

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ENGERIX-B safely and effectively. See full prescribing information for ENGERIX-B.

### ENGERIX-B [Hepatitis B Vaccine (Recombinant)]

#### Suspension for Intramuscular Injection

Initial U.S. Approval: 1989

#### INDICATIONS AND USAGE

ENGERIX-B is a vaccine indicated for immunization against infection caused by all known subtypes of hepatitis B virus. (1)

#### DOSAGE AND ADMINISTRATION

For intramuscular administration. (2, 2.2)

- Persons from birth through 19 years of age: A series of 3 doses (0.5 mL each) on a 0-, 1-, 6-month schedule. (2.3)
- Persons 20 years of age and older: A series of 3 doses (1 mL each) on a 0-, 1-, 6-month schedule. (2.3)
- Adults on hemodialysis: A series of 4 doses (2 mL each) as a single 2-mL dose or as two 1-mL doses on a 0-, 1-, 2-, 6-month schedule. (2.3)

#### DOSAGE FORMS AND STRENGTHS

ENGERIX-B is a sterile suspension available in the following presentations:

- 0.5-mL (10 mcg) single-dose vials and prefilled syringes (3)
- 1-mL (20 mcg) single-dose vials and prefilled syringes (3)

#### CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis B-containing vaccine, or to any component of ENGERIX-B, including yeast. (4)

#### WARNINGS AND PRECAUTIONS

- The tip caps of the prefilled syringes may contain natural rubber latex which may cause allergic reactions in latex-sensitive individuals. (5.1)

- Syncope (fainting) can occur in association with administration of injectable vaccines, including ENGERIX-B. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.2)
- Temporarily defer vaccination of infants with a birth weight less than 2,000 g born to HBsAg-negative mothers. (5.3)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including ENGERIX-B, to infants born prematurely should be based on consideration of the infant's medical status, and the potential benefits and possible risks of vaccination. (5.4)

#### ADVERSE REACTIONS

The most common solicited adverse events were injection site soreness (22%) and fatigue (14%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or [www.vaers.hhs.gov](http://www.vaers.hhs.gov).

#### DRUG INTERACTIONS

Do not mix ENGERIX-B with any other vaccine or product in the same syringe or vial. (7.1)

#### USE IN SPECIFIC POPULATIONS

- Safety and effectiveness of ENGERIX-B have not been established in pregnant women and nursing mothers. ENGERIX-B should only be given to a pregnant woman if clearly needed. (8.1, 8.3)
- Antibody responses are lower in persons older than 60 years of age than in younger adults. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: XX/XXXX

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### FULL PRESCRIBING INFORMATION

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

- 2.1 Preparation for Administration
- 2.2 Administration
- 2.3 Recommended Dose and Schedule
- 2.4 Alternate Dosing Schedules
- 2.5 Booster Vaccinations
- 2.6 Known or Presumed Exposure to Hepatitis B Virus

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 Latex
- 5.2 Syncope
- 5.3 Infants Weighing Less than 2,000 g at Birth
- 5.4 Apnea in Premature Infants
- 5.5 Preventing and Managing Allergic Vaccine Reactions
- 5.6 Moderate or Severe Acute Illness
- 5.7 Altered Immunocompetence
- 5.8 Multiple Sclerosis
- 5.9 Limitations of Vaccine Effectiveness

#### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

#### 7 DRUG INTERACTIONS

- 7.1 Concomitant Administration with Vaccines and Immune Globulin
- 7.2 Interference with Laboratory Tests

#### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action

#### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### 14 CLINICAL STUDIES

- 14.1 Efficacy in Neonates
- 14.2 Efficacy and Immunogenicity in Specific Populations
- 14.3 Immunogenicity in Neonates
- 14.4 Immunogenicity in Children and Adults
- 14.5 Interchangeability with Other Hepatitis B Vaccines

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

3 ENGERIX-B<sup>®</sup> is indicated for immunization against infection caused by all known subtypes of  
4 hepatitis B virus.

5 **2 DOSAGE AND ADMINISTRATION**

6 For intramuscular administration. See Section 2.2 for subcutaneous administration in persons at  
7 risk of hemorrhage.

8 **2.1 Preparation for Administration**

9 Shake well before use. With thorough agitation, ENGERIX-B is a homogeneous, turbid white  
10 suspension. Do not administer if it appears otherwise. Parenteral drug products should be  
11 inspected visually for particulate matter and discoloration prior to administration, whenever  
12 solution and container permit. If either of these conditions exists, the vaccine should not be  
13 administered.

14 For the prefilled syringes, attach a sterile needle and administer intramuscularly.

15 For the vials, use a sterile needle and sterile syringe to withdraw the vaccine dose and administer  
16 intramuscularly. Changing needles between drawing vaccine from a vial and injecting it into a  
17 recipient is not necessary unless the needle has been damaged or contaminated. Use a separate  
18 sterile needle and syringe for each individual.

