

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**TWINRIX [Hepatitis A & Hepatitis B (Recombinant) Vaccine]**  
**Suspension for Intramuscular Injection**  
**Initial U.S. Approval: 2001**

### RECENT MAJOR CHANGES

Dosage and Administration, Preparation for Administration X/XXXX (2.1)

### INDICATIONS AND USAGE

TWINRIX is a vaccine indicated for active immunization against disease caused by hepatitis A virus and infection by all known subtypes of hepatitis B virus. TWINRIX is approved for use in persons 18 years of age or older. (1)

### DOSAGE AND ADMINISTRATION

- TWINRIX is administered by intramuscular injection. (2.2)
- Standard Dosing: A series of 3 doses (1 mL each) given on a 0-, 1-, and 6-month schedule. (2.3)
- Accelerated Dosing: A series of 4 doses (1 mL each) given on days 0, 7, and 21 to 30 followed by a booster dose at month 12. (2.3)

### DOSAGE FORMS AND STRENGTHS

Suspension for injection available in 1-mL single-dose vials and prefilled syringes. (3, 11, 16)

### CONTRAINDICATIONS

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

### WARNINGS AND PRECAUTIONS

- The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions. (5.1)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including TWINRIX. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.2)

### ADVERSE REACTIONS

Following any dose of TWINRIX, the most common ( $\geq 10\%$ ) solicited injection site reactions were injection site soreness (35% to 41%) and redness (8% to 11%); the most common solicited systemic adverse events were headache (13% to 22%) and fatigue (11% to 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 TWINRIX with any other vaccine or product in the same syringe or vial. (7.1)

### USE IN SPECIFIC POPULATIONS

- Safety and effectiveness of TWINRIX have not been established in pregnant women, nursing mothers, and pediatric patients. (8.1, 8.3, 8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: X/201X

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1 **FULL PRESCRIBING INFORMATION**

2 **1 INDICATIONS AND USAGE**

3 TWINRIX® is indicated for active immunization against disease caused by hepatitis A virus and  
4 infection by all known subtypes of hepatitis B virus. TWINRIX is approved for use in persons  
5 18 years of age or older.

6 **2 DOSAGE AND ADMINISTRATION**

7 **2.1 Preparation for Administration**

8 The vaccine should be re-suspended before use. When re-suspended, the vaccine will have a  
9 uniform hazy white appearance.

10 Upon storage, a fine white deposit with a clear colorless layer above may be present. Re-suspend  
11 the vaccine following the steps below.

- 12 1. Hold the syringe upright in a closed hand.
- 13 2. Shake the syringe by tipping it upside down and back upright again.
- 14 3. Repeat this action vigorously for at least 15 seconds.
- 15 4. Inspect the vaccine again:
  - 16 • If the vaccine appears as a uniform hazy white suspension, it is ready to use – the  
17 appearance should not be clear.
  - 18 • If the vaccine still does not appear as a uniform hazy white suspension, tip upside down  
19 and back upright again for at least another 15 seconds then inspect again.

20 Parenteral drug products should be inspected visually for particulate matter and discoloration  
21 prior to administration, whenever solution and container permit. If either of these conditions  
22 exists, the vaccine should not be administered.

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

24 For the vials, use a sterile needle and sterile syringe to withdraw the 1-mL dose and administer  
25 intramuscularly. Changing needles between drawing vaccine from a vial and injecting it into a  
26 recipient is not necessary unless the needle has been damaged or contaminated. Use a separate  
27 sterile needle and syringe for each individual.

28 **2.2 Administration**

29 TWINRIX should be administered by intramuscular injection only as a 1-mL dose. Administer in  
30 the deltoid region. Do not administer in the gluteal region; such injections may result in a  
31 suboptimal response.

32 Do not administer this product intravenously, intradermally, or subcutaneously.

### 33 **2.3 Recommended Dose and Schedule**

34 Standard dosing schedule consists of 3 doses (1-mL each), given intramuscularly at 0, 1, and 6  
35 months. Alternatively, an accelerated schedule of 4 doses (1-mL each), given intramuscularly on  
36 Days 0, 7, and 21 to 30 followed by a booster dose at Month 12 may be used.

