AUSTRALIAN PRODUCT INFORMATION

ENGERIX-B (hepatitis B surface antigen recombinant (yeast)) vaccine, suspension for injection

1 NAME OF THE MEDICINE

Hepatitis B surface antigen recombinant (yeast)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ENGERIX-B PAEDIATRIC DOSE: 10 µg dose vaccine

1 dose (0.5 mL) contains:

Hepatitis B surface antigen [1, 2]	10 micrograms
[1]Adsorbed on aluminium hydroxide hydrate	Total: 0.25 milligrams Al^{3+}

[2]Produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology

ENGERIX-B: 20 µg dose vaccine

1 dose (1 mL) contains:

Hepatitis B surface antigen[1, 2]	20 micrograms
[1]Adsorbed on aluminium hydroxide hydrate	Total: 0.50 milligrams Al^{3+}

[2]Produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

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.

3 PHARMACEUTICAL FORM

Suspension for injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ENGERIX-B is indicated for active immunisation against hepatitis B virus infection. The use of the vaccine should be in accordance with official recommendations.

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.

4.2 DOSE AND METHOD OF ADMINISTRATION

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 participants protected after the first and second doses.

The 20 μg vaccine can also be used in participants 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. For details on the recommended vaccination schedule, including use in pre-term babies, refer to the Australian Immunisation Handbook.

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

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	0.5 mL	0.5 mL	0.5 mL
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	0.5 mL	0.5 mL	0.5 mL

* after first dose

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

The 20 μg vaccine may be administered in participants 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 Section 5.1 PHARMACODYNAMIC PROPERTIES). 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.

∇ For details on the recommended vaccination schedule, including use in pre-term babies, refer to the Australian Immunisation Handbook.

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

	Vaccine Dose	At birth	1 month*	6 months*
ENGERIX-B vaccine	10 μg	0.5 mL	0.5 mL	0.5 mL
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 Section 5.1 PHARMACODYNAMIC PROPERTIES). 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.

Dosage adjustment

Renal impairment/dialysis

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 40 μg. The 40 μg (2 mL) dose may be administered as 2 x 20 μg in one injection site or in each arm.

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

* 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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 need for a booster dose in healthy individuals who have received a full primary vaccination course has not been established. Thus, a booster dose is not recommended in these circumstances. Booster doses are recommended for haemodialysis patients and other immunocompromised patients. Refer to the Australian Immunisation Handbook for further guidance.

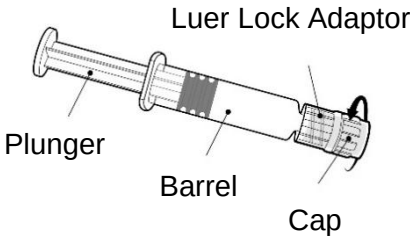
Method of administration

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.

The vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance prior to administration. In the event of either being observed, do not administer the vaccine. The vaccine should be discarded.

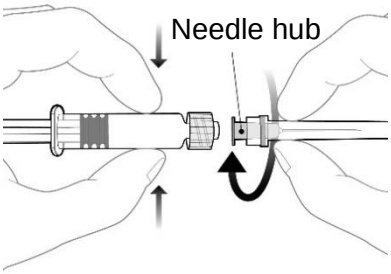
The pre-filled syringe presentations are for use in a single patient only and any residue must be discarded.

Instructions for the pre-filled syringe



Hold the syringe by the barrel, not by the plunger.

Unscrew the syringe cap by twisting it anticlockwise.



To attach the needle, connect the hub to the Luer Lock Adaptor and rotate a quarter turn clockwise until you feel it lock.

Do not pull the syringe plunger out of the barrel. If it happens, do not administer the vaccine.

Any unused product or waste material should be disposed of in accordance with local requirements.

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.

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

4.3 CONTRAINDICATIONS

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

As for any vaccine, ENGERIX-B should not be administered to participants 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 Section 4.2 DOSE AND METHOD OF 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 participants 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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Chronic adult haemodialysis patients/Patients with impaired renal function (creatinine clearance <30 mL/min) 16 years of age and above).

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.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

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 ≤ 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 hepatic impairment

No data available.

Use in renal impairment

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE above, for use in haemodialysis patients.

Use in the elderly

No data available.

Paediatric use

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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.

ENGERIX-B can be given concomitantly with Human Papillomavirus (HPV) vaccine (CERVARIX).

