PRODUCT MONOGRAPH

ENGERIX®-B

Hepatitis B vaccine (recombinant)

Available as: 0.5 mL and 1.0 mL suspensions
of 20 µg/mL hepatitis B surface antigen

Injectable vaccine for active immunization against infection caused by all known subtypes of hepatitis B virus

GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
L5N 6L4

Control No: 165871 Date of Approval: August 9, 2013

Table of Contents

ENGERIX®-B

Hepatitis B vaccine (recombinant)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular Injection	Injection 0.5 mL and 1.0 mL suspensions of 20 µg/mL hepatitis B surface antigen	Aluminum hydroxide. The 0.5 mL and 1.0 mL formulations are thimerosal free. *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

DESCRIPTION

The hepatitis B virus induces a severe form of viral hepatitis. Other causative agents are hepatitis A virus, and the non-A, non-B hepatitis viruses. Hepatitis D virus, a defective virus requiring the "keeper function" of the hepatitis B virus, occurs either as a co-infection or super-infection in a HBsAg carrier.

Transmission of the virus occurs through percutaneous contact with contaminated blood, serum or plasma. Infection may also occur by the exposure of mucous surfaces, or intact or damaged skin to other body fluids such as saliva, mucosal secretions and semen.

There is no specific treatment for hepatitis. The incubation period may be as long as 6 months, followed by a very complex clinical course of an acute or chronic nature, often leading to hospitalization.

Viral hepatitis caused by hepatitis B virus is a major worldwide health problem, though the incidence and epidemiology vary widely among geographical areas and population subgroups.

In Canada, the United States and Northern Europe, 4% to 6% of the population are infected during their lifetime (mostly young adults); between 5% and 10% of infections lead to persistent viremia (carrier state). Certain population subgroups in these areas, however, are at high risk (see INDICATIONS AND CLINICAL USE).

In Asia, infection often occurs early in life, leading to a hepatitis B marker prevalence of more than 70% in the general population and a carrier rate of up to 20%.

It is estimated that the reservoir of persistent hepatitis B surface antigen carriers amounts to 350 million people worldwide. Carriers are at a high risk of developing chronic liver disease which may lead to cirrhosis or primary hepatocellular carcinoma. A significant reduction in the incidence of hepatocellular carcinoma has been observed in children aged 6 to14 years following a nationwide hepatitis B vaccination in Taiwan. This resulted from a significant decline in the prevalence of hepatitis B antigen, the persistence of which is an essential factor in the development of hepatocellular carcinoma.

Vaccination against hepatitis B is expected in the long term to reduce the overall incidence of both hepatitis B and the chronic complications such as chronic active hepatitis and cirrhosis.

INDICATIONS AND CLINICAL USE

ENGERIX®-B (hepatitis B vaccine (recombinant)) is indicated for:

- active immunization against hepatitis B virus infection.

The vaccine will not protect against infection caused by hepatitis A and non-A non-B hepatitis viruses. As hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection or carrier state, it can be expected that hepatitis D will also be prevented by vaccination with ENGERIX®-B.

The vaccine can be administered at any age from birth onwards. It may be used to start a primary course of vaccination or as a booster dose. It may also be used to complete a primary course of vaccination started with plasma-derived or yeast-derived vaccines or as a booster dose in subjects who have previously received a primary course of vaccination with plasma-derived or yeast-derived vaccines.

In areas of low prevalence of hepatitis B, vaccination is strongly recommended in subjects who are at increased risk of infection. These include the following groups:

- *Health professionals:*
  - physicians and surgeons;
  - oral surgeons and dentists;
  - nurses, dental nurses, dental hygienists, podiatrists;
  - IV teams and operating room personnel;
  - paramedical personnel in close contact with patients;
  - staff in hemodialysis, nephrology, hepatology, hematology and oncology units;
  - laboratory personnel handling blood and other clinical specimens;
  - blood bank and plasma fractionation workers;
  - pathologists and morgue attendants;
  - cleaning staff who handle waste in hospitals;
  - emergency and first aid workers;

- ambulance staff;
- dental, medical and nursing students.

- *Patients:*
  - patients receiving frequent blood transfusion or clotting factor concentrates, such as those in oncology units and those with thalassemia, sickle-cell anemia, cirrhosis, hemophilia, etc.;
  - patients on hemodialysis.

- *Personnel and residents of institutions:*
  - persons with frequent and/or close contacts with high-risk groups;
  - prisoners and prison staff;
  - residents and staff of institutions for the developmentally challenged (those who are in contact with aggressive biting residents being at highest risk).

- *Persons at increased risk due to their sexual practices:*
  - males having sexual contact with other males;
  - others with multiple sexual partners or with a recent history of sexually transmitted disease.