19 **2.2 Administration**

20 ENGERIX-B should be administered by intramuscular injection. The preferred administration  
21 site is the anterolateral aspect of the thigh for infants younger than 1 year and the deltoid muscle  
22 in older children (whose deltoid is large enough for an intramuscular injection) and adults.  
23 ENGERIX-B should not be administered in the gluteal region; such injections may result in  
24 suboptimal response.

25 ENGERIX-B may be administered subcutaneously to persons at risk of hemorrhage (e.g.,  
26 hemophiliacs). However, hepatitis B vaccines administered subcutaneously are known to result  
27 in a lower antibody response. Additionally, when other aluminum-adsorbed vaccines have been  
28 administered subcutaneously, an increased incidence of local reactions including subcutaneous  
29 nodules has been observed. Therefore, subcutaneous administration should be used only in  
30 persons who are at risk of hemorrhage with intramuscular injections.

31 Do not administer this product intravenously or intradermally.

32 **2.3 Recommended Dose and Schedule**

33 Persons from Birth through 19 Years of Age

34 Primary immunization for infants (born of hepatitis B surface antigen [HBsAg]-negative or  
35 HBsAg-positive mothers), children (birth through 10 years of age), and adolescents (11 through  
36 19 years of age) consists of a series of 3 doses (0.5 mL each) given on a 0-, 1-, and 6-month  
37 schedule.

38 Persons 20 Years of Age and Older

39 Primary immunization for persons 20 years of age and older consists of a series of 3 doses (1 mL  
40 each) given on a 0-, 1-, and 6-month schedule.

41 Adults on Hemodialysis

42 Primary immunization consists of a series of 4 doses (2 mL each) given as a single 2-mL dose or  
43 two 1-mL doses on a 0-, 1-, 2-, and 6-month schedule. In hemodialysis patients, antibody  
44 response is lower than in healthy persons and protection may persist only as long as antibody  
45 levels remain above 10 mIU/mL. Therefore, the need for booster doses should be assessed by  
46 annual antibody testing. A 2-mL booster dose (as a single 2-mL dose or two 1-mL doses) should  
47 be given when antibody levels decline below 10 mIU/mL.<sup>1</sup> [See *Clinical Studies (14.2).*]

48 **Table 1. Recommended Dosage and Administration Schedules**

Group	Dose <sup>a</sup>	Schedules
Infants born of: HBsAg-negative mothers	0.5 mL	0, 1, 6 months
HBsAg-positive mothers <sup>b</sup>	0.5 mL	0, 1, 6 months
Children: Birth through 10 years of age	0.5 mL	0, 1, 6 months
Adolescents: 11 through 19 years of age	0.5 mL	0, 1, 6 months
Adults: 20 years of age and older	1 mL	0, 1, 6 months
Adults on hemodialysis	2 mL <sup>c</sup>	0, 1, 2, 6 months

49 HBsAg = Hepatitis B surface antigen.

50 <sup>a</sup> 0.5 mL (10 mcg); 1 mL (20 mcg).

51 <sup>b</sup> Infants born to HBsAg-positive mothers should receive vaccine and hepatitis B immune  
52 globulin (HBIG) within 12 hours after birth [see *Dosage and Administration (2.6)*].

53 <sup>c</sup> Given as a single 2-mL dose or as two 1-mL doses.

54 **2.4 Alternate Dosing Schedules**

55 There are alternate dosing and administration schedules which may be used for specific  
56 populations (e.g., neonates born of hepatitis B–infected mothers, persons who have or might

57 have been recently exposed to the virus, and travelers to high-risk areas) (Table 2). For some of  
 58 these alternate schedules, an additional dose at 12 months is recommended for prolonged  
 59 maintenance of protective titers.

60 **Table 2. Alternate Dosage and Administration Schedules**

Group	Dose <sup>a</sup>	Schedules
Infants born of: HBsAg-positive mothers <sup>b</sup>	0.5 mL	0, 1, 2, 12 months
Children: Birth through 10 years of age	0.5 mL	0, 1, 2, 12 months
5 through 10 years of age	0.5 mL	0, 12, 24 months <sup>c</sup>
Adolescents: 11 through 16 years of age	0.5 mL	0, 12, 24 months <sup>c</sup>
11 through 19 years of age	1 mL	0, 1, 6 months
11 through 19 years of age	1 mL	0, 1, 2, 12 months
Adults: 20 years of age and older	1 mL	0, 1, 2, 12 months

61 HBsAg = Hepatitis B surface antigen.

62 <sup>a</sup> 0.5 mL (10 mcg); 1 mL (20 mcg).

63 <sup>b</sup> Infants born to HBsAg-positive mothers should receive vaccine and hepatitis B immune  
 64 globulin (HBIG) within 12 hours after birth [see *Dosage and Administration (2.6)*].

65 <sup>c</sup> For children and adolescents for whom an extended administration schedule is  
 66 acceptable based on risk of exposure.

