

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

ENGERIX-B

Hepatitis B vaccine (recombinant)

0.5 mL and 1.0 mL suspensions of 20 mcg/mL hepatitis B surface antigen for injection

Active immunizing agent against infection
caused by all known subtypes of hepatitis B virus

ATC Code: J07BC01

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

Date of Initial Approval:
November 06, 1987

Date of Revision:
April 3, 2019

Submission Control No: 219320

© 2019 GSK group of companies or its licensor
Trademarks are owned by or licensed to the GSK group of companies

RECENT MAJOR LABEL CHANGES

Warnings and Precautions, Immune (7) 10/2015
Clinical Trials, Special Populations and Conditions (13.2) 10/2015
Dosage and Administration, Administration (3.3) 08/2018
Dosage and Administration, Administration (3.3) 04/2019

TABLE OF CONTENTS

RECENT MAJOR LABEL CHANGES	2
TABLE OF CONTENTS	2
PART I: HEALTH PROFESSIONAL INFORMATION	4
1 INDICATIONS	4
1.1 Pediatrics	4
2 CONTRAINDICATIONS.....	4
3 DOSAGE AND ADMINISTRATION	5
3.1 Dosing Considerations	5
3.2 Recommended Dose and Dosage Adjustment	5
3.3 Administration	7
4 OVERDOSAGE	9
5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.....	10
6 DESCRIPTION.....	11
7 WARNINGS AND PRECAUTIONS	11
7.1 Special Populations.....	12
7.1.1 Pregnant Women	12
7.1.2 Breast-feeding.....	12
7.1.3 Pediatrics	12
8 ADVERSE REACTIONS.....	12
8.1 Clinical Trial Adverse Reactions.....	12
8.2 Post-Market Adverse Reactions.....	14
9 DRUG INTERACTIONS.....	14
9.1 Overview	14
9.2 Drug-Drug Interactions	14
9.3 Drug-Food Interactions.....	15
9.4 Drug-Herb Interactions	15
9.5 Drug-Laboratory Test Interactions.....	15
10 ACTION AND CLINICAL PHARMACOLOGY	15
10.1 Mechanism of Action.....	15
10.2 Duration of Protection	15

11	STORAGE, STABILITY AND DISPOSAL	15
	PART II: SCIENTIFIC INFORMATION	16
12	PHARMACEUTICAL INFORMATION	16
13	CLINICAL TRIALS	17
	13.1 Trial Design and Study Demographics.....	17
	13.2 Study Results.....	19
	PATIENT MEDICATION INFORMATION.....	23

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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.

The hepatitis B virus induces a severe form of viral hepatitis. 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 B. 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 developing chronic liver disease which may lead to cirrhosis or primary hepatocellular carcinoma.

The National Advisory Committee of Immunization (NACI) provides additional guidance on the use of hepatitis B vaccines in Canada, including a list of recommended individuals for vaccination against hepatitis B. Please refer to the Canadian Immunization Guide.

1.1 Pediatrics

Pediatrics (0 – 19 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of ENGERIX-B in pediatric patients has been established; therefore, Health Canada has authorized an indication for pediatric use (see Clinical Trials, Special Populations and Conditions).

2 CONTRAINDICATIONS

ENGERIX-B (hepatitis B vaccine (recombinant)) is contraindicated in patients 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 vaccine components, see Dosage Forms, Strengths, Composition and Packaging.

ENGERIX-B 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).

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

- ENGERIX-B (hepatitis B vaccine (recombinant)) should be injected intramuscularly and must not be given intravenously or intradermally
- ENGERIX-B may be given to pediatric patients, patients with renal insufficiency and to immunocompromised patients as per the dosing recommendations below

3.2 Recommended Dose and Dosage Adjustment

Table 1 Dosage and Administration

Vaccination Schedule	Age	Dose/Volume (mcg/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	

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).

Primary Immunization

Adults 20 years and over:

A dose of 20 mcg of antigen protein in 1.0 mL suspension is recommended for adults (see Table 1).

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

A dose of 10 mcg of antigen protein in 0.5 mL suspension is recommended for neonates, infants, children and adolescents up to 19 years of age inclusive (see Table 1).

