Engerix™-B

1. NAME OF THE MEDICINAL PRODUCT

Engerix™-B
Hepatitis B (rDNA) vaccine (adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

10 µg dose vaccine
1 dose (0.5 ml) contains:
Hepatitis B surface antigen [1, 2] 10 micrograms

[1]Adsorbed on aluminium hydroxide, hydrated Total: 0.25 milligrams Al^{3+}
[2]Produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology

20 µg dose vaccine
1 dose (1 ml) contains:
Hepatitis B surface antigen[1, 2] 20 micrograms

[1]Adsorbed on aluminium hydroxide, hydrated Total: 0.50 milligrams Al^{3+}
[2]Produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology

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

3. PHARMACEUTICAL FORM

Suspension for injection.
Turbid white suspension.
Upon storage, a fine white deposit with a clear colourless supernatant may be observed.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

Engerix™-B is indicated for active immunisation against hepatitis B virus (HBV) infection caused by all known subtypes in subjects of all ages considered at risk of exposure to HBV. It can be expected that hepatitis D will also be prevented by immunisation with **Engerix™-B** as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

Immunisation against hepatitis B is expected in the long term to reduce not only the incidence of this disease, but also its chronic complications such as chronic active hepatitis B and hepatitis B associated cirrhosis.

In areas of **low prevalence** of hepatitis B, immunisation is particularly recommended for those belonging to groups identified at increased risk of infection (see below), however, universal immunisation of all infants and adolescents will contribute to the control of hepatitis B on a population basis.

In areas of **intermediate and high prevalence** of hepatitis B, with most of the population at risk of acquiring the HBV, the best strategy is to provide universal immunisation of neonates, infants, children and adolescents, as well as adults belonging to groups at increased risk of infection.

The WHO, the US Immunisation Practices Advisory Committee (ACIP) and the American Academy of Paediatrics advocate that the vaccination of new-borns and/or the vaccination of adolescents is the optimal strategy for the control of hepatitis B in all countries.

Groups identified at increased risk of infection:

- **Health Care Personnel.**
- **Patients frequently receiving blood products.**
- **Personnel and residents of institutions.**
- **Persons at increased risk due to their sexual behaviour.**
- **Illicit users of addictive injectable drugs.**
- **Travellers to areas with a high endemicity of HBV.**
- **Infants born of mothers who are HBV carriers.**
- **Persons originating from areas with a high endemicity of HBV.**
- **Patients with sickle-cell anaemia.**
- **Patients who are candidates for organ transplantation.**
- **Household contacts of any of the above groups and of patients with acute or chronic HBV infection.**
- **Subjects with chronic liver disease (CLD) or at risk of developing CLD (e.g. Hepatitis C virus carriers, persons who abuse alcohol).**
- **Others:** Police personnel, fire brigade personnel, armed forces personnel and anybody who through their work or personal lifestyle may be exposed to HBV.

4.2 Posology and Method of Administration

Posology

20 μg dose vaccine. The 20 μg dose (in 1.0 ml suspension) is intended for use in subjects 20 years of age and older.

10 μg dose vaccine. The 10 μg dose (in 0.5 ml suspension) is intended for use in neonates, infants and children up to and including the age of 19 years.

However, the 20 μg vaccine can also be used in subjects from 11 years up to and including 15 years of age as a 2-dose schedule in situations when there is a low risk of hepatitis B infection during the vaccination course and when compliance with the complete vaccination course can be assured (see section 5.1 Pharmacodynamic Properties).

Primary immunisation schedules

<u>All subjects</u>

A 0, 1 and 6 months schedule gives optimal protection at month 7 and produces high antibody titres. An accelerated schedule, with immunisation at 0, 1 and 2 months, will confer protection more quickly and is expected to provide better patient compliance. With this schedule, a fourth dose should be administered at 12 months to assure long term protection as titres after the third dose are lower than those obtained after the 0, 1, 6 months schedule. In infants this schedule will allow for simultaneous administration of hepatitis B with other childhood vaccines.

<u>Subjects 20 years of age and above</u>

In exceptional circumstances in adults, where an even more rapid induction of protection is required, e.g. persons travelling to areas of high endemicity and who commence a course of vaccination against hepatitis B within one month prior to departure, a schedule of three intramuscular injections given at 0, 7 and 21 days may be used. When this schedule is applied, a fourth dose is recommended 12 months after the first dose (see section 5.1 Pharmacodynamic Properties for seroconversion rates).

