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 or older. Primary immunization should be administered at least 2 weeks prior to expected exposure to HAV. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Children and adolescents: A single 0.5-mL dose and a 0.5-mL booster dose administered between 6 to 12 months later. (2.2)
- Adults: A single 1-mL dose and a 1-mL booster dose administered between 6 to 12 months later. (2.2)
- For intramuscular use only. (2.2)

---------- 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 ----------

HAVRIX is available in vials and 2 types of prefilled syringes. One type of prefilled syringe has a tip cap which may contain natural rubber latex. The other type has a tip cap and a rubber plunger which contain dry natural latex rubber. Use of these syringes may cause allergic reactions in latex-sensitive individuals. (5.1, 16)

---------- 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: xx/xxxx

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

HAVRIX® is 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.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

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

2.2 Recommended Dose and Schedule

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

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

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

3 DOSAGE FORMS AND STRENGTHS

Suspension for injection available in the following presentations:

- 0.5-mL single-dose vials and prefilled TIP-LOK® syringes.
- 1-mL single-dose vials and prefilled TIP-LOK syringes.

4 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, is a contraindication to administration of HAVRIX *[see Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Latex

HAVRIX is available in vials and 2 types of prefilled syringes. One type of prefilled syringe has a tip cap which may contain natural rubber latex. The other type has a tip cap and a rubber plunger which contain dry natural latex rubber. Use of these syringes may cause allergic reactions in latex-sensitive individuals. The vial stopper does not contain latex. *[See How Supplied/Storage and Handling (16).]*

5.2 Preventing and Managing Allergic Vaccine Reactions

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

5.3 Altered Immunocompetence

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

5.4 Limitations of Vaccine Effectiveness

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

The safety of HAVRIX has been evaluated in 61 clinical trials involving more than 34,000 individuals receiving doses of 360 EL.U., 720 EL.U., or 1440 EL.U.

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

Incidence 1% to 10% of Injections: *Metabolism and Nutrition Disorders:* Anorexia.

Gastrointestinal Disorders: Nausea.

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

Incidence <1% of Injections: *Infections and Infestations:* Pharyngitis, upper respiratory tract infections.

Blood and Lymphatic System Disorders: Lymphadenopathy.

Psychiatric Disorders: Insomnia.

Nervous System Disorders: Dysgeusia, hypertonia.

Eye Disorders: Photophobia.

Ear and Labyrinth Disorders: Vertigo.

Gastrointestinal Disorders: Abdominal pain, diarrhea, vomiting.

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

Musculoskeletal and Connective Tissue Disorders: Arthralgia, myalgia.

General Disorders and Administration Site Conditions: Injection site hematoma.

Investigations: Creatine phosphokinase increased.

Studies of HAVRIX 720 EL.U./0.5 mL in Children 11 to 25 Months of Age: In 4 studies, 3,152 children 11 to 25 months of age received at least one dose of HAVRIX 720 EL.U. administered alone or concomitantly with other routine childhood vaccinations *[see Clinical Studies (14.2, 14.5)]*. The studies included HAV 210 (N = 1,084), HAV 232 (N = 394), HAV 220 (N = 433), and HAV 231 (N = 1,241).

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

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

Table 1. Solicited Local Adverse Reactions and General Adverse Events Occurring Within 4 Days of Vaccination[a] in Children 15 to 24 Months of Age With HAVRIX Administered 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

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

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

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

[a] Within 4 days of vaccination defined as day of vaccination and the next 3 days.

[b] MMR = measles, mumps, and rubella vaccine; V = varicella vaccine.

Serious Adverse Events in Children 11 to 25 Months of Age: Among these 4 studies, 0.9% (29/3,152) of subjects reported a serious adverse event within the 31-day period following vaccination with HAVRIX. Among subjects administered HAVRIX alone 1.0% (13/1,332) reported a serious adverse event. Among subjects who received HAVRIX concomitantly with other childhood vaccines, 0.9% (8/909) reported a serious adverse event. In these 4 studies, there were 4 reports of seizure within 31 days post-vaccination: these occurred 2, 9, and 27 days following the first dose of HAVRIX administered alone and 12 days following

the second dose of HAVRIX. In one subject who received INFANRIX and Hib conjugate vaccine followed by HAVRIX 6 weeks later, bronchial hyperreactivity and respiratory distress were reported on the day of administration of HAVRIX alone.

