

ENGERIX®-B PRODUCT INFORMATION

(Hepatitis B surface antigen (rys))

DESCRIPTION

ENGERIX-B is a non-infectious recombinant DNA hepatitis B vaccine containing the purified surface antigen of the virus.

ENGERIX-B is a sterile suspension. The vaccine is available as a 1mL dose, consisting of a suspension of 20µg of antigen protein adsorbed on 0.5mg Al⁺⁺⁺ as aluminium hydroxide. A 0.5mL dose is also available, consisting of a suspension of 10µg of antigen protein adsorbed on 0.25mg Al⁺⁺⁺ as aluminium hydroxide. Excipients include: sodium phosphate, sodium acid phosphate, polysorbate 20 (maximum 0.01mg), sodium chloride, water for injection. Multidose presentations also contain 2-phenoxyethanol as a preservative. Each 1mL dose of ENGERIX-B contains <2µg (1:500,000) of thiomersal.

ENGERIX-B is produced by culture of genetically-engineered *Saccharomyces cerevisiae* yeast cells which carry the relevant gene of an adw subtype of the surface antigen of hepatitis B virus (HBsAg). The surface antigen expressed in yeast cells, is purified by several physico-chemical steps and formulated as a suspension of the antigen adsorbed onto aluminium hydroxide. Standardised fermentation and purification procedures ensure batch to batch consistency of ENGERIX-B.

The manufacture of this product includes exposure to bovine derived materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

ENGERIX-B is highly purified, and meets the WHO requirements for recombinant hepatitis B vaccines. No substances of human origin are used in its manufacture.

CLINICAL PHARMACOLOGY

ENGERIX-B induces the production of specific humoral antibodies (anti-HBs), which confer immunity against hepatitis B. A peak anti-HBs antibody titre of ≥10 IU/L correlates with long-term protection against hepatitis B virus (HBV) infection (seroprotection).

Seroconversion (SC) is defined as the appearance of antibodies ≥ 1 IU/L in a previously seronegative subject.

Clinical trials demonstrated SC rates of ≥ 97% (SP rates of ≥ 96%) in normal immunocompetent adults and children following a 0, 1, 6 months schedule, and SC rates of >90% in neonates following injections at 0, 1, 2 months.

Following a 0, 1, 6 month schedule, SC rates of 96.6% and 99% (corresponding to SP rates of 92.3% and 93%) were obtained in mentally retarded individuals and male homosexuals respectively. In a clinical trial where thalassaemic patients received three doses of 20µg at 0, 1, 6 months, SC rates as well as SP rates were 100% (17 subjects tested).

In healthy adults administered vaccine doses according to a 0, 1, 2 month primary schedule with a 12 month booster, seroprotective rates of 15% and 89% were achieved one month after the first and third doses respectively. One month after the 12 month booster dose, 95.8% of vaccinees achieved seroprotective antibody levels. In healthy adults administered a 0, 7, 21 day primary schedule with a 12 month booster, seroprotective rates of 65.2% and 76.4% were achieved one week and one month respectively following the third vaccine dose. One month after the 12 month booster dose, 98.6% of vaccinees achieved seroprotective antibody levels.

In healthy adolescents (from 11 years up to and including 15 years of age) administered doses of 20 µg at 0 and 6 months, SP rates were 11.3% at month 2, 26.4% at month 6 and 96.7% at month 7. Immunogenicity in this study was measured by the development of antibody to HBsAg as detected by enzyme immunoassay (seropositivity cut-off: 3.3 mIU/ml), using a titre of ≥ 10 IU/L as indicative of seroprotection.

The following table compares seroprotection rates (SP) obtained with the two different dosages and schedules recommended in subjects from 11 years up to and including 15 years of age:

Vaccine groups	Anti-HBs Month 2 SP (%)	Anti-HBs Month 6 SP (%)	Anti-HBs Month 7 SP (%)
ENGERIX-B 10 µg (0, 1, 6 months schedule)	55.8	87.6	98.2
ENGERIX-B 20 µg (0, 6 months schedule)	11.3	26.4	96.7

In patients 16 years of age and above with impaired renal function, including patients undergoing haemodialysis administered 40 µg (2 x 20 µg) doses at 0, 1, 2 and 6 months, SP rates were 55.4% at month 3 and 87.1% at month 7.

