Engerix-B

Version GDSv15-IPIv11

Engerix-B

Hepatitis B vaccine (rDNA) (adsorbed)

Suspension for injection

Qualitative and Quantitative Composition

10 µg Dose Vaccine

1 serving (0.5 ml) contains:

Hepatitis B surface antigen[1, 2]	10 micrograms

1Adsorbed in aluminum hydroxide, total hydrate: 0.25 milligrams Al3+

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

20 µg Dose Vaccine

1 serving (1 ml) contains:

Hepatitis B1 surface antigen, 2	20 micrograms

1Adsorbed in aluminum hydroxide, total hydrate: 0.50 milligrams of Al3+

2Produced in yeast cells (Saccharomyces cerevisiae) by recombinant DNA technology.

The vaccine is highly purified and exceeds WHO requirements for recombinant hepatitis B vaccines.

Cloudy white suspension.

After storage, a fine white deposit with a transparent colourless supernatant can be observed.

Clinical Information

Directions

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. Hepatitis D can also be expected to be prevented by immunization with ***ENGERIX-B,*** since hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

It is expected that in the long term, immunization against hepatitis B will reduce not only the incidence of this disease but also its chronic complication such as chronic active hepatitis B and cirrhosis associated with hepatitis B.

In areas of low hepatitis B **prevalence**, immunization is particularly recommended for those in groups identified as being at higher risk of infection (see below); however, universal immunization of all infants and adolescents will contribute to hepatitis B control in the population.

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

WHO, the U.S. Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics support that vaccination of newborns and/or adolescents is the optimal strategy for hepatitis B control in all countries.

Groups Identified at Higher Risk of Infection

- Health care personnel.
- Patients who frequently receive blood products.
- Staff and residents of institutions.
- People at higher risk because of their sexual behavior.
- Illicit users of addictive injecting drugs.
- Travelers to areas with high HBV endemicity.
- Infants born to HBV-carrying mothers.
- People from areas with high HBV endemicity.
- Patients with sickle cell disease.
- Patients who are candidates for organ transplantation.
- Household contacts of any of the groups mentioned above and of patients with acute or chronic HBV infection.
- Subjects with chronic liver disease or at risk of developing it (e.g., carriers of hepatitis C virus, people who abuse alcohol consumption).
- Other: Police, fire brigade, armed forces, and anyone who may be exposed to HBV through their work or personal lifestyle.

Dosage and Administration

Dosage

Vaccine Dose of 20 gµ

The 20 g dose (in 1 ml suspension) is for use in subjects 20 years of age or older.µ

Vaccine Dose of 10 gµ

The dose of 10 g (in 0.5 ml suspension) is for use in newborns, infants and children up to and including 19 years of age. µ

However, the 20 µg vaccine can also be used in subjects 11 to 15 years of age inclusive, in the form of a 2-dose schedule in cases of low risk of hepatitis B infection during the vaccination cycle and when compliance with the full course of vaccination can be ensured (see "Pharmacodynamics").

Primary Vaccination Program

All Subjects

A 0-, 1- and 6-month program provides optimal protection at month 7 and produces high antibody titers. An accelerated program, with immunization at 0, 1 and 2 months, will protect more quickly, and is expected to invite better patient compliance. With this schedule, a fourth dose should be given at 12 months to ensure long-term protection, as titers after the third dose are lower than those obtained after the 0, 1, and 6-month program. In infants, this program will allow the simultaneous administration of hepatitis B vaccine with other childhood vaccines.

Subjects 20 Years of Age and Older

In exceptional circumstances in adults, when even more rapid induction of protection is required, e.g. people travelling to highly endemic areas and those starting a course of hepatitis B vaccination in the month before leaving, a schedule of three intramuscular injections to be administered on days 0 may be followed, 7 and 21. When applying this schedule, a fourth dose is recommended 12 months after the first dose (see "Pharmacodynamics" for seroconversion rates).

Subjects 11 to 15 Years of Age Inclusive

The 20 µg vaccine may be administered to subjects 11 to 15 years of age inclusive, according to a 0- and 6-month schedule. However, in this case, protection against hepatitis B may not be obtained until after the second dose (see "Pharmacodynamics"). Therefore, this schedule should only be followed when there is a low risk of hepatitis B infection during the vaccination cycle and when it can be guaranteed that the two-dose vaccination course will be completed. If both conditions cannot be guaranteed (e.g., haemodialysis patients, travellers to endemic areas, and persons in close contact with infected subjects), the 3-dose schedule or accelerated 10 µg vaccine should be followed.