Subjects from 11 years up to and including 15 years of age

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 section 5.1 Pharmacodynamic Properties). Therefore, this schedule should be used only when there is a low risk of hepatitis B infection during the vaccination course and when completion of the two-dose vaccination course can be assured. If both conditions can not be assured (for instance patients undergoing haemodialysis, travellers to endemic regions and close contacts of infected subjects), the three-dose or the accelerated schedule of the 10 μg vaccine should be used.

Patients with renal insufficiency including patients undergoing haemodialysis 16 years of age and above

The primary immunisation schedule for patients with renal insufficiency including patients undergoing haemodialysis is four double doses (2 x 20 μg) at elected date, 1 month, 2 months and 6 months from the date of the first dose. The immunisation schedule should be adapted in order to ensure that the anti-HBs antibody titre remains equal to or higher than the accepted protective level of 10 IU/L.

Patients with renal insufficiency including patients undergoing haemodialysis up to and including 15 years of age, including neonates

Patients with renal insufficiency, including patients undergoing haemodialysis, have a reduced immune response to hepatitis B vaccines. Either the 0, 1, 2 and 12 months or the 0, 1, 6 months schedule of **Engerix™-B** 10 μg can be used. Based on adult experience, vaccination with a higher dosage of antigen may improve the immune response. Consideration should be given to serological testing following vaccination. Additional doses of vaccine may be needed to ensure a protective anti-HBs level ≥ 10 IU/L.

Known or presumed exposure to HBV

In circumstances where exposure to HBV has recently occurred (eg needlestick with contaminated needle) the first dose of **Engerix™-B** can be administered simultaneously with hepatitis B immune globulins (HBIg) which however must be given at a separate injection site (see section 4.5 Interaction with Other Medicinal Products and Other Forms of Interactions). The 0, 1, 2-12 months immunisation schedule should be advised.

Neonates born of mothers who are HBV carriers

The immunisation with **Engerix™-B** (10 μg) of these neonates should start at birth, and one of the two immunisation schedules have to be followed. Either the 0, 1, 2 and 12 months or the 0, 1 and 6 months schedule can be used; however, the former schedule provides a more rapid immune response. When available, HBIg should be given simultaneously with **Engerix™-B** at a separate injection site as this may increase the protective efficacy.

These immunisation schedules may be adjusted to accommodate local immunisation practices with regard to the recommended age of administration of other childhood vaccines.

Booster dose

The need for a booster dose in healthy individuals who have received a full primary vaccination course has not been established; however, some official vaccination programmes currently include a recommendation for a booster and these should be respected.

For haemodialysis and other immunocompromised patients, booster doses are recommended in order to ensure an antibody level of ≥ 10 IU/L.

Booster data are available. The booster dose is as well tolerated as the primary vaccination course.

Method of administration
Engerix™-B should be injected intramuscularly in the deltoid region in adults and children or in the anterolateral thigh in neonates, infants and young children. Exceptionally the vaccine may be administered subcutaneously in patients with thrombocytopenia or bleeding disorders.

Engerix™-B should not be administered in the buttock or intradermally since this may result in a lower immune response.

4.3 Contraindication
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.

HIV infection is not considered as a contraindication for hepatitis B vaccination.

4.4 Special Warnings and Precautions for Use
As with other vaccines, the administration of **Engerix™-B** should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection, however, is not a contraindication for immunisation.

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

The vaccine will not prevent infection caused by other pathogens known to infect the liver such as hepatitis A, hepatitis C and hepatitis E virus.

The immune response to hepatitis B vaccines is related to a number of factors, including older age, male gender, obesity, smoking habits and route of administration. In subjects who may respond less well to the administration of the hepatitis B vaccines (e.g. more than 40 years of age etc.), additional doses may be considered.

In patients with renal insufficiency including patients undergoing haemodialysis , HIV infected patients and persons with an impaired immune system, adequate anti-HBs antibody titres may not be obtained after the primary immunisation course and such patients may therefore require administration of additional doses of vaccine. (see section 4.2 Posology and Method of Administration-Patients with renal insufficiency including patients undergoing haemodialysis).

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

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.

Engerix™-B should not be administered in the buttock or intradermally since this may result in a lower immune response.