## 67 **2.5 Booster Vaccinations**

68 Whenever administration of a booster dose is appropriate, the dose of ENGERIX-B is 0.5 mL for  
 69 children 10 years of age and younger and 1 mL for persons 11 years of age and older. Studies  
 70 have demonstrated a substantial increase in antibody titers after booster vaccination with  
 71 ENGERIX-B. See Section 2.3 for information on booster vaccination for adults on hemodialysis.

## 72 **2.6 Known or Presumed Exposure to Hepatitis B Virus**

73 Persons with known or presumed exposure to the hepatitis B virus (e.g., neonates born of  
 74 infected mothers, persons who experienced percutaneous or permucosal exposure to the virus)  
 75 should be given hepatitis B immune globulin (HBIG) in addition to ENGERIX-B in accordance  
 76 with Advisory Committee on Immunization Practices recommendations and with the package  
 77 insert for HBIG. ENGERIX-B can be given on either dosing schedule (0, 1, and 6 months or 0,  
 78 1, 2, and 12 months).

## 79 **3 DOSAGE FORMS AND STRENGTHS**

80 ENGERIX-B is a sterile suspension available in the following presentations:

- 81 • 0.5-mL (10 mcg) single-dose vials and prefilled TIP-LOK<sup>®</sup> syringes  
82 • 1-mL (20 mcg) single-dose vials and prefilled TIP-LOK syringes

83 *[See Description (11), How Supplied/Storage and Handling (16).]*

#### 84 **4 CONTRAINDICATIONS**

85 Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis B-containing  
86 vaccine, or to any component of ENGERIX-B, including yeast, is a contraindication to  
87 administration of ENGERIX-B *[see Description (11)].*

#### 88 **5 WARNINGS AND PRECAUTIONS**

##### 89 **5.1 Latex**

90 The tip caps of the prefilled syringes may contain natural rubber latex which may cause allergic  
91 reactions in latex-sensitive individuals.

##### 92 **5.2 Syncope**

93 Syncope (fainting) can occur in association with administration of injectable vaccines, including  
94 ENGERIX-B. Syncope can be accompanied by transient neurological signs such as visual  
95 disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to  
96 avoid falling injury and to restore cerebral perfusion following syncope.

##### 97 **5.3 Infants Weighing Less than 2,000 g at Birth**

98 Hepatitis B vaccine should be deferred for infants with a birth weight <2,000 g if the mother is  
99 documented to be HBsAg negative at the time of the infant's birth. Vaccination can commence at  
100 chronological age 1 month or hospital discharge. Infants born weighing <2,000 g to HBsAg-  
101 positive mothers should receive vaccine and hepatitis B immune globulin (HBIG) within 12  
102 hours after birth. Infants born weighing <2,000 g to mothers of unknown HBsAg status should  
103 receive vaccine and HBIG within 12 hours after birth if the mother's HBsAg status cannot be  
104 determined within the first 12 hours of life. The birth dose in infants born weighing <2,000 g  
105 should not be counted as the first dose in the vaccine series and it should be followed with a full  
106 3-dose standard regimen (total of 4 doses).<sup>2</sup> *[See Dosage and Administration (2).]*

##### 107 **5.4 Apnea in Premature Infants**

108 Apnea following intramuscular vaccination has been observed in some infants born prematurely.  
109 Decisions about when to administer an intramuscular vaccine, including ENGERIX-B, to infants  
110 born prematurely should be based on consideration of the infant's medical status, and the  
111 potential benefits and possible risks of vaccination. For ENGERIX-B, this assessment should  
112 include consideration of the mother's hepatitis B antigen status and the high probability of  
113 maternal transmission of hepatitis B virus to infants born of mothers who are HBsAg positive if  
114 vaccination is delayed.

115 **5.5 Preventing and Managing Allergic Vaccine Reactions**

116 Prior to immunization, the healthcare provider should review the immunization history for  
117 possible vaccine sensitivity and previous vaccination-related adverse reactions to allow an  
118 assessment of benefits and risks. Epinephrine and other appropriate agents used for the control of  
119 immediate allergic reactions must be immediately available should an acute anaphylactic  
120 reaction occur. [See *Contraindications (4)*.]

121 **5.6 Moderate or Severe Acute Illness**

122 To avoid diagnostic confusion between manifestations of an acute illness and possible vaccine  
123 adverse effects, vaccination with ENGERIX-B should be postponed in persons with moderate or  
124 severe acute febrile illness unless they are at immediate risk of hepatitis B infection (e.g., infants  
125 born of HBsAg-positive mothers).

126 **5.7 Altered Immunocompetence**

127 Immunocompromised persons may have a diminished immune response to ENGERIX-B,  
128 including individuals receiving immunosuppressant therapy.

