

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

HAVRIX (Hepatitis A Vaccine)
Suspension for Intramuscular Injection
Initial U.S. Approval: 1995

INDICATIONS AND USAGE

HAVRIX is a vaccine indicated for active immunization against disease caused by hepatitis A virus (HAV). HAVRIX is approved for use in persons 12 months of age and older. Primary immunization should be administered at least 2 weeks prior to expected exposure to HAV. (1)

DOSAGE AND ADMINISTRATION

- HAVRIX is administered by intramuscular injection. (2.2)
- Children and adolescents: A single 0.5-mL dose and a 0.5-mL booster dose administered between 6 to 12 months later. (2.3)
- Adults: A single 1-mL dose and a 1-mL booster dose administered between 6 to 12 months later. (2.3)

DOSAGE FORMS AND STRENGTHS

- Suspension for injection available in the following presentations:
- 0.5-mL single-dose vials and prefilled syringes. (3)
- 1-mL single-dose vials and prefilled syringes. (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

- In studies of adults and children 2 years of age and older, the most common solicited adverse events were injection-site soreness (56% of adults and 21% of children) and headache (14% of adults and less than 9% of children). (6.1)
- In studies of children 11 to 25 months of age, the most frequently reported solicited local reactions were pain (32%) and redness (29%). Common solicited general adverse events were irritability (42%), drowsiness (28%), and loss of appetite (28%). (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.

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

Safety and effectiveness of HAVRIX have not been established in pregnant women and nursing mothers. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: X/201X

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

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Latex
- 5.2 Syncope
- 5.3 Preventing and Managing Allergic Vaccine Reactions
- 5.4 Altered Immunocompetence
- 5.5 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 Immunosuppressive Therapies

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Pediatric Effectiveness Studies
- 14.2 Immunogenicity in Children and Adolescents
- 14.3 Immunogenicity in Adults
- 14.4 Duration of Immunity
- 14.5 Immune Response to Concomitantly Administered 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 HAVRIX[®] is indicated for active immunization against disease caused by hepatitis A virus
4 (HAV). HAVRIX is approved for use in persons 12 months of age and older. Primary
5 immunization should be administered at least 2 weeks prior to expected exposure to HAV.

6 2 DOSAGE AND ADMINISTRATION

7 2.1 Preparation for Administration

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

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

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

18 2.2 Administration

19 HAVRIX should be administered by intramuscular injection only. HAVRIX should not be
20 administered in the gluteal region; such injections may result in suboptimal response.

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

22 2.3 Recommended Dose and Schedule

23 Children and Adolescents

24 Primary immunization for children and adolescents (12 months through 18 years of age) consists
25 of a single 0.5-mL dose and a 0.5-mL booster dose administered anytime between 6 and
26 12 months later. The preferred sites for intramuscular injections are the anterolateral aspect of
27 the thigh in young children or the deltoid muscle of the upper arm in older children.

28 Adults

29 Primary immunization for adults consists of a single 1-mL dose and a 1-mL booster dose
30 administered anytime between 6 and 12 months later. In adults, the injection should be given in
31 the deltoid region.

32 **3 DOSAGE FORMS AND STRENGTHS**

33 Suspension for injection available in the following presentations:

- 34 • 0.5-mL single-dose vials and prefilled TIP-LOK[®] syringes.
35 • 1-mL single-dose vials and prefilled TIP-LOK syringes. [*See How Supplied/Storage and*
36 *Handling (16).*]

37 **4 CONTRAINDICATIONS**

38 Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis A-containing
39 vaccine, or to any component of HAVRIX, including neomycin, is a contraindication to
40 administration of HAVRIX [*see Description (11)*].

41 **5 WARNINGS AND PRECAUTIONS**

42 **5.1 Latex**

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

45 **5.2 Syncope**

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

50 **5.3 Preventing and Managing Allergic Vaccine Reactions**

51 Appropriate medical treatment and supervision must be available to manage possible
52 anaphylactic reactions following administration of the vaccine [*see Contraindications (4)*].

53 **5.4 Altered Immunocompetence**

54 Immunocompromised persons may have a diminished immune response to HAVRIX, including
55 individuals receiving immunosuppressant therapy.

