1 NAME OF THE MEDICINAL PRODUCT

Engerix B10MCG
Engerix B 20MCG

Suspension for injection
Hepatitis B (rDNA) vaccine (adsorbed) (HBV)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ENGERIX B 10MCG vaccine – 1 dose (0.5 ml) contains:
Purified hepatitis B 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

ENGERIX B 20MCG vaccine – 1 dose (1 ml) contains :
Purified hepatitis B 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

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Suspension for injection.
The suspension is turbid white.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Engerix B is indicated for active immunisation against hepatitis B virus infection (HBV) caused by all known subtypes in non immune subjects . The 20 µg dose vaccine in 1.0 ml suspension is intended for use in subjects 16 years of age and above. The 10 µg dose vaccine in 0.5 ml suspension is intended for use in subjects up to and including 15 years of age, including neonates. The categories within the population to be immunised are determined on the basis of official recommendations.

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.

4.2 Posology and method of administration

Posology

Dosage

The 20 µg dose vaccine in 1.0 ml suspension is intended for use in subjects 16 years of age and above. The 10 µg dose vaccine in 0.5 ml suspension is intended for use in subjects up to and including 15 years of age, including neonates.

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 below and section 5.1).

Primary Immunisation schedules

Subjects up to and including 15 years of age:

Two primary immunisation schedules can be recommended:

A 0, 1, 6 months schedule which gives optimal protection at month 7 and produces high antibody concentrations.

An accelerated schedule, with immunisation at 0, 1 and 2 months, which 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 antibody concentrations 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.

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

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 mIU/ml.

Neonates born of mothers who are HBV carriers:

The immunisation with Engerix B (10 mcg) of these neonates should start at birth, and two immunisation schedules have been 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 , hepatitis B immune globulins (HBIg) should be given simultaneously with Engerix B at a separate injection site as this may increase the protective efficacy

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

The 20 µg/1 ml 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). 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 cannot 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/0.5 ml vaccine should be used.

Subjects 16 years of age and above:

Two primary immunisation schedules can be recommended:

A 0, 1, 6 months schedule which gives optimal protection at month 7 and produces high antibody concentrations.

An accelerated schedule, with immunisation at 0, 1 and 2 months, which 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 antibody concentrations after the third dose are lower than those obtained with the 0, 1, 6 months schedule.

Subjects 18 years of age and above:

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.

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 concentrations remain equal to or higher than the accepted protective level of 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 HBIg which, however, must be given at a separate injection site (see section 4.5). The 0, 1, 2-12 months immunisation schedule should be advised.

Subjects up to and including 15 years of age:
These immunisation schedules may be adjusted to accommodate local immunisation practices with regard to the recommended age of administration of other childhood vaccines.

Subjects 16 years of age and above:
These immunisation schedules may be adjusted to accommodate local immunisation practices.

Booster dose

Current data do not support the need for booster vaccination among immunocompetent subjects who have responded to a full primary vaccination course .
However, in immunocompromised subjects (eg subjects with chronic renal failure, haemodialysis patients, HIV positive subjects), boosters should be administered to maintain anti-HBs antibody concentrations equal or higher than the accepted protective level of 10 mIU/ml. For these immunocompromised subjects, post-vaccination testing every 6-12 months is advised.

National recommendations on booster vaccination should be considered.

Interchangeability of hepatitis B vaccines

See section 4.5.

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.

4.3 Contra-indications

Engerix B should not be administered to subjects with known hypersensitivity to the active substances or to any of the excipients listed in section 6.1, or to subjects having shown signs of hypersensitivity after previous Engerix B administration.

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.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name of the administered product should be clearly recorded. is recommended to record the batch number as well.

Precautions for use

Syncope (fainting) can occur following, or even before any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. 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 all injectable vaccines, appropriate medical treatment should always be readily available in case of rare anaphylactic reactions following the administration of the vaccine.