129 **5.8 Multiple Sclerosis**

130 Results from 2 clinical studies indicate that there is no association between hepatitis B  
131 vaccination and the development of multiple sclerosis,<sup>3</sup> and that vaccination with hepatitis B  
132 vaccine does not appear to increase the short-term risk of relapse in multiple sclerosis.<sup>4</sup>

133 **5.9 Limitations of Vaccine Effectiveness**

134 Hepatitis B has a long incubation period. ENGERIX-B may not prevent hepatitis B infection in  
135 individuals who had an unrecognized hepatitis B infection at the time of vaccine administration.  
136 Additionally, it may not prevent infection in individuals who do not achieve protective antibody  
137 titers.

138 **6 ADVERSE REACTIONS**

139 **6.1 Clinical Trials Experience**

140 Because clinical trials are conducted under widely varying conditions, adverse reaction rates  
141 observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical  
142 trials of another vaccine and may not reflect the rates observed in practice.

143 The most common solicited adverse events were injection site soreness (22%) and fatigue (14%).

144 In 36 clinical studies, a total of 13,495 doses of ENGERIX-B were administered to 5,071 healthy  
145 adults and children who were initially seronegative for hepatitis B markers, and healthy  
146 neonates. All subjects were monitored for 4 days post-administration. Frequency of adverse  
147 events tended to decrease with successive doses of ENGERIX-B.

148 Using a symptom checklist, the most frequently reported adverse events were injection site  
149 soreness (22%) and fatigue (14%). Other events are listed below. Parent or guardian completed  
150 forms for children and neonates. Neonatal checklist did not include headache, fatigue, or  
151 dizziness.

152 Incidence 1% to 10% of Injections

153 *Nervous System Disorders:* Dizziness, headache.

154 *General Disorders and Administration Site Conditions:* Fever (>37.5°C), injection site  
155 erythema, injection site induration, injection site swelling.

156 Incidence <1% of Injections

157 *Infections and Infestations:* Upper respiratory tract illnesses.

158 *Blood and Lymphatic System Disorders:* Lymphadenopathy.

159 *Metabolism and Nutrition Disorders:* Anorexia.

160 *Psychiatric Disorders:* Agitation, insomnia.

161 *Nervous System Disorders:* Somnolence, tingling.

162 *Vascular Disorders:* Flushing, hypotension.

163 *Gastrointestinal Disorders:* Abdominal pain/cramps, constipation, diarrhea, nausea, vomiting.

164 *Skin and Subcutaneous Tissue Disorders:* Erythema, petechiae, pruritus, rash, sweating,  
165 urticaria.

166 *Musculoskeletal and Connective Tissue Disorders:* Arthralgia, back pain, myalgia,  
167 pain/stiffness in arm, shoulder, or neck.

168 *General Disorders and Administration Site Conditions:* Chills, influenza-like symptoms,  
169 injection site ecchymosis, injection site pain, injection site pruritus, irritability, malaise,  
170 weakness.

171 In a clinical trial, 416 adults with type 2 diabetes and 258 control subjects without type 2  
172 diabetes who were seronegative for hepatitis B markers received at least one dose of  
173 ENGERIX-B. Subjects were monitored for solicited adverse events for 4 days following each  
174 vaccination. The most frequently reported solicited adverse events in the entire study population  
175 were injection site pain (reported in 39% of diabetic subjects and 45% of control subjects) and  
176 fatigue (reported in 29% of diabetic subjects and 27% of control subjects). Serious adverse  
177 events were monitored through 30 days following the last vaccination. Serious adverse events  
178 (SAEs) occurred in 3.8% of diabetic subjects and 1.6% of controls. No SAEs were deemed  
179 related to ENGERIX-B.

180 **6.2 Postmarketing Experience**

181 In addition to reports in clinical trials, worldwide voluntary reports of adverse events received  
182 for ENGERIX-B since market introduction (1990) are listed below. This list includes serious  
183 adverse events or events that have a suspected causal connection to components of ENGERIX-B.

184 Because these events are reported voluntarily from a population of unknown size, it is not always  
185 possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

186 Infections and Infestations

187 Herpes zoster, meningitis.

188 Blood and Lymphatic System Disorders

189 Thrombocytopenia.

190 Immune System Disorders

191 Allergic reaction, anaphylactoid reaction, anaphylaxis. An apparent hypersensitivity syndrome  
192 (serum sickness-like) of delayed onset has been reported days to weeks after vaccination,  
193 including: arthralgia/arthritis (usually transient), fever, and dermatologic reactions such as  
194 urticaria, erythema multiforme, ecchymoses, and erythema nodosum.

195 Nervous System Disorders

196 Encephalitis, encephalopathy, migraine, multiple sclerosis, neuritis, neuropathy including  
197 hypoesthesia, paresthesia, Guillain-Barré syndrome and Bell's palsy, optic neuritis, paralysis,  
198 paresis, seizures, syncope, transverse myelitis.