## 37 **3 DOSAGE FORMS AND STRENGTHS**

38 Suspension for injection available in 1-mL single-dose vials and prefilled TIP-LOK<sup>®</sup> syringes  
39 [*see Description (11), How Supplied/Storage and Handling (16)*].

## 40 **4 CONTRAINDICATIONS**

41 Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis A-containing or  
42 hepatitis B-containing vaccine, or to any component of TWINRIX, including yeast and  
43 neomycin, is a contraindication to administration of TWINRIX [*see Description (11)*].

## 44 **5 WARNINGS AND PRECAUTIONS**

### 45 **5.1 Latex**

46 The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic  
47 reactions.

### 48 **5.2 Syncope**

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

### 53 **5.3 Preventing and Managing Allergic Vaccine Reactions**

54 Prior to immunization, the healthcare provider should review the immunization history for  
55 possible vaccine sensitivity and previous vaccination-related adverse reactions to allow an  
56 assessment of benefits and risks. Appropriate medical treatment and supervision must be  
57 available to manage possible anaphylactic reactions following administration of the vaccine. [*See*  
58 *Contraindications (4)*.]

### 59 **5.4 Moderate or Severe Acute Illness**

60 To avoid diagnostic confusion between manifestations of an acute illness and possible vaccine  
61 adverse effects, vaccination with TWINRIX should be postponed in persons with moderate or  
62 severe acute febrile illness unless they are at immediate risk of hepatitis A or hepatitis B  
63 infection.

64 **5.5 Altered Immunocompetence**

65 Immunocompromised persons, including individuals receiving immunosuppressive therapy, may  
66 have a diminished immune response to TWINRIX.

67 **5.6 Multiple Sclerosis**

68 Results from 2 clinical studies indicate that there is no association between hepatitis B  
69 vaccination and the development of multiple sclerosis,<sup>1</sup> and that vaccination with hepatitis B  
70 vaccine does not appear to increase the short-term risk of relapse in multiple sclerosis.<sup>2</sup>

71 **5.7 Limitations of Vaccine Effectiveness**

72 Hepatitis A and hepatitis B have relatively long incubation periods. The vaccine may not prevent  
73 hepatitis A or hepatitis B infection in individuals who have an unrecognized hepatitis A or  
74 hepatitis B infection at the time of vaccination. Additionally, vaccination with TWINRIX may  
75 not protect all individuals.

76 **6 ADVERSE REACTIONS**

77 **6.1 Clinical Trials Experience**

78 Because clinical trials are conducted under widely varying conditions, adverse reaction rates  
79 observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical  
80 trials of another vaccine and may not reflect the rates observed in practice. As with any vaccine,  
81 there is the possibility that broad use of TWINRIX could reveal adverse events not observed in  
82 clinical trials.

83 Following any dose of TWINRIX, the most common ( $\geq 10\%$ ) solicited injection site reactions  
84 were injection site soreness (35% to 41%) and redness (8% to 11%); the most common solicited  
85 systemic adverse events were headache (13% to 22%) and fatigue (11% to 14%).

86 The safety of TWINRIX has been evaluated in clinical trials involving the administration of  
87 approximately 7,500 doses to more than 2,500 individuals.

88 In a US study, 773 subjects (aged 18 to 70 years) were randomized 1:1 to receive TWINRIX (0-,  
89 1-, and 6-month schedule) or concurrent administration of ENGERIX-B (0-, 1-, and 6-month  
90 schedule) and HAVRIX (0- and 6-month schedule). Solicited local adverse reactions and  
91 systemic adverse events were recorded by parents/guardians on diary cards for 4 days (Days 0 to  
92 3) after vaccination. Unsolicited adverse events were recorded for 31 days after vaccination.  
93 Solicited events reported following the administration of TWINRIX or ENGERIX-B and  
94 HAVRIX are presented in Table 1.