Protection

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 viruses.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

A number of factors have been observed to reduce the immune response to hepatitis B vaccines. These factors include older age, male gender, obesity, smoking, route of administration and some chronic underlying diseases. Consideration should be given to serological testing of those subjects who may be at risk of not achieving seroprotection following a complete course of Engerix B. Additional doses may need to be considered for persons who do not respond or have a sub-optimal response to a course of vaccinations.

Special population

Patients with chronic liver disease or with HIV infection or hepatitis C carriers should not be precluded from vaccination against hepatitis B. The vaccine could be advised since HBV infection can be severe in these patients: the HB vaccination should thus be considered on a case by case basis by the physician. In HIV infected patients, as also in patients with renal insufficiency including patients undergoing haemodialysis and persons with an impaired immune system, adequate anti-HBs antibody concentrations may not be obtained after the primary immunisation course and such patients may therefore require administration of additional doses of vaccine.

Preterm infants

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunization 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.

Sodium content
This vaccine contains less than 1mmol sodium (23 mg) per dose , that is to say essentially "sodium free".

4.5 Interaction with other medicinal products 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 concentrations provided that they are administered at separate injection sites.

Engerix B can be given concomitantly with *Haemophilus influenzae* b, BCG, hepatitis A, polio, measles, mumps, rubella, diphtheria, tetanus and pertussis vaccines.

Engerix B can be given concomitantly with Human Papillomavirus (HPV) vaccine. 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 subjects reaching anti-HBs ≥ 10mIU/ml was 97.9% for concomitant vaccination and 100% for Engerix B alone.

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

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, if it is desired to administer a booster dose, it may be administered to subjects who have previously received a primary immunisation course with plasma-derived or with other genetically-engineered hepatitis B vaccines.

It may be expected that in patients receiving immunosuppressive treatment or patients with immunodeficiency, an adequate immune response may not be elicited (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

The effect of the HBsAg on foetal development has not been assessed.

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.

Breast-feeding

The effect on breastfed infants of the administration of Engerix B to their mothers has not been evaluated in clinical studies, as information concerning the excretion into the breast milk is not available.

No contraindication has been established.

Fertility

Engerix B has not been evaluated in fertility studies.

4.7 Effects on ability to drive and use machines

Engerix B has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety profile presented below is based on data from 5329 subjects followed in 23 studies.

The current formulation of Engerix B does not contain thiomersal (an organomercuric compound). The following undesirable effects have been

reported following the use of the thiomersal containing formulations as well as the thiomersal free formulation.

In one clinical study conducted in adults with the current formulation (thiomersal free formulation), the incidence of pain, redness, swelling, fatigue, gastro-enteritis, headache and fever was comparable to the incidence observed in the clinical studies conducted with former thiomersal containing vaccine formulations.

In one clinical study conducted in children with the current formulation (thiomersal free formulation), the incidence of pain, redness, swelling, drowsiness, irritability, loss of appetite and fever was comparable to the incidence observed in the clinical studies conducted with former thiomersal containing vaccine formulations.

Tabulated summary of adverse reactions

Frequencies per dose are defined as follows:

Very common: ≥1/10
Common: ≥1/100 to <1/10
Uncommon: ≥1/1000 to <1/100
Rare; ≥1/10,000 to <1/1000
Very rare: <1/10,000