199 Eye Disorders

200 Conjunctivitis, keratitis, visual disturbances.

201 Ear and Labyrinth Disorders

202 Earache, tinnitus, vertigo.

203 Cardiac Disorders

204 Palpitations, tachycardia.

205 Vascular Disorders

206 Vasculitis.

207 Respiratory, Thoracic, and Mediastinal Disorders

208 Apnea, bronchospasm including asthma-like symptoms.

209 Gastrointestinal Disorders

210 Dyspepsia.

211 Skin and Subcutaneous Tissue Disorders

212 Alopecia, angioedema, eczema, erythema multiforme including Stevens-Johnson syndrome,  
213 erythema nodosum, lichen planus, purpura.

214 Musculoskeletal and Connective Tissue Disorders

215 Arthritis, muscular weakness.

216 General Disorders and Administration Site Conditions

217 Injection site reaction.

218 Investigations

219 Abnormal liver function tests.

220 **7 DRUG INTERACTIONS**

221 **7.1 Concomitant Administration with Vaccines and Immune Globulin**

222 ENGERIX-B may be administered concomitantly with immune globulin.

223 When concomitant administration of other vaccines or immune globulin is required, they should  
224 be given with different syringes and at different injection sites. Do not mix ENGERIX-B with  
225 any other vaccine or product in the same syringe or vial.

226 **7.2 Interference with Laboratory Tests**

227 Hepatitis B surface antigen (HBsAg) derived from hepatitis B vaccines has been transiently  
228 detected in blood samples following vaccination. Serum HBsAg detection may not have  
229 diagnostic value within 28 days after receipt of a hepatitis B vaccine, including ENGERIX-B.

230 **8 USE IN SPECIFIC POPULATIONS**

231 **8.1 Pregnancy**

232 Pregnancy Category C

233 Animal reproduction studies have not been conducted with ENGERIX-B. It is also not known  
234 whether ENGERIX-B can cause fetal harm when administered to a pregnant woman or can  
235 affect reproduction capacity. ENGERIX-B should be given to a pregnant woman only if clearly  
236 needed.

237 **8.3 Nursing Mothers**

238 It is not known whether ENGERIX-B is excreted in human milk. Because many drugs are  
239 excreted in human milk, caution should be exercised when ENGERIX-B is administered to a  
240 nursing woman.

241 **8.4 Pediatric Use**

242 Safety and effectiveness of ENGERIX-B have been established in all pediatric age groups.  
243 Maternally transferred antibodies do not interfere with the active immune response to the  
244 vaccine. [See *Adverse Reactions* (6), *Clinical Studies* (14.1, 14.3, 14.4).]

245 The timing of the first dose in infants weighing less than 2,000 g at birth depends on the HBsAg  
246 status of the mother. [See *Warnings and Precautions* (5.3).]

## 247 **8.5 Geriatric Use**

248 Clinical studies of ENGERIX-B used for licensure did not include sufficient numbers of subjects  
249 65 years of age and older to determine whether they respond differently from younger subjects.  
250 However, in later studies it has been shown that a diminished antibody response and  
251 seroprotective levels can be expected in persons older than 60 years of age.<sup>5</sup> [See *Clinical Studies*  
252 (14.2).]

## 253 **11 DESCRIPTION**

254 ENGERIX-B [Hepatitis B Vaccine (Recombinant)] is a sterile suspension of noninfectious  
255 hepatitis B virus surface antigen (HBsAg) for intramuscular administration. It contains purified  
256 surface antigen of the virus obtained by culturing genetically engineered *Saccharomyces*  
257 *cerevisiae* cells, which carry the surface antigen gene of the hepatitis B virus. The HBsAg  
258 expressed in the cells is purified by several physicochemical steps and formulated as a  
259 suspension of the antigen adsorbed on aluminum hydroxide. The procedures used to manufacture  
260 ENGERIX-B result in a product that contains no more than 5% yeast protein.

261 Each 0.5-mL pediatric/adolescent dose contains 10 mcg of HBsAg adsorbed on 0.25 mg  
262 aluminum as aluminum hydroxide.

263 Each 1-mL adult dose contains 20 mcg of HBsAg adsorbed on 0.5 mg aluminum as aluminum  
264 hydroxide.

265 ENGERIX-B contains the following excipients: Sodium chloride (9 mg/mL) and phosphate  
266 buffers (disodium phosphate dihydrate, 0.98 mg/mL; sodium dihydrogen phosphate dihydrate,  
267 0.71 mg/mL).

268 ENGERIX-B is available in vials and prefilled syringes. The tip caps of the prefilled syringes  
269 may contain natural rubber latex; the plungers are not made with natural rubber latex. The vial  
270 stoppers are not made with natural rubber latex.

271 ENGERIX-B is formulated without preservatives.

## 272 **12 CLINICAL PHARMACOLOGY**

### 273 **12.1 Mechanism of Action**

274 Infection with hepatitis B virus can have serious consequences including acute massive hepatic  
275 necrosis and chronic active hepatitis. Chronically infected persons are at increased risk for  
276 cirrhosis and hepatocellular carcinoma.

