

**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) for persons ≥12 months of age. 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**

- HAVRIX is a sterile suspension available in the following presentations:
- 0.5 mL single-dose vials and prefilled syringes. (3, 11, 16)
- 1.0 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 vaccine, or to any component of HAVRIX, including neomycin. (4)

**WARNINGS AND PRECAUTIONS**

- The needleless prefilled syringes contain dry natural latex rubber and may cause allergic reactions. (5.1)

- Immunocompromised persons may have a diminished immune response to HAVRIX. (5.2)
- HAVRIX may not prevent hepatitis A infection in individuals with unrecognized hepatitis A infection at the time of vaccination. (5.3)

**ADVERSE REACTIONS**

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)

**To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 and www.vaers.hhs.gov.**

**DRUG INTERACTIONS**

- Do not mix HAVRIX with any other vaccine or product in the same syringe or vial. (7.1)
- HAVRIX may be given concurrently at different injection sites with (7.1):
  - INFANRIX® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP).
  - *Haemophilus influenzae* type b (Hib) conjugate vaccine (PRP-T).
  - pneumococcal 7-valent conjugate vaccine.
  - immune globulin.

**USE IN SPECIFIC POPULATIONS**

Safety and effectiveness of HAVRIX have not been established in pregnant women and nursing mothers. HAVRIX should only be given to a pregnant woman if clearly needed. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: January 2010

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

HAVRIX is a vaccine indicated for active immunization against disease caused by hepatitis A virus (HAV) for persons  $\geq 12$  months of age. 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 vial or syringe well before withdrawal and use. Inspect HAVRIX visually for particulate matter, discoloration, and cracks in the vial or syringe prior to administration, whenever solution and container permit. If any of these conditions exist, the vaccine should not be administered. With thorough agitation, HAVRIX is a homogeneous, turbid, white suspension. Discard if it appears otherwise.

#### 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 in order to ensure the highest antibody titers. The preferred sites for intramuscular injections are the anterolateral aspect of the thigh in infants and 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 order to ensure the highest antibody titers. In adults, the injection should be given in the deltoid region.

### 3 DOSAGE FORMS AND STRENGTHS

HAVRIX is a sterile suspension available in the following presentations:

- 0.5 mL single-dose vials and prefilled TIP-LOK<sup>®</sup> syringes.
- 1.0 mL single-dose vials and prefilled TIP-LOK<sup>®</sup> syringes.

*[See Description (11) and How Supplied (16) for a listing of vaccine components.]*

### 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 Hypersensitivity**

HAVRIX may cause severe allergic reaction.

The tip cap and the rubber plunger of the needleless prefilled syringes contain dry natural latex rubber that may cause allergic reactions in latex sensitive individuals. The vial stopper is latex-free.

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

### **5.2 Altered Immunocompetence**

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

### **5.3 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, it may not prevent infection in individuals who do not achieve protective antibody titers (although the lowest titer needed to confer protection has not been determined).

## **6 ADVERSE REACTIONS**

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 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 60 clinical trials involving approximately 32,900 individuals receiving doses ranging from 360 EL.U. to 1440 EL.U.

The frequency of solicited adverse events tended to decrease with successive doses of HAVRIX.

Of solicited adverse events in clinical trials, the most frequently reported by volunteers was injection-site soreness (56% of adults and 21% of children); however, 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 (>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.

**Outbreak Setting and a Field Efficacy Trial:** Safety data were obtained from 2 additional sources in which large populations were vaccinated. In an outbreak setting in which 4,930 individuals were immunized with a single dose of either 720 EL.U. or 1440 EL.U. of HAVRIX, no serious adverse events due to vaccination were reported. Overall, less than 10% of vaccinees reported solicited general adverse events following the vaccine. The most common solicited local adverse reaction was pain at the injection site, reported in 22% (650/2,911) of subjects at 24 hours and decreasing to 2% (71/2,838) by 72 hours.

In a field efficacy trial, 19,037 children received the 360 EL.U. dose of HAVRIX. The most commonly reported adverse events by children from 2 selected schools following administration of HAVRIX were injection-site pain (10%, 68/719) and tenderness (8%, 58/719), following first doses of HAVRIX. Pain was slightly higher following the first dose of HAVRIX (10%) compared to the group who received the comparison vaccine ENGERIX-B<sup>®</sup> (6%) but was similar between vaccines following the second dose (6% for both groups). Likewise, tenderness was slightly higher following the first dose of HAVRIX (8%) compared to the group who received the comparison vaccine ENGERIX-B (5%) but was similar between vaccines following the second dose (4% for both groups). The large trial further allowed for analysis of rare adverse events, including hospitalization and death. No significant differences were found between the cohorts.

**HAVRIX 720 EL.U./0.5 mL at 11 Months of Age and Older:** In a US multicenter study, parents/guardians recorded local and general adverse events on diary cards for 4 days (Days 0 to 3) after vaccination [see *Clinical Studies (14.2)*]. In the 3 groups of children who received HAVRIX alone, safety data were available for 723 children who received 1,396 documented doses of HAVRIX. Additional safety data were available for 181 children who received HAVRIX coadministered with INFANRIX<sup>®</sup> (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) (DTaP) and *Haemophilus influenzae* type b (Hib) conjugate vaccine (tetanus toxoid conjugate) (PRP-T) (Sanofi Pasteur SA).

