AUSTRALIAN PRODUCT INFORMATION - H-B-VAX® II Hepatitis B vaccine (recombinant) Hepatitis B surface antigen (recombinant)

1 NAME OF THE MEDICINE

Hepatitis B surface antigen recombinant

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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 aluminium (as amorphous aluminium hydroxyphosphate sulfate – 0.5 mg), each 0.5 mL dose of the paediatric formulation vaccine contains 5 µg of hepatitis B surface antigen adsorbed onto aluminium (as amorphous aluminium hydroxyphosphate sulfate – 0.25 mg), and each 1.0 mL dose of the dialysis formulation contains 40 µg of hepatitis B surface antigen adsorbed onto aluminium (as amorphous aluminium hydroxyphosphate sulfate – 0.5 mg). The vaccine is of the *adw* subtype.

All formulations of the vaccine are preservative-free.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Suspension for injection.

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

Copyright © 2019 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA. All rights reserved.

4.2 DOSE AND METHOD OF 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[2] (11 - 19 years)	Paediatric	3 x 5 μg
Adolescents [2](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.

[2] 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 Section 5.1 Pharmacodynamic Properties, Clinical trials, Immunogenicity).

Dosage for Infants Born of HBsAg Positive Mothers

(See Section 5.1 Pharmacodynamic Properties, Clinical trials, Immunogenicity)

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 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	-	0.5 mL*	0.5 mL	0.5 mL
Hepatitis B Immune Globulin	0.5 mL	-	-	-

*The first 5 μg / 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.

4.3 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 Section 5.1 Pharmacodynamic Properties, Immunogenicity).

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 renal impairment
See Section 5.1 Pharmacodynamic Properties, Immunogenicity.

Use in the elderly
No data available at time of registration.

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 Section 4.2 Dose and Method of 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.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
H-B-VAX II has not been evaluated for its potential to impair fertility.

Use in pregnancy – 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 (≥ 37.8°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 Section 4.4 Special Warnings and Precautions for Use).
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 ≥ 1% of doses given in studies were as follows:

Ages 0-1: irritability (3.2%), fever ≥ 38.3°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 ≥ 38.3°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°F or > 38°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.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
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.

Clinical trials
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 ≥ 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.

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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
Not applicable

Distribution
Not applicable

Metabolism
Not applicable

Excretion
Not applicable

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Mutagenicity
H-B-VAX II has not been evaluated for its mutagenic potential.

Carcinogenicity
H-B-VAX II has not been evaluated for its carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

aluminum (as amorphous aluminium hydroxyphosphate sulfate)
Borax
Sodium chloride
Water for injection

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

The expiry date can be found on the packaging. In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store vials and syringes at 2-8°C. *Do not freeze since freezing destroys potency.* Protect from light. Storage above or below the recommended temperature may reduce potency.

6.5 NATURE AND CONTENTS OF CONTAINER

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.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure
Not applicable

CAS number
Not applicable

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8 SPONSOR

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

Macquarie Park NSW 2113
www.msd-australia.com.au

Distributor
Seqirus Pty Ltd
63 Poplar Road, Parkville, 3052
Victoria, Australia

9 DATE OF FIRST APPROVAL

17 November 2000

10 DATE OF REVISION

13 February 2020

IPC-V232-I-052018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All sections	Reformat and text update to align with new Australian Product Information format released 20 Nov 2017.
6.4	Added “Protect from light”