

PRODUCT INFORMATION

NAME OF THE MEDICINE:

Injection
H-B-VAX® II
(hepatitis B vaccine (recombinant))

DESCRIPTION:

H-B-VAX® II [hepatitis B vaccine (recombinant)] is a non-infectious subunit viral vaccine derived from surface antigen (HBsAg or Australia antigen) of hepatitis B virus produced in yeast cells.

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 vaccine contains no detectable yeast DNA but may contain up to 1% yeast protein.

The vaccine against hepatitis B is free of association with human blood or blood products.

Each 1.0 mL dose of adult formulation vaccine contains 10 µg of hepatitis B surface antigen adsorbed onto approximately 0.5 mg aluminium hydroxide, each 0.5 mL dose of the paediatric formulation vaccine contains 5 µg of hepatitis B surface antigen adsorbed onto approximately 0.25 mg aluminium hydroxide, and each 1.0 mL dose of the dialysis formulation contains 40 µg of hepatitis B surface antigen adsorbed onto approximately 0.5 mg of aluminium hydroxide. The vaccine is of the *adw* subtype.

All formulations of the vaccine are preservative-free.

PHARMACOLOGY:

CLINICAL PHARMACOLOGY

IMMUNOGENICITY

Clinical studies have established that H-B-VAX II when injected into the deltoid muscle induced protective levels of antibody (defined as ≥ 10 mIU/mL anti-HBs) in 96% of 1213 healthy adults who received the recommended 3-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 titres were measured 1 to 2 months after the third dose. 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 3-dose regimen of vaccine.

Predialysis and haemodialysis patients respond less well to H-B-VAX II than do healthy individuals. In two studies, where 40 µg doses of vaccine were administered in the deltoid muscle, 89% of 28 participants developed anti-HBs with 86% achieving levels \geq 10mIU/mL. Serological data on the proposed dosage regimen are limited to 28 subjects only; antibody levels achieved in these subjects were considerably lower than in normal subjects. No information is available on the persistence of antibodies in these subjects beyond 6 months after the last dose of the vaccine.

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, randomised multicentre study. The proportion of the adolescents receiving the two-dose regimen who developed a protective antibody level 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 received the first 10 µg dose of the two-dose regimen, the proportion who developed a protective antibody level was approximately 72%.

The protective efficacy of 5 µg doses of H-B-VAX II 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 H-B-VAX II, 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 H-B-VAX II when compared to historical controls who received only a single dose of Hepatitis B Immune Globulin.

It has been demonstrated that doses of up to 3 mL of Hepatitis B Immune Globulin, when administered simultaneously with the first dose of H-B-VAX II at separate body sites, did not interfere with the induction of protective antibodies against hepatitis B virus elicited by the three-dose vaccine regimen.

The duration of protective effect of H-B-VAX II is unknown at present, and the need for booster doses not defined.

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:

H-B-VAX II is indicated for immunisation against infection caused by all known subtypes of hepatitis B virus.

Adolescent vaccination is not necessary for children who have received a primary course of hepatitis B vaccine.

Vaccination is recommended in adults who are at substantial risk of hepatitis B virus infection and have been demonstrated or judged to be susceptible.

Vaccination of individuals who have antibodies against hepatitis B virus from a previous infection is not necessary.

CONTRAINDICATIONS;

Hypersensitivity to any component of the vaccine.

Hypersensitivity to yeast (*Saccharomyces cerevisiae*).

Patients who develop symptoms suggestive of hypersensitivity after an injection should not receive further injections of H-B-VAX II.

PRECAUTIONS:

Persons with immuno-deficiency or those receiving immunosuppressive therapy require larger vaccine doses and respond less well than healthy individuals. Included in this group are haemodialysis patients for whom 40 µg doses are recommended. (See CLINICAL PHARMACOLOGY).

Because of the long incubation period for hepatitis B, it is possible for unrecognised infection to be present at the time H-B-VAX II is given. H-B-VAX II may not prevent hepatitis B in such patients.

Further study is required to determine the effectiveness of H-B-VAX II in preventing hepatitis when the vaccine regimen is begun after an exposure to the hepatitis B virus has already occurred (i.e. use for post-exposure prophylaxis). Information available so far suggests that efficacy is reduced in such cases.

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, adrenaline should be available for immediate use should anaphylaxis or an anaphylactoid reaction occur.

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

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

Use in Pregnancy (Category B2):

There is no convincing evidence of risk to the foetus from immunisation of pregnant women using inactivated virus vaccines, bacterial vaccines, or toxoids.

Animal reproduction studies have not been conducted with H-B-VAX II. It is not known whether H-B-VAX II can cause foetal harm when administered to a pregnant woman or can affect reproductive capacity. H-B-VAX II should be given to a pregnant woman only if clearly needed.

Use in lactation:

It is not known whether H-B-VAX II is excreted in human milk. However studies with H-B-VAX II in 12 lactating women have failed to reveal evidence of this vaccine being excreted.