- *Persons who use injectable drugs illicitly.*

- *Travellers to areas of high endemicity and their close contacts.*

- *Household contacts of any of the above groups and of patients with acute or chronic hepatitis B infection.*

- *Infants born of HBsAg-positive mothers.*

- *Chronic Liver Disease (CLD):*
  - subjects with chronic liver disease;
  - subjects at risk of developing CLD (e.g. Hepatitis C virus carriers, persons who abuse alcohol).

- *Others:*
  - police;
  - fire fighters;
  - armed forces personnel;
  - morticians and embalmers;
  - those who through their work or personal lifestyle may be exposed to the hepatitis B virus.

In areas of both low and high prevalence, vaccination should be offered to all young children and neonates at risk, as well as to adult high risk groups.

CONTRAINDICATIONS

ENGERIX®-B (hepatitis B vaccine (recombinant)):

- should not be administered to subjects with known hypersensitivity to any component of the vaccine or having shown signs of hypersensitivity after previous ENGERIX®-B administration. For a complete listing of the components, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.

- should not be administered to subjects with severe febrile infections as for any vaccine. However, the presence of a minor infection does not contraindicate vaccination.

Human immunodeficiency virus (HIV) infection is not considered as a contraindication for hepatitis B vaccination (see WARNINGS AND PRECAUTIONS).

WARNINGS AND PRECAUTIONS

General

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

ENGERIX®-B (hepatitis B vaccine (recombinant)) should not be administered in the gluteal region or intradermally since these routes of administration may result in a lower immune response. Intradermal administration may also result in severe local reactions.

The vaccine must never be administered intravenously.

A new sterile syringe and a new sterile needle should always be used to prevent the transmission from one subject to another of infectious agents, such as the hepatitis B virus, non-A, non-B hepatitis virus or the human immunodeficiency virus (HIV).

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.

Hepatic

Patients with chronic liver disease or hepatitis C carriers should not be precluded from vaccination against hepatitis B. The vaccine could be advised since hepatitis B virus (HBV) infection can be severe in these patients. The HBV vaccination should be considered on a case by case basis by the physician.

Immune

Because hepatitis B has a long incubation period it is possible that there may be latent infection at the time of vaccination. ENGERIX®-B may not prevent hepatitis B in such cases.

Patients who develop symptoms suggestive of hypersensitivity after an injection should not receive further injections of ENGERIX®-B (see CONTRAINDICATIONS).

The immune response to hepatitis B vaccine 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 vaccine (e.g. more than 40 years of age, etc.), additional doses may be considered.

Patients with HIV infection should not be precluded from vaccination against hepatitis B. The vaccine could be advised since hepatitis B virus (HBV) infection can be severe in these patients. The HBV vaccination should be considered on a case by case basis by the physician.

In HIV infected patients and persons with an impaired immune system, adequate anti-HBs antibody titers may not be obtained after the primary immunization course and such patients may therefore require administration of additional doses of vaccine (see DOSAGE AND ADMINISTRATION).

Renal

In hemodialysis patients, adequate anti-HBs antibody titers may not be obtained after the primary immunization course and such patients may therefore require administration of additional doses of vaccine (see DOSAGE AND ADMINISTRATION).

Special Populations

Pregnant Women: The effect of the antigen (HBsAg) on fetal development is unknown as adequate studies with ENGERIX®-B have not been conducted during pregnancy and adequate animal reproduction studies are not available. However, vaccination of a pregnant woman may be considered in order to prevent hepatitis B in high-risk situations.

Nursing Women: Adequate human data on use during lactation and adequate animal reproduction studies are not available. It is not known whether ENGERIX®-B is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ENGERIX®-B is administered to a nursing woman.

Pediatrics: The potential risk of apnoea and the need for respiratory monitoring for 48-72 hours 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.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety profile presented below is based on data from more than 5300 subjects.

Frequency	Adverse Event	System/Organ Class
Very Common: ≥ 10%	irritability	Psychiatric disorders
	headache (with 10 µg formulation)	Nervous system disorders
	pain and redness at the injection site, fatigue	General disorders and administration site conditions
Common: ≥ 1% and < 10%	appetite loss	Metabolism and nutrition disorders
	headache (with 20 µg formulation), drowsiness	Nervous system disorders
	gastrointestinal symptoms (such as nausea, vomiting, diarrhea, abdominal pain)	Gastrointestinal disorders
	swelling at the injection site, malaise, injection site reaction (such as induration), fever (≥37.5°C)	General disorders and administration site conditions
Uncommon: ≥ 0.1% and < 1%	dizziness	Nervous system disorders
	myalgia	Musculoskeletal and connective tissue disorders
	Influenza-like illness	General disorders and administration site conditions
Rare: ≥ 0.01% and < 0.1%	lymphadenopathy	Blood and lymphatic system disorders
	paraesthesia	Nervous system disorders
	rash, pruritus, urticaria	Skin and subcutaneous tissue disorders
	arthralgia	Musculoskeletal and connective tissue disorders

Post-Market Adverse Drug Reactions

The following adverse reactions have been reported with ENGERIX®-B.