The following table shows seroprotection rates (SP) obtained with 40 µg (2 x 20 µg) doses in haemodialysis and pre-haemodialysis patients.

Group	Timing	N	SP	
			n	%
Pre-haemodialysis patients	Month 1	42	3	7.1
	Month 2	42	5	11.9
	Month 3	42	18	42.9
	Month 6	38	21	55.3
	Month 7	39	31	79.5
	Month 12	36	27	75.0
Haemodialysis patients	Month 1	41	1	2.4
	Month 2	41	13	31.7
	Month 3	40	25	62.5
	Month 6	39	30	76.9
	Month 7	38	34	89.5
	Month 12	34	27	79.4

Immunogenicity was measured by the development of antibody to HBsAg as detected by enzyme immunoassay (seropositivity cut-off: 3.3 mIU/mL), using a titre of ≥ 10 IU/L as indicative of seroprotection.

A significant reduction in the incidence of hepatocellular carcinoma was observed in Taiwanese children aged 6 - 14 years, following a nationwide hepatitis B vaccination program.

Interchangeability of hepatitis B vaccines

Although no clinical data has been submitted, there is no reason to believe that the use of a different formulation of hepatitis B vaccine used either during a primary vaccination course or during booster dosing will not be satisfactory.

INDICATIONS

ENGERIX-B is indicated for active immunisation against hepatitis B virus infection. The NH&MRC* recommend all infants, young children and unvaccinated adolescents receive a primary course of immunisation against hepatitis B.

The NH&MRC also recommends immunisation for persons who are at substantial risk and have been demonstrated or judged to be susceptible to the hepatitis B virus. Groups identified at increased risk of acquiring HBV infection include:

- Infants born to carrier (HBsAg-positive) mothers.
- Individuals for whom post-exposure prophylaxis for hepatitis B is indicated.
- Household contacts (other than sexual partners) of acute and chronic hepatitis B cases and carriers.
- Susceptible sexual contacts. Risk occurs in susceptible (anti-HBs negative) partners of HBV carriers and patients with acute hepatitis B. Susceptible clients of STD (sexually transmitted disease) clinics, and sexually active men who have sex with men are also at increased risk of infection.
- Injecting drug users.
- Haemodialysis patients, HIV-positive individuals and other immunosuppressed adults.
- Patients receiving certain blood products especially patients with clotting disorders receiving blood product concentrates.
- Individuals with chronic liver disease and / or hepatitis C.
- Staff and residents of facilities for the intellectually disabled, including both residential and non-residential care of this group.
- Liver transplant recipients. Such individuals should be vaccinated prior to transplantation if seronegative for hepatitis B, as they may be at increased risk of infection from the transplanted organ.
- Staff and inmates of long term correctional facilities.
- Health care workers, dentists, embalmers, tattooists and body-piercers. All staff directly involved in patient care, embalming, or in the handling of human blood or tissue should be vaccinated.
- Individuals adopting children from overseas. These children should be tested for hepatitis B, and if HBsAg positive, members of the adoptive family should be vaccinated.
- Others in whom vaccination may be justified include police, members of the armed forces and emergency services staff, depending on the risks of exposure associated with assigned duties. Long term travellers to regions of high endemicity, and those residing for some time in such regions who may anticipate close personal contact with local residents, should be vaccinated. Short-term tourists or business travellers are at very little risk of hepatitis B, provided they avoid exposure through sexual contact, injecting drug use, tattooing and body piercing. Although the risk of hepatitis B infection in contact sports is low, immunisation of those involved should not be discouraged. As the risk in Australian schools is very low, vaccination of classroom contacts is seldom indicated. Nevertheless, vaccination of school children and adolescents should be encouraged.

As hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection, it can be expected that hepatitis D will also be prevented by vaccination with ENGERIX-B. The vaccine will not protect against infection caused by hepatitis A, hepatitis C and hepatitis E viruses, and other pathogens known to infect the liver.

CONTRAINDICATIONS

ENGERIX-B should not be administered to subjects with known hypersensitivity to any component of the vaccine, or to subjects having shown signs of hypersensitivity after previous ENGERIX-B administration.

As for any vaccine, ENGERIX-B should not be administered to subjects with severe febrile infections. However, the presence of minor infections without fever does not contraindicate vaccination.

HIV infection is not considered a contraindication to hepatitis B vaccination.

PRECAUTIONS

The vaccine should never be administered intravenously.

As with all injectable vaccines, appropriate medical treatment (ie adrenaline) and supervision should always be readily available in case of anaphylactic reactions following the administration of the vaccine.

It is good clinical practice that any vaccination be preceded by a review of medical history (especially with regard to previous vaccinations and possible adverse events) and a clinical examination.

ENGERIX-B should not be administered in the gluteal region or intradermally/subcutaneously since these routes of administration may not result in an optimum immune response. Exceptionally in patients with thrombocytopenia or severe bleeding disorders (eg. haemophiliacs) the vaccine may be administered subcutaneously, since bleeding after intramuscular injection may occur in these patients (see DOSAGE AND ADMINISTRATION).

The immune response to hepatitis B vaccines is related to a number of factors including route of administration, age (more than 40 years of age), male gender, obesity, and smoking habits. As individuals in these groups may respond less optimally to hepatitis B vaccines, the administration of additional vaccine doses may be considered.

In dialysis patients, HIV infected patients and subjects who have impairment of the immune system, adequate antibody concentrations may not be obtained after the recommended primary vaccination course. The need for monitoring antibody levels in such patients should be considered. (see DOSAGE AND ADMINISTRATION - chronic adult haemodialysis patients)

Caution should be exercised in administering the vaccine to patients in whom a systemic reaction due to the vaccine may pose a significant risk; eg in patients with severely compromised cardiopulmonary function.

Because of the long incubation period of hepatitis B, it is possible for unrecognised infection to be present at the time of vaccination. The vaccine may not prevent hepatitis B in such cases.

The vaccine may not prevent infection in individuals who do not achieve protective antibody titres.

The vaccine will not protect against infection caused by hepatitis A, hepatitis C and hepatitis E viruses, and other pathogens known to infect the liver.

The potential risk of apnoea and the need for respiratory monitoring for 48-72 hours should be considered when administering the primary immunisation series to very premature infants (born \leq 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Use in Pregnancy (Category B2)

Adequate human data on use during pregnancy and adequate animal reproduction studies are not available. Therefore, vaccination of pregnant women cannot be recommended, unless expected benefits outweigh potential risks, as might occur in high risk situations.

Use in Lactation

Adequate human data on use during lactation and adequate animal reproduction studies are not available.

Use in impaired hepatic function

No information available.

Use in impaired renal function

See under PRECAUTIONS for use in haemodialysis patients.

Interaction with other drugs

ENGERIX-B SHOULD NOT BE MIXED IN THE SAME SYRINGE WITH OTHER VACCINES.

ENGERIX-B may be administered concomitantly with the following vaccines: diphtheria-tetanus-pertussis (DTP), diphtheria-tetanus (DT), poliomyelitis (oral or injectable), measles-mumps-rubella, *Haemophilus influenzae* type b (Hib), and hepatitis A, providing separate syringes and separate injection sites are used.

The simultaneous administration of ENGERIX-B and hepatitis B immunoglobulin (HBIG) does not result in reduced anti-HBs antibody titres provided separate injection sites are used.

Effects on the ability to drive and use machinery

The vaccine is considered unlikely to affect the ability to drive and operate machinery.

ADVERSE REACTIONS

ENGERIX-B is generally well tolerated.