Patients with Renal Impairment, Including Hemodialysis Patients 16 Years and Older

The primary immunization schedule for patients with renal impairment, including patients with hemodialysis, is four double doses [4x(2 x 20 µg)] on the chosen day, one month, 2 months and 6 months from the date of the first dose. The immunisation programme should be adjusted to ensure that the hepatitis B antibody titer remains at or above the accepted level of protection of 10 IU/l.

Patients with Renal Impairment, Including Hemodialysis Patients Up to and Including 15 Years of Age, Including Newborns

Patients with renal impairment, including patients on hemodialysis, have a lower immune response to hepatitis B vaccines. The 0, 1, 2 and 12 month or 0, 1 and 6 month program of ***ENGERIX B*** 10 µg can be used. Based on experience in adults, vaccination with a higher dose of antigens may improve the immune response. Serological testing after vaccination should be considered. Additional doses of vaccine may be required to ensure a level of protection against hepatitis B of 10 IU/l.≥

Suspected or Known Exposure to HBV

In circumstances where exposure to HBV has recently occurred (e.g . stuck with a contaminated needle), the first dose of ***ENGERIX*** B may be administered simultaneously with immunoglobulina against hepatitis B (HBig), which should, however, be administered at a different location (see "Interactions"). The immunization schedule of 0, 1, 2 and 12 months is advised.

Newborns whose mothers are carriers of HBV

Immunisation with ENGERIX B (10 µg) of these infants should be initiated at birth, and one of the two immunisation programmes should be followed. The 0, 1, 2 and 12 month programme or the 0, 1 and 6 month programme may be used; However, the first program provides a faster immune response. Where available, HBig should be administered simultaneously with ***ENGERIX B*** at a different injection site as this may increase protective efficacy.

These immunization schedules can be adjusted to suit local immunization practices with respect to the recommended age of administration of other childhood vaccines.

Booster Dose

The need for a booster dose in healthy subjects who have received the complete primary vaccination series has not been established; However, some official vaccination programmes currently recommend a booster dose that must be respected.

For haemodialysis or immunocompromised patients, booster doses are recommended to ensure an antibody level 10 IU/l.

Data are available on the booster dose, which indicate that it is tolerated in the same way as the primary vaccination course.

Route of Administration

ENGERIX B should be injected intramuscularly into the deltoid region in adults and children or into the anterolateral thigh region in newborns, infants and young children. The vaccine can exceptionally be administered subcutaneously in patients with thrombocytopenia or coagulation disorders.

ENGERIX B should not be administered in the gluteal region or intradermally, as this may lead to a lower immune response.

Contraindications

ENGERIX B must not be administered to subjects with known hypersensitivity to any of the components of the vaccine, or to subjects who have shown signs of hypersensitivity after prior administration of ***ENGERIX-B***.

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

Warnings and Precautions

As with other vaccines, administration of ***ENGERIX B*** should be postponed in subjects suffering from severe acute febrile illness. However, the presence of a minor infection is not a contraindication to immunization.

Because of the long incubation period of hepatitis B, infection may be undiagnosed at the time of immunization. The vaccine may not prevent hepatitis B infection in such cases.

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

The immune response to hepatitis B vaccines is related to several factors, including older age, male sex, obesity, smoking and route of administration. Additional doses may be considered in subjects who may be less responsive to administration (e.g., over 40 years of age, etc.) of hepatitis B vaccines.

In patients with renal impairment, including haemodialysis patients, HIV-infected patients and persons with an impaired immune system, adequate anti-HBs antibody titers may not be obtained after the primary course of immunization and therefore such patients may require administration of additional doses of the vaccine (see section "Posology" - Patients with renal impairment, including patients on haemodialysis).

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

Syncope (fainting) may occur after, or even before, any vaccination as a psychogenic response to needle injection. It is important that proper procedures are in place to prevent fainting injuries.

ENGERIX B should not be applied to the gluteal region or intradermally, as this may result in a lower immune response.

Under no circumstances should ENGERIX B be administered intravascularly.

As with any vaccine, a protective immune response may not be elicited in all vaccinated persons (see "Pharmacodynamics").

When administering the primary vaccination series in preterm infants ≤ 28 weeks' gestation and especially in those with a prior history of respiratory immaturity, both the potential risk of apnoea and the need for respiratory monitoring for 48-72 hours should be considered. As the benefit of vaccination is high in this group of children, vaccination should not be prevented or delayed.