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 mcg 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 Table 1) (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 mcg) 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 mcg (2 x 20 mcg) 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.

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.

3.3 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.

Vial Instructions

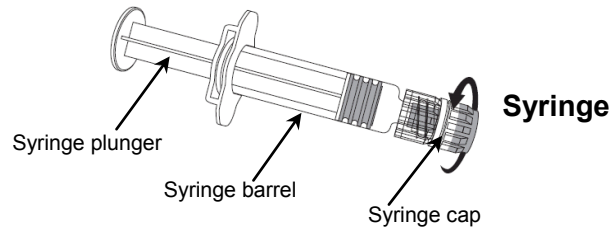
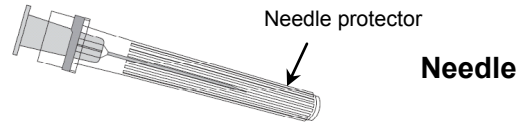
When using vial, use different needles to pierce the rubber stopper and to inject the vaccine.

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.

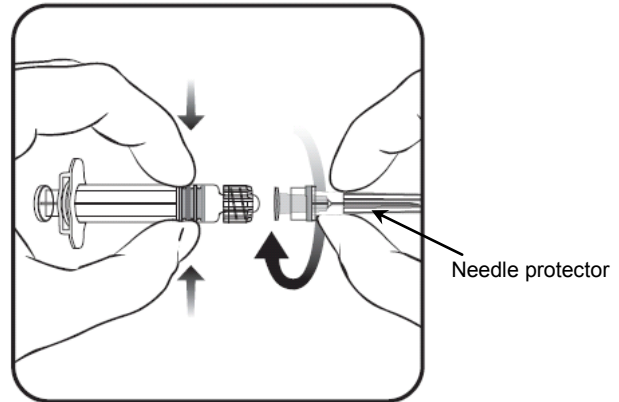
Syringe Instructions

To attach the needle to the syringe, refer to the drawing below

1. Holding the syringe **barrel** in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.



2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock (see drawing).

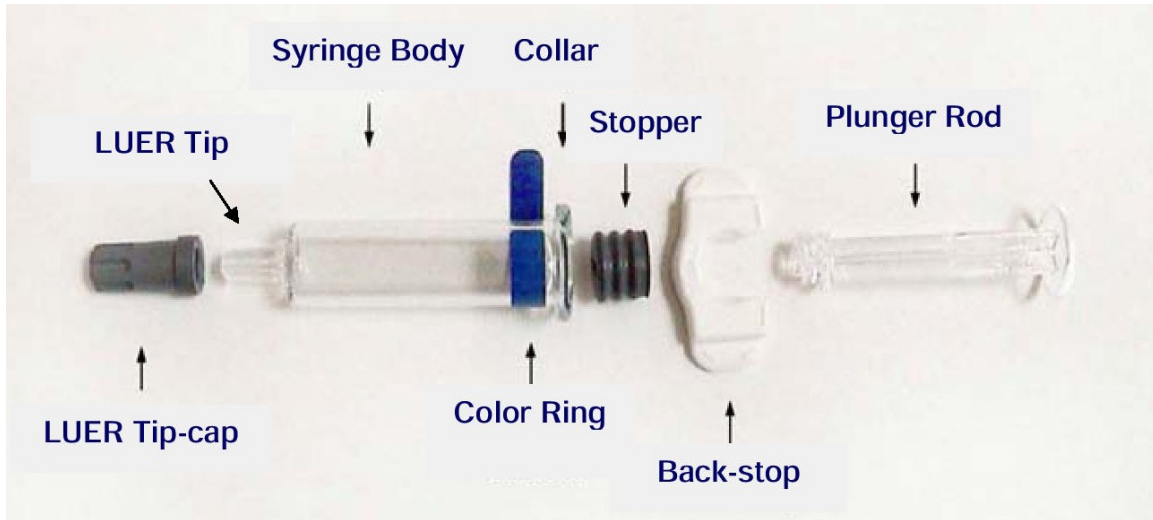


3. Remove the needle protector, which on occasion can be a little stiff.

4. Administer the vaccine.

Note: The syringe provided with ENGERIX-B might be slightly different (without screw thread) than the syringe in the above drawing. In that case, the needle should be attached following the below instructions.