277 Antibody concentrations  $\geq 10$  mIU/mL against HBsAg are recognized as conferring protection  
278 against hepatitis B virus infection.<sup>1</sup> Seroconversion is defined as antibody titers  $\geq 1$  mIU/mL.

## 279 **13 NONCLINICAL TOXICOLOGY**

### 280 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

281 ENGERIX-B has not been evaluated for carcinogenic or mutagenic potential, or for impairment  
282 of fertility.

## 283 **14 CLINICAL STUDIES**

### 284 **14.1 Efficacy in Neonates**

285 Protective efficacy with ENGERIX-B has been demonstrated in a clinical trial in neonates at  
286 high risk of hepatitis B infection.<sup>6,7</sup> Fifty-eight neonates born of mothers who were both HBsAg-  
287 positive and hepatitis B “e” antigen (HBeAg)-positive were given ENGERIX-B  
288 (10 mcg/0.5 mL) at 0, 1, and 2 months, without concomitant hepatitis B immune globulin  
289 (HBIG). Two infants became chronic carriers in the 12-month follow-up period after initial  
290 inoculation. Assuming an expected carrier rate of 70%, the protective efficacy rate against the  
291 chronic carrier state during the first 12 months of life was 95%.

### 292 **14.2 Efficacy and Immunogenicity in Specific Populations**

#### 293 Homosexual Men

294 ENGERIX-B (20 mcg/1 mL) given at 0, 1, and 6 months was evaluated in homosexual men 16  
295 to 59 years of age. Four of 244 subjects became infected with hepatitis B during the period prior  
296 to completion of the 3-dose immunization schedule. No additional subjects became infected  
297 during the 18-month follow-up period after completion of the immunization course.

#### 298 Adults with Chronic Hepatitis C

299 In a clinical trial of 67 adults 25 to 67 years of age with chronic hepatitis C, ENGERIX-B  
300 (20 mcg/1 mL) was given at 0, 1, and 6 months. Of the subjects assessed at Month 7 (N = 31),  
301 100% responded with seroprotective titers. The geometric mean antibody titer (GMT) was  
302 1,260 mIU/mL (95% Confidence Interval [CI]: 709, 2,237).

#### 303 Adults on Hemodialysis

304 Hemodialysis patients given hepatitis B vaccines respond with lower titers, which remain at  
305 protective levels for shorter durations than in normal subjects. In a clinical trial of 56 adults who  
306 had been on hemodialysis for a mean period of 56 months, ENGERIX-B (40 mcg/2 mL given as  
307 two 1-mL doses) was given at 0, 1, 2, and 6 months. Two months after the fourth dose, 67%

308 (29/43) of patients had seroprotective antibody levels ( $\geq 10$  mIU/mL) and the GMT among  
309 seroconverters was 93 mIU/mL.

### 310 Adults with Type 2 Diabetes Mellitus

311 In a descriptive study, 674 adult subjects with type 2 diabetes (diagnosed within the preceding 5  
312 years) or without type 2 diabetes were enrolled and stratified by age and body mass index (BMI).  
313 The per-protocol immunogenicity cohort included 378 diabetic subjects and 189 matched control  
314 subjects who received ENGERIX-B (20 mcg/1 mL) at 0, 1, and 6 months. Among these subjects,  
315 the mean age was 54 years (range: 20 to 82 years); mean BMI was 32 kg/m<sup>2</sup> (range: 17 to 64  
316 kg/m<sup>2</sup>); 51% were male; 88% were white, 3% were American Indian or Alaskan Native, 3%  
317 were black, 2% were Asian, 4% were other racial groups; 2% were Hispanic or Latino.

318 The overall seroprotection rates (1 month after the third dose) were 75% (95% CI: 71, 80) in  
319 patients with diabetes and 82% (95% CI: 76, 87) in control subjects. The seroprotection rates in  
320 those with diabetes aged 20 to 39 years, 40 to 49 years, 50 to 59 years, and at least 60 years were  
321 89%, 81%, 83%, and 58%, respectively. The seroprotection rates in those without diabetes in  
322 these same age-groups were 100%, 86%, 82% and 70%, respectively. Subjects with diabetes and  
323 a BMI of at least 30 kg/m<sup>2</sup> had a seroprotection rate of 72% compared with 80% in diabetic  
324 subjects with lower BMIs. In control subjects, seroprotection rates were 82% in those with a  
325 BMI of at least 30 kg/m<sup>2</sup> and 83% in those with lower BMIs.

### 326 **14.3 Immunogenicity in Neonates**

327 In clinical studies, neonates were given ENGERIX-B (10 mcg/0.5 mL) at 0, 1, and 6 months or  
328 at 0, 1, and 2 months of age. The immune response to vaccination was evaluated in sera obtained  
329 1 month after the third dose of ENGERIX-B.