56 **5.5 Limitations of Vaccine Effectiveness**

57 Hepatitis A virus has a relatively long incubation period (15 to 50 days). HAVRIX may not
58 prevent hepatitis A infection in individuals who have an unrecognized hepatitis A infection at the
59 time of vaccination. Additionally, vaccination with HAVRIX may not protect all individuals.

60 **6 ADVERSE REACTIONS**

61 **6.1 Clinical Trials Experience**

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

65 The safety of HAVRIX has been evaluated in 61 clinical trials involving approximately 37,000
66 individuals receiving doses of 360 EL.U. (n = 21,928 in 3- or 4-dose schedule), 720 EL.U.
67 (n = 12,274 in 2- or 3-dose schedule), or 1440 EL.U. (n = 2,782 in 2- or 3-dose schedule).

68 Of solicited adverse events in clinical trials of adults, who received HAVRIX 1440 EL.U., and
69 children (2 years of age and older), who received either HAVRIX 360 EL.U. or 720 EL.U., the
70 most frequently reported was injection-site soreness (56% of adults and 21% of children); less
71 than 0.5% of soreness was reported as severe. Headache was reported by 14% of adults and less
72 than 9% of children. Other solicited and unsolicited events occurring during clinical trials are
73 listed below.

74 Incidence 1% to 10% of Injections

75 *Metabolism and Nutrition Disorders:* Anorexia.

76 *Gastrointestinal Disorders:* Nausea.

77 *General Disorders and Administration Site Conditions:* Fatigue, fever >99.5°F (37.5°C),
78 induration, redness, and swelling of the injection site; malaise.

79 Incidence <1% of Injections

80 *Infections and Infestations:* Pharyngitis, upper respiratory tract infections.

81 *Blood and Lymphatic System Disorders:* Lymphadenopathy.

82 *Psychiatric Disorders:* Insomnia.

83 *Nervous System Disorders:* Dysgeusia, hypertonia.

84 *Eye Disorders:* Photophobia.

85 *Ear and Labyrinth Disorders:* Vertigo.

86 *Gastrointestinal Disorders:* Abdominal pain, diarrhea, vomiting.

87 *Skin and Subcutaneous Tissue Disorders:* Pruritus, rash, urticaria.

88 *Musculoskeletal and Connective Tissue Disorders:* Arthralgia, myalgia.

89 *General Disorders and Administration Site Conditions:* Injection site hematoma.

90 *Investigations:* Creatine phosphokinase increased.

91 Coadministration Studies of HAVRIX in Children 11 to 25 Months of Age

92 In 4 studies, 3,152 children 11 to 25 months of age received at least one dose of HAVRIX
93 720 EL.U. administered alone or concomitantly with other routine childhood vaccinations [*see*
94 *Clinical Studies (14.2, 14.5)*]. The studies included HAV 210 (N = 1,084), HAV 232 (N = 394),
95 HAV 220 (N = 433), and HAV 231 (N = 1,241).

96 In the largest of these studies (HAV 231) conducted in the US, 1,241 children 15 months of age
97 were randomized to receive: Group 1) HAVRIX alone; Group 2) HAVRIX concomitantly with
98 measles, mumps, and rubella (MMR) vaccine (manufactured by Merck and Co.) and varicella
99 vaccine (manufactured by Merck and Co.); or Group 3) MMR and varicella vaccines. Subjects in
100 Group 3 who received MMR and varicella vaccines received the first dose of HAVRIX 42 days
101 later. A second dose of HAVRIX was administered to all subjects 6 to 9 months after the first
102 dose of HAVRIX. Solicited local adverse reactions and general events were recorded by
103 parents/guardians on diary cards for 4 days (days 0 to 3) after vaccination. Unsolicited adverse
104 events were recorded on the diary card for 31 days after vaccination. Telephone follow-up was
105 conducted 6 months after the last vaccination to inquire about serious adverse events, new onset
106 chronic illnesses and medically significant events. A total of 1,035 children completed the 6-
107 month follow-up. Among subjects in all groups combined, 53% were male; 69% of subjects were
108 white, 16% were Hispanic, 9% were black and 6% were other racial/ethnic groups.