Clinical Trials Experience

Based on clinical trial symptom sheet data, the incidence of local side effects is 24% and of systemic side effects 8%; both local and systemic side effects occurred in approximately 13% of subjects. The incidence of local and systemic reactions was comparable to those of plasma derived hepatitis B vaccines.

In a comparative trial in subjects from 11 years up to and including 15 years of age, the incidence of local and general solicited symptoms reported after a two-dose regimen of ENGERIX-B 20 µg was overall similar to that reported after the standard three-dose regimen of ENGERIX-B 10 µg.

The safety profile presented below is based on data from more than 5,300 subjects. Events are listed within body systems and categorised by frequency according to the following definitions:

Frequencies are reported as:

Very common: (≥ 1/10)

Common: (≥1/100, <1/10)

Uncommon: (≥1/1,000, <1/100)

Rare: (≥1/10,000, <1/1,000)

Very rare: (<1/10,000) including isolated reports

Blood and lymphatic system disorders: *Rare:* lymphadenopathy

Metabolism and nutrition disorders: *Common:* appetite lost

Psychiatric disorders: *Very common:* irritability

Nervous system disorders: *Common:* headache (very common with 10 µg formulation), drowsiness; *Uncommon:* dizziness; *Rare:* paresthesia

Gastrointestinal disorders: *Common:* gastrointestinal symptoms (such as nausea, vomiting, diarrhea, abdominal pain)

Skin and subcutaneous tissue disorders: *Rare:* rash, pruritus, urticaria

Musculoskeletal and connective tissue disorders: *Uncommon:* myalgia; *Rare:* arthralgia

General disorders and administration site conditions: *Very common:* pain and redness at injection site, fatigue; *Common:* swelling at injection site, malaise, injection site reaction (such as induration), fever (≥37.5°C); *Uncommon:* influenza-like illness

Post-marketing Data

The following adverse events have been reported following widespread use of the vaccine. As with other hepatitis B vaccines, in many instances the causal relationship to the vaccine has not been established.

Autonomic nervous system:

Rare: flushing, sweating

Body as a whole:

Rare: fever, fatigue, malaise, chills

Very rare: anaphylaxis, delayed hypersensitivity reactions, serum sickness

Unknown frequency: allergic reactions including anaphylactoid reactions

Cardiovascular

Very rare: syncope, hypotension

Central and peripheral nervous system:

Rare: paraesthesia, dizziness, headache

Very rare: paralysis, neuropathy (including Guillain-Barre syndrome, facial paralysis, optic neuritis [visual disturbance] and multiple sclerosis), encephalitis, encephalopathy, meningitis, neck stiffness, neuritis and vertigo, convulsions

Unknown frequency: hypoaesthesia

Gastrointestinal system:

Rare: nausea, vomiting, diarrhoea, abdominal pain

Very rare: anorexia

Hearing and Vestibular:

Very rare: tinnitus

Liver and biliary system:

Rare: abnormal liver function tests

Local reactions:

Common: transient soreness, pain, induration, erythema, and swelling at the injection site have been reported. These reactions are usually mild and subside within two days.

Very rare: ecchymosis at the injection site

Musculoskeletal system:

Rare: arthralgia, myalgia

Very rare: arthritis

Unknown frequency: muscular weakness

Platelet bleeding and clotting:

Very rare: thrombocytopenia

Psychiatric:

Very rare: disturbed sleep

Respiratory system:

Very rare: bronchospasm-like symptoms, pharyngitis or other upper respiratory infection, cough

Skin and appendages:

Rare: urticaria, rash, pruritus

Very rare: severe skin disorders such as erythema multiforme, angioedema

Unknown frequency: lichen planus

Urinary system:

Very rare: dysuria

Vascular extracardiac:

Very rare: vasculitis

White cell and reticulo-endothelial system:

Very rare: lymphadenopathy

DOSAGE AND ADMINISTRATION

The vaccine is a ready-to-use suspension. It must be shaken well before use, since upon storage, the vaccine settles down as a fine white deposit with a clear colourless supernatant. After shaking, the vaccine is a slightly opaque, white suspension. Discard if the contents of the vial appear otherwise. All parenteral drug and vaccine products should be inspected visually prior to administration for discolouration or particulate matter.