Engerix™-B should under no circumstances be administered intravascularly.

As with any vaccine, a protective immune response may not be elicited in all vaccinees (see section 5.1 Pharmacodynamic Properties).

The potential risk of apnoea and the need for respiratory monitoring for 48-72h 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.

4.5 Interaction with Other Medicinal Products and Other Forms of Interactions

The simultaneous administration of **Engerix™-B** and a standard dose of HBIg does not result in lower anti-HBs antibody titres provided that they are administered at separate injection sites.

Engerix™-B can be given concomitantly with DTP, DT and/or polio vaccines, if this fits conveniently in an immunisation scheme recommended by the country Health Authority.

Engerix™-B can be administered together with measles-mumps-rubella vaccines, *Haemophilus influenzae* b vaccine, hepatitis A vaccine and BCG.

Engerix™-B can be given concomitantly with Human Papillomavirus (HPV) vaccine (Cervarix™).

Administration of **Engerix™-B** at the same time as Cervarix™ 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 subjects reaching anti-HBs ≥ 10 mIU/ml was 97.9% for concomitant vaccination and 100% for **Engerix™-B** alone.

Different injectable vaccines should always be administered at different injection sites.

Interchangeability of hepatitis B vaccines

Engerix™-B may be used to complete a primary immunisation course started either with plasma-derived or with other genetically-engineered hepatitis B vaccines, or as a booster dose in subjects who have previously received a primary immunisation course with plasma-derived or with other genetically-engineered hepatitis B vaccines.

4.6 Pregnancy and Lactation

Pregnancy

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

However, as with all inactivated viral vaccines one does not expect harm for the foetus. **Engerix™-B** should be used during pregnancy only when clearly needed, and the possible advantages outweigh the possible risks for the foetus.

Lactation

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

No contraindication has been established.

4.7 Effects on Ability to Drive and Use Machine
The vaccine is unlikely to produce an effect on the ability to drive and use machines.

4.8 Undesirable Effects
The safety profile presented below is based on data from more than 5,300 subjects.

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

System Organ Class	Frequency	Adverse reactions
Clinical trials		
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, diarrhoea, 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		
Infections and infestations	Meningitis	
Blood and lymphatic system disorders	Thrombocytopenia	
Immune system disorders	Anaphylaxis, allergic reactions including anaphylactoid reactions and mimicking serum sickness	
Nervous system disorders	Paralysis, convulsions, hypoaesthesia, encephalitis, encephalopathy, neuropathy, neuritis	
Vascular disorders	Hypotension, vasculitis	
Skin and subcutaneous tissue disorders	Angioneurotic oedema, lichen planus, erythema multiforme	
Musculoskeletal and connective tissue disorders	Arthritis, muscular weakness	

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 similar overall to that reported after the standard three-dose regimen of **Engerix™-B** 10 μg.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmaco-therapeutic group: Heaptitis B vaccine, ATC code J07BC01

Engerix™-B induces specific humoral antibodies against HBsAg (anti-HBs antibodies). Anti-HBs antibody concentrations ≥ 10 IU/L correlate with protection to HBV infection.

- ***Protective efficacy***

At risk groups

In field studies, a protective efficacy between 95% and 100% was demonstrated in neonates, children and adults at risk.

A 95% protective efficacy was demonstrated in neonates of HBeAg positive mothers, immunised according to the 0, 1, 2 and 12 or 0, 1 and 6 schedules without the concomitant administration of HBIg at birth. However, simultaneous administration of HBIg and vaccine at birth increased the protective efficacy to 98%.

Twenty years after primary vaccination during infancy, subjects born to mothers who were HBV carriers, received a challenge dose of **Engerix™-B**. One month later, at least 93% of subjects (N=75) mounted an anamnestic response demonstrating immune memory.