Paediatric Use:

H-B-VAX II has been shown to be immunogenic and usually well tolerated in infants and children of all ages. Newborns also respond well; maternally transferred antibodies do not interfere with the active immune response to the vaccine. See DOSAGE AND ADMINISTRATION for recommended paediatric dosage and for recommended dosage for infants born to HBsAg-positive mothers.

The safety profile and effectiveness of the dialysis formulation in children has not been established.

ADVERSE EFFECTS:

H-B-VAX II is generally well tolerated. No adverse experiences were reported during clinical trials which could be related to changes in the titres 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.

The following adverse reactions were reported in clinical studies in healthy adults.

Incidence Equal to or Greater than 1% of Injections:

LOCAL REACTION (INJECTION SITE) (26% OF DOSES)

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

BODY AS A WHOLE

The most frequent systemic complaints include fatigue/asthenia (4.2%), fever ($\geq 37.8^{\circ}\text{C}$) (3.2%), malaise (1.2%).

DIGESTIVE SYSTEM

Nausea (1.8%), diarrhoea (1.1%).

NERVOUS SYSTEM

Headache (4.1%)

RESPIRATORY SYSTEM

Pharyngitis (1.2%), upper respiratory infection (1.0%).

Incidence Less than 1% of Injections:

BODY AS A WHOLE

Sweating, achiness, sensation of warmth, chills, flushing.

DIGESTIVE SYSTEM

Vomiting, abdominal pains/cramps, dyspepsia, diminished appetite.

RESPIRATORY SYSTEM

Rhinitis, influenza, cough.

NERVOUS SYSTEM

Vertigo/dizziness, paraesthesia, lightheadedness.

INTEGUMENTARY SYSTEM

Pruritus, rash (non-specified), angioedema, urticaria.

MUSCULOSKELETAL SYSTEM

Arthralgia including mono-articular, myalgia, back pain, neck pain, shoulder pain, neck stiffness.

HAEMIC/LYMPHATIC SYSTEM

Lymphadenopathy.

PSYCHIATRIC/BEHAVIOURAL

Insomnia/disturbed sleep.

SPECIAL SENSES

Earache.

UROGENITAL SYSTEM

Dysuria.

CARDIOVASCULAR SYSTEM

Hypotension.

Additional adverse effects:

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.

Hypersensitivity

Anaphylaxis and symptoms of immediate hypersensitivity reactions including oedema, dyspnoea, 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-Barre syndrome, exacerbation of multiple sclerosis, multiple sclerosis, optic neuritis, seizure, febrile seizure, encephalitis, vasovagal syncope.

Special Senses

Tinnitus

Uveitis

Haematologic

Increased erythrocyte sedimentation rate, thrombocytopenia.

Infants and Young Children:

The nature and incidence of systemic adverse reactions is different in infants and young children. In clinical studies, in infants 0-1 years of age and children 1-10 years of age, reactions reported $\geq 1\%$ of doses given in studies were as follows:

Ages 0-1: irritability (3.2%), fever $\geq 38.3^{\circ}\text{C}$ (2.8%), diminished appetite (2.8%), diarrhoea (2.5%), vomiting (1.8%), cough (1.4%), cold symptoms (1.1%).

Ages 1-10: cold symptoms (2.7%), viral infection (2.7%), fever $\geq 38.3^{\circ}\text{C}$ (2.1%), cough (2.1%), injection site reactions (1.6%), diarrhoea (1.1%), rhinitis (1.1%), headache (1.1%).

H-B-VAX II (hepatitis B vaccine [recombinant], MSD), (5 μg /0.5 mL [without preservative]) is available for use in individuals for whom a thiomersal-free vaccine is advisable (e.g. infants who may receive other vaccines containing thiomersal).

In a group of studies, 1636 doses of H-B-VAX II 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 ($> 101^{\circ}\text{F}$ or $> 38^{\circ}\text{C}$ oral equivalent), crying, diarrhoea, vomiting, diminished appetite and insomnia.

Potential Adverse Effects:

In addition, a variety of adverse effects, not observed in clinical trials with H-B-VAX II have been reported with H-B-VAX (plasma-derived hepatitis B vaccine). Those listed below are to serve as alerting information to physicians.

Hypersensitivity: Body as a Whole: Irritability.

Nervous System: Neurological disorders such as myelitis including transverse myelitis; acute radiculoneuropathy and herpes zoster.

Haematological: Thrombocytopenia.

Special Senses: Visual disturbances.

DOSAGE AND ADMINISTRATION:

DO NOT INJECT INTRAVENOUSLY OR INTRADERMALLY.

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

As the plasma derived vaccine has been shown to be immunogenic by the subcutaneous route, H-B-VAX II may also be administered subcutaneously to persons at risk of haemorrhage following intramuscular injections. However, when other aluminium-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., haemophiliacs) at risk of haemorrhage 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.

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 discolouration prior to administration. After thorough agitation, H-B-VAX II is a slightly opaque, white suspension.

