by injection. A three-dose series should be given according to the following schedule:
• First dose: at elected date
• Second dose: >1 month after first injection
• Third dose >1 month after second injection

For adolescents, 11 to 15 years of age, a two-dose series may be given according to the following schedule:
• First dose: at elected date
• Second dose: 4 to 6 months later

NOTE: For infants born to mothers infected with HBV, the first dose of the hepatitis B vaccination series should be given at birth, or as soon thereafter as possible, in addition to an injection of hepatitis B immune globulin.

At present, it is not known whether a booster dose will be necessary. See your doctor for more details.

Overdose:

In case of overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Your doctor will decide when to give the missed dose

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Any vaccine may have unintended or undesirable effects, so-called side effects. RECOMBIVAX HB® is generally well tolerated. The side effects seen in children, adolescents, and adults include injection-site reactions such as soreness, redness, swelling, itching, bruising, warmth and a hard lump. Generalized reactions include fatigue, headache, fever, nausea, diarrhea, and vomiting. Serious side effects occur less frequently and can include allergic reactions, certain severe types of rash, joint pain, muscle disorders, and nerve disorders such as Guillain-Barré Syndrome, seizure, or convulsion accompanied by a very high fever, and fainting. Other side effects also reported include bleeding or bruising more easily than normal.

Your doctor has a more complete list of side effects.
Tell your doctor promptly about these or any other unusual symptoms. If the condition persists or worsens, seek medical attention.

In addition, tell your doctor if you experienced any symptoms that suggest an allergic reaction after any dose in the vaccination series.

HOW TO STORE IT

Store refrigerated at 2-8°C. Do not freeze.

All vaccines must be discarded after the expiration date.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects case reports on adverse events following immunization.

For health care professionals:
If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events following Immunization (AEFI) Form and send it to your local Health Unit in **your province/territory.**

For the General Public:
Should you experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events following Immunization (AEFI) Form.

If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada
By toll-free telephone: 866-844-0018
By toll-free fax: 866-844-5931
Email: caefi@phac-aspc.gc.ca
Web: http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php__http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php

Mail:
The Public Health Agency of Canada
Vaccine Safety Section 130 Colonnade Road ,
A/L 6502A
Ottawa , ON K1A 0K9

or at Merck Canada Inc. by one of the following 2 ways:

- Call toll-free: 1-800-567-2594
- Complete an Adverse Events following Immunization (AEFI) Form and:
  - Fax toll-free 1-800-369-3090, or
  - Mail to: Merck Canada Inc.
    Pharmacovigilance
    P.O. Box 1005
    Pointe-Claire - Dorval, QC H9R 4P8

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.merck.ca
or by contacting the sponsor, Merck Canada Inc.,
at: 1-800-567-2594.

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