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	Very common	Headache (paediatric use)
	Common	Drowsiness, headache (adult use)
	Uncommon	Dizziness
	Rare	Paraesthesia
Gastrointestinal disorders	Common	Gastrointestinal symptoms (such as nausea, vomiting, diarrhoea, abdominal pain)
Skin and subcutaneous tissue disorders	Rare	Urticaria, pruritus, rash
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	Fever (≥37.5°C), malaise, swelling at injection site, injection site reaction (such as induration)
	Uncommon	Influenza-like illness
Post-marketing surveillance		
Infections and infestations	Not known (cannot be estimated from the available data)	Meningitis
Blood and lymphatic system disorders	Not known (cannot be estimated from the available data)	Thrombocytopenia
Immune system disorders	Not known (cannot be estimated from the available data)	Anaphylaxis, allergic reactions including anaphylactoid reactions and mimicking serum sickness
Nervous system disorders	Not known (cannot be estimated from the available data)	Encephalitis, encephalopathy, convulsions, paralysis, neuritis (including Guillain-Barré syndrome, optic neuritis and multiple sclerosis), neuropathy, hypoaesthesia
Vascular disorders	Not known (cannot be estimated from the available data)	Vasculitis, hypotension
Respiratory thoracic and mediastinal disorders	Not known (cannot be estimated from the available data)	Apnoea in very premature infants (≤ 28 weeks of gestation) (see section 4.4)
Skin and subcutaneous tissue disorders	Not known (cannot be estimated from the	Erythema multiforme, angioneurotic oedema, lichen planus

	available data)	
Musculoskeletal and connective tissue disorders	Not known (cannot be estimated from the available data)	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/1 ml was similar overall to that reported after the standard three-dose regimen of Engerix B 10 µg/0.5 ml.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il.
Additionally, you should also report to GSK Israel (il.safety@gsk.com)

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

Pharmacotherapeutic group: Hepatitis B vaccine, ATC code: J07BC01

Mechanism of action

Engerix B induces specific humoral antibodies against HBsAg (anti-HBs antibodies). Anti-HBs antibody concentrations ≥ m10 IU/ml correlate with protection to HBV infection.

Pharmacodynamic effects
Subjects with increased risk of HBV exposure In field studies, a protective efficacy between 95% and 100% was demonstrated in neonates, children and adults at risk.

In healthy subjects in high risk area, one month after the last vaccine dose, a 95% protective efficacy (serum anti HBs IgG ≥ 10 mIU/ml) was demonstrated in neonates

of HBeAg positive mothers, immunised according to the 0, 1, 2 and 12 month or 0, 1 and 6 month schedules without concomitant administration of hepatitis B immunoglobulin (HBIg) at birth. However, simultaneous administration of HBIg and vaccine at birth increased the protective efficacy to 98%.

Neonates born to mothers who were hepatitis B virus carriers (HBsAg positive with or without HBeAg) and who did not receive HBIg at birth received a challenge dose of Engerix B twenty years after primary vaccination (3-dose or 4-dose schedules).
The seroprotection rate before and after the challenge dose has been evaluated:

Seroprotection rate	**N**	**n**	**%**	**95% CI**	
				LL	**UL**
Pre-challenge	72	39	54.2	42.0	66.0
Post-challenge	75	74	98.7	92.8	100

N = number of subjects with available results

n = number of subjects with concentration equal to or above 10mIU/ml

% = percentage of subjects with concentration equal to or above 10mIU/ml

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

PRE = at the time of administration of the challenge dose / POST = one month after challenge dose

The anamnestic response according to the pre-challenge serostatus was also evaluated:

	Anamnestic response				
				95% CI	
Pre-challenge status	**N**	**n**	**%**	**LL**	**UL**
Subjects < 10 mIU/ml	33	31	93.9	79.8	99.3
Subjects ≥ 10 mIU/ml	39	39	100	91.0	100
Total	72	70	97.2	90.3	99.7

Stratification based on last available time point prior to challenge dose:

- subjects <10 mIU/ml = subjects with antibody concentration <10 mIU/ml prior to the challenge dose
- subjects ≥10 mIU/ml = subjects with antibody concentration ≥10 mIU/ml prior to the challenge dose

Anamnestic response is defined as:

- anti-HBs antibody concentrations ≥ 10 mIU/ml in subjects who were seronegative before the challenge dose, or
- an increase in anti-HBs antibody concentrations by at least 4-fold in subjects who were seropositive before the challenge dose.