109 Percentages of subjects with solicited local adverse reactions and general adverse events
110 following HAVRIX administered alone (Group 1) or concomitantly with MMR and varicella
111 vaccines (Group 2) are presented in Table 1. The solicited adverse events from the 3 additional
112 coadministration studies conducted with HAVRIX were comparable to those from Study
113 HAV 231.

114 **Table 1. Solicited Local Adverse Reactions and General Adverse Events occurring within**
 115 **4 Days of Vaccination^a in Children 15 to 24 Months of Age with HAVRIX Administered**
 116 **Alone or Concomitantly with MMR and Varicella Vaccines (TVC)**

	Group 1 HAVRIX Dose 1 %	Group 2 HAVRIX+ MMR+V^b Dose 1 %	Group 1 HAVRIX Dose 2 %	Group 2 HAVRIX Dose 2 %
Local (at injection site for HAVRIX)				
N	298	411	272	373
Pain, any	23.8	23.6	24.3	30.3
Redness, any	20.1	20.0	22.8	23.9
Swelling, any	8.7	10.2	9.6	9.9
General				
N	300	417	271	375
Irritability, any	33.3	43.9	31.0	27.2
Irritability, grade 3	0.3	1.9	1.5	0.3
Drowsiness, any	22.3	35.3	21.0	20.8
Drowsiness, grade 3	1.0	2.2	1.1	0.0
Loss of appetite, any	18.3	26.1	19.9	20.5
Loss of appetite, grade 3	1.0	1.4	0.4	0.3
Fever ≥100.6°F (38.1°C)	3.0	4.8	3.3	2.7
Fever ≥101.5°F (38.6°C)	2.0	2.6	1.8	1.6
Fever ≥102.4°F (39.1°C)	0.7	0.7	0.4	1.1

117 Total vaccinated cohort (TVC) = all subjects who received at least one dose of vaccine.

118 N = number of subjects who received at least one dose of vaccine and for whom diary card
 119 information was available.

120 Grade 3: drowsiness defined as prevented normal daily activities; irritability/fussiness defined as
 121 crying that could not be comforted/prevented normal daily activities; loss of appetite defined
 122 as no eating at all.

123 ^a Within 4 days of vaccination defined as day of vaccination and the next 3 days.

124 ^b MMR = measles, mumps, and rubella vaccine; V = varicella vaccine.

125 *Serious Adverse Events in Children 11 to 25 Months of Age:* Among these 4 studies, 0.9%
 126 (29/3,152) of subjects reported a serious adverse event within the 31-day period following
 127 vaccination with HAVRIX. Among subjects administered HAVRIX alone 1.0% (13/1,332)

128 reported a serious adverse event. Among subjects who received HAVRIX concomitantly with
129 other childhood vaccines, 0.9% (8/909) reported a serious adverse event. In these 4 studies, there
130 were 4 reports of seizure within 31 days post-vaccination: these occurred 2, 9, and 27 days
131 following the first dose of HAVRIX administered alone and 12 days following the second dose
132 of HAVRIX. In one subject who received INFANRIX and Hib conjugate vaccine followed by
133 HAVRIX 6 weeks later, bronchial hyperreactivity and respiratory distress were reported on the
134 day of administration of HAVRIX alone.

135 **6.2 Postmarketing Experience**

136 In addition to reports in clinical trials, worldwide voluntary reports of adverse events received
137 for HAVRIX since market introduction of this vaccine are listed below. This list includes serious
138 adverse events or events which have a suspected causal connection to components of HAVRIX
139 or other vaccines or drugs. Because these events are reported voluntarily from a population of
140 uncertain size, it is not always possible to reliably estimate their frequency or establish a causal
141 relationship to the vaccine.

142 Infections and Infestations

143 Rhinitis.

144 Blood and Lymphatic System Disorders

145 Thrombocytopenia.

146 Immune System Disorders

147 Anaphylactic reaction, anaphylactoid reaction, serum sickness–like syndrome.

148 Nervous System Disorders

149 Convulsion, dizziness, encephalopathy, Guillain-Barré syndrome, hypoesthesia, multiple
150 sclerosis, myelitis, neuropathy, paresthesia, somnolence, syncope.