Interactions

Concurrent administration of ***ENGERIX B*** and a standard dose of HBig does not result in low titers of anti-HBs antibodies, as long as they are administered at different sites.

ENGERIX B can be administered concomitantly with DTP, DT and/or polio vaccines, if this is adequately aligned with the immunization schedule recommended by the country's Health Authorities.

ENGERIX B can also be given in conjunction with measles-mumps-rubella, *Haemophilus influenzae* type b, hepatitis A and BCG vaccines.

ENGERIX B can be administered concomitantly with the Human Papillomavirus (HPV) vaccine (***Cervarix***).

Administration of ***ENGERIX B*** at the same time as ***Cervarix*** has not shown any clinically relevant interference in the antibody response to HPV antigens. Geometric means of anti-HBs antibody concentrations were lower at co-administration, but the clinical significance of this observation is unknown because seroprotection indices were not affected. The proportion of subjects achieving anti-HBs levels ≥ 10 mIU/ml was 97.9% for concomitant vaccination and 100% for ***ENGERIX B*** alone.

Different injectable vaccines should always be given at different sites.

Interchangeability of Hepatitis B Vaccines

ENGERIX B can be used to complete a primary immunization schedule initiated with either plasma-derived or genetically engineered hepatitis B vaccines, or as a booster dose in subjects who have previously received a course of primary immunization with plasma-derived or genetically engineered hepatitis B vaccines.

Pregnancy and Lactation

Pregnancy

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

However, as with all inactivated viral vaccines, no harm to the fetus is expected. ***ENGERIX B*** should be used during pregnancy only when clearly necessary and the potential benefits outweigh the potential risks to the foetus.

Nursing

Adequate data on the use of the vaccine during lactation and adequate studies on animal reproduction are not available.

No contraindication has been established.

Effects on the Ability to Drive and Use Machines

The vaccine is unlikely to have any effect on the ability to drive and use machinery.

Adverse Reactions

The safety profile given below is based on data obtained from more than 5300 patients.

Frequencies are communicated as:

Very common(≥1/10)
Common(≥1/100 to <1/10)
Uncommon(≥1/1000 to <1/100)
Rare(≥1/10000 to <1/1000)
Very rare(<1/10000)

Type of Organ System	Frequency	Adverse Reactions
Clinical trials		
Haematological and lymphatic system disorders	Rare	Lymphadenopathy
Nutrition and metabolism disorders	Frequent	Loss of appetite
Psychiatric disorders	Very common	Irritability
Nervous system disorders	Frequent	Headache (very common with the 10 µg formulation), drowsiness
	Rare	Dizziness
	Rare	Paresthesia
Gastrointestinal disorders	Frequent	Gastrointestinal symptoms (such as nausea, vomiting, diarrhea, abdominal pain)
Skin and subcutaneous tissue disorders	Rare	Rash, pruritus, hives
Disorders of the musculoskeletal system and connective tissue	Rare	Myalgia
	Rare	Arthralgia
General disorders and administration site disorders	Very common	Pain and redness at the injection site, fatigue
	Frequent	Swelling at the injection site, malaise, injection site reaction (such as induration), fever (37.5°C)≥
	Rare	Flu-like symptoms
Post-marketing data		
Infections and infestations	Meningitis	
Haematological and lymphatic system disorders	Thrombocytopenia	
Immune disorders	Anaphylaxis, allergic reactions including anaphylactoid reactions and serum sickness-like reactions	
Nervous system disorders	Paralysis, convulsions, hypoesthesia, encephalitis, encephalopathy, neuropathy, neuritis	
Vascular disorders	Hypotension, vasculitis	
Skin and subcutaneous tissue disorders	Angioneurotic edema, lichen planus, erythema multiforme	
Disorders of the musculoskeletal system and connective tissue	Arthritis, muscle weakness	

In a comparative study in subjects aged 11 years to 15 years inclusive, the incidence of requested local and general symptoms reported after a two-dose schedule of ENGERIX B 20 µg was globally similar to the incidence reported after the conventional three-dose schedule of ***ENGERIX B*** 10 µg.

Overdose

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

Pharmacological properties

Pharmacodynamics

Pharmacotherapeutic group: Hepatitis B vaccine, ATC code J07BC01

ENGERIX B induces the production of specific humoral antibodies against HBsAg (anti-HBs antibodies). Anti-HBs antibody concentrations 10 IU/L correlate with protection against HBV infection.≥

Protective Efficacy

Groups at Risk

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

A protective efficacy of 95% was demonstrated in newborns of HBsAg-positive mothers, immunized according to schedules 0, 1, 2 and 12 months or 0, 1 and 6 months, without concomitant administration of HBIG at birth. However, simultaneous administration of HBIg and vaccine at birth increased protective efficacy to 98%.