6.2 Postmarketing Experience

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

Infections and Infestations: Rhinitis.

Blood and Lymphatic System Disorders: Thrombocytopenia.

Immune System Disorders: Anaphylactic reaction, anaphylactoid reaction, serum sickness–like syndrome.

Nervous System Disorders: Convulsion, dizziness, encephalopathy, Guillain-Barré syndrome, hypoesthesia, multiple sclerosis, myelitis, neuropathy, paresthesia, somnolence, syncope.

Vascular Disorders: Vasculitis.

Respiratory, Thoracic, and Mediastinal Disorders: Dyspnea.

Hepatobiliary Disorders: Hepatitis, jaundice.

Skin and Subcutaneous Tissue Disorders: Angioedema, erythema multiforme, hyperhidrosis.

Congenital, Familial, and Genetic Disorders: Congenital anomaly.

Musculoskeletal and Connective Tissue Disorders: Musculoskeletal stiffness.

General Disorders and Administration Site Conditions: Chills, influenza-like symptoms, injection site reaction, local swelling.

7 DRUG INTERACTIONS

7.1 Concomitant Administration With Vaccines and Immune Globulin

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

- INFANRIX (DTaP);
- Hib conjugate vaccine;
- pneumococcal 7-valent conjugate vaccine;
- MMR vaccine;
- varicella vaccine.

HAVRIX may be administered concomitantly with immune globulin.

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

7.2 Immunosuppressive Therapies

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

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

8.5 Geriatric Use

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

8.6 Hepatic Impairment

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

11 DESCRIPTION

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

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

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

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

HAVRIX is formulated without preservatives.

HAVRIX is available in vials and 2 types of prefilled syringes. One type of prefilled syringe has a tip cap which may contain natural rubber latex. The other type has a tip cap and a rubber plunger which contain dry natural latex rubber. The vial stopper does not contain latex. *[See How Supplied/Storage and Handling (16).]*

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

14.1 Pediatric Effectiveness Studies

Protective efficacy with HAVRIX has been demonstrated in a double-blind, randomized controlled study in school children (age 1 to 16 years) in Thailand who were at high risk of HAV infection. A total of 40,119 children were randomized to be vaccinated with either HAVRIX 360 EL.U. or ENGERIX-B 10 mcg at 0, 1, and 12 months. Of these, 19,037 children received 2 doses of HAVRIX (0 and 1 months) and 19,120 children received 2 doses of control vaccine, ENGERIX-B (0 and 1 months). A total of 38,157 children entered surveillance at day 138 and were observed for an additional 8 months. Using the protocol-defined endpoint (≥2 days absence from school, ALT level >45 U/mL, and a positive result in the HAVAB-M test), 32 cases of clinical hepatitis A occurred in the control group. In the HAVRIX group, 2 cases were identified. These 2 cases were mild in terms of both biochemical and clinical indices of hepatitis A disease.

Thus the calculated efficacy rate for prevention of clinical hepatitis A was 94% (95% Confidence Interval [CI]: 74, 98).

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

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

14.2 Immunogenicity in Children and Adolescents

Immune Response to HAVRIX 720 EL.U./0.5 mL at 11 to 25 Months of Age (Study HAV 210): In this prospective, open-label, multicenter study, 1,084 children were administered study vaccine in one of 5 groups:

(1) Children 11 to 13 months of age who received HAVRIX on a 0- and 6-month schedule;

(2) Children 15 to 18 months of age who received HAVRIX on a 0- and 6-month schedule;

(3) Children 15 to 18 months of age who received HAVRIX coadministered with INFANRIX and Haemophilus b (Hib) conjugate vaccine (no longer US-licensed) at month 0 and HAVRIX at month 6;

(4) Children 15 to 18 months of age who received INFANRIX coadministered with Hib conjugate vaccine at month 0 and HAVRIX at months 1 and 7;

(5) Children 23 to 25 months of age who received HAVRIX on a 0- and 6-month schedule.