Infections and infestations	Meningitis
Blood and lymphatic system disorder	Thrombocytopenia
Immune system disorders	Anaphylaxis, allergic reactions including anaphylactoid reactions and mimicking serum sickness
Nervous system disorders	Encephalopathy, encephalitis, neuritis, neuropathy, paralysis, convulsions, hypoaesthesia, multiple sclerosis*, optic neuritis, Guillain-Barre syndrome*
Vascular disorders	Hypotension, vasculitis, syncope
Skin and subcutaneous tissue disorders	Angioneurotic oedema, lichen planus, erythema multiforme
Musculoskeletal and connective tissue disorders	Arthritis, muscular weakness
Hepatic system disorders	Abnormal liver function tests
Respiratory system disorders	Bronchospasm

* "A number of studies have demonstrated no link between hepatitis B vaccine and multiple sclerosis, Guillain-Barre syndrome (GBS), …." (Canadian Immunization Guide 7th Edition 2006).

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 (hepatitis B vaccine (recombinant)) 20 µg was similar overall to that reported after the standard three-dose regimen of ENGERIX®-B 10 µg.

DRUG INTERACTIONS

ENGERIX®-B 10 µg/0.5mL dose may be administered concomitantly with the Human Papillomavirus vaccine (CERVARIX®). Administration of the 10 µg/0.5mL dose of ENGERIX®-B at the same time as CERVARIX® has shown no clinically relevant interference in the antibody response to the HPV16/18 antigens in CERVARIX®. Anti-hepatitis B geometric mean antibody titers were lower on co-administration of the vaccines but the percentage of subjects reaching anti-HB ≥ 10mIU/ml (seroprotection) was 97.8% for concomitant vaccination with ENGERIX®-B, and 100% for ENGERIX®-B given alone. The clinical relevance of the reduced antibody titre and the risk of a substantially reduced immune response to hepatitis B if doses of hepatitis B vaccine are missed are not known.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

For optimal protection the recommended Standard schedule for ENGERIX®-B (hepatitis B vaccine [recombinant]) is three doses administered at 0, 1 and 6 months.

For more Accelerated protection a three dose schedule (0, 1, 2 with a booster dose at month 12) results in the development of protective anti-HBs titres by 3 months. The booster dose (at 12 months) is required to maintain prolonged protective anti-HBs titres.

In circumstances in adults, where a very 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 booster dose should be administered 12 months after the first dose for longer term protection (see ACTION AND CLINICAL PHARMACOLOGY for seroconversion rates).

Dosage:

Adults 20 years and over:

A dose of 20 µg of antigen protein in 1.0 mL suspension is recommended for adults.

Neonates, infants, children and adolescents up to 19 years inclusive:

A dose of 10 µg of antigen protein in 0.5 mL suspension is recommended for neonates, infants, children and adolescents up to 19 years of age inclusive.

When the pediatric presentation is not available, other presentations may be used for withdrawing the appropriate dose.

Alternative Dosing (Adolescents 11-15 years)
A dose of 20 μg of antigen protein in 1.0 mL suspension may be administered in subjects from 11 years up to and including 15 years of age according to a 0, 6 months schedule if low compliance is anticipated (see ACTION AND CLINICAL PHARMACOLOGY).

Patients with renal insufficiency including patients undergoing hemodialysis 16 years of age and above:
The primary immunization schedule for patients with renal insufficiency including patients undergoing hemodialysis 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 immunization schedule should be adapted in order to ensure that the anti-HBs antibody titre remains above the accepted protective level of 10 IU/L.

Patients with renal insufficiency including patients undergoing hemodialysis up to and including 15 years of age:
Patients with renal insufficiency including patients undergoing hemodialysis have a reduced immune response to hepatitis B vaccine. Consideration should be given to serological testing following a complete course of ENGERIX®-B. Additional doses of vaccine may need to be considered to ensure a protective anti-HBs level >10 IU/L.

Immunocompromised patients:
A 2.0 mL (2 x 1.0 mL) dose of ENGERIX®-B 40 μg (2 x 20 μg) is recommended (see ACTION AND CLINICAL PHARMACOLOGY).

ENGERIX®-B can effectively boost anti-HBs responses initially elicited by either plasma-derived or yeast-derived vaccines.

For individuals in whom a primary vaccination schedule has been initiated with a plasma-derived vaccine, dosing may be continued with ENGERIX®-B.