95 **Table 1. Rates of Local Adverse Reactions and Systemic Adverse Events within 4 Days of**  
 96 **Vaccination<sup>a</sup> with TWINRIX<sup>b</sup> or ENGERIX-B and HAVRIX<sup>c</sup>**

Local	TWINRIX			ENGERIX-B			HAVRIX	
	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2
	(n = 385) %	(n = 382) %	(n = 374) %	(n = 382) %	(n = 376) %	(n = 369) %	(n = 382) %	(n = 369) %
Soreness	37	35	41	41	25	30	53	47
Redness	8	9	11	6	7	9	7	9
Swelling	4	4	6	3	5	5	5	5
Systemic	TWINRIX			ENGERIX-B and HAVRIX				
	Dose 1	Dose 2	Dose 3	Dose 1 <sup>d</sup>	Dose 2 <sup>e</sup>	Dose 3 <sup>d</sup>		
	(n = 385) %	(n = 382) %	(n = 374) %	(n = 382) %	(n = 376) %	(n = 369) %		
Headache	22	15	13	19	12	14		
Fatigue	14	13	11	14	9	10		
Diarrhea	5	4	6	5	3	3		
Nausea	4	3	2	7	3	5		
Fever	4	3	2	4	2	4		
Vomiting	1	1	0	1	1	1		

97 <sup>a</sup> Within 4 days of vaccination defined as day of vaccination and the next 3 days.

98 <sup>b</sup> 389 subjects received at least 1 dose of TWINRIX.

99 <sup>c</sup> 384 subjects received at least 1 dose each of ENGERIX-B and HAVRIX.

100 <sup>d</sup> Doses 1 and 3 included ENGERIX-B and HAVRIX in the control group receiving separate  
 101 vaccinations.

102 <sup>e</sup> Dose 2 included only ENGERIX-B in the control group receiving separate vaccinations.

103 Most solicited local adverse reactions and systemic adverse events seen with TWINRIX were  
 104 considered by the subjects as mild and self-limiting and did not last more than 48 hours.

105 In a clinical trial in which TWINRIX was given on a 0-, 7-, and 21- to 30-day schedule followed  
 106 by a booster dose at 12 months, solicited local adverse reactions or systemic adverse events were  
 107 comparable to those seen in other clinical trials of TWINRIX given on a 0-, 1-, and 6-month  
 108 schedule.

109 Among 2,299 subjects in 14 clinical trials, the following adverse events were reported to occur  
 110 within 30 days following vaccination:

111 Incidence 1% to 10% of Injections, Seen in Clinical Trials with TWINRIX

112 *Infections and Infestations*: Upper respiratory tract infections.

113 *General Disorders and Administration Site Conditions*: Injection site induration.

114 Incidence <1% of Injections, Seen in Clinical Trials with TWINRIX

115 *Infections and Infestations*: Respiratory tract illnesses.

116 *Metabolism and Nutrition Disorders*: Anorexia.

117 *Psychiatric Disorders*: Agitation, insomnia.

118 *Nervous System Disorders*: Dizziness, migraine, paresthesia, somnolence, syncope.

119 *Ear and Labyrinth Disorders*: Vertigo.

120 *Vascular Disorders*: Flushing.

121 *Gastrointestinal Disorders*: Abdominal pain, vomiting.

122 *Skin and Subcutaneous Tissue Disorders*: Erythema, petechiae, rash, sweating, urticaria.

123 *Musculoskeletal and Connective Tissue Disorders*: Arthralgia, back pain, myalgia.

124 *General Disorders and Administration Site Conditions*: Injection site ecchymosis, injection

125 site pruritus, influenza-like symptoms, irritability, weakness.

126 Incidence <1% of Injections, Seen in Clinical Trials with HAVRIX and/or ENGERIX-B

127 *Blood and Lymphatic System Disorders*: Lymphadenopathy.<sup>a+b</sup>

128 *Nervous System Disorders*: Dysgeusia,<sup>a</sup> hypertonia,<sup>a</sup> tingling.<sup>b</sup>

129 *Eye Disorders*: Photophobia.<sup>a</sup>

130 *Vascular Disorders*: Hypotension.<sup>b</sup>

131 *Gastrointestinal Disorders*: Constipation.<sup>b</sup>

132 *Investigations*: Creatine phosphokinase increased.<sup>a</sup>

133 <sup>a+b</sup> Following either HAVRIX or ENGERIX-B.

