Hepatitis-B Vaccine (recombinant DNA)

Revac-B$^+$

20 mcg /mL
Suspension for Injection (IM)

FORMULATION

Each mL single-dose (Adult Dose) vial contains:
Purified HBsAg (>98% purity) ....20 mcg
Aluminum Hydroxide Gel (as Al^{+++}) .... 0.5 mg
Thiomersal (as preservative) ....0.05 mg

PRODUCT DESCRIPTION

Recombinant Hepatitis B vaccine (Revac-B$^+$) is a sterile suspension for injection containing purified, non-infectious major surface antigen of the hepatitis B virus (HBV) and is manufactured by recombinant DNA technology. The antigen is adsorbed onto high affinity aluminum hydroxide gel molecules, hence, the suspension appears almost white and translucent. The vaccine fulfills WHO Requirements for Hepatitis B vaccine made by recombinant DNA techniques.

Recombinant Hepatitis B vaccine (Revac-B$^+$) is presented in USP type 1 glass vial. The content upon storage may present a fine white deposit with a clear colorless supernatant. The vaccine is slightly opaque once shaken.

Recombinant Technology

The Hepatitis B surface antigen (HBsAg) is produced in genetically engineered yeast cells of *Pichia pastoris* which carry the gene that codes for the major surface antigen protein of the HBV. The HBsAg expressed in yeast cells is purified by complex physical, chemical and biochemical processes. The resultant highly purified surface antigen assembles spontaneously into spherical particles of an average diameter of 20-24 nm containing non-glycosylated polypeptides in a lipid matrix. **No substance of human origin is used in the manufacture of HBsAg protein.**

CLINICAL PHARMACOLOGY

Hepatitis B virus is a DNA virus consisting of antigenically distinct surface and core components. The major antigenic determinant of the viral surface is HBsAg. The presence of HBsAg in serum indicates the presence of an acute or chronic HBV infection or a chronic carrier state.

Hepatitis B virus is one of several hepatitis viruses that cause a systemic infection which results in major pathologic changes in the liver. The incubation period for HBV infection after exposure to the virus to onset of symptoms is 6 weeks to 6 months.

Hepatitis B virus infection can have serious consequences including acute massive hepatic necrosis, chronic active hepatitis, liver cirrhosis and even hepatocellular carcinoma (HC). Studies have shown a clear link between chronic hepatitis infection and hepatocellular carcinoma and 80% of HCs are caused by HBV. Hepatitis B vaccine has been recognized as the first vaccine against cancer because it can prevent primary liver cancer.

Hepatitis B vaccine stimulates active immunity to HBV infection. The HBsAg, which is present in recombinant hepatitis B vaccine, promotes the production of antibody to HBsAg (anti-HBs); anti-HBs neutralize HBV so that its pathogenic or infective properties are inhibited.

Protection against HBV infection is virtually complete in individuals who develop adequate antibody levels after hepatitis B vaccine immunization. The duration of protection and the need for booster doses after primary immunization with hepatitis B vaccine has not been fully determined.

Immunogenicity in Adults:

Results of a study in adults (n=226), with a mean age of 27.65 years old, given a 3-dose regimen (0, 30th and 60th days) of 20 mcg doses of a recombinant hepatitis B vaccine derived from *Pichia pastoris* showed a seroconversion rate of 91.2% by the 30th day, and 100% by the 60th and 90th days. The seroprotection rates were 71% by the 30th day, 99.6% by the 60th day, and 100% by the 90th day. The geometric mean antibody titer (GMT) increased from 230.9 mIU/mL at 30th day to 12,480.2 mIU/mL at 90th day. No serious adverse events or death had been reported. These results were comparable with two other commercially available recombinant hepatitis B vaccines (one derived from *Saccharomyces cerevisiae*, and another from *Pichia pastoris*).

Immunogenicity in Patients with Hepatitis C virus (HCV) infection:

The immunologic response to hepatitis B vaccine may be decreased in patients with HCV infection and may be adversely affected by HCV viral overload.

Immunogenicity in Hemodialysis and Immunocompromised Patients:

In general, the immunologic response to hepatitis B vaccine is less in hemodialysis patients and other immunocompromised individuals than in healthy adults, and adequate levels generally persist for shorter periods.

INDICATION

Hepatitis B vaccine 20 mcg/mL dose is for the active immunization against hepatitis B infection in adults and children >10 years old.

- For primary immunization against HBV infection caused by all known subtypes, and to stimulate active immunity to HBV in individuals, who are, or will be, at increased risk of potential exposure to HBV or HBsAg-positive materials (e.g., blood, plasma, serum).