Table 1: Dosage and Administration

Vaccination Schedule	Age	Dose/Volume (µg/mL)	Dosing Schedule (months)				
			0	1	2	6	12
Standard (3 dose)	≥20 years of age	20/1.0	x	x		x	
Standard	0 - 19 years of age	10/0.5	x	x		x	
Accelerated	≥ 20 years of age	20/1.0	x	x	x		x
	0 - 19 years of age	10/0.5	x	x	x		x
Rapid	≥ 20 years of age	20/1.0	0,7d, 21d xxx d=days				x
Alternative	11 - 15 years of age	20/1.0	x			x	

Booster Doses
Routine booster vaccinations in immunocompetent persons are not recommended since protection has been shown to last for at least 15 years. Studies of long term protective efficacy, however, will determine whether booster doses of vaccine are ever needed. It is important to recognize that absence of detectable anti-HBs does not mean lack of protection, because immune memory persists. Booster doses in this situation are not indicated.

Immunocompromised persons often respond suboptimally to the vaccine. Subsequent hepatitis B virus (HBV) exposures in these individuals can result in disease or the carrier state. Therefore, booster doses may be necessary in this population. The optimal timing of booster doses for immunocompromised individuals who are at continued risk of HBV exposure is not known and should be based on the severity of the compromised state and annual monitoring for the presence of anti-HBs.

Administration
Check the expiry date of the vaccine carefully. Do not use vaccine beyond its expiry date.

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 resuspend the sediment of fine white particles of adjuvant (aluminium hydroxide) which settles during storage and to obtain a slightly opaque, white suspension. Discard if the content appears otherwise.

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

Clean the skin at the site of injection with a suitable antiseptic and dry with a piece of dry sterile cotton. Disinfect the rubber stopper with antiseptic; wipe it dry with a dry, sterile cotton swab; then using a sterile needle, withdraw the vaccine from the vial into a sterile syringe.

ENGERIX®-B should be injected intramuscularly. In adults the injection should be given in the deltoid region. In neonates and infants it may be preferable to inject ENGERIX®-B in the anterolateral thigh because of the small size of their deltoid muscle. In special circumstances the vaccine may be administered subcutaneously in patients with severe bleeding tendencies (e.g., hemophiliacs).

ENGERIX®-B must not be given intravenously or intradermally.
ENGERIX®-B may be administered simultaneously with hepatitis B immunoglobulin (HBIG); however it must be administered at a separate injection site.

OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional Poison Control Centre

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

ENGERIX®-B induces specific humoral antibodies against HBsAg (anti-HBs antibodies). It is generally accepted that an anti-HBs titre greater than 10 IU/L correlates with protection against hepatitis B virus infection. More than 90% of healthy adults, children and neonates developed protective anti-HBs titres one month after completing a primary vaccination schedule of ENGERIX®-B (hepatitis B vaccine (recombinant)).

STORAGE AND STABILITY

ENGERIX®-B (hepatitis B vaccine (recombinant)) should be shipped under refrigeration and stored at 2 to 8°C. **Do not freeze.** Vaccine which has been frozen is no longer potent and should be discarded.

The single dose container does not contain a preservative. The entire contents of a single dose container must be withdrawn and should be used immediately upon withdrawal.

For multidose vaccine, discard unused portion no longer than 24 hours after first puncture.

When stored at 2 to 8°C, ENGERIX®-B is stable until the expiry date shown on the label.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ENGERIX®-B (hepatitis B vaccine (recombinant)) is available in two size formats:

- 0.5 mL single pediatric dose vial containing 10 µg of hepatitis B surface antigen per vial in a carton with Prescribing Information leaflet.

- 1.0 mL adult dose vial containing 20 µg of hepatitis B surface antigen per vial in a carton with Prescribing Information leaflet.

Each 1.0 mL adolescent/adult dose of vaccine contains 20 µg of hepatitis B surface antigen adsorbed onto 0.5 mg of Al^{3+} as aluminum hydroxide. Each 0.5 mL pediatric dose contains 10 µg of hepatitis B surface antigen adsorbed onto 0.25 mg of Al^{3+} as aluminum hydroxide. The ENGERIX®-B 0.5 mL and 1.0 mL formulations are thimerosal free.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	hepatitis B vaccine (recombinant)
Physicochemical properties:	The active ingredient is the hepatitis B surface antigen (HBsAg) produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology. It is adsorbed on aluminum hydroxide, hydrated. The HBsAg expressed in yeast cells is purified by several physicochemical 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 HBV component is formulated in phosphate buffered saline.

Product Characteristics

The vaccine is a slightly opaque, white, sterile suspension. A slow settling of the white aluminum hydroxide may occur during storage leaving a clear colourless supernatant liquid.

CLINICAL TRIALS

Clinical data supports the following four dosing schedules (see DOSAGE AND ADMINISTRATION):

- The 3-dose Standard schedule is 0, 1 and 6 months.
- The 3-dose Accelerated schedule is 0, 1, 2 with a booster dose at 12 months.
- In situations where very rapid protection is required, a Rapid schedule of 0, 7 and 21 days with a booster dose at 12 months may be used.
- The 2-dose Alternative schedule is 0 and 6 months for adolescents 11 to 15 years of age.