The monodose vial and pre-filled syringe presentations are for use in a single patient only and any residue must be discarded.

Dosage

The vaccine can be administered at any age from birth onwards. Vaccination of individuals who have antibodies against hepatitis B virus from a previous infection is not necessary.

Adults and adolescents older than 19 years:

A dose of 20 µg of antigen protein in 1 mL is recommended in a 0, 1, 6 month schedule.

Adolescents:

In adolescents from the age of 10 years, up to and including 19 years, a 10 µg dose is recommended provided the immunisation is carried out in the 0, 1, 6 month schedule, in circumstances which will ensure compliance to the full vaccination course. If compliance cannot be assured, then a 20 µg dose should be used to increase the proportion of subjects protected after the first and second doses.

The 20 µg vaccine can also be used in subjects from 11 years up to and including 15 years of age in a 0 and 6 month schedule in situations when there is a relatively low risk of hepatitis B infection during the vaccination course and when compliance with the complete vaccination course can be anticipated.

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

Neonates, infants and children below 10 years of age:

A dose of 10 µg of antigen protein in 0.5 mL suspension is recommended in a 0, 1, 6 months schedule. A dose of 20 µg may, however, be used when a paediatric presentation is not available. For details on the recommended vaccination schedule, refer to the NH&MRC* Handbook.

In neonates and infants, maternally transferred antibodies do not interfere with the active immune response to the vaccine.

Administration

ENGERIX-B should be injected intramuscularly. In adults, the injection should be given in the deltoid region but it may be preferable to inject ENGERIX-B in the anterolateral thigh in neonates and infants because of the small size of their deltoid muscle. Exceptionally, the vaccine may be administered subcutaneously in patients with thrombocytopenia or severe bleeding tendencies (e.g. haemophiliacs).

ENGERIX-B MUST NOT BE GIVEN INTRAVENOUSLY.

Vaccination Schedules

For primary vaccination of adults, adolescents and children not previously exposed to the hepatitis B virus, the schedules are as follows:

	Vaccine dose	Initial	1 month*	6 months*
Adults and adolescents over 19 years	20 µg	1 mL	1 mL	1 mL
Adolescents from 10 up to and including 19 years ‡	10 µg	0.5mL	0.5mL	0.5mL
Adolescents from 11 years up to and including 15 years of age #	20 µg	1 mL	-	1 mL
Neonates [∇] and children younger than 10 years	10 µg	0.5mL	0.5mL	0.5mL

* after first dose

‡ if compliance cannot be assured a 20µg dose should be used.

The 20 µg vaccine may be administered in subjects from 11 years up to and including 15 years of age according to a 0,6 months schedule. However, in this case, protection against hepatitis B infections may not be obtained until after the second dose (see Clinical Pharmacology). Therefore this schedule should be used only when there is a relatively low risk of hepatitis B infection during

the vaccination course and when completion of the two-dose vaccination course can be anticipated. If this cannot be anticipated, the three-dose schedule of the 10 µg vaccine should be used.

∇ The recommended schedule for hepatitis B vaccine in neonates is 0, 2, 4 and 6 months (refer to the NH&MRC Handbook).

The recommended treatment regimen for infants born to HBsAg positive mothers (irrespective of the mother's HBeAg status) is as follows:

	<u>Vaccine Dose</u>	At birth	1 month*	6 months*
ENGERIX-B vaccine	10 µg	0.5mL	0.5mL	0.5mL
Hepatitis B Immunoglobulin (HBIG)	-	100 IU	-	-

* after first dose

The first dose of vaccine and immunoglobulin should preferably be given within 12 hours of birth at separate sites. The efficacy of HBIG decreases markedly if treatment is delayed beyond 48 hours. If this is not possible, vaccination should not be delayed beyond 7 days after birth.