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

Table 2. Anti-Hepatitis A Immune Response Following 2 Doses of HAVRIX 720 EL.U./0.5 mL Administered 6 Months Apart in Children Given the First Dose of 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

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

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

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

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

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

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

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

14.3 Immunogenicity in Adults

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

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

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

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

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

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

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

14.4 Duration of Immunity

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

14.5 Immune Response to Concomitantly Administered Vaccines

In 3 clinical studies HAVRIX was administered concomitantly with other routinely recommended US-licensed vaccines: Study HAV 232: Diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (INFANRIX, DTaP) and Haemophilus b (Hib) conjugate vaccine (tetanus toxoid conjugate) (manufactured by sanofi pasteur SA); Study HAV 220: Pneumococcal 7-valent conjugate vaccine (PCV-7) (manufactured by Pfizer), and Study HAV 231: MMR and varicella vaccines. *[See Adverse Reactions (6.1).]*

Concomitant Administration With DTaP and Hib Conjugate Vaccine (Study HAV 232): In this US multicenter study, 468 subjects, children 15 months of age were randomized to receive: Group 1) HAVRIX coadministered with INFANRIX and Hib conjugate vaccine (n = 127); Group 2) INFANRIX and Hib conjugate vaccine alone followed by a first dose of HAVRIX one month later (n = 132); or Group 3) HAVRIX alone (n = 135). All subjects received a second dose of HAVRIX alone 6 to 9 months following the first dose. Among subjects in all groups combined, 53% were male; 64% of subjects were white, 12% were black, 6% were Hispanic, and 18% were other racial/ethnic groups.

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

Concomitant Administration With Pneumococcal 7-Valent Conjugate Vaccine (Study HAV 220): In this US multicenter study, 433 children 15 months of age were randomized to receive: Group 1) HAVRIX coadministered with PCV-7 vaccine (n = 137); Group 2) HAVRIX administered alone (n = 147); or Group 3) PCV-7 vaccine administered alone (n = 149) followed by a first dose of HAVRIX one month later. All subjects received a second dose of HAVRIX 6 to 9 months after the first dose. Among subjects in all groups combined, 53% were female; 61% of subjects were white, 16% were Hispanic, 15% were black, and 8% were other racial/ethnic groups.

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

Concomitant Administration With MMR and Varicella Vaccines (Study HAV 231):

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

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

HAVRIX is available in single-dose vials (contain no latex) and prefilled TIP-LOK syringes (may contain latex) (packaged without needles) (Preservative Free Formulation):

720 EL.U./0.5 mL

NDC 58160-825-01 Vial (contains no latex) in Package of 10: NDC 58160-825-11
NDC 58160-825-43 Syringe (tip cap may contain latex) in Package of 10: NDC 58160-825-52
NDC 58160-825-41 Syringe (tip cap and plunger contain latex) in Package of 5: NDC 58160-825-46
NDC 58160-825-41 Syringe (tip cap and plunger contain latex) in Package of 10: NDC 58160-825-51

1440 EL.U./mL

NDC 58160-826-01 Vial (contains no latex) in Package of 10: NDC 58160-826-11
NDC 58160-826-43 Syringe (tip cap may contain latex) in Package of 5: NDC 58160-826-48
NDC 58160-826-32 Syringe (tip cap and plunger contain latex) in Package of 1: NDC 58160-826-32
NDC 58160-826-41 Syringe (tip cap and plunger contain latex) in Package of 5: NDC 58160-826-46

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

17 PATIENT COUNSELING INFORMATION

- Inform vaccine recipients and parents or guardians of the potential benefits and risks of immunization with HAVRIX.
- Emphasize, when educating vaccine recipients and parents or guardians regarding potential side effects, that HAVRIX contains non-infectious killed viruses and cannot cause hepatitis A infection.
- Instruct vaccine recipients and parents or guardians to report any adverse events to their healthcare provider.

- Give vaccine recipients and parents or guardians the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

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