Study Results

Immunogenicity in Healthy Adults and Adolescents

The table below summarizes seroprotection rates (i.e. percentages of subjects with anti-HBs antibody titer ≥ 10 IU/L) obtained in clinical studies with the different schedules mentioned in the DOSAGE AND ADMINISTRATION section.

Table 2: Seroprotection Rates

Vaccination Schedule	Population	Dosing Schedule	Seroprotection Rate
Standard	Healthy subjects	0, 1, 6 months	at month 7: ≥ 96%
Accelerated	Healthy subjects	0, 1, 2 - 12 months	at month 1: 15% at month 3: 89% at month 13: 95.8%
Rapid	Healthy Adults	0, 7, 21 days - 12 months	at day 28: 65.2% at month 2: 76% at month 13: 98.6%
Alternative	Healthy subjects from 11 years up to and including 15 years of age	0, 6 months	at month 2: 11.3% at month 6: 26.4% at month 7: 96.7%

Females generally seroconverted more quickly than males. As well, anti-HBs titres are higher in females than in males after 3 doses of yeast-derived or plasma-derived vaccine. However, protective anti-HBs titres develop in the same proportion in both sexes.

In a comparative study (HBV-280) performed in adolescents 11 to 15 years of age, onset of seroprotection (SP) was slower with the 2-dose schedule of ENGERIX®-B 20 µg (11.3% at month 2, 26.4% at month 6) compared to the 3-dose schedule of ENGERIX®-B 10 µg (55.8% at month 2, 87.6% at month 6). However, high seroprotection rates were reached one month after primary vaccination course with both schedules (96.7% with the 2-dose vs 98.2% with the 3-dose schedule). Geometric mean titers were 2739 mIU/mL and 7238 mIU/mL for 2-dose and 3-dose schedules respectively. Anti-HBs seroprotection rates observed in long-term follow-up phase of the study are presented in Table 3 below.

Table 3: Anti-HBs seroprotection rates observed at month 30, 42, 54 and 66 in long-term follow-up phase of study HBV-280

	Dosing schedule	Anti-HBs seroprotection rate (%)*			
		30 months	42 months	54 months	66 months
ENGERIX®-B 20 µg	0, 6 months	87.1	83.7	84.4	79.5
ENGERIX®-B 10 µg	0, 1, 6 months	96.9	92.5	94.7	91.4

* Percentage of subjects with anti-HBs antibody titer ≥10 IU/L

Special Populations and Conditions

Pediatrics:

Immunogenicity in Children

The anti-HBs response of children is similar to that of adults.

Immunogenicity in Neonates

In ongoing studies, the anti-HBs response of neonates of both carrier and non-carrier mothers to ENGERIX®-B has been shown to be similar to that obtained in adults and children with regard to seroconversion rate and anti-HBs titres attained. Preliminary data indicate that administration of hepatitis B immunoglobulin (HBIG) to the neonate at birth does not appear to affect the immune response to ENGERIX®-B.

Geriatrics:

Immunogenicity in Older Subjects

Anti-HBs titres tend to be slightly lower in older subjects than in younger subjects. This influence of age is found for both yeast-derived and plasma-derived vaccines.

Hepatic Insufficiency:

Immunogenicity in Subjects with Chronic Hepatitis C

After the completion of the vaccination course, all subjects were seroprotected with respect to hepatitis B (anti-HBs levels ≥ 10 mIU/mL), and GMTs were ≥ 1000 mIU/mL. The immune response of chronic liver disease (CLD) patients was similar to that of ENGERIX®-B in healthy subjects.

Renal Insufficiency:

Hemodialysis Patients

The anti-HBs response of patients on chronic hemodialysis is known to be impaired. However, experience from clinical studies shows that two months after 4 double doses, i.e., 40 µg (at months 0, 1, 2 and 6), 67% of vaccinees developed protective antibody titres. Anti-HBs titres remained relatively low compared to anti-HBs titres in healthy subjects. In a subsequent study conducted in 83 uremic patients, a seroprotection rate of 87% was achieved one month after four double doses of ENGERIX®-B, and 79% six months after last vaccine dose.

Other Clinical Studies:
In one study, four of 244 (1.6%) adults (homosexual men) at high risk of contracting hepatitis B virus became infected during the period prior to completion of three doses of ENGERIX®-B (20 µg at 0, 1, 6 months). No additional patients became infected during the 18-month follow-up period after completion of the immunization course.

The anti-HBs response to the recombinant yeast-derived vaccine is at least as high as that obtained by plasma-derived vaccines in patients affected by thalassemia major.
The anti-HBs response to ENGERIX®-B in residents of institutions for the developmentally challenged is similar to that observed in the general population.

The anti-HBs response in drug addicts does not differ from the response in the general population.