151 Vascular Disorders

152 Vasculitis.

153 Respiratory, Thoracic, and Mediastinal Disorders

154 Dyspnea.

155 Hepatobiliary Disorders

156 Hepatitis, jaundice.

157 Skin and Subcutaneous Tissue Disorders

158 Angioedema, erythema multiforme, hyperhidrosis.

159 Congenital, Familial, and Genetic Disorders

160 Congenital anomaly.

161 Musculoskeletal and Connective Tissue Disorders

162 Musculoskeletal stiffness.

163 General Disorders and Administration Site Conditions

164 Chills, influenza-like symptoms, injection site reaction, local swelling.

165 **7 DRUG INTERACTIONS**

166 **7.1 Concomitant Administration with Vaccines and Immune Globulin**

167 In clinical studies HAVRIX was administered concomitantly with the following vaccines [*see*
168 *Adverse Reactions (6.1) and Clinical Studies (14.5)*]:

- 169 • INFANRIX (DTaP);
- 170 • Hib conjugate vaccine;
- 171 • pneumococcal 7-valent conjugate vaccine;
- 172 • MMR vaccine;
- 173 • varicella vaccine.

174 HAVRIX may be administered concomitantly with immune globulin.

175 When concomitant administration of other vaccines or immune globulin is required, they should
176 be given with different syringes and at different injection sites. Do not mix HAVRIX with any
177 other vaccine or product in the same syringe or vial.

178 **7.2 Immunosuppressive Therapies**

179 Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic
180 drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune
181 response to HAVRIX.

182 **8 USE IN SPECIFIC POPULATIONS**

183 **8.1 Pregnancy**

184 Pregnancy Category C

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

188 **8.3 Nursing Mothers**

189 It is not known whether HAVRIX is excreted in human milk. Because many drugs are excreted
190 in human milk, caution should be exercised when HAVRIX is administered to a nursing woman.

191 **8.4 Pediatric Use**

192 The safety and effectiveness of HAVRIX, doses of 360 EL.U. or 720 EL.U., have been evaluated
193 in more than 22,000 subjects 1 year to 18 years of age.

194 The safety and effectiveness of HAVRIX have not been established in subjects younger than
195 12 months of age.

196 **8.5 Geriatric Use**

197 Clinical studies of HAVRIX did not include sufficient numbers of subjects 65 years of age and
198 older to determine whether they respond differently from younger subjects. Other reported
199 clinical experience has not identified differences in overall safety between these subjects and
200 younger adult subjects.

201 **8.6 Hepatic Impairment**

202 Subjects with chronic liver disease had a lower antibody response to HAVRIX than healthy
203 subjects [see *Clinical Studies (14.3)*].

204 **11 DESCRIPTION**

205 HAVRIX (Hepatitis A Vaccine) is a sterile suspension of inactivated virus for intramuscular
206 administration. The virus (strain HM175) is propagated in MRC-5 human diploid cells. After
207 removal of the cell culture medium, the cells are lysed to form a suspension. This suspension is
208 purified through ultrafiltration and gel permeation chromatography procedures. Treatment of this
209 lysate with formalin ensures viral inactivation. Viral antigen activity is referenced to a standard
210 using an enzyme linked immunosorbent assay (ELISA), and is therefore expressed in terms of
211 ELISA Units (EL.U.).

212 Each 1-mL adult dose of vaccine contains 1440 EL.U. of viral antigen, adsorbed on 0.5 mg of
213 aluminum as aluminum hydroxide.

214 Each 0.5-mL pediatric dose of vaccine contains 720 EL.U. of viral antigen, adsorbed onto
215 0.25 mg of aluminum as aluminum hydroxide.

216 HAVRIX contains the following excipients: Amino acid supplement (0.3% w/v) in a
217 phosphate-buffered saline solution and polysorbate 20 (0.05 mg/mL). From the manufacturing
218 process, HAVRIX also contains residual MRC-5 cellular proteins (not more than 5 mcg/mL),
219 formalin (not more than 0.1 mg/mL), and neomycin sulfate (not more than 40 ng/mL), an
220 aminoglycoside antibiotic included in the cell growth media.

