Engerix™-B

1. Trade name of medicinal product
Engerix-B.

2. Qualitative and quantitative composition
Engerix-B, hepatitis B vaccine is a sterile suspension containing the purified major surface antigen of the virus manufactured by recombinant DNA technology, adsorbed onto aluminium hydroxide.
The antigen is produced by culture of genetically-engineered yeast cells (*Saccharomyces cerevisiae*) which carry the gene which codes for the major surface antigen of the hepatitis B virus (HBV). This hepatitis B surface antigen (HBsAg) expressed in yeast cells is purified by several physico-chemical steps. The HBsAg assembles spontaneously, in the absence of chemical treatment, into spherical particles of 20 nm in average diameter containing non-glycosylated HBsAg polypeptides and a lipid matrix consisting mainly of phospholipids. Extensive tests have demonstrated that these particles display the characteristic properties of natural HBsAg.
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.
A 20 µg dose vaccine (in 1.0 ml suspension) contains 20 µg HBsAg.
A 10 µg dose vaccine (in 0.5 ml suspension) contains 10 µg HBsAg.

3. Pharmaceutical form
Suspension for injection.

4. Clinical particulars
4.1 Therapeutic indications
Engerix-B is indicated for active immunisation against 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 complication 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
- 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 Dosage and method of administration

Dosage

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

10 µg dose vaccine. A 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. In children aged 10 to 19 years, the adult dose of 20 µg can be employed if low compliance is anticipated, since a higher percentage of vaccinees with protective antibody levels (≥ 10 IU/l) is obtained after two injections at this dosage.

IMMUNISATION SCHEDULE

A series of three intramuscular injections is required to achieve optimal protection. Two primary immunisation schedules can be recommended.

- Schedules which have more time between the second and third doses, such as immunisation at 0, 1 and 6 months, may take longer to confer protection, but will produce higher anti-HBs antibody titres after three doses. This schedule is intended for use in children up to and including 19 years of age with a 10 µg dose of **Engerix™-B**
- A schedule, with immunisation at 0, 1 and 2 months, will confer protection more quickly and is expected to provide better patient compliance. A booster should be administered at 12 months. In infants this schedule will allow for simultaneous administration of hepatitis B with other childhood vaccines.

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. Thus a booster dose is not recommended in these circumstances. Booster data are available. The booster dose is as well tolerated as the primary vaccination course.

Dosage recommendation for chronic lever disease (CLD)
The immunisation schedule for chronic liver disease patients is three doses of 20 mcg at 0, 7 and 21 days.

Dosage recommendation for known or presumed exposure to HBV.
In circumstances where exposure to HBV has recently occurred (e.g. needlestick with contaminated needle) the first dose of **Engerix-B** can be administered simultaneously with HBIg which however must be given at a separate injection site. The rapid immunisation schedule should be advised.

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 under no circumstances be administered intravenously.

4.3 Contra-indications
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 contra-indication for hepatitis B vaccination.

4.4 Special warnings and special 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 contra-indication 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 agents such as hepatitis A, hepatitis C and hepatitis E and other pathogens known to infect the liver.
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 haemodialysis patients, 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.
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. **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 intravenously.

4.5 Interaction with other medicaments and other forms of interaction
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 OPV, if this fits conveniently in an immunisation scheme recommended by the country Health Authority. **Engerix-B** can also be administered together with measles-mumps-rubella vaccines, Haemophilus influenzae b vaccine, hepatitis A vaccine and BCG. 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 contra-indication has been established.

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

4.8 Undesirable effects
Engerix-B is generally well tolerated.
The following undesirable effects, usually mild and transient have been reported following the widespread use of the vaccine. As with other hepatitis B vaccines, in many instances, the causal relationship with the vaccine has not been established.

Common:
Application site: redness, pain, swelling at injection site

Rare:
Body as a whole : fatigue, fever, malaise, influenza-like symptoms
Central and peripheral nervous system : dizziness, headache, paresthesia
Gastro-intestinal system : nausea, vomiting, diarrhoea, abdominal pain
Liver and biliary system : abnormal liver function tests
Musculoskeletal system : arthralgia, myalgia
Skin and appendages : rash, pruritus, urticaria

Very rare:
Body as a whole : anaphylaxis, allergic reactions including anaphylactoid reactions and mimicking serum sickness
Cardiovascular : syncope, hypotension.
Central and peripheral nervous system : paralysis, neuropathy, neuritis (including Guillain-Barré syndrome, optic neuritis and multiple sclerosis), encephalitis, encephalopathy, meningitis, convulsions.

Haematological disorders : thrombocytopenia
Musculoskeletal system : arthritis
Respiratory system : bronchospasm like symptoms
Skin and appendages : angioedema, erythema multiforme
Vascular extracardiac : vasculitis
White cell and reticulo-endothelial system : lymphadenopathy

4.9 Overdose
Not applicable.

5. Pharmacological properties
5.1 Pharmacodynamic Properties
Engerix-B induces specific humoral antibodies against HBsAg (anti-HBs antibodies). An anti-HBs antibody titre above 10 IU/l correlates with protection to HBV infection.
Protective efficacy in risk groups
In field studies, a protective efficacy between 95% and 100% was demonstrated in neonates, children and adults at risk.
Seroconversion rate in healthy subjects
When the 0, 1 and 6 month schedule is followed, ≥ 96% of vaccinees have seroprotective levels of antibody 7 months after the first dose.
When the 0, 1 and 2 month primary schedule plus a booster at month, 12 is followed, 15% of vaccinees have seropositive levels of antibody one month after the first dose and 89% of vaccinees have seropositive levels of antibody one month after completion of the primary schedule.
One month after the booster dose 95.8% of vaccinees achieved seroprotective levels of antibody.
For use in exceptional circumstances, the immunisation schedule of 0, 7 and 21 day primary schedule plus a booster at month 12 results in 65.2% and 76% of vaccinees having seroprotective levels of antibody within 1 and 5 weeks respectively following completion of the primary schedule. One month after the booster dose 98.6% of vaccinees achieved seroprotective levels of antibody.

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 Pharmacokinetic properties
Not applicable

5.3 Preclinical safety data
Appropriate safety tests have been performed.

6. Pharmaceutical particulars

6.1 List of excipients

Aluminium hydroxide, sodium chloride, sodium phosphate dihydrate, sodium dihydrogen phosphate, polysorbate 20, water for injections.
Multidose presentations contain 2-phenoxyethanol as preservative.

6.2 Incompatibilities

Engerix-B should not be mixed with other vaccines.

6.3 Shelf life

The shelf life of Engerix-B is three years from the date of manufacture when stored at +2°C to +8°C. The expiry date of the vaccine is indicated on the label and packaging.

6.4 Special precautions for storage

New and partially used vials should be stored at +2°C to +8°C.
DO NOT FREEZE; discard if vaccine has been frozen.

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 under 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 immunogenicity in man.

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.
The content, upon storage may present a fine white deposit with a clear colourless supernatant. Once shaken the vaccine is slightly opaque.

6.6 Instructions for use/handling and disposal (if necessary)

The vaccine should be inspected visually for any foreign particulate matter and/or coloration prior to administration. Before use of **Engerix-B**, the vaccine should be well shaken to obtain a slightly opaque, white suspension. Discard if the content appears otherwise.
When using a multidose vial, each dose should be taken with a sterile needle and syringe. As with other vaccines, a dose of vaccine should be withdrawn under strict aseptic conditions and precautions taken to avoid contamination of the contents.
When using a vial, use different needles to pierce the rubber stopper and to inject the vaccine. For additional information please refer to the manufacturer.

Engerix-B is a trademark.