Immunogenicity with Thimerosal-free Formulation
Study HBV-269 enrolled 652 healthy adults aged 18 to 50 years with a 20 µg HBsAg/dose, compared the responses elicited one month after the completion of the primary vaccination course (three doses given at 0, 1 and 6 months) by ENGERIX®-B vaccine formulated to contain 50 µg/mL of thiomersal as preservative (referred to as ENGERIX®-B) with those induced by preservative-free ENGERIX®-B (PF- ENGERIX®-B, single dose formulation containing traces of thimerosal from the production process) and by single dose thimerosal-free ENGERIX®-B (TF- ENGERIX®-B, current formulation manufactured using the thimerosal-free process).

Study HBV-277 enrolled 589 infants with a 10 µg HBsAg/dose compared the responses elicited one month after the completion of the primary vaccination course (three doses given at 0, 1 and 6 months) by TF- ENGERIX®-B with that elicited by PF- ENGERIX®-B in infants when the first dose was administered during the first two weeks of life.

The immune response to the HBsAg antigen manufactured using the thiomersal-free process was not rendered inferior by the change in process. Seroprotection rates are presented in the table below.

Table 4: Anti-HBs Seroprotection Rates at Month 7, ATP Cohort, Non-inferiority Studies with Monovalent Vaccine: Study HBV-269 in Adults and Study HBV-277 in Infants

Study	Schedule	Seroprotection Rate (%)	
HBV-269	HBsAg 20µg/dose 0, 1 and 6 months	ENGERIX®-B	94.4
		PF-ENGERIX®-B	98.9
		TF-ENGERIX®-B	96.6
HBV-277	HBsAg 10µg/dose 0, 1 and 6 months	PF-ENGERIX®-B	98.1
		TF-ENGERIX®-B	96.9

DETAILED PHARMACOLOGY

Not applicable.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

Not applicable.

REFERENCES

1. Andre FE, Shapiro F, Heath RB, Hoffbrand BI. Prospects for control of hepatitis B. Postgrad Med J 1987; 63(Suppl 2).

2. Blumberg BS, Hepburn A, Andre FE. International Conference on Prospects for Eradication of Hepatitis B Virus. Vaccine 1990;(Supplement 8).

3. Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. N Engl J Med 1997; 336(26):1855-1859.

4. Cristofani C, Marchi S, Costa F. Role of HCV infection of immune response to hepatitis B vaccination in chronic renal failure patients on hemodialysis. Hepatology 1994; 19(4):54 Abstract 66.

5. De Wilde M, Cabezon T, Harford N, Rutgers T, Simoen E, Van Wijnendaele F. Production in yeast of hepatitis B surface antigen by R-DNA technology. Dev Biol Stand 1985; 59:99-107.

6. Goilav C. Immunization of homosexual men with a recombianant DNA vaccine against hepatitis B: immunology and protection. VIral hepatitis and liver disease, Alan R Liss, Inc 1988;1057-1058.

7. Goilav C, Prinsen H, Piot P. Protective efficacy of a recombinant DNA vaccine against hepatitis B in male homosexuals: results at 36 months. Vaccine 1990;(8 Suppl):S50-S52.

8. Goilav C, Prisen H, Safary A. Four year follow-up with a yeast derived Hepatitis B vaccine (YDV). Internationl Symposium on Viral Hepatitis and Liver Disease 1990;112.

9. Grosheide P, Damme PV. Prevention and Control of Hepatitis B in the Community. Communicable Diseases Series 1986.

10. Harford N, Cabezon T, Crabeel M, Simoen E, Rutgers A, De Wilde M. Expression of hepatitis B surface antigen in yeast. Dev Biol Stand 1983; 54:125-130.

11. Hollinger FB. Factors influencing the immune response to hepatitis B vaccine, booster dose guidelines, and vaccine protocol recommendations. Am J Med 1989; 87(3A):36S-40S.

12. Immunization Practices Advisory Committee (ACIP) USA. Hepatitis B Virus: A comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination. Morbidity and Mortality Weekly Report Nov 22 1991; 40((RR-13)):1-25.

13. Kamel M, el Manialawi M, Miller FD. Recombinant hepatitis B vaccine immunogenicity in presence of hepatitis C virus seropositivity. Lancet 1994; 343(8896):552.

14. Kuwert E, Scheiermann N, Gesemann M, Paar D, Safary A, Simoen E et al. Dose range study in healthy volunteers of a hepatitis B vaccine produced in yeast. Antiviral Res 1985; Suppl 1:281-288.

15. Lee SD, Chan CY, Yu MI, Wang YJ, Chang FY, Lo KJ et al. Safety and immunogenicity of inactivated hepatitis A vaccine in patients with chronic liver disease. J Med Virol 1997; 52(2):215-218.

16. Meheus A, Alisjahbana A, Vranckx R, Sukadi A, Usman A, Ngantung W et al. Immunogenicity of a recombinant DNA hepatitis B vaccine in neonates. Postgrad Med J 1987; 63 Suppl 2:139-141.