Twenty years after primary vaccination during early childhood, newborns whose mothers were HBV carriers received an exposure dose of ***ENGERIX-B***. One month later, at least 93% of subjects (N=75) had an anamnestic response, demonstrating the development of immune memory.

Healthy Subjects

The attached table summarizes the levels of seroprotection (i.e. percentage of subjects with anti-HBs antibody concentrations ≥ 10 IU/l) obtained in clinical trials with different vaccination schedules mentioned in "Posology".

Population	Scheme	Seroprotection levels
Healthy subjects	0, 1, 6 months	per month 7: 96 %≥
	0, 1, 2 – 12 months	per month 1: 15 % per month 3: 89 % per month 13: 95.8 %
Healthy subjects 20 years and older	0, 7, 21 days – 12 months	on day 28: 65.2 % per month 2: 76 % per month 13: 98.6 %

The seroprotection (SP) indices obtained with the two different doses and authorized schedules in subjects 11 to 15 years of age inclusive, were evaluated up to 66 months after the first dose of 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 10 µg (0, 1, 6 month program)	55.8 %	87.6 %	98.2 %	96.9 %	92.5 %	94.7 %	91.4 %
ENGERIX B 20 µg (0.6 month program)	11.3 %	26.4 %	96.7 %	87.1 %	83.7 %	84.4 %	79.5 %

These data show that primary vaccination with ***ENGERIX B*** vaccine induces circulating anti-HBs antibodies that persist for at least 66 months. After completion of the primary vaccination series, no clinically significant difference in seroprotection indices is observed at any point in time when comparing the 2 vaccine groups. Indeed, all subjects in both vaccine groups (including subjects with anti-HBs antibody concentrations < 10 IU/L) received an exposure dose between 72 and 78 months after primary vaccination. One month after the exposure dose, all subjects had an anamnestic response to the exposure dose and were found to be seroprotected (i.e., with anti-HBs antibody concentrations of 10 IU/L). These data suggest that protection against hepatitis B could still occur through immune memory in all subjects who responded to primary vaccination but had lost the level of seroprotection of anti-HBs antibodies.≥

Repetition of Exposure in Healthy Subjects

One exposure dose was administered to subjects (N=284) aged 12 to 13 years vaccinated during early childhood with 3 doses of ***ENGERIX-B***. A month later, it was observed that 98.9% of the subjects were seroprotected.

Patients with Renal Insufficiency Including Patients Undergoing Hemodialysis

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

Patients with Type II Diabetes

Age (years)	Plan	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

In children 6 to 14 years of age, a significant reduction in the incidence of hepatocellular carcinoma has been observed after national hepatitis B vaccination in Taiwan. There was a significant decrease in the prevalence of hepatitis B antigen, whose persistence is an essential factor in the development of hepatocellular carcinoma.

Preclinical Safety Data

Appropriate safety tests have been carried out.

Pharmaceutical Characteristics

List of Excipients

Sodium chloride, sodium phosphate dihydrate, sodium diacid phosphate, water for injection.

Polysorbate 20 is present as a residue from the manufacturing process.

Shelf Life

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

Special Storage Precautions

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Keep the product in the original container to protect from light.

Stability data indicate that ***ENGERIX B*** is stable at temperatures up to 37ºC for 3 days or up to 25ºC for 7 days. This data is intended to guide healthcare professionals in case of a temporary temperature excursion only. The storage conditions are detailed on the packaging.

Nature and Content of the Container

ENGERIX B is available in glass vials or prefilled glass syringes.

The vials and prefilled syringes are made of type I neutral glass, which meets the requirements of the European Pharmacopoeia.

Not all presentations are available in all countries.

Incompatibilities

ENGERIX B must not be mixed with other vaccines.

Instructions for Use/Handling

When stored, the contents may present a fine white deposit with a transparent colorless supernatant. Before use, the vaccine should be shaken well to obtain a slightly opaque white suspension.

Prior to administration, the vaccine should be inspected visually for any foreign particles and/or abnormal physical appearance. If any of these abnormalities are observed, do not administer the vaccine.

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

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

Version GDSv15/IPIv11
Date of issue12 December 2019.

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