134 <sup>a</sup> Following HAVRIX.

135 <sup>b</sup> Following ENGERIX-B.

136 Adverse events within 30 days of vaccination in the US clinical trial of TWINRIX given on a 0-,

137 7-, and 21- to 30-day schedule followed by a booster dose at 12 months were comparable to

138 those reported in other clinical trials.

139 **6.2 Postmarketing Experience**

140 The following adverse events have been identified during postapproval use of TWINRIX,  
141 HAVRIX, or ENGERIX-B. Because these events are reported voluntarily from a population of  
142 uncertain size, it is not possible to reliably estimate their frequency or establish a causal  
143 relationship to product exposure.

144 Postmarketing Experience with TWINRIX

145 The following list includes serious events or events which have suspected causal connection to  
146 components of TWINRIX.

147 *Infections and Infestations:* Herpes zoster, meningitis.

148 *Blood and Lymphatic System Disorders:* Thrombocytopenia, thrombocytopenic purpura.

149 *Immune System Disorders:* Allergic reaction, anaphylactoid reaction, anaphylaxis, serum  
150 sickness–like syndrome days to weeks after vaccination (including arthralgia/arthritis, usually  
151 transient; fever; urticaria; erythema multiforme; ecchymoses; and erythema nodosum).

152 *Nervous System Disorders:* Bell's palsy, convulsions, encephalitis, encephalopathy,  
153 Guillain-Barré syndrome, hypoesthesia, myelitis, multiple sclerosis, neuritis, neuropathy, optic  
154 neuritis, paralysis, paresis, transverse myelitis.

155 *Eye Disorders:* Conjunctivitis, visual disturbances.

156 *Ear and Labyrinth Disorders:* Earache, tinnitus.

157 *Cardiac Disorders:* Palpitations, tachycardia.

158 *Vascular Disorders:* Vasculitis.

159 *Respiratory, Thoracic, and Mediastinal Disorders:* Bronchospasm including asthma-like  
160 symptoms, dyspnea.

161 *Gastrointestinal Disorders:* Dyspepsia.

162 *Hepatobiliary Disorders:* Hepatitis, jaundice.

163 *Skin and Subcutaneous Tissue Disorders:* Alopecia, angioedema, eczema, erythema  
164 multiforme, erythema nodosum, hyperhidrosis, lichen planus.

165 *Musculoskeletal and Connective Tissue Disorders:* Arthritis, muscular weakness.

166 *General Disorders and Administration Site Conditions:* Chills; immediate injection site pain,  
167 stinging, and burning sensation; injection site reaction; malaise.

168 *Investigations:* Abnormal liver function tests.

169 Postmarketing Experience with HAVRIX and/or ENGERIX-B

170 The following list includes serious events or events which have suspected causal connection to  
171 components of HAVRIX and/or ENGERIX-B, not already reported above for TWINRIX.

172 *Eye Disorders: Keratitis.*<sup>a</sup>

173 *Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome.*<sup>a</sup>

174 *Congenital, Familial, and Genetic Disorders: Congenital abnormality.*<sup>b</sup>

175 <sup>a</sup> Following ENGERIX-B.

176 <sup>b</sup> Following HAVRIX.

## 177 **7 DRUG INTERACTIONS**

### 178 **7.1 Concomitant Administration with Vaccines and Immune Globulin**

179 Do not mix TWINRIX with any other vaccine or product in the same syringe or vial.

180 When concomitant administration of immunoglobulin is required, it should be given with a  
181 different syringe and at a different injection site.

182 There are no data to assess the concomitant use of TWINRIX with other vaccines.

### 183 **7.2 Immunosuppressive Therapies**

184 Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic  
185 drugs, and corticosteroids (used in greater-than-physiologic doses), may reduce the immune  
186 response to TWINRIX.