17. National Advisory Committee on Immunization. Statement on immunizing agents for the prevention of viral hepatitis. Canada Diseases Weekly Report June 6 1987;(13-22):99-106.

18. National Institutes of Health Consensus Development Statement. Management of Hepatitis C 1997.

19. Poovorawan Y, Sanpavat S, Pongpunlert W, Chumdermpadetsuk S, Sentrakul P, Safary A. Protective efficacy of a recombinant DNA hepatitis B vaccine in neonates of HBe antigen-positive mothers. JAMA 1989; 261(22):3278-3281.

20. Public Health Agency of Canada. Canadian Immunization Guide. 2006; Seventh Edition. Available from: http://www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php.

21. Tong MJ, Poovorawan Y, and CP. Immunoprophylaxis of neonates against hepatitis B. Proceeding of 1990 international symposium on viral hepatitis and liver disease: Contemporary issues and future prospects 1990;849-855.

22. Tsai JF, Jeng JE, Ho MS, Chang WY, Hsieh MY, Lin ZY et al. Effect of hepatitis C and B virus infection on risk of hepatocellular carcinoma: a prospective study. Br J Cancer 1997; 76(7):968-974.

23. Tsega E, Tafesse B, Horton J, Nordenfelt E, Wolde-Hawariat G, Hansson BG et al. Immunogenicity, reactogenicity and comparison of two doses of recombinant DNA yeast-derived hepatitis B vaccine in Ethiopian children. Trop Geogr Med 1991; 43(1-2):220-227.

24. Van Thiel DH, Gavaler JS. Response to HBV vaccination in patients with severe liver disease. Absence of an HLA effect. Dig Dis Sci 1992; 37(9):1447-1451.

25. Weltman MD, Brotodihardjo A, Crewe EB, Farrell GC, Bilous M, Grierson JM et al. Coinfection with hepatitis B and C or B, C and delta viruses results in severe chronic liver disease and responds poorly to interferon-alpha treatment. J Viral Hepat 1995; 2(1):39-45.

26. Wiedermann G, Scheiermann N, Goubau P, Ambrosch F, Gesemann M, De Bel C et al. Multicentre dose range study of a yeast-derived hepatitis B vaccine. Vaccine 1987; 5(3):179-183.

27. Zarski JP, Bohn B, Bastie A, Pawlotsky JM, Baud M, Bost-Bezeaux F et al. Characteristics of patients with dual infection by hepatitis B and C viruses. J Hepatol 1998; 28(1):27-33.

PART III: CONSUMER INFORMATION

ENGERIX®-B
Hepatitis B vaccine (recombinant)

This leaflet is part III of a three-part "Product Monograph" published for ENGERIX®-B approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ENGERIX®-B. Contact your doctor or pharmacist if you have any questions about the drug.

Keep this leaflet until you have finished the complete vaccination course. You may need to read it again.

This vaccine has been prescribed for you or your child and should not be passed on to others.

ABOUT THIS VACCINE

What the vaccine is used for:
ENGERIX®-B is a vaccine used to prevent hepatitis B disease.

It can be expected that hepatitis D will also be prevented by immunization with ENGERIX®-B as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

Vaccination is the best way to protect against this disease. The vaccine does not contain live virus and cannot cause hepatitis B infection.

What it does:
The vaccine works by causing the body to produce its own protection (antibodies) against the disease.

When it should not be used:
ENGERIX®-B:

- should not be given if you or your child have previously had any allergic reaction to ENGERIX®-B, or any ingredient contained in this vaccine.
- should not be administered if you or your child have a severe febrile infection pertaining to a fever.
- in healthy subjects the presence of a minor infection, however, is not a contraindication for vaccination.

What the medicinal ingredient is:
Each 1.0 mL adolescent/adult dose of vaccine contains 20 µg of hepatitis B surface antigen adsorbed onto 0.5 mg of Al^{3+} as aluminum hydroxide.
Each 0.5 mL pediatric dose contains 10 µg of hepatitis B surface antigen adsorbed onto 0.25 mg of Al^{3+} as aluminum hydroxide.

What the important nonmedicinal ingredients are:
Aluminum hydroxide.
For a full listing of nonmedicinal ingredients see Part 1 of the Product Monograph.

What dosage forms it comes in:
ENGERIX®-B is available in two size formats:

- 0.5 mL single pediatric dose vial containing 10 µg of hepatitis B surface antigen per vial.
- 1.0 mL adult dose vial containing 20 µg of hepatitis B surface antigen per vial.