Administration of ENGERIX-B at the same time as CERVARIX (HPV vaccine) has shown no clinically relevant interference in the antibody response to the HPV antigens. Anti-HBs geometric mean antibody concentrations were lower on co-administration, but the clinical significance of this observation is not known since the seroprotection rates remain unaffected.

The proportion of participants reaching anti-HBs ≥ 10mIU/mL was 97.9% for concomitant vaccination and 100% for ENGERIX-B alone.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

(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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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 participants. The incidence of local and systemic reactions was comparable to those of plasma derived hepatitis B vaccines.

In a comparative trial in participants 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.

Adverse effects data from patients who received a challenge dose of ENGERIX-B 10 μg (preservative free) at 72 to 78 months after primary vaccination is shown in the below table. The Group 1 participants had received 2 doses of thiomersal-free ENGERIX-B (20 μg) at 0

and 6 months, with placebo at Month 1. The Group 2 participants had received 3 doses of preservative-free ENGERIX-B (10 μg) at 0, 1 and 6 months.

Table 1: Adverse effects data from patients who received a challenge dose of ENGERIX-B 10 μg at 72 to 78 months after primary vaccination

Incidence and Nature of Symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total Vaccinated cohort)													
		Group 1 (N=55)				Group 2 (N=22)				Pooled (N=77)			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
Any symptom		38	69.1	55.2	80.9	14	63.6	40.7	82.8	52	67.5	55.9	77.8
General symptoms		26	47.3	33.7	61.2	12	54.5	32.2	75.6	38	49.4	37.8	61.0
Local symptoms		31	56.4	42.3	69.7	5	22.7	7.8	45.4	36	46.8	35.3	58.5
Solicited local symptoms													
Pain	Any	22	40.0	27.0	54.1	4	18.2	5.2	40.3	26	33.8	23.4	45.4
	Grade 3	0	0.0	0.0	6.5	0	0.0	0.0	15.4	0	0.0	0.0	4.7
	M.A	0	0.0	0.0	6.5	0	0.0	0.0	15.4	0	0.0	0.0	4.7
Redness (mm)	Any	11	20.0	10.4	33.0	1	4.5	0.1	22.8	12	15.6	8.3	25.6
	≥ 50mm	0	0.0	0.0	6.5	0	0.0	0.0	15.4	0	0.0	0.0	4.7
	M.A	0	0.0	0.0	6.5	0	0.0	0.0	15.4	0	0.0	0.0	4.7
Swelling (mm)	Any	9	16.4	7.8	28.8	0	0.0	0.0	15.4	9	11.7	5.5	21.0
	≥ 50mm	0	0.0	0.0	6.5	0	0.0	0.0	15.4	0	0.0	0.0	4.7
	M.A	0	0.0	0.0	6.5	0	0.0	0.0	15.4	0	0.0	0.0	4.7
Solicited General Symptoms													
Fatigue	Any	19	34.5	22.2	48.6	7	31.8	13.9	54.9	26	33.8	23.4	45.4
	Grade 3	1	1.8	0.0	9.7	0	0.0	0.0	15.4	1	1.3	0.0	7.0
	Related	15	27.3	16.1	41.0	7	31.8	13.9	54.9	22	28.6	18.8	40.0
	Grade 3 Related	0	0.0	0.0	6.5	0	0.0	0.0	15.4	0	0.0	0.0	4.7
	M.A	1	1.8	0.0	9.7	0	0.0	0.0	15.4	1	1.3	0.0	7.0
Fever/ (Axillary) (°C)	Any	1	1.8	0.0	9.7	0	0.0	0.0	15.4	1	1.3	0.0	7.0
	≥ 37.5°C	1	1.8	0.0	9.7	0	0.0	0.0	15.4	1	1.3	0.0	7.0
	>38.0°C	0	0.0	0.0	6.5	0	0.0	0.0	15.4	0	0.0	0.0	4.7
	Related	0	0.0	0.0	6.5	0	0.0	0.0	15.4	0	0.0	0.0	4.7
	>39.5°C Related	0	0.0	0.0	6.5	0	0.0	0.0	15.4	0	0.0	0.0	4.7
	M.A	1	1.8	0.0	9.7	0	0.0	0.0	15.4	1	1.3	0.0	7.0
Gastro-intestinal symptoms	All	7	12.7	5.3	24.5	4	18.2	5.2	40.3	11	14.3	7.4	24.1
	Grade 3	0	0.0	0.0	6.5	0	0.0	0.0	15.4	0	0.0	0.0	4.7
	Related	7	12.7	5.3	24.5	2	9.1	1.1	29.2	9	11.7	5.5	21.0
	Grade 3 Related	0	0.0	0.0	6.5	0	0.0	0.0	15.4	0	0.0	0.0	4.7
	M.A	0	0.0	0.0	6.5	0	0.0	0.0	15.4	0	0.0	0.0	4.7
Headache	All	14	25.5	14.7	39.0	4	18.2	5.2	40.3	18	23.4	14.5	34.4
	Grade 3	0	0.0	0.0	6.5	0	0.0	0.0	15.4	0	0.0	0.0	4.7
	Related	11	20.0	10.4	33.0	3	13.6	2.9	34.9	14	18.2	10.3	28.6