Do not remove the white back-stop from the syringe. Prior to administration, ensure that the plunger rod is firmly attached to the rubber stopper by turning the plunger clockwise until slight resistance is felt. **Do not** over tighten. Remove syringe LUER Tip-cap and needle cap. Attach needle by pressing and twisting in a clockwise rotation until secured to the 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.

4 OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular Injection	<p>Suspensions/20 mcg/mL hepatitis B surface antigen</p> <p>Each 0.5 mL pediatric/ adolescent dose of vaccine contains 10 mcg of hepatitis B surface antigen adsorbed onto 0.25 mg of Al³⁺ as aluminium hydroxide.</p> <p>Each 1.0 mL adult dose of vaccine contains 20 mcg of hepatitis B surface antigen adsorbed onto 0.5 mg of Al³⁺ as aluminium hydroxide.</p>	<p>Aluminium (as aluminium hydroxide), disodium phosphate dihydrate, sodium chloride, sodium dihydrogen phosphate dihydrate, and water for injection.</p> <p>The 0.5 mL and 1.0 mL formulations are thimerosal free.</p>

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

Packaging

0.5 mL single dose vials or prefilled syringes* are packaged in a 1 pack carton with a Package Leaflet.

1.0 mL single dose vials or prefilled syringes* are packaged in a 1 or 25 pack carton with a Package Leaflet.

**Only prefilled syringes in a 1 pack carton are currently available in Canada*

6 DESCRIPTION

ENGERIX-B (hepatitis B vaccine (recombinant)) is a sterile, non-live, thimerosal free vaccine for intramuscular injection. The vaccine is supplied as a single dose vial/syringe of hepatitis B surface antigen (HBsAg) adsorbed onto Al³⁺ as aluminium hydroxide, available in a pediatric and adult dose.

7 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).

Hepatic/Biliary/Pancreatic

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, individuals with type 2 diabetes, 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).

Neurologic

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.

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).

7.1 Special Populations

7.1.1 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.

There is no experience on the extent of exposure during clinical trials.

7.1.2 Breast-feeding

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, precaution should be exercised.

7.1.3 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 \leq 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.

8 ADVERSE REACTIONS

8.1 Clinical Trial Adverse 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 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 mcg 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 mcg 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

8.2 Post-Market Adverse Reactions

The following adverse reactions have been reported with ENGERIX-B (hepatitis B vaccine (recombinant)).

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 20 mcg was similar overall to that reported after the standard three-dose regimen of ENGERIX-B 10 mcg.

9 DRUG INTERACTIONS

9.1 Overview

ENGERIX-B (hepatitis B vaccine (recombinant)) 10 mcg/0.5mL dose may be administered concomitantly with the Human Papillomavirus vaccine (CERVARIX). Administration of the 10 mcg/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 \geq 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.

9.2 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.3 Drug-Food Interactions

Interactions with food have not been established.

9.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Hepatitis B vaccine (recombinant) 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 hepatitis B vaccine (recombinant).

10.2 Duration of Protection

Routine booster vaccinations in immunocompetent persons are not recommended since protection has been shown to last for at least 15 years (see Dosage and Administration, Booster Doses).

11 STORAGE, STABILITY AND DISPOSAL

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.

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

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

Keep out of reach and sight of children.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: hepatitis B vaccine (recombinant)

Product Characteristics

The active ingredient is the hepatitis B surface antigen (HBsAg) produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology. It is adsorbed on aluminium 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.