Healthy subjects

The table below summarizes seroprotection rates (i.e. percentages of subjects with anti-HBs antibody concentrations ≥ 10 IU/L) obtained in clinical studies with the different schedules mentioned in section 4.2 Posology and Method of Administration:

Population	Schedule	Seroprotection rate
Healthy subjects	0, 1, 6 months 0, 1, 2 – 12 months	at month 7: ≥ 96% at month 1: 15% at month 3: 89% at month 13: 95.8%
Healthy subjects 20 years of age and above	0, 7, 21 days – 12 months	at day 28 : 65.2% at month 2: 76% at month 13: 98.6%

The seroprotection rates (SP) obtained with the two different dosages and schedules licensed in subjects 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 the Table below:

Vaccine groups	Seroprotection rate						
	Month 2	Month 6	Month 7	Month 30	Month 42	Month 54	Month 66
Engerix™-B 10µg (0, 1, 6 months schedule)	55.8%	87.6%	98.2%	96.9%	92.5%	94.7%	91.4%
Engerix™-B 20µg (0, 6 months schedule)	11.3%	26.4%	96.7%	87.1%	83.7%	84.4%	79.5%

These data show that a primary vaccination with **Engerix™-B** vaccine induces circulating anti-HBs antibodies that persist for at least 66 months. After having completed the primary course, at each time point there is no clinically significant difference in the seroprotection rates when comparing the 2 vaccine groups. Indeed, all subjects in both vaccine groups (including subjects 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 subjects 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 subjects who responded to primary vaccination but lost seroprotection level of anti-HBs antibodies.

Rechallenge in healthy subjects
Subjects (N=284) aged 12 to 13 years vaccinated during infancy with 3 doses of **Engerix™-B** received a challenge dose. One month later, 98.9% of subjects were shown to be seroprotected.

Patients with renal insufficiency including patients undergoing haemodialysis

Age (years)	Schedule	Seroprotection rate
16 and above	0, 1, 2, 6 months (2 x 20 µg)	at month 3: 55.4% at month 7: 87.1%

Patients with type II diabetes

Age (years)	Schedule	Seroprotection rate at Month 7
20-39	0, 1, 6 months (20 µg)	88.5%
40-49		81.2%
50-59		83.2%
≥ 60		58.2%

· ***Reduction in the incidence of hepatocellular carcinoma in children***
A significant reduction in the incidence of hepatocellular carcinoma has been observed in children aged 6-14 years following a nationwide hepatitis B vaccination in Taiwan. There was a significant decline in the prevalence of hepatitis B antigen, the persistence of which is an essential factor in the development of hepatocellular carcinoma.

5.2 Pre-clinical Safety Data
Appropriate safety tests have been performed.

6. PHARMACEUTICAL PARTICULARS
6.1 List of Excipients
Monodose presentation
Sodium chloride, sodium phosphate dihydrate, sodium dihydrogen phosphate, water for injections.
Polysorbate 20 is present as residual from the manufacturing process.

Multidose presentation
Sodium chloride, sodium phosphate dihydrate, sodium dihydrogen phosphate, water for injections, 2-phenoxyethanol as preservative.
Polysorbate 20 is present as residual from the manufacturing process.

6.2 Incompatibilities
Engerix™-B should not be mixed with other vaccines.

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

6.4 Special Precautions for Storage
The vaccine should be stored at +2°C to +8°C.
Partially used vials must be used the same day.
DO NOT FREEZE; discard if vaccine has been frozen.
Store in the original package in order to protect from light.

Additional information on the stability
The following experimental data give an indication of the stability of the vaccines and are not recommendations for storage (see section 6.4 Special Precautions for Storage).

Engerix™-B has been kept in a refrigerator at +2°C to +8°C for 48 months without significant loss of potency.

Engerix™-B has been kept at 37°C for 1 month and 45°C for 1 week without loss of its potency.

6.5 Nature and Contents of Container
Engerix™-B is presented in a glass vial or glass prefilled syringes.
The vials and prefilled syringes are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements.

6.6 Instructions for Use and Handling
Upon storage, a fine white deposit with a clear colourless supernatant may be observed. The vaccine should be well shaken before use to obtain 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, the vaccine should be discarded.

When using a multidose vial, each dose should be withdrawn with a sterile needle and syringe. As with other vaccines, a dose of vaccine should be withdrawn under strict aseptic conditions and precautions be taken to avoid contamination of the contents.

When using a vial, use different needles to pierce the rubber stopper and to inject the vaccine.

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

Not all presentations are available in every country.

7. MARKETING AUTHORIZATION HOLDER
GlaxoSmithKline (Thailand) Ltd.

8. MARKETING AUTHORIZATION NUMBER
1C 963/29

9. DATE OF AUTHORIZATION
22 Dec 1986

Engerix-B and **Cervarix** are trademarks of the GSK group of companies.

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