N = number of subjects with both pre- and post-vaccination results available

n = number of responders

% = percentage of responders

95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit

<u>General paediatric population:</u>

- Seroprotection rates in healthy subjects up to and including 15 years of age:

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:

Population	Schedule	Seroprotection rate
Healthy subjects up to and including 15 years of age	0, 1, 6 months	at month 7: ≥ 96 %
	0, 1, 2 – 12 months	at month 1: 15 % at month 3: 89 % at month 13: 95.8 %

The data in the above table were generated with thiomersal containing vaccines. Two additional clinical studies conducted with the current formulation of Engerix B, which does not contain thiomersal, among healthy infants and adults, elicit similar seroprotection rates as compared to former thiomersal containing formulations of Engerix B.

- Persistence of immune response in healthy subjects from 11 years up to and including 15 years of age:

The long-term immune response was assessed in a clinical trial in subjects from 11 years up to and including 15 years of age at the time of primary vaccination. Seroprotection rates (i.e. percentages of subjects with anti-HBs antibody concentrations ≥ 10 IU/l) with the two different dosages and schedules were evaluated up to 66 months after the first dose of the primary vaccination and are presented in the table below (ATP cohort for efficacy):

	Months after the first vaccine dose:						
Vaccination schedule	**2**	**6**	**7**	**30**	**42**	**54**	**66**
	Seroprotection rate						
Engerix B 10µg (0, 1, 6 months)	55.8%	87.6%	98.2%*	96.9%	92.5%	94.7%	91.4%
Engerix B 20µg (0, 6 months)	11.3%	26.4%	96.7%*	87.1%	83.7%	84.4%	79.5%

* At month 7, 97.3% and 88.8% of subjects aged 11 to 15 years vaccinated with Engerix B 10 µg/0.5 ml (0, 1, 6 months schedule) or Engerix B 20 µg/1 ml (0, 6 months schedule) respectively developed anti-HBs antibody concentrations ≥ 100mIU/ml. Geometric Mean Concentrations (GMC) were 7238 mIU/ml and 2739 mIU/ml respectively.

All subjects in both vaccine groups (N=74) received a challenge dose 72 to 78 months after primary vaccination. One month later, all subjects mounted an

anamnestic response with a GMC increase of 108 and 95 fold from the pre to the post challenge time points in the 2-dose and 3-dose priming schedule respectively and were shown to be seroprotected. These data suggest that immune memory was induced in all subjects who responded to primary vaccination, even among those who had lost seroprotection at Month 66.

- Healthy subjects 16 years of age and above:

The table below summarizes seroprotection rates (i.e. percentages of subjects with anti-HBs antibody concentrations ≥ 10 IU/l) obtained in clinical studies with Engerix B 20µg, given according to the different schedules mentioned in Section 4.2:

Population	Schedule	Seroprotection rate
Healthy subjects 16 years of age and above	0, 1, 6 months	at month 7: ≥ 96 %
	0, 1, 2 – 12 months	at month 1: 15 % at month 3: 89 % at month 13: 95.8 %
Healthy subjects 18 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 data in the above table were generated with thiomersal containing vaccines. Two additional clinical studies conducted with the current formulation of Engerix B, which contains no thiomersal, among healthy infants and adults, elicit similar seroprotection rates as compared to former thiomersal containing formulations of Engerix B.

- Persistence of immune response and rechallenge of subjects aged 15 to 16 years, 14 years after primary vaccination:

Seroprotection rates before and after a challenge dose have been evaluated in subjects aged 15 to 16 years who were vaccinated with 3 doses of ENGERIX B during the first two years of life:

Seroprotection rate	**N**	**n**	**%**	**95% CI**	
				LL	**UL**
Pre-challenge	292	191	65.4	59.6	70.9
Post-challenge	292	286	97.9	95.6	99.2