221 HAVRIX is formulated without preservatives.

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

225 **12 CLINICAL PHARMACOLOGY**

226 **12.1 Mechanism of Action**

227 The hepatitis A virus belongs to the picornavirus family. It is one of several hepatitis viruses that
228 cause systemic disease with pathology in the liver.

229 The incubation period for hepatitis A averages 28 days (range: 15 to 50 days).¹ The course of
230 hepatitis A infection is extremely variable, ranging from asymptomatic infection to icteric
231 hepatitis and death.

232 The presence of antibodies to HAV confers protection against hepatitis A infection. However,
233 the lowest titer needed to confer protection has not been determined.

234 **13 NONCLINICAL TOXICOLOGY**

235 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

236 HAVRIX has not been evaluated for its carcinogenic potential, mutagenic potential, or potential
237 for impairment of fertility.

238 **14 CLINICAL STUDIES**

239 **14.1 Pediatric Effectiveness Studies**

240 Protective efficacy with HAVRIX has been demonstrated in a double-blind, randomized
241 controlled study in school children (age 1 to 16 years) in Thailand who were at high risk of HAV
242 infection. A total of 40,119 children were randomized to be vaccinated with either HAVRIX
243 360 EL.U. or ENGERIX-B 10 mcg at 0, 1, and 12 months. Of these, 19,037 children received 2
244 doses of HAVRIX (0 and 1 months) and 19,120 children received 2 doses of control vaccine,
245 ENGERIX-B (0 and 1 months). A total of 38,157 children entered surveillance at day 138 and
246 were observed for an additional 8 months. Using the protocol-defined endpoint (≥ 2 days absence
247 from school, ALT level >45 U/mL, and a positive result in the HAVAB-M test), 32 cases of
248 clinical hepatitis A occurred in the control group. In the HAVRIX group, 2 cases were identified.
249 These 2 cases were mild in terms of both biochemical and clinical indices of hepatitis A disease.
250 Thus the calculated efficacy rate for prevention of clinical hepatitis A was 94% (95% Confidence
251 Interval [CI]: 74, 98).

252 In outbreak investigations occurring in the trial, 26 clinical cases of hepatitis A (of a total of 34
253 occurring in the trial) occurred. No cases occurred in vaccinees who received HAVRIX.

254 Using additional virological and serological analyses post hoc, the efficacy of HAVRIX was
255 confirmed. Up to 3 additional cases of mild clinical illness may have occurred in vaccinees.
256 Using available testing, these illnesses could neither be proven nor disproven to have been
257 caused by HAV. By including these as cases, the calculated efficacy rate for prevention of
258 clinical hepatitis A would be 84% (95% CI: 60, 94).

259 **14.2 Immunogenicity in Children and Adolescents**

260 Immune Response to HAVRIX 720 EL.U./0.5 mL at 11 to 25 Months of Age (Study
 261 HAV 210)

262 In this prospective, open-label, multicenter study, 1,084 children were administered study
 263 vaccine in one of 5 groups:

- 264 (1) Children 11 to 13 months of age who received HAVRIX on a 0- and 6-month schedule;
 265 (2) Children 15 to 18 months of age who received HAVRIX on a 0- and 6-month schedule;
 266 (3) Children 15 to 18 months of age who received HAVRIX coadministered with INFANRIX
 267 and Haemophilus b (Hib) conjugate vaccine (no longer US-licensed) at month 0 and HAVRIX at
 268 month 6;
 269 (4) Children 15 to 18 months of age who received INFANRIX coadministered with Hib
 270 conjugate vaccine at month 0 and HAVRIX at months 1 and 7;
 271 (5) Children 23 to 25 months of age who received HAVRIX on a 0- and 6-month schedule.

272 Among subjects in all groups, 52% were male; 61% of subjects were white, 9% were black, 3%
 273 were Asian, and 27% were other racial/ethnic groups. The anti-hepatitis A antibody vaccine
 274 responses and GMTs, calculated on responders for groups 1, 2, and 5 are presented in Table 2.
 275 Vaccine response rates were similar among the 3 age groups that received HAVRIX. One month
 276 after the second dose of HAVRIX, the GMT in each of the younger age groups (11 to 13 and 15
 277 to 18 months of age) was shown to be similar to that achieved in the 23 to 25 months of age
 278 group.