WARNINGS AND PRECAUTIONS

BEFORE you use ENGERIX®-B talk to your doctor or pharmacist if:

- you are or think you may be pregnant or if you intend to become pregnant. Your doctor will discuss with you the possible risks and benefits of having ENGERIX®-B during pregnancy.
- you are breast-feeding. It is not known if ENGERIX®-B passes into breast-milk.
- you have a poor immune system due to illness or drug treatment.
- you or your child have a severe infection with a high temperature (over 38°C). In these cases, the vaccination will be postponed until you or your child have recovered. A minor infection such as a cold should not be a problem, but talk to your doctor first.
- you or your child have a bleeding problem or bruise(s) easily.
- you or your child is taking any other medicine or have recently received any other vaccine.

A poor response to the vaccine, possibly without achieving protection against hepatitis B, is more common in older people, men rather than women, smokers, obese people, and people with long standing illnesses, or people on some type of drug treatments. Your doctor may advise you or your child to have a blood test after you have or your child has completed the course of vaccinations to check if you have or your child has made a satisfactory response or an adequate (immune) response. If not, your doctor will advise you or your child on the possible need to have extra doses.

In these cases, your doctor can determine the right time and schedule of vaccination for you or your child.

If your child has breathing difficulties, please contact your doctor. This may be more common in the first three days following vaccination if your child is born prematurely (before or at 28 weeks of pregnancy).

Fainting can occur following, or even before, any needle injection; therefore, tell the doctor or nurse if you or your child fainted with a previous injection.

INTERACTIONS WITH THIS VACCINE

ENGERIX®-B 10 µg/0.5mL dose can be given at the same time as CERVARIX®, a Human Papillomavirus vaccine.

PROPER USE OF THIS VACCINE

Usual dose:
The doctor will give ENGERIX®-B as an injection into your upper arm muscle or into the thigh muscle of your child.

The vaccine should not be given (deep) into the skin or intramuscularly into the buttock because protection may be less.

The vaccine should never be given into a vein.

Make sure you or your child finish the complete vaccination course of injections. If not, you or your child may not be fully protected against the disease.

Your doctor will advise on the possible need for extra doses, and future booster dosing.

For optimal protection, the recommended Standard schedule for ENGERIX®-B is three doses given at 0, 1 and 6 months.

For more Accelerated protection a three dose schedule (0, 1, 2 with a booster dose at month 12) results in the development of protective anti-HBs titres by 3 months. The booster dose (at 12 months) is required to maintain prolonged protective anti-HBs titres.

Dosage and Administration Table

Vaccination Schedule	Age	Dose / Volume (µg/mL)	Dosing Schedule (months)				
			0	1	2	6	12
Standard (3 dose)	≥ 20 years of age	20/1.0	x	x		x	
Standard*	0-19 years of age	10/0.5	x	x		x	
Accelerated	≥ 20 years of age	20/1.0	x	x	x		x
	0-19 years of age	10/0.5	x	x	x		x
Rapid	≥ 20 years of age	20/1.0	0,7d, 21d xxx d=days				x
Alternative	11-15 years of age	20/1.0	x			x	

Overdose

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose
If you or your child miss a schedule injection, talk to your doctor and arrange another visit.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Any vaccine may have some side effects.

ENGERIX®-B has been widely used and the list below includes side effects that are not necessarily linked to the vaccine.

Very common (more than 1 in 10 doses of vaccine):
- irritability
- pain and redness at the injection site
- tiredness

Common (up to 1 in 10 doses of vaccine):
- loss of appetite
- headache, drowsiness
- nausea, vomiting, diarrhoea, abdominal pain
- hard lump and swelling at the injection site
- fever, generally feeling unwell

Uncommon (up to 1 in 100 doses of vaccine):
- dizziness
- aching muscles
- flu-like symptoms, such as high temperature, sore throat, runny nose, cough and chills

Rare (up to 1 in 1000 doses of vaccine):
- paresthesia (abnormal sensation of the skin)
- rash, pruritus (itching of the skin), urticaria (hives)
- arthralgia (pain in the joints)
- abnormal liver function tests

Do not be alarmed by this list of possible side effects. It is possible that you or your child have no side effects from vaccination.

This is not a complete list of side effects. For any unexpected effects while taking ENGERIX®-B, *contact your doctor or pharmacist.*

HOW TO STORE IT

Keep out of the reach and sight of children.
Store at 2 - 8°C (in a refrigerator).

Do not freeze. Freezing destroys the vaccine.

Store in the original package in order to protect from light.

Do not use after the expiry date shown on the label.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects case reports on adverse events following immunization.

For health care professionals:
If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events following Immunization (AEFI) Form and send it to your local Health Unit in your province/territory.

For the General Public:
Should you experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events following Immunization (AEFI) Form.

If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada:

By toll-free telephone: 866-844-0018
By toll-free fax: 866-844-5931
By email: caefi@phac-aspc.gc.ca
Web: http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php

Mail:
The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road, A/L6502A
Ottawa, ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.gsk.ca
or by contacting the sponsor, GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
L5N 6L4
1-800-387-7374
This leaflet was prepared by GlaxoSmithKline Inc.

Last revised: August 1, 2013