	Grade 3 Related	0	0.0	0.0	6.5	0	0.0	0.0	15.4	0	0.0	0.0	4.7
	M.A	1	1.8	0.0	9.7	0	0.0	0.0	15.4	1	1.3	0.0	7.0

Group 1 = received two doses of *ENGERIX-B* (20 µg HBsAg) in the primary study
Group 2 = received three doses of *ENGERIX-B* (10 µg HBsAg) in the primary study
N = number of participants who received the vaccine
n (%) = number (percentage) of participants who reported the symptom at least once
95% CI = Exact 95% confidence interval; LL = Lower limit, UL = Upper limit
Any = all reports of the specified symptom irrespective of intensity grade and relationship to vaccination
Grade 3 pain, fatigue, gastrointestinal symptoms, headache = pain, fatigue, gastrointestinal symptoms, headache that prevented normal activity
Related = symptoms considered by the investigator to have causal relationship to vaccination
Grade 3 Related = adverse event which prevented normal everyday activities and was assessed as causally related to vaccination
M.A. = symptoms for which the participants received medical attention
Pooled = Pooled results of Group 1 and Group 2

The safety profile presented below is based on data from more than 5,300 participants. 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.

Infections and Infestations: Herpes zoster

Autonomic nervous system: *Rare***:** flushing, sweating

Body as a whole: *Rare:* fever, fatigue, malaise, chills**;** *Very rare:* anaphylaxis, delayed hypersensitivity reactions, mimicking 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, myelitis including transverse myelitis

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

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

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

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

ENGERIX-B induces the production of specific humoral antibodies (anti-HBs), which confer immunity against hepatitis B. A peak anti-HBs antibody concentration 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 participant.

Clinical trials

Protective Efficacy

Clinical trials demonstrated SC rates of ≥ 97% (seroprotection (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.

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 seroprotection rates (SP) obtained with the two different dosages and schedules recommended in participants from 11 years up to and including 15 years of age were evaluated up to 66 months after the first dose of the primary vaccination and are presented in Table 2.

Table 2: Seroprotection Rates obtained with two different dosages in participants 11 to 15 years

Vaccine groups	Anti-HBs Month 2 SP (%)	Anti-HBs Month 6 SP (%)	Anti-HBs Month 7 SP (%)	Anti-HBs Month 30 SP (%)	Anti-HBs Month 42 SP (%)	Anti-HBs Month 54 SP (%)	Anti-HBs Month 66 SP (%)
ENGERIX-B 10 µg (0, 1, 6 months schedule)	55.8 (46.1-65.1)[1]	87.6 (80.1-93.1)[1]	98.2 (93.8-99.8)[1]	96.9 (89.2-99.6)[1]	92.5 (84.4-97.2)[1]	94.7 (87.1-98.5)[1]	91.4 (82.3-96.8)[1]
ENGERIX-B 20 µg (0, 6 months schedule)	11.3 (7.5-15.9)[1]	26.4 (20.9-32.4)[1]	96.7 (93.6-98.6)[1]	87.1 (80.4-92.2)[1]	83.7 (77.2-89.0)[1]	84.4 (77.5-89.8)[1]	79.5 (71.7-86.1)[1]

[1] 95% confidence interval, (lower limit – upper limit)

These data show that a primary vaccination with ENGERIX-B vaccine induces circulating anti-HBs antibodies that persist for at least 66 months. From one month after completion of the primary course through to 66 months i.e. Month 7 to Month 66, the Seroprotection rates were comparable between the 2 groups but tended to be lower in the 20 µg Group (0, 6 months schedule) compared to the 10 µg Group (0, 1, 6 month schedule) at all timepoints. The seroprotection rates at Month 66 were 79.5% (95%CI 71.7%, 86.1%) and 91.4% (95%CI 82.3%, 96.8%) in the 20 µg Group and 10 µg Group respectively. All participants in both vaccine groups (including participants with anti-HBs antibody concentrations < 10 IU/L) received a challenge dose 72 to 78 months after primary vaccination. One month after the challenge dose, all participants mounted an anamnestic response to the challenge dose and were shown to be seroprotected (i.e. anti-HBs antibody concentrations ≥ 10 IU/L). These data suggest that protection against hepatitis B may still be conferred through immune memory in

all participants who responded to primary vaccination but lost seroprotection level of anti-HBs antibodies.