330 Among infants administered ENGERIX-B at 0, 1, and 6 months, 100% of evaluable subjects  
331 (N = 52) seroconverted by Month 7. The GMT was 713 mIU/mL. Of these, 97% had  
332 seroprotective levels ( $\geq 10$  mIU/mL).

333 Among infants enrolled (N = 381) to receive ENGERIX-B at 0, 1, and 2 months of age, 96% had  
334 seroprotective levels ( $\geq 10$  mIU/mL) by Month 4. The GMT among seroconverters (N = 311)  
335 (antibody titer  $\geq 1$  mIU/mL) was 210 mIU/mL. A subset of these children received a fourth dose  
336 of ENGERIX-B at 12 months of age. One month following this dose, seroconverters (N = 126)  
337 had a GMT of 2,941 mIU/mL.

### 338 **14.4 Immunogenicity in Children and Adults**

#### 339 Persons 6 Months through 10 Years of Age

340 In clinical trials, children (N = 242) 6 months through 10 years of age were given ENGERIX-B  
341 (10 mcg/0.5 mL) at 0, 1, and 6 months. One to 2 months after the third dose, the seroprotection  
342 rate was 98% and the GMT of seroconverters was 4,023 mIU/mL.

#### 343 Persons 5 through 16 Years of Age

344 In a separate clinical trial including both children and adolescents 5 through 16 years of age,  
345 ENGERIX-B (10 mcg/0.5 mL) was administered at 0, 1, and 6 months (N = 181) or 0, 12, and  
346 24 months (N = 161). Immediately before the third dose of vaccine, seroprotection was achieved  
347 in 92.3% of subjects vaccinated on the 0-, 1-, and 6-month schedule and 88.8% of subjects on the  
348 0-, 12-, and 24-month schedule (GMT: 117.9 mIU/mL versus 162.1 mIU/mL, respectively,  
349  $P = 0.18$ ). One month following the third dose, seroprotection was achieved in 99.5% of children  
350 vaccinated on the 0-, 1-, and 6-month schedule compared with 98.1% of those on the 0-, 12-, and  
351 24-month schedule. GMTs were higher ( $P = 0.02$ ) for children receiving vaccine on the 0-, 1-,  
352 and 6-month schedule compared with those on the 0-, 12-, and 24-month schedule  
353 (5,687.4 mIU/mL versus 3,158.7 mIU/mL, respectively).

#### 354 Persons 11 through 19 Years of Age

355 In clinical trials with healthy adolescent subjects 11 through 19 years of age, ENGERIX-B  
356 (10 mcg/0.5 mL) given at 0, 1, and 6 months produced a seroprotection rate of 97% at Month 8  
357 (N = 119) with a GMT of 1,989 mIU/mL (N = 118, 95% CI: 1,318, 3,020). Immunization with  
358 ENGERIX-B (20 mcg/1 mL) at 0, 1, and 6 months produced a seroprotection rate of 99% at  
359 Month 8 (N = 122) with a GMT of 7,672 mIU/mL (N = 122, 95% CI: 5,248, 10,965).

#### 360 Persons 16 through 65 Years of Age

361 Clinical trials in healthy adult and adolescent subjects (16 through 65 years of age) have shown  
362 that following a course of 3 doses of ENGERIX-B (20 mcg/1 mL) given at 0, 1, and 6 months,  
363 the seroprotection (antibody titers  $\geq 10$  mIU/mL) rate for all individuals was 79% at Month 6  
364 (5 months after second dose) and 96% at Month 7 (1 month after third dose); the GMT for  
365 seroconverters was 2,204 mIU/mL at Month 7 (N = 110).

366 An alternate 3-dose schedule (20 mcg/1 mL given at 0, 1, and 2 months) designed for certain  
367 populations (e.g., individuals who have or might have been recently exposed to the virus and  
368 travelers to high-risk areas) was also evaluated. At Month 3 (1 month after third dose), 99% of  
369 all individuals were seroprotected and remained protected through Month 12. On the alternate  
370 schedule, a fourth dose of ENGERIX-B (20 mcg/1 mL) at 12 months produced a GMT of  
371 9,163 mIU/mL at Month 13 (1 month after fourth dose) (N = 373).

#### 372 Persons 40 Years of Age and Older

373 Among subjects 40 years of age and older given ENGERIX-B (20 mcg/1 mL) at 0, 1, and  
374 6 months, the seroprotection rate 1 month after the third dose was 88% and the GMT for  
375 seroconverters was 610 mIU/mL (N = 50). In adults older than 40 years of age, ENGERIX-B  
376 produced anti-HBsAg antibody titers that were lower than those in younger adults.