N = number of subjects with available results

n = number of subjects with concentration equal to or above 10mIU/ml

% = percentage of subjects with concentration equal to or above 10mIU/ml

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

PRE = prior to the challenge dose / POST= one month after challenge dose

Anamnestic response has been evaluated according to pre-challenge serostatus in subjects aged 15 to 16 years who were vaccinated with 3 doses of ENGERIX B during the first two years of life:

	Anamnestic response				
				95% CI	
Pre-challenge status	**N**	**n**	**%**	**LL**	**UL**
Subjects < 10 mIU/ml	101	95	94.1	87.5	97.8
Subjects ≥ 10 mIU/ml	190	187	98.4	95.5	99.7
Total	291	282	96.9	94.2	98.6

Stratification based on last available time point prior to booster dose:

- subjects <10 mIU/ml = subjects with antibody concentration <10 mIU/ml prior to the challenge dose
- subjects ≥10 mIU/ml = subjects with antibody concentration ≥10 mIU/ml prior to the challenge dose

Anamnestic response is defined as:

- anti-HBs antibody concentrations ≥ 10 mIU/ml in subjects who were seronegative before the challenge dose, or
- an increase in anti-HBs antibody concentrations by at least 4-fold in subjects who were seropositive before the challenge dose.

N = number of subjects with both pre- and post-vaccination results available

n = number of responders

% = percentage of responders

95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit

The primary endpoint of the study, defined as the percentage of subjects with anti-HBs antibody concentrations ≥ 100 mIU/mL one month after the challenge dose, was calculated at 90.8% (95% CI: 86.8; 93.8). The anti-HBs antibody GMC increased by 156-fold (from 26.5 to 4134.9 mIU/mL) as a response to the challenge dose.

Similar data with respect to seroprotection rates and anamnestic response were obtained in subjects (N=279) aged 12 - 13 years.

- Patients with renal insufficiency including patients undergoing haemodialysis:

The seroprotection rates in subjects 16 years of age and above with renal insufficiency including patient undergoing haemodialysis were evaluated 3 and 7 months after the first dose of the primary vaccination and are presented in the Table below:

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:

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 the Table below:

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 clear link has been demonstrated between hepatitis B infection and the occurrence of hepatocellular carcinoma (HCC). The prevention of hepatitis B by vaccination results in a reduction of the incidence of HCC, as has been observed in Taiwan in children aged 6-14 years.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

The preclinical safety data satisfy the requirements of the WHO.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Disodium phosphate dihydrate

Sodium dihydrogen phosphate dihydrate
Water for injections

For adsorbent, see section 2.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the vaccine is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).
Do not freeze; Do not use if the vaccine has been frozen.
Store in the original package, in order to protect from light

6.5 Nature and contents of container

Engerix B10MCG
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.

Pack sizes of 1,10,25 and 50, with or without needles.

0.5 ml of suspension in a vial (type I glass) with a stopper (butyl rubber).

Pack sizes of 1, 10, 25,50 and 100.

The tip cap and rubber plunger stopper of the pre-filled syringe and the stopper of the vial are made with synthetic rubber.

Engerix B20MCG
1 ml of suspension in a pre-filled syringe (type I glass) with a plunger stopper (butyl rubber) and with a rubber tip cap.

Pack sizes of 1, 10 , 25, 50 and 100, with or without needles.

1 ml of suspension in a vial (type I glass) with a stopper (butyl rubber).

Pack sizes of 1, 10, 25, 50 and 100.

The tip cap and rubber plunger stopper of the pre-filled syringe and the stopper of the vial are made with synthetic rubber.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

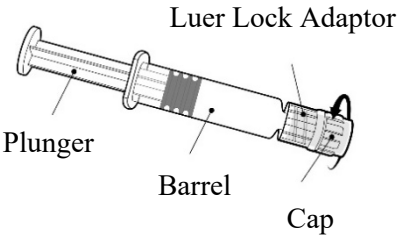
Shake before use.

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

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.