Rechallenge in healthy participants

In a clinical study conducted in Germany, healthy participants (N=284) aged 12 to 13 years vaccinated during infancy with 3 doses of ENGERIX-B received a challenge dose of ENGERIX-B. One month later, 98.9% of participants were shown to be seroprotected.

At risk groups:

In clinical studies performed in Thailand twenty years after primary vaccination during infancy, participants born to mothers who were HBV carriers, received a challenge dose of ENGERIX-B. One month later, at least 93% of participants (N=75) mounted an anamnestic response i.e. at least (greater than or equal to) a 4-fold rise in post-challenge dose anti-HB's antibody concentrations in subjects seropositive at the previous available long-term time-point, demonstrating immune memory.

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 intellectually impaired individuals and male homosexuals respectively. In a clinical trial where thalassaemic patients received three doses of 20 μg at 0, 1, 6 months, SC rates as well as SP rates were 100% (17 participants tested).

Patients with renal insufficiency

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.

Table 3: Seroprotection Rates (SP) obtained with 40 μg (2 x 20 μg) doses in haemodialysis and pre-haemodialysis patients 16 years of age and above

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.

Patients with type II diabetes

The seroprotection rates in subjects 20 years of age and above with type II diabetes were evaluated one month after the last dose of the primary vaccination and are presented in Table 4.

Table 4: Seroprotection Rates (SP) in subjects 20 years of age and above with type II diabetes

Age (years)	**Schedule**	**Seroprotection rate at month 7 ≥ 10 mIU/mL**		
		%	**95 % CI**	
			LL	**UL**
20-39 <BMI 30 kg/m2	0, 1, 6 months (20 µg)	85.7	57.2	98.2
20-39 ≥BMI 30 kg/m2		89.5	75.2	97.1
40-49 <BMI 30 kg/m2		80.8	60.6	93.4
40-49 ≥BMI 30 kg/m2		81.4	69.1	90.3
50-59 <BMI 30 kg/m2		90.2	79.8	96.3
50-59 ≥BMI 30 kg/m2		75.9	62.8	86.1
[3] 60 <BMI 30 kg/m2		66.7	53.3	78.3

**Data source: Study 115918 (HBV-323) Table 42 Seropositivity rates, Seroprotection rates and geometric mean concentrations (GMCs) for anti-HBs antibody concentrations by groups before first dose of vaccination and one month after third dose of vaccination by stratified groups by age and BMI (ATP cohort for Immunogenicity)*

Reduction in the incidence of hepatocellular carcinoma in children

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.

5.2 PHARMACOKINETIC PROPERTIES

Not relevant to vaccines.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The final vaccines also contain dibasic sodium phosphate dihydrate, monobasic sodium phosphate, sodium chloride, aluminium hydroxide hydrate and water for injections and traces of polysorbate 20. ENGERIX-B contains no thiomersal.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

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.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

ENGERIX-B must be 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.

6.5 NATURE AND CONTENTS OF CONTAINER

ENGERIX-B 20 μg (Adult dose):

- 1 mL of suspension in a pre-filled syringe (type I glass) with a plunger stopper (butyl rubber) and with a rubber tip cap.

Pre-filled syringes in packs of 1, 10 and 25.

ENGERIX-B PAEDIATRIC DOSE 10 μg:

- 0.5 mL of suspension in a pre-filled syringe (type I glass) with a plunger stopper (butyl rubber) and with a rubber tip cap.

Pre-filled syringe in packs of 1, 10 and 25.

The tip cap and rubber plunger stopper of the pre-filled syringe are not made with natural rubber latex.

Not all pack sizes and container types may be distributed in Australia.

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

Not relevant to vaccines.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

GlaxoSmithKline Australia Pty Ltd
Level 4, 436 Johnston Street,
Abbotsford, Victoria, 3067
Australia

9 DATE OF FIRST APPROVAL

24 July 2006

10 DATE OF REVISION

05 March 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2	Editorial changes to the vaccination schedules in ‘Neonates, infants and children below 10 years of age’ in table footnote. Booster dosing updated to align with the Australian Immunisation Handbook (AIH).

Version 14.0

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