- Hepatitis D occurs only in the presence of hepatitis B. By immunizing against hepatitis B, hepatitis D infection may be prevented.

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

DOSAGE AND ADMINISTRATION

- For deep intramuscular (IM) injection into the deltoid muscle in adults and adolescents.

- **Do not inject intravenously or intradermally.** The vaccine may be administered subcutaneously (SC) in patients with thrombocytopenia or bleeding disorders.

- Do not inject into the gluteal muscle since this route of administration may result in lower immune response.

A. Primary Immunization Schedule

1st dose: On selected date
2nd dose: 30 days after the first dose
3rd dose: 180 days after the first dose

Note: This vaccine may be used to complete a primary immunization course in patients who have previously received another hepatitis B vaccine. Booster dose is not routinely recommended.

B. Special Dosage Recommendations

- For persons involuntarily exposed by accident to HBV infection but still negative for HBsAg and IgM anti-HBc:

1st dose:	On selected date
2nd dose:	30 days after the first dose
3rd dose:	60 days after the first dose
4th dose:	1 year after the first dose

- Immunocompromised patients will require additional dosage as follows:

1st dose of 40 mcg (2mL): On selected date
2nd dose of 40 mcg (2mL): 30 days after the first dose
3rd dose of 40 mcg (2mL): 60 days after the first dose
4th dose of 40 mcg (2mL): 180 days after the first dose

Or, as prescribed by a physician.

Directions for Use:

- Inspect visually for particulate matter and discoloration prior to administration.

- The vaccine should be well shaken before use to obtain a uniform, whitish translucent suspension.

- No dilution or reconstitution is necessary.

- Recombinant Hepatitis B vaccine (Revac-B^{+}) should not be mixed with other vaccines.

- Strict aseptic technique should be observed when drawing up the contents of the vial. If contaminated, it has the potential to become a source of infection to patients.

- Any vaccine remaining in a single-dose vial should be discarded properly.

- Whenever a dose of this vaccine is administered, a record should be made of the specific type of vaccine given, manufacturer, lot number, age of the patient, and date of administration.

Stability and Potency:

- Recombinant Hepatitis B vaccine (Revac-B^{+}) is stable and potent for 36 months at +2°C to +8°C.
- Exposure of the vaccine to higher temperatures, at 37°C for 1 month and 45°C for 1 week did not result in the loss of its immunogenicity.

CONTRAINDICATIONS

- Known hypersensitivity to hepatitis B-containing vaccine or any component of the vaccine, including yeast.

- Severe febrile illness

WARNINGS AND PRECAUTIONS

- Prior to immunization, the patient's medical history should be reviewed for possible sensitivity to the vaccine. As with any vaccine, appropriate medical treatment including epinephrine should be available for immediate use in case of an anaphylactoid reaction.

- Patients who develop hypersensitivity reactions after an injection should not receive further injections of the vaccine.

- Sensitization reactions may occur since thiomersal has been used in the manufacturing process of this vaccine and residues of it are present in the final product.

- Any serious active infection including febrile illness is a reason for delaying use of the vaccine except when, in the opinion of the physician, withholding the vaccine entails a greater risk to the patient.

- Use with caution in individuals with severely compromised cardiopulmonary status or to others in whom a febrile or adverse systemic reaction could pose a significant risk.

- Exacerbation of multiple sclerosis has been rarely reported after hepatitis B vaccine administration; no causal relationship has been established. Thus, in patients 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.

- Immunocompromised and hemodialysis patients generally require higher vaccine doses than healthy individuals to stimulate adequate circulating antibody titers **[see Special Dosage Recommendations]**. For those receiving immunosuppressive therapy, deferral of vaccination for at least 3 months after therapy may be considered **[see Interactions with Other Medicaments].**

- Since hepatitis B virus has a long incubation period to manifest the symptoms of infection, some patients may receive the vaccine while the infection remains unrecognized. In such cases, the vaccine may not prevent HBV infection. Moreover, it may not prevent infection in individuals who do not achieve protective antibody titers.

- A number of factors have been associated with the reduction in immune response to hepatitis B vaccines. These include older age, male gender, obesity, smoking, route of administration and some chronic underlying diseases. Serological testing should be considered in those individuals who may be at risk of not achieving seroprotection after a complete course of hepatitis B vaccine.

- Patients with chronic liver disease or with HIV infection or hepatitis C carriers should not be precluded from vaccination against hepatitis B. The vaccine could be recommended since hepatitis B infection can be severe in these patients: vaccination should thus be considered on a case to case basis by the physician.

- As with any vaccine, a protective immune response may not be elicited in all vaccinees.