## 187 **8 USE IN SPECIFIC POPULATIONS**

### 188 **8.1 Pregnancy**

189 Pregnancy Category C

190 Animal reproduction studies have not been conducted with TWINRIX. It is also not known  
191 whether TWINRIX can cause fetal harm when administered to a pregnant woman or can affect  
192 reproduction capacity. TWINRIX should be given to a pregnant woman only if clearly needed.

### 193 **8.3 Nursing Mothers**

194 It is not known whether TWINRIX is excreted in human milk. Because many drugs are excreted  
195 in human milk, caution should be exercised when TWINRIX is administered to a nursing  
196 woman.

### 197 **8.4 Pediatric Use**

198 Safety and effectiveness in pediatric patients younger than 18 years have not been established.

### 199 **8.5 Geriatric Use**

200 Clinical studies of TWINRIX did not include sufficient numbers of subjects aged 65 years and  
201 older to determine whether they respond differently from younger subjects [*see Clinical Studies*  
202 (*14.1, 14.3*)].



203 **11 DESCRIPTION**

204 TWINRIX [Hepatitis A & Hepatitis B (Recombinant) Vaccine] is a bivalent vaccine containing  
205 the antigenic components used in producing HAVRIX<sup>®</sup> (Hepatitis A Vaccine) and  
206 ENGERIX-B<sup>®</sup> [Hepatitis B Vaccine (Recombinant)]. TWINRIX is a sterile suspension for  
207 intramuscular administration that contains inactivated hepatitis A virus (strain HM175) and  
208 noninfectious hepatitis B virus surface antigen (HBsAg). The hepatitis A virus is propagated in  
209 MRC-5 human diploid cells and inactivated with formalin. The purified HBsAg is obtained by  
210 culturing genetically engineered *Saccharomyces cerevisiae* yeast cells, which carry the surface  
211 antigen gene of the hepatitis B virus. Bulk preparations of each antigen are adsorbed separately  
212 onto aluminum salts and then pooled during formulation.

213 A 1-mL dose of vaccine contains 720 ELISA Units of inactivated hepatitis A virus and 20 mcg  
214 of recombinant HBsAg protein. One dose of vaccine also contains 0.45 mg of aluminum in the  
215 form of aluminum phosphate and aluminum hydroxide as adjuvants, amino acids, sodium  
216 chloride, phosphate buffer, polysorbate 20, and Water for Injection. From the manufacturing  
217 process each 1-mL dose of TWINRIX also contains residual formalin (not more than 0.1 mg),  
218 MRC-5 cellular proteins (not more than 2.5 mcg), neomycin sulfate (an aminoglycoside  
219 antibiotic included in the cell growth media; not more than 20 ng), and yeast protein (no more  
220 than 5%).

221 TWINRIX is available in vials and prefilled syringes. The tip caps of the prefilled syringes  
222 contain natural rubber latex; the plungers are not made with natural rubber latex. The vial  
223 stoppers are not made with natural rubber latex.

224 TWINRIX is formulated without preservatives.

225 **12 CLINICAL PHARMACOLOGY**

226 **12.1 Mechanism of Action**

227 Hepatitis A

228 The course of infection with hepatitis A virus (HAV) is extremely variable, ranging from  
229 asymptomatic infection to fulminant hepatitis.<sup>3</sup>

230 The presence of antibodies to HAV (anti-HAV) confers protection against hepatitis A disease.  
231 However, the lowest titer needed to confer protection has not been determined. Natural infection  
232 provides lifelong immunity even when antibodies to hepatitis A are undetectable. Seroconversion  
233 is defined as antibody titers equal to or greater than the assay cut-off (cut-off values vary  
234 depending on the assay used) in those previously seronegative.

235 Hepatitis B

236 Infection with hepatitis B virus (HBV) can have serious consequences including acute massive  
237 hepatic necrosis and chronic active hepatitis. Chronically infected persons are at increased risk  
238 for cirrhosis and hepatocellular carcinoma.