279 **Table 2. Anti-Hepatitis A Immune Response following 2 Doses of HAVRIX**
 280 **720 EL.U./0.5 mL Administered 6 Months Apart in Children Given the First Dose of**
 281 **HAVRIX at 11 to 13 Months of Age, 15 to 18 Months of Age, or 23 to 25 Months of Age**

Age group	N	Vaccine Response		GMT (mIU/mL)
		%	95% CI	
11-13 months (Group 1)	218	99	97, 100	1,461 ^a
15-18 months (Group 2)	200	100	98, 100	1,635 ^a
23-25 months (Group 5)	211	100	98, 100	1,911

282 Vaccine response = Seroconversion (anti-HAV \geq 15 mIU/mL [lower limit of antibody
 283 measurement by assay]) in children initially seronegative or at least the maintenance of the
 284 pre-vaccination anti-HAV concentration in initially seropositive children.

285 CI = Confidence Interval; GMT = Geometric mean antibody titer.

286 ^a Calculated on vaccine responders one month post-dose 2. GMTs in children 11 to 13 months
 287 of age and 15 to 18 months of age were non-inferior (similar) to the GMT in children 23 to
 288 25 months of age (i.e., the lower limit of the two-sided 95% CI on the GMT ratio for
 289 Group 1/Group 5 and for Group 2/Group 5 were both \geq 0.5).

290 In 3 additional clinical studies (HAV 232, HAV 220, and HAV 231), children received either 2
291 doses of HAVRIX alone or the first dose of HAVRIX concomitantly administered with other
292 routinely recommended US-licensed vaccines followed by a second dose of HAVRIX. After the
293 second dose of HAVRIX, there was no evidence for interference with the anti-HAV response in
294 the children who received concomitantly administered vaccines compared to those who received
295 HAVRIX alone. [See Adverse Reactions (6.1) and Clinical Studies (14.5).]

296 Immune Response to HAVRIX 360 EL.U. among Individuals 2 to 18 Years of Age

297 In 6 clinical studies, 762 subjects 2 to 18 years of age received 2 doses of HAVRIX (360 EL.U.)
298 given 1 month apart (GMT ranged from 197 to 660 mIU/mL). Ninety-nine percent of subjects
299 seroconverted following 2 doses. When a third dose of HAVRIX 360 EL.U. was administered
300 6 months following the initial dose, all subjects were seropositive (anti-HAV ≥ 20 mIU/mL)
301 1 month following the third dose, with GMTs rising to a range of 3,388 to 4,643 mIU/mL. In
302 1 study in which children were followed for an additional 6 months, all subjects remained
303 seropositive.

304 Immune Response to HAVRIX 720 EL.U./0.5 mL among Individuals 2 to 19 Years of 305 Age

306 In 4 clinical studies, 314 children and adolescents ranging from 2 to 19 years of age were
307 immunized with 2 doses of HAVRIX 720 EL.U./0.5 mL given 6 months apart. One month after
308 the first dose, seroconversion (anti-HAV ≥ 20 mIU/mL [lower limit of antibody measurement by
309 assay]) ranged from 96.8% to 100%, with GMTs of 194 mIU/mL to 305 mIU/mL. In studies in
310 which sera were obtained 2 weeks following the initial dose, seroconversion ranged from 91.6%
311 to 96.1%. One month following the booster dose at month 6, all subjects were seropositive, with
312 GMTs ranging from 2,495 mIU/mL to 3,644 mIU/mL.

313 In an additional study in which the booster dose was delayed until 1 year following the initial
314 dose, 95.2% of the subjects were seropositive just prior to administration of the booster dose.
315 One month later, all subjects were seropositive, with a GMT of 2,657 mIU/mL.

316 **14.3 Immunogenicity in Adults**

317 More than 400 healthy adults 18 to 50 years of age in 3 clinical studies were given a single
318 1440 EL.U. dose of HAVRIX. All subjects were seronegative for hepatitis A antibodies at
319 baseline. Specific humoral antibodies against HAV were elicited in more than 96% of subjects
320 when measured 1 month after vaccination. By day 15, 80% to 98% of vaccinees had already
321 seroconverted (anti-HAV ≥ 20 mIU/mL [lower limit of antibody measurement by assay]). GMTs
322 of seroconverters ranged from 264 to 339 mIU/mL at day 15 and increased to a range of 335 to
323 637 mIU/mL by 1 month following vaccination.