INTERACTIONS WITH OTHER MEDICAMENTS

- **Hepatitis B Immunoglobulin (HBIg):** To avoid neutralization, hepatitis B vaccine and HBIg should not be administered in the same syringe and should not be injected at the same site.

- **Other Vaccines** [e.g., vaccine against Hepatitis A, *Haemophilus influenzae* type b Conjugate (Hib), BCG, polio, measles, mumps, rubella, diphtheria, tetanus, pertussis, influenza, pneumococcal): In general, simultaneous administration of these vaccines has not resulted in impaired antibody responses or increased adverse effects. Separate sites and syringes should be used for simultaneous administration of injectable vaccines.

- **Anti-infective agents:** In general, concomitant therapy with these agents does not affect the immune response to inactivated vaccines, including hepatitis B vaccine.

- **Immunosuppressive agents** (e.g., corticotropin, corticosteroids, alkylating agents, antimetabolites, radiation): Individuals receiving such agents may have a reduced response.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

- **Pregnancy: Pregnancy Category C**. There are no well-controlled studies in pregnant women. Hepatitis B vaccine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

- **Lactation:** It is not known whether hepatitis B vaccine is excreted in human milk. Since many medicines are excreted in human milk, the vaccine should be used with caution in breastfeeding women.

- **Children:** Hepatitis B vaccine is well-tolerated and highly immunogenic in children.

- **Elderly:** Hepatitis B vaccine is less immunogenic in adults 65 years old and above compared with younger patients. No overall differences in safety were observed between the elderly and younger adult subjects.

UNDESIRABLE EFFECTS

Recombinant Hepatitis B vaccine is generally well tolerated. The following undesirable effects have been reported after the use of hepatitis B vaccine; however, in many instances the causal relationship to the vaccine has not been established.

Injection Site Reactions: Burning, ecchymoses, erythema, induration, inflammation/swelling, local pain, nodule formation, pruritus, soreness, tenderness, warmth

Body as a Whole: Achiness, chills, fatigue/asthenia, fever (>37.5°C), flushing, influenza-like symptoms, malaise, paresis, tingling, sweating, sensation of warmth, weakness

Dermatologic/Hypersensitivity Reactions: Anaphylaxis and symptoms of immediate hypersensitivity reactions including rash, pruritus, urticaria, edema, angioedema, dyspnea, chest discomfort, bronchial spasm (including asthma-like symptoms), palpitation or symptoms consistent with a hypotensive episode have been reported within the first few hours after administration of hepatitis B vaccine; alopecia, angioneurotic edema, eczema, petechiae; an apparent serum-sickness reaction with delayed onset has been reported days to weeks after administration of the vaccine, this reaction consists of dermatologic reactions such as erythema multiforme (including Stevens-Johnson syndrome) and erythema nodosum; purpura, polyarteritis nodosa, systemic lupus erythematosus (SLE), lupus-like syndrome

Musculoskeletal System: Arthralgia (including monoarticular), arthritis, pain/stiffness in arm, shoulder, back and/or neck, myalgia, muscle weakness

Cardiovascular System: Hypotension, syncope, tachycardia/palpitations, vasculitis

Nervous System: Agitation, convulsions, demyelinating disease of the CNS, disturbed sleep/insomnia, encephalitis, encephalopathy, facial paralysis, irritability, headache, herpes zoster, lightheadedness, meningitis, migraine, multiple sclerosis, exacerbation of multiple sclerosis, neuritis (including Guillain-Barré syndrome, optic neuritis, myelitis including transverse myelitis), paresthesia, polyradiculoneuritis, peripheral neuropathy (including Bell's palsy and hypoesthesia), radiculopathy, vertigo/dizziness, seizure, febrile seizure, somnolence, tiredness, vasovagal syncope; crying in infants and children

Respiratory System: Bronchospasm (including asthma-like symptoms), cough, influenza, nosebleed, pharyngitis, rhinitis, symptoms of upper respiratory illnesses

Gastrointestinal Disorders: Abdominal pain/cramps, constipation, diarrhea, diminished appetite/anorexia, dyspepsia, nausea, vomiting

Urogenital System: Dysuria

Hepatobiliary Disorders: Abnormal liver function tests

Hematologic: Increased erythrocyte sedimentation rate; lymphadenopathy, thrombocytopenia

Special Senses: Earache, tinnitus, conjunctivitis, keratitis, optic neuritis, visual disturbances

OVERDOSE AND TREATMENT

No case of overdose has been reported.

STORAGE CONDITIONS

- Store at 2°C to 8°C.
- Do not freeze. Discard if product has been frozen.
- Keep the product out of sight and reach of children.

AVAILABILITY

Box of 1's (1 mL vial)

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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