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

Table 3 - Summary of patient demographics for clinical trials studying active immunization against hepatitis B virus infection

Study #	Trial design	Dosage, route of administration and duration	Study subjects vaccinated (n)	Mean age (Range)	Sex
HBV-269	Phase II, double blind, randomised, active controlled, multicentre study in healthy adults	<p>3 dose schedule:</p> <p>Group 1: Preservative-free (PF) ENGERIX-B 20 mcg (thiomersal <2 mcg/ml)</p> <p>Group 2: ENGERIX-B (ENG): ENGERIX-B 20 mcg (thiomersal 50 mcg/ml)</p> <p>Group 3: Thiomersal-free (TF): ENGERIX-B 20 mcg (no thiomersal)</p> <p>0, 1 and 6 months Follow-up: 18 months</p>	652	30.4 (18-58) years*	Males: 287 Females: 365
HBV-277	Phase III, double blind, randomised, multicentre study in healthy infants	<p>3 dose schedule: ENGERIX-B 10 mcg</p> <p>0, 1 and 6 months</p>	587	6.6 (0-14) years	Males: 307 Females: 280
HBV-280	Phase III, single-blind, randomized, multicentre study in healthy subjects 11-15 years of age	<p>2 dose schedule: ENGERIX-B 20 mcg</p> <p>0, 6 months</p> <p>3 dose schedule: ENGERIX-B 10 mcg 0, 1, 6 months</p> <p>Follow-up: 66 months</p>	384	12.8 (11-15) years	Male: 191 Female: 193

Study #	Trial design	Dosage, route of administration and duration	Study subjects vaccinated (n)	Mean age (Range)	Sex
HBV-234	Phase IV, open-label, randomized, multicentre study in healthy adults	3 dose schedule + booster: Group 1: ENGERIX-B 20 mcg 0, 1, 2, 12 months Group 2: ENGERIX-B 20 mcg 0, 14, 28 days and 12 months Group 3: ENGERIX-B 20 mcg 0, 7, 21 days and 12 months	524	27.2 (18-59) years	Males: 190 Females: 333**
HBV-323	Phase IV, open-label, multicenter study with 2:1 ratio of adults with or without type 2 diabetes mellitus	ENGERIX-B 20 mcg: 0, 1, 6 months	674	51.8 (20-82) years	Female: 334 Male: 340

*HBV-269 mean age, age range and sex was calculated on the Total Cohort, n = 652. Of the 652 subjects enrolled, age was not known for 3 subjects

**HBV-234 mean age, age range and sex was calculated on the analysis of reactogenicity cohort, n = 524. The total number of Study subjects vaccinated (n = 524) is greater than the number allotted to the Sex category because Sex was not noted for some individuals

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.

13.2 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 (HBV-269, HBV-277, HBV-280 and HBV-234) with the different schedules mentioned in the Dosage and Administration section.

Table 4 Seroprotection Rates

Vaccination Schedule	Population	Dosing Schedule	Seroprotection Rate
Standard	Healthy subjects	0, 1, 6 months	at month 7: $\geq 96\%$
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 mcg (11.3% at month 2, 26.4% at month 6) compared to the 3-dose schedule of ENGERIX-B 10 mcg (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 5 below.

Table 5 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 mcg	0, 6 months	87.1	83.7	84.4	79.5
ENGERIX-B 10 mcg	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 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 mcg (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.

Immunogenicity in Subjects with Type 2 Diabetes Mellitus

The table below summarizes seroprotection rates from study HBV-323 (i.e. percentages of subjects with anti-HBs antibody concentrations ≥ 10 mIU/mL) in subjects with type 2 diabetes mellitus and control subjects without type 2 diabetes.

Table 6 Seroprotection rates in subjects with type 2 diabetes and control subjects without type 2 diabetes

Age (Years)	Dosing Schedule (Strength)	Patients with Type II diabetes		Control Subjects	
		Seroprotection Rate at Month 7 (%)	95% CI	Seroprotection Rate at Month 7 (%)	95% CI
20-39	0, 1, 6 months (20 mcg)	88.5	76.6-95.6	100	86.8-100
40-49		81.2	71.2-88.8	86.4	72.6-94.8
50-59		83.2	75.2-89.4	82.3	70.5-90.8
≥ 60		58.2	48.9-67.1	70.2	56.6-81.6

Patients with Type II Diabetes = subjects diagnosed with type 2 diabetes within the past five years.

Control Subjects = subjects with no diagnosis or documented history of diabetes.