324 The GMTs obtained following a single dose of HAVRIX are at least several times higher than
325 that expected following receipt of immune globulin.

326 In a clinical study using 2.5 to 5 times the standard dose of immune globulin (standard
327 dose = 0.02 to 0.06 mL/kg), the GMT in recipients was 146 mIU/mL at 5 days
328 post-administration, 77 mIU/mL at month 1, and 63 mIU/mL at month 2.

329 In 2 clinical trials in which a booster dose of 1440 EL.U. was given 6 months following the
330 initial dose, 100% of vaccinees (n = 269) were seropositive 1 month after the booster dose, with
331 GMTs ranging from 3,318 mIU/mL to 5,925 mIU/mL. The titers obtained from this additional
332 dose approximate those observed several years after natural infection.

333 In a subset of vaccinees (n = 89), a single dose of HAVRIX 1440 EL.U. elicited specific
334 anti-HAV neutralizing antibodies in more than 94% of vaccinees when measured 1 month after
335 vaccination. These neutralizing antibodies persisted until month 6. One hundred percent of
336 vaccinees had neutralizing antibodies when measured 1 month after a booster dose given at
337 month 6.

338 Immunogenicity of HAVRIX was studied in subjects with chronic liver disease of various
339 etiologies. 189 healthy adults and 220 adults with either chronic hepatitis B (n = 46), chronic
340 hepatitis C (n = 104), or moderate chronic liver disease of other etiology (n = 70) were
341 vaccinated with HAVRIX 1440 EL.U. on a 0- and 6-month schedule. The last group consisted of
342 alcoholic cirrhosis (n = 17), autoimmune hepatitis (n = 10), chronic hepatitis/cryptogenic
343 cirrhosis (n = 9), hemochromatosis (n = 2), primary biliary cirrhosis (n = 15), primary sclerosing
344 cholangitis (n = 4), and unspecified (n = 13). At each time point, geometric mean antibody titers
345 (GMTs) were lower for subjects with chronic liver disease than for healthy subjects. At month 7,
346 the GMTs ranged from 478 mIU/mL (chronic hepatitis C) to 1,245 mIU/mL (healthy). One
347 month after the first dose, seroconversion rates in adults with chronic liver disease were lower
348 than in healthy adults. However, 1 month after the booster dose at month 6, seroconversion rates
349 were similar in all groups; rates ranged from 94.7% to 98.1%. The relevance of these data to the
350 duration of protection afforded by HAVRIX is unknown.

351 In subjects with chronic liver disease, local injection site reactions with HAVRIX were similar
352 among all 4 groups, and no serious adverse events attributed to the vaccine were reported in
353 subjects with chronic liver disease.

354 **14.4 Duration of Immunity**

355 The duration of immunity following a complete schedule of immunization with HAVRIX has
356 not been established.

357 **14.5 Immune Response to Concomitantly Administered Vaccines**

358 In 3 clinical studies HAVRIX was administered concomitantly with other routinely
359 recommended US-licensed vaccines: Study HAV 232: Diphtheria and tetanus toxoids and
360 acellular pertussis vaccine adsorbed (INFANRIX, DTaP) and Haemophilus b (Hib) conjugate
361 vaccine (tetanus toxoid conjugate) (manufactured by sanofi pasteur SA); Study HAV 220:

362 Pneumococcal 7-valent conjugate vaccine (PCV-7) (manufactured by Pfizer), and Study
363 HAV 231: MMR and varicella vaccines. [See Adverse Reactions (6.1).]

364 Concomitant Administration with DTap and Hib Conjugate Vaccine (Study HAV 232)

365 In this US multicenter study, 468 subjects, children 15 months of age were randomized to
366 receive: Group 1) HAVRIX coadministered with INFANRIX and Hib conjugate vaccine
367 (n = 127); Group 2) INFANRIX and Hib conjugate vaccine alone followed by a first dose of
368 HAVRIX one month later (n = 132); or Group 3) HAVRIX alone (n = 135). All subjects
369 received a second dose of HAVRIX alone 6 to 9 months following the first dose. Among
370 subjects in all groups combined, 53% were male; 64% of subjects were white, 12% were black,
371 6% were Hispanic, and 18% were other racial/ethnic groups.