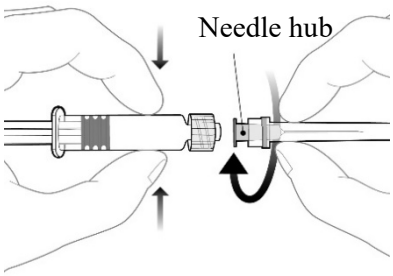
The entire contents of a mono-dose container must be withdrawn and should be used immediately.

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.

Disposal

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

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals S.A., Rixensart, Belgium

8 LICENSE HOLDER

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva

9 LICENSE NUMBER

Engerix B 20 mcg	20MCG/ml	035-60-25829
Engerix B10 mcg	10mcg/0.50ml	055-06-26267

Revised on December 2023 according to MOHs guidelines

Eng B Dr V12

תאריך עדכון העלון	פרקים שהתעדכנו	אסמכתא לעדכון	הערות
12/04/2018	4.1, 4.2 **- section 4.**1 Update of indication section in line with the UK indication -**section 4.**2 Update of 2 dose regimen from 10-15 years to 11-15 years in line with the UK	UK SPC (4/2017)	
05/2019		UK SPC (4/2017) UK PIL (10/2017)	לאחר אישור הועדה המייעצת של משרד הבריאות, נשלחות הצעות עלונים עדכניות על פי בקשת משרד הבריאות
11/2020	2, 4.7, 6.6	EU mutual recognition 28 August 2020	עד כה עלון הרפרנס עבור התכשיר היה עלון UK. בעקבות הברקסיט נתבקשנו על ידי החברה להחליף את מדינת הרפרנס. הוחלט לעבור לעלון EU mutual recognition שזהה בתוכנו לעלון UK הנוכחי.

			ההבדל היחיד הוא שב-UK יש עלון לרופא אחד בו איחדו את המידע לעלון אחד משותף עבור שני המינונים, וה-EU mutual recognition יצר עלון לרופא נפרד עבור שני מינון. התוכן של העלונים בסופו של דבר זהה בין UK ל-EU . לגבי העלונים לצרכן, גם ב-UK וגם ב-EU העלונים מפוצלים, וזהים בתוכנם בין הרשויות. אצלינו קיים עלון לרופא ולצרכן משותף לשני המינונים והוחלט להשאירו כך, משותף. העידכון לעלון נעשה בהתאם לעדכונים שהיו בעלון EU mutual recognition האחרון מאוגוסט 2020. בעדכון העלון לרופא היה גם עדכון במידע היציבות לאחר פתיחה בסעיף 6.4 . ביקשנו להוסיף את המידע בנספח לתעודת האיכות בתהליך החידוש שכרגע בעיצומו. ברגע שהמידע יאושר בנספח לתעודת האיכות נעדכן גם את העלון. בסעיף 2 בוצע עדכון לאופן רישום החומר הפעיל בהתאם למאושר ברישיון.
14/10/2021	6.4	עידכון עקב סיום תהליך חידוש ועדכון בנספח לתעודת איכות בתנאי האיחסון (במקום לזרוק אם קפא, לא להשתמש אם קפא)	עידכון עקב סיום תהליך חידוש ועדכון בנספח לתעודת איכות בתנאי האיחסון (במקום לזרוק אם קפא, לא להשתמש אם קפא) נשלח במסלול של שינוי באישור רוקח ממונה
24/02/2022	4.4, 6.3	עלון אירופאי לרופא עודכן בהתאם ל EU excipients guideline ובנוסף הוסף מידע על Traceability	העידכון בעלון לרופא בלבד. אין צורך בעדכון בעלון לצרכן.
23/04/2023	4.2, 4.4, 4.5,5	עודכן בהתאם לעלון Engerix B10mcg EU SmPC from Mar 2023	עידכון לעלון לרופא בלבד
12/2023	6.5 6.6	EU SmPC 26/04/2023	עידכון הוראות שימוש. עידכון עלון בהמשך לתיק שינוי של ה-ONE PFS