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 mcg 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 mcg 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 mcg/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).

In Study HBV-277, 587 infants were vaccinated with a 10 mcg HBsAg/dose and 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 were compared 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 7 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 20 mcg/dose 0, 1 and 6 months	ENGERIX-B	94.4
		PF-ENGERIX-B	98.9
		TF-ENGERIX-B	96.6
HBV-277	HBsAg 10 mcg/dose 0, 1 and 6 months	PF-ENGERIX-B	98.1
		TF-ENGERIX-B	96.9

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR VACCINE

PATIENT MEDICATION INFORMATION

ENGERIX-B **Hepatitis B vaccine (recombinant)** **Suspension for Injection**

Read this carefully before you receive **ENGERIX-B**. This leaflet is a summary and will not tell you everything about this vaccine. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ENGERIX-B**.

What is ENGERIX-B 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.

How does ENGERIX-B work?

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

What are the ingredients in ENGERIX-B?

Medicinal ingredients:

- Each 1.0 mL adult dose of vaccine contains 20 mcg of hepatitis B surface antigen adsorbed onto 0.5 mg of Al³⁺ as aluminium hydroxide.
- Each 0.5 mL pediatric/ adolescent dose of vaccine contains 10 mcg of hepatitis B surface antigen adsorbed onto 0.25 mg of Al³⁺ as aluminium hydroxide.

Non-medicinal ingredients: Aluminium (as aluminium hydroxide), disodium phosphate dihydrate, sodium chloride, sodium dihydrogen phosphate dihydrate, and water for injection.

ENGERIX-B comes in the following dosage forms:

- 0.5 mL single pediatric dose vials or prefilled syringes* containing 10 mcg of hepatitis B surface antigen per vial.
- 1.0 mL adult dose vials or prefilled syringes* containing 20 mcg of hepatitis B surface antigen per vial.

**Only prefilled syringes are currently available in Canada*

Do not use ENGERIX-B if:

- you or your child have previously had any allergic reaction to ENGERIX-B, or any ingredient contained in this vaccine.
- you or your child have a severe febrile infection pertaining to a fever.

In healthy subjects the presence of a minor infection is not a contraindication for vaccination.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ENGERIX-B. Talk about any health conditions or problems you may have, including 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.

Other warnings you should know about:

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, people with type 2 diabetes, 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.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may be given with ENGERIX-B:

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

How to take ENGERIX-B:

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 (mcg/ 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: Some cases of overdose have been reported. In general, the side effects reported are similar to those seen after administration of the recommended dose of ENGERIX-B.

In case of drug overdose, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you or your child misses a scheduled injection, talk to your doctor and arrange another visit.

What are possible side effects from using ENGERIX-B?

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.

These are not all the possible side effects you may feel when taking ENGERIX-B. If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional. Please also see the To help avoid side effects and Other warnings you should know about, sections.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on [Adverse Reaction Reporting \(http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php\)](http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Reporting Suspected Side Effects following immunization

For the general public: Should you experience a side effect following immunization, please report it to your doctor, nurse, or pharmacist.

Should you require information related to the management of the side effect, please contact your healthcare provider. The Public Health Agency of Canada, Health Canada and GlaxoSmithKline Canada Inc. cannot provide medical advice.

For healthcare professionals: If a patient experiences a side effect following immunization, please complete the Adverse Events Following Immunization (AEFI) Form appropriate for your province/territory by inquiring with your local Public Health Unit or the national form available at <http://www.phac-aspc.gc.ca/im/ae-fi-essi-form-eng.php>, and send it to your local Public Health Unit.

Storage:

Store at 2 - 8°C (in a refrigerator).

Keep out of reach and sight of children.

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.

If you want more information about ENGERIX-B:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the latest available Patient Medication Information by visiting the [Health Canada website](#); the manufacturer's website www.gsk.ca, or by calling 1-800-387-7374.

This leaflet was prepared by GlaxoSmithKline Inc.

Last Revised: March 13, 2019

©2019 GSK group of companies or its licensor.
Trademarks are owned by or licensed to the GSK group of companies.