The following ranges of solicited adverse event rates were observed among 3 groups of children that received their first dose of HAVRIX alone at between 11 and 25 months of age: Injection site pain in 15 to 21% of subjects, redness in 16 to 21% of subjects, swelling in 8% of subjects, irritability in 24 to 36% of subjects, loss of appetite in 16 to 19% of subjects, drowsiness in 15 to 17% of subjects and fever (>39.5°C) in ≤2% of subjects. Following the

booster dose of HAVRIX, among local reactions: Pain was reported in 16 to 21% of subjects, redness in 17 to 22%, swelling in 8 to 10% of subjects. Following the booster dose of HAVRIX, among general events, irritability was reported in 19 to 29% of subjects, loss of appetite in 14 to 18% of subjects, drowsiness in 13 to 16% of subjects and fever ( $>39.5^{\circ}\text{C}$ ) in  $\leq 1\%$  of subjects.

Drowsiness and loss of appetite occurred at higher rates in subjects 15 to 18 months of age who received Hib conjugate vaccine and INFANRIX concomitantly with HAVRIX as compared to subjects 15 to 18 months of age who received Hib conjugate vaccine and INFANRIX (drowsiness 34% and 22% and loss of appetite 29% and 19%, respectively). With the exception of fever ( $>39.5^{\circ}\text{C}$ ), the solicited general symptoms occurred at higher rates in subjects 15 to 18 months of age who received Hib conjugate vaccine and INFANRIX concomitantly with HAVRIX as compared to subjects 15 to 18 months of age who received HAVRIX alone (irritability 46% and 30%, drowsiness 34% and 17%, and loss of appetite 29% and 17%, respectively).

A febrile seizure was reported in an 18-month-old subject 2 days after receiving the first dose of HAVRIX. Other serious adverse events reported during the course of this study with the use of HAVRIX alone included a single case each of hepatitis  $\sim 5$  months post dose 1, insulin-dependent diabetes  $\sim 4$  months post dose 1, and Kawasaki's disease  $\sim 3\frac{1}{2}$  months post dose 1. The association of these events with vaccination is unknown.

In an open-label, randomized, US multicenter study, children 15 months of age received the 2-dose series of HAVRIX. The second dose of HAVRIX was given 6 to 9 months after the first dose. One group received HAVRIX alone ( $n = 122$ ); a second group received the first dose of HAVRIX coadministered with INFANRIX and Hib conjugate vaccine (PRP-T) (Sanofi Pasteur SA) ( $n = 129$ ); and a third group received INFANRIX and Hib conjugate vaccine coadministered and the first dose of HAVRIX one month later ( $n = 115$ ). [*See Clinical Studies (14.5).*] The percentages of subjects for whom solicited local adverse events (days 0 to 3) were reported following the first dose of HAVRIX alone, HAVRIX coadministered with INFANRIX and Hib conjugate, and coadministration of INFANRIX and Hib conjugate were as follows: Pain (21%, 45%, 40%), redness (15%, 42%, 42%) and swelling (8%, 30%, 30%). The percentages of subjects for whom solicited local symptoms at the HAVRIX injection site were reported after the first dose of HAVRIX in the HAVRIX alone group compared to subjects who received HAVRIX coadministered with INFANRIX and Hib conjugate vaccine were as follows: Pain (21% versus 35%), redness (15% versus 30%), and swelling (8% versus 16%).

Solicited general adverse events (days 0 to 3) reported among children following the first dose of HAVRIX alone, HAVRIX coadministered with INFANRIX and Hib conjugate vaccine, and coadministration of INFANRIX and Hib conjugate vaccine were as follows: Irritability (33%, 43%, 34%), drowsiness (25%, 34%, 24%), loss of appetite (16%, 24%, 17%), and fever [ $>38.0^{\circ}\text{C}$ ] (8%, 16%, 19%).

In this trial, 14 subjects reported 24 serious adverse events, including 6 subjects in the HAVRIX group (status asthmaticus, asthma [2 events], failure to thrive, gastroenteritis, arthritis bacterial, developmental delay, expressive language disorder, dehydration [3 events]), 3 subjects

in the group who received HAVRIX coadministered with INFANRIX and Hib conjugate vaccine (dehydration, gastroenteritis rotavirus, gastroenteritis, pyrexia, tachycardia), and 5 subjects in the group that received the INFANRIX and Hib conjugate vaccine followed by HAVRIX (bronchial hyperreactivity, respiratory distress, developmental delay, expressive language disorder, dehydration [2 events], gastroenteritis rotavirus, tonsillar hypertrophy). All events were reported as recovered or recovering by the end of the study. No fatalities occurred.

In another US multicenter study, children 15 months of age (range 14 to 16 months) received either HAVRIX coadministered with a US-licensed pneumococcal 7-valent conjugate vaccine (Wyeth Pharmaceuticals Inc.) followed by a second dose of HAVRIX 6 to 9 months later; HAVRIX administered alone followed by a second dose of HAVRIX 6 to 9 months later; or pneumococcal 7-valent conjugate vaccine administered alone followed by a first dose of HAVRIX one month later and a second dose of HAVRIX 6 to 9 months after the first [*see