239 Antibody concentrations  $\geq 10$  mIU/mL against HBsAg are recognized as conferring protection  
240 against hepatitis B virus infection.<sup>4</sup>

## 241 **13 NONCLINICAL TOXICOLOGY**

### 242 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

243 TWINRIX has not been evaluated for its carcinogenic or mutagenic potential, or for impairment  
244 of fertility.

## 245 **14 CLINICAL STUDIES**

### 246 **14.1 Immunogenicity: Standard 0-, 1-, and 6-Month Dosing Schedule**

247 In 11 clinical trials, sera from 1,551 healthy adults aged 17 to 70 years, including 555 male  
248 subjects and 996 female subjects, were analyzed following administration of 3 doses of  
249 TWINRIX on a 0-, 1-, and 6-month schedule. Seroconversion (defined as equal to or greater than  
250 assay cut-off depending on assay used) for antibodies against HAV was elicited in 99.9% of  
251 vaccinees, and protective antibodies (defined as  $\geq 10$  mIU/mL) against HBV surface antigen were  
252 detected in 98.5% of vaccinees, 1 month after completion of the 3-dose series (Table 2).

253 **Table 2. Seroconversion and Seroprotection Rates in Worldwide Clinical Trials**

<b>Dose of TWINRIX</b>	<b>n</b>	<b>% Seroconversion for Hepatitis A<sup>a</sup></b>	<b>% Seroprotection for Hepatitis B<sup>b</sup></b>
1	1,587	93.8	30.8
2	1,571	98.8	78.2
3	1,551	99.9	98.5

254 <sup>a</sup> Anti-HAV titer  $\geq$  assay cut-off: 20 mIU/mL (HAVAB Test) or 33 mIU/mL  
255 (ENZYMUN-TEST<sup>®</sup>).

256 <sup>b</sup> Anti-HBsAg titer  $\geq 10$  mIU/mL (AUSAB<sup>®</sup> Test).

257 One of the 11 trials was a comparative trial conducted in a US population given either  
258 TWINRIX (on a 0-, 1-, and 6-month schedule) or HAVRIX (0- and 6-month schedule) and  
259 ENGERIX-B (0-, 1-, and 6-month schedule). The monovalent vaccines were given  
260 concurrently in opposite arms. Of the 773 adults (aged 18 to 70 years) enrolled in this trial, an  
261 immunogenicity analysis was performed in 533 subjects who completed the study according to  
262 protocol. Of these, 264 subjects received TWINRIX and 269 subjects received HAVRIX and  
263 ENGERIX-B. Seroconversion rates against HAV and seroprotection rates against HBV are  
264 presented in Table 3; geometric mean titers (GMTs) are presented in Table 4. The absolute  
265 difference in anti-HAV seropositivity rates between groups was 0.36% (90% CI: -1.8, 3.1).  
266 Non-inferiority in terms of anti-HAV response was demonstrated (lower limit of the 90% CI  
267 was higher than the pre-specified non-inferiority criterion of -4.3%). The absolute difference in  
268 anti-HBsAg seroprotection rates between groups was 2.8% (90% CI: -1.3, 7.7). Non-inferiority

269 in terms of anti-HBV response was demonstrated (lower limit of the 90% CI was higher than  
 270 the pre-specified non-inferiority criterion of -9.4%).

271 **Table 3. Seroconversion and Seroprotection Rates in a US Clinical Trial**

Vaccine	n	Timepoint	% Seroconversion for Hepatitis A <sup>a</sup> (95% CI)	% Seroprotection for Hepatitis B <sup>b</sup> (95% CI)
TWINRIX	264	Month 1	91.6	17.9
		Month 2	97.7	61.2
		Month 7	99.6 (97.9, 100.0)	95.1 (91.7, 97.4)
HAVRIX and ENGERIX-B	269	Month 1	98.1	7.5
		Month 2	98.9	50.4
		Month 7	99.3 (97.3, 99.9)	92.2 (88.3, 95.1)

272 CI = Confidence Interval.

273 <sup>a</sup> Anti-HAV titer  $\geq$  assay cut-off: 33 mIU/mL (ENZYMUN-TEST).