This product is for one dose in one patient only. Once the single-dose vial has been penetrated, the withdrawn vaccine should be used promptly, and the vial and residue must be discarded.

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

1st Dose	at elected date
2nd Dose	one month later
3rd Dose	six months after the first dose

Two-Dose Regimen - Adolescents (11-15 years of age). An alternate two-dose regimen is available for routine vaccination of adolescents (11-15 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	four - six months later

The formulation, dose and regimen of H-B-VAX II for specific populations is as follows:

Group	Formulation	Regimen*
Infants Children (0-10 years)	Paediatric	3 x 5 µg
Children and Adolescents [‡] (11 - 19 years)	Paediatric	3 x 5 µg
Adolescents [‡] (11-15 years)	Adult	2 x 10 µg
Adults	Adult	3 x 10 µg
Adult Dialysis & Pre-Dialysis Patients	Dialysis	3 x 40 µg

* The appropriate dosage can be achieved from another formulation provided that the total volume of vaccine administered does not exceed 1.0 mL. However the 40 µg/1.0 mL can be used only for adult predialysis/ dialysis patients.

[‡] Adolescents (11 to 15 years of age) may receive either the 3x5 µg or the 2x10 µg regimen.

Revaccination

The duration of protective effect of H-B-VAX II is unknown at present, and the need for booster doses is not yet defined. One 10 µg dose of H-B-VAX II induced an anamnestic response in 94% of 31 healthy adults who had been vaccinated five to seven years previously with H-B-VAX II (hepatitis B Vaccine [recombinant], MSD). Whenever revaccination or administration of a booster dose is appropriate, H-B-VAX II may be used (see CLINICAL PHARMACOLOGY).

Dosage for Infants Born of HBsAg Positive Mothers

(See CLINICAL PHARMACOLOGY)

Results from clinical studies indicate that administration of one 0.5mL dose of hepatitis B immune globulin at birth and three 5 µg (0.5mL) doses of H-B-VAX II, 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 treatment regimen for infants born of HBsAg positive mothers is as follows:

Treatment	Birth	Within 7 Days	1 Month	6 Months
Paediatric Formulation 5 µg/ 0.5 mL	-	0.5mL*	0.5mL	0.5mL
Hepatitis B Immune Globulin	0.5mL	-	-	-

*The first 5µg / 0.5 mL dose of H-B-VAX II 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.

Known or Presumed Exposure to HBsAg

There are no prospective studies directly testing the efficacy of a combination of Hepatitis B Immune Globulin (Human) and H-B-VAX II in preventing clinical hepatitis B following percutaneous, ocular or mucous membrane exposure to hepatitis B virus. However, since most persons with such exposure (e.g. health-care workers) are candidates for H-B-VAX II and since combined Hepatitis B Immune Globulin (Human) plus vaccine is more efficacious than Hepatitis B Immune Globulin (Human) 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 (Human) (0.06 mL/kg) should be given intramuscularly as soon as possible after exposure and within 24 hours if possible. H-B-VAX II (see dosage recommendation) should be given intramuscularly at a separate site within seven days of exposure and second and third doses given one and six months, respectively, after the first dose.

Withdraw the recommended dose from the vial using a sterile needle and syringe free of preservatives, antiseptics, and detergents.

PRESENTATION AND STORAGE CONDITIONS:

Presentation:

H-B-VAX II is supplied as a 0.5 mL (Paediatric) single dose vial containing 5 µg of hepatitis B surface antigen per vial. Available in single packs and packs of 10.

H-B-VAX II is supplied as a 1 mL (Adult) single dose vial containing 10 µg of hepatitis B surface antigen per vial. Available in single packs and packs of 10.

H-B-VAX II is supplied as a 1 mL (Dialysis) single dose vial containing 40 µg of hepatitis B surface antigen per vial. Available in single packs only.

H-B-VAX II is supplied as a 1 mL (Adult) single dose prefilled syringe containing 10 µg of hepatitis B surface antigen per syringe. Available in single packs and packs of 10.

H-B-VAX II is supplied as a 0.5 mL (Paediatric) single dose prefilled syringe containing 5 µg of hepatitis B surface antigen per syringe. Available in single packs and packs of 10.

Storage Conditions:

Store vials and syringes at 2-8°C.

Storage above or below the recommended temperature may reduce potency.

Do not freeze since freezing destroys potency.

NAME AND ADDRESS OF THE SPONSOR:

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A
26 Talavera Road
Macquarie Park NSW 2113
Australia

NAME AND ADDRESS OF THE DISTRIBUTOR:

bioCSL Pty Ltd
63 Poplar Road, Parkville, 3052
Victoria, Australia

POISION SCHEDULE OF THE MEDICINE:

Prescription Only Medicine (S4)

Date of last TGA approval:

This product information was approved by the Therapeutic Goods Administration on 17 November 2000.

Date of most recent amendment:

21 October 2014