372 There was no evidence for reduced antibody response to diphtheria and tetanus toxoids
373 (percentage of subjects with antibody levels ≥ 0.1 mIU/mL to each antigen), pertussis antigens
374 (percentage of subjects with seroresponse, antibody concentrations ≥ 5 EL.U./mL in seronegative
375 subjects or post-vaccination antibody concentration ≥ 2 times the pre-vaccination antibody
376 concentration in seropositive subjects, and GMTs), or Hib (percentage of subjects with antibody
377 levels ≥ 1 mcg/mL to polyribosyl-ribitol phosphate, PRP) when HAVRIX was administered
378 concomitantly with INFANRIX and Hib conjugate vaccine (Group 1) relative to INFANRIX and
379 Hib conjugate vaccine administered together (Group 2).

380 Concomitant Administration with Pneumococcal 7-Valent Conjugate Vaccine (Study
381 HAV 220)

382 In this US multicenter study, 433 children 15 months of age were randomized to receive:
383 Group 1) HAVRIX coadministered with PCV-7 vaccine (n = 137); Group 2) HAVRIX
384 administered alone (n = 147); or Group 3) PCV-7 vaccine administered alone (n = 149) followed
385 by a first dose of HAVRIX one month later. All subjects received a second dose of HAVRIX 6
386 to 9 months after the first dose. Among subjects in all groups combined, 53% were female; 61%
387 of subjects were white, 16% were Hispanic, 15% were black, and 8% were other racial/ethnic
388 groups.

389 There was no evidence for reduced antibody response to PCV-7 (GMC to each serotype) when
390 HAVRIX was administered concomitantly with PCV-7 vaccine (Group 1) relative to PCV-7
391 administered alone (Group 3).

392 Concomitant Administration with MMR and Varicella Vaccines (Study HAV 231)

393 In a US multicenter study, there was no evidence for interference in the immune response to
394 MMR and varicella vaccines (the percentage of subjects with pre-specified
395 seroconversion/seroresponse levels) administered at 15 months of age concomitantly with
396 HAVRIX relative to the response when MMR and varicella vaccines are administered without
397 HAVRIX. [See Adverse Reactions (6.1).]

398 **15 REFERENCES**

- 399 1. Centers for Disease Control and Prevention. Prevention of hepatitis A through active or
400 passive immunization: Recommendations of the Immunization Practices Advisory
401 Committee (ACIP). *MMWR* 2006;55(RR-7):1-23.

402 **16 HOW SUPPLIED/STORAGE AND HANDLING**

403 HAVRIX is available in single-dose vials and prefilled disposable TIP-LOK syringes (packaged
404 without needles) (Preservative Free Formulation):

405 720 EL.U./0.5 mL

406 NDC 58160-825-01 Vial in Package of 10: NDC 58160-825-11

407 NDC 58160-825-43 Syringe in Package of 10: NDC 58160-825-52

408 1440 EL.U./mL

409 NDC 58160-826-01 Vial in Package of 10: NDC 58160-826-11

410 NDC 58160-826-05 Syringe in Package of 1: NDC 58160-826-34

411 NDC 58160-826-43 Syringe in Package of 10: NDC 58160-826-52

412 Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has
413 been frozen. Do not dilute to administer.

414 **17 PATIENT COUNSELING INFORMATION**

- 415 • Inform vaccine recipients and parents or guardians of the potential benefits and risks of
416 immunization with HAVRIX.
- 417 • Emphasize, when educating vaccine recipients and parents or guardians regarding potential
418 side effects, that HAVRIX contains non-infectious killed viruses and cannot cause hepatitis
419 A infection.
- 420 • Instruct vaccine recipients and parents or guardians to report any adverse events to their
421 healthcare provider.
- 422 • Give vaccine recipients and parents or guardians the Vaccine Information Statements, which
423 are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to
424 immunization. These materials are available free of charge at the Centers for Disease Control
425 and Prevention (CDC) website (www.cdc.gov/vaccines).

426

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