274 <sup>b</sup> Anti-HBsAg titer  $\geq$  10 mIU/mL (AUSAB Test).

275 **Table 4. Geometric Mean Titers in a US Clinical Trial**

Vaccine	n	Timepoint	GMT to Hepatitis A (95% CI)	GMT to Hepatitis B (95% CI)
TWINRIX	263	Month 1	335	8
	259	Month 2	636	23
	264	Month 7	4756 (4152, 5448)	2099 (1663, 2649)
HAVRIX and ENGERIX-B	268	Month 1	444	6
	269	Month 2	257	18
	269	Month 7	2948 (2638, 3294)	1871 (1428, 2450)

276 GMT = Geometric mean titer; CI = Confidence Interval.

277 Since the immune responses to hepatitis A and hepatitis B induced by TWINRIX were  
 278 non-inferior to the monovalent vaccines, efficacy is expected to be similar to the efficacy for  
 279 each of the monovalent vaccines.

280 The antibody titers achieved 1 month after the final dose of TWINRIX were higher than titers  
 281 achieved 1 month after the final dose of HAVRIX in this clinical trial. This may have been due  
 282 to a difference in the recommended dosage regimens for these 2 vaccines, whereby vaccinees  
 283 receiving TWINRIX received 3 doses of 720 EL.U. of hepatitis A antigen at 0, 1, and 6 months,  
 284 whereas vaccinees receiving HAVRIX received 2 doses of 1440 EL.U. of the same antigen (at 0  
 285 and 6 months). However, these differences in peak titer have not been shown to be clinically  
 286 significant.

287 **14.2 Immunogenicity: Accelerated Dosing Schedule (Day 0, 7, and 21-30, Month**  
 288 **12)**

289 In 496 healthy adults, the safety and immunogenicity of TWINRIX given on a 0-, 7-, and 21- to  
 290 30-day schedule followed by a booster dose at 12 months (n = 250), was compared with separate  
 291 vaccinations with monovalent hepatitis A vaccine (HAVRIX at 0 and 12 months) and hepatitis B  
 292 vaccine (ENGERIX-B at 0, 1, 2, and 12 months) as a control group (n = 246).

293 Following a booster dose at Month 12, seroprotection rates for hepatitis B and seroconversion  
 294 rates for hepatitis A at Month 13 following TWINRIX were non-inferior to the control group.  
 295 The absolute difference in anti-HBs seroprotection rates between groups (HAVRIX +  
 296 ENGERIX-B minus TWINRIX) was -2.99 (95% CI: -7.80, 1.49). Non-inferiority was  
 297 demonstrated as the upper limit of the 95% CI was lower than the pre-defined limit of 7%. The  
 298 absolute difference in anti-HAV seroprotection rates between groups (HAVRIX + ENGERIX-B  
 299 minus TWINRIX) was 0 (95% CI: -1.91, 1.94). Non-inferiority was demonstrated as the upper  
 300 limit of the 95% CI was lower than the pre-defined limit of 7%. The immune responses are  
 301 presented in Table 5.

302 **Table 5. Seroconversion and Seroprotection Rates up to 1 Month after the Last Dose of**  
 303 **Vaccines (According-to-Protocol Cohort)**

	Timepoint	TWINRIX <sup>a</sup>	HAVRIX and ENGERIX-B <sup>b</sup>
		(n = 194-204)	(n = 197-207)
% Seroconversion for Hepatitis A <sup>c</sup> (95% CI)	Day 37	98.5 (95.8, 99.7)	98.6 (95.8, 99.7)
	Day 90	100 (98.2, 100)	95.6 (91.9, 98.0)
	Month 12	96.9 (93.4, 98.9)	86.9 (81.4, 91.2)
	Month 13	100 (98.1, 100)	100 (98.1, 100)
% Seroprotection for Hepatitis B <sup>d</sup> (95% CI)	Day 37	63.2 (56.2, 69.9)	43.5 (36.6, 50.5)
	Day 90	83.2 (77.3, 88.1)	76.7 (70.3, 82.3)
	Month 12	82.1 (75.9, 87.2)	77.8 (71.3, 83.4)
	Month 13	96.4 (92.7, 98.5)	93.4 (89.0, 96.4)

304 CI = Confidence Interval.

305 <sup>a</sup> TWINRIX given on a 0-, 7-, and 21- to 30-day schedule followed by a booster at Month 12.