#### 377 **14.5 Interchangeability with Other Hepatitis B Vaccines**

378 A controlled study (N = 48) demonstrated that completion of a course of immunization with 1  
379 dose of ENGERIX-B (20 mcg/1 mL) at Month 6 following 2 doses of RECOMBIVAX HB<sup>®</sup>  
380 (10 mcg) at Months 0 and 1 produced a similar GMT (4,077 mIU/mL) to immunization with 3

381 doses of RECOMBIVAX HB (10 mcg) at Months 0, 1, and 6 (GMT: 2,654 mIU/mL). Thus,  
382 ENGERIX-B can be used to complete a vaccination course initiated with RECOMBIVAX HB.<sup>8</sup>

## 383 **15 REFERENCES**

- 384 1. Centers for Disease Control and Prevention. Hepatitis B. In: Atkinson W, Wolfe C,  
385 Humiston S, Nelson R, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*.  
386 6th ed. Atlanta, GA: Public Health Foundation; 2000:207-229.
- 387 2. Centers for Disease Control and Prevention. A Comprehensive Immunization Strategy to  
388 Eliminate Transmission of Hepatitis B Virus Infection in the United States.  
389 Recommendations of the Advisory Committee on Immunization Practices (ACIP). Part 1:  
390 Immunization of Infants, Children, and Adolescents, *MMWR* 2005;54(RR-16);1-23.
- 391 3. Ascherio A, Zhang SM, Hernán MA, et al. Hepatitis B vaccination and the risk of multiple  
392 sclerosis. *N Engl J Med*. 2001;344(5):327-332.
- 393 4. Confavreux C, Suissa S, Saddier P, et al. Vaccination and the risk of relapse in multiple  
394 sclerosis. *N Engl J Med*. 2001-344(5):319-326.
- 395 5. Centers for Disease Control and Prevention. A Comprehensive Immunization Strategy to  
396 Eliminate Transmission of Hepatitis B Virus Infection in the United States.  
397 Recommendations of the Advisory Committee on Immunization Practices (ACIP). Part 2:  
398 Immunization of Adults, *MMWR* 2006;55(RR-16);1-25.
- 399 6. André FE, Safary A. Clinical experience with a yeast-derived hepatitis B vaccine. In:  
400 Zuckerman AJ, ed. *Viral Hepatitis and Liver Disease*. New York, NY: Alan R Liss, Inc.;  
401 1988:1025-1030.
- 402 7. Poovorawan Y, Sanpavat S, Pongpunlert W, et al. Protective efficacy of a recombinant DNA  
403 hepatitis B vaccine in neonates of HBe antigen-positive mothers. *JAMA*. 1989;261(22):3278-  
404 3281.
- 405 8. Bush LM, Moonsammy GI, Boscia JA. Evaluation of initiating a hepatitis B vaccination  
406 schedule with one vaccine and completing it with another. *Vaccine*. 1991;9(11):807-809.

## 407 **16 HOW SUPPLIED/STORAGE AND HANDLING**

408 ENGERIX-B is available in single-dose vials and prefilled disposable TIP-LOK syringes  
409 (packaged without needles) (Preservative-Free Formulation):

410 10-mcg/0.5 mL Pediatric/Adolescent Dose

411 NDC 58160-820-01 Vial in Package of 10: NDC 58160-820-11

412 NDC 58160-820-43 Syringe in Package of 10: NDC 58160-820-52

413 20-mcg/mL Adult Dose

414 NDC 58160-821-01 Vial in Package of 10: NDC 58160-821-11  
415 NDC 58160-821-05 Syringe in Package of 1: NDC 58160-821-34  
416 NDC 58160-821-43 Syringe in Package of 10: NDC 58160-821-52  
417 Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze; discard if product has been  
418 frozen. Do not dilute to administer.

419 **17 PATIENT COUNSELING INFORMATION**

- 420 • Inform vaccine recipients and parents or guardians of the potential benefits and risks of  
421 immunization with ENGERIX-B.
- 422 • Emphasize, when educating vaccine recipients and parents or guardians regarding potential  
423 side effects, that ENGERIX-B contains non-infectious purified HBsAg and cannot cause  
424 hepatitis B infection.
- 425 • Instruct vaccine recipients and parents or guardians to report any adverse events to their  
426 healthcare provider.
- 427 • Give vaccine recipients and parents or guardians the Vaccine Information Statements, which  
428 are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to  
429 immunization. These materials are available free of charge at the Centers for Disease Control  
430 and Prevention (CDC) website ([www.cdc.gov/vaccines](http://www.cdc.gov/vaccines)).

431  
432 ENGERIX-B and TIP-LOK are registered trademarks of the GSK group of companies.  
433 The other brand listed is a trademark of the respective owner and is not a trademark of the GSK  
434 group of companies. The maker of this brand is not affiliated with and does not endorse the GSK  
435 group of companies or its products.  
436



437  
438 Manufactured by **GlaxoSmithKline Biologicals**  
439 Rixensart, Belgium, US License No. 1617  
440 Distributed by **GlaxoSmithKline**  
441 Research Triangle Park, NC 27709

442  
443 ©201X, the GSK group of companies. All rights reserved.

444  
445 ENG:XXPI