Testing for HBsAg and anti-HBs is suggested at 12-15 months of age. If HBsAg is not detectable and anti-HBs is present, the child has been protected.

Accelerated schedules

In circumstances where more rapid protection is required (e.g. contacts of carriers, immunisation of travellers and newborns to carrier women) two accelerated vaccination schedules of 0, 1 and 2 months or 0, 7 and 21 days may be used. However, as higher seroprotective rates are observed following the 0, 1, 2 month schedule, it is recommended the 0, 7, 21 day schedule be administered only to adults, and only in exceptional circumstances (e.g travellers commencing hepatitis B primary vaccination within one month of departure). (see CLINICAL PHARMACOLOGY) Since the peak antibody levels reached after these shorter schedules of primary vaccination are lower compared to the 0, 1 and 6 month schedule, it is recommended that a fourth dose (booster) be given at 12 months after the first dose of vaccine, in order to ensure adequate seroprotection rates.

Chronic adult haemodialysis patients/Patients with impaired renal function (creatinine clearance <30 mL/min) 16 years of age and above

The primary vaccination schedule for chronic adult haemodialysis patients or patients with impaired renal function 16 years of age and above consists of four doses of 40µg. The 40 µg (2mL) dose may be administered as 2 x 20 µg in one injection site or in each arm.

	Vaccine dose	Initial	1 month*	2 months*	6months*
Chronic haemodialysis or Impaired renal function patients	40 µg	2mL	2mL	2mL	2mL

* after first dose

As vaccine-induced protection in haemodialysis patients is less complete, boosting should be adapted in order to ensure the anti-HBs antibody titre remains above 10IU/L (see PRECAUTIONS). The need for booster dosing should be assessed by antibody testing at six to twelve monthly intervals. ENGERIX-B booster doses of 40 µg (2 x 20 µg) are recommended for these patients.

Post-exposure prophylaxis

There are no adequately controlled studies on the effectiveness of hepatitis B immunoglobulin administration, along with the vaccine, in adults and older children exposed to hepatitis B virus through 1) needlestick, ocular or mucous membrane exposure to blood known or presumed to contain HBsAg; 2) human bites by known or presumed HBsAg carriers that penetrate the skin; 3) following intimate sexual contact with known or presumed HBsAg carriers.

Hepatitis B immunoglobulin (human) (400 IU) should be given intramuscularly as soon as possible (must be within 72 hours of exposure). ENGERIX-B should be given at a separate site within 7 days and then at 1 month and 6 months. Passive immunisation will not interfere with active response to ENGERIX-B.

Booster dose

The NH&MRC* recommends that booster doses against hepatitis B are not required in immunocompetent individuals, since there is good evidence that a completed primary course of hepatitis B vaccination provides long lasting protection in these individuals. This applies to adults, children and all subgroups (such as health care workers). Booster doses are recommended for immunosuppressed individuals, for people living with HIV infection or with renal failure. The timing for boosting in these individuals should be decided by regular monitoring of hepatitis B antibody levels at six to twelve monthly intervals.

OVERDOSAGE

Cases of overdose have been reported during post-marketing surveillance. Adverse events reported following overdose were similar to those reported with normal vaccine administration.

STORAGE

The shelf-life of ENGERIX-B is three years from the date of manufacture when stored between +2°C to +8°C. DO NOT FREEZE, discard if the vaccine has been frozen.

The expiry date of the vaccine is indicated on the label and packaging.

PRESENTATIONS

ENGERIX-B 20 µg (Adult dose):

Monodose vials (1mL) in packs of 1 and 10.

Pre-filled syringes in packs of 1 and 10.

ENGERIX-B 10 µg (Paediatric dose):

Monodose vials (0.5mL) in packs of 1 and 10.

NB: Each vaccination should be carried out with a separate syringe.

The vials and syringes are made of neutral glass type 1, which conforms to European Pharmacopoeia requirements.

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