306 <sup>b</sup> HAVRIX 1440 EL.U./1 mL given on a 0- and 12-month schedule and ENGERIX-B  
 307 20 mcg/1 mL given on a 0-, 1-, 2-, and 12-month schedule.

308 <sup>c</sup> Anti-HAV titer ≥ assay cut-off: 15 mIU/mL (anti-HAV Behring Test).

309 <sup>d</sup> Anti-HBsAg titer ≥ 10 mIU/mL (AUSAB Test).

310 **14.3 Immunogenicity in Adults Older than 40 Years**

311 The effect of age on immune response to TWINRIX was studied in 2 trials. The first trial  
 312 evaluated subjects aged 41 to 63 years (N = 72; mean age = 50). All subjects were seropositive

313 for anti-HAV antibodies following the third dose of TWINRIX. For the hepatitis B response,  
314 94% of subjects were seroprotected after the third dose of TWINRIX.

315 The second trial included subjects aged 19 years and older with a comparison between those  
316 older than 40 years (n = 183, aged 41 to 70 years; mean age = 48) and those aged 40 years or  
317 younger (n = 191; aged 19 to 40 years; mean age 33). More than 99% of subjects in both age  
318 groups achieved a seropositive response for anti-HAV antibodies, and GMTs were comparable  
319 between the age groups. In the older subjects who received TWINRIX, 92.9% (95% CI: 88.2,  
320 96.2) achieved seroprotection against hepatitis B compared with 96.9% (95% CI: 93.3, 98.8) of  
321 the younger subjects. The GMT was 1,890 mIU/mL in the older subjects compared with  
322 2,285 mIU/mL in the younger subjects.

#### 323 **14.4 Duration of Immunity**

324 Two clinical trials involving a total of 129 subjects demonstrated that antibodies to both HAV  
325 and HBV surface antigen persisted for at least 4 years after the first vaccine dose in a 3-dose  
326 series of TWINRIX, given on a 0-, 1-, and 6-month schedule. For comparison, after the  
327 recommended immunization regimens for HAVRIX and ENGERIX-B, respectively, similar  
328 studies involving a total of 114 subjects have shown that seropositivity to HAV and HBV also  
329 persists for at least 4 years.

### 330 **15 REFERENCES**

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### 339 **16 HOW SUPPLIED/STORAGE AND HANDLING**

340 TWINRIX is available in 1-mL single-dose vials and 1-mL single-dose prefilled disposable  
341 TIP-LOK syringes (packaged without needles) (Preservative-Free Formulation):

342 NDC 58160-815-01 Vial in Package of 10: NDC 58160-815-11

343 NDC 58160-815-05 Syringe in Package of 1: NDC 58160-815-34

344 NDC 58160-815-43 Syringe in Package of 10: NDC 58160-815-52

345 Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze; discard if product has been  
346 frozen.

347 **17 PATIENT COUNSELING INFORMATION**

- 348 • Inform vaccine recipients of the potential benefits and risks of immunization with  
349 TWINRIX.
- 350 • Emphasize, when educating vaccine recipients regarding potential side effects, that  
351 components of TWINRIX cannot cause hepatitis A or hepatitis B infection.
- 352 • Instruct vaccine recipients to report any adverse events to their healthcare provider.
- 353 • Inform that safety and efficacy have not been established in pregnant women.
- 354 • Give vaccine recipients the Vaccine Information Statements, which are required by the  
355 National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These  
356 materials are available free of charge at the Centers for Disease Control and Prevention  
357 (CDC) website ([www.cdc.gov/vaccines](http://www.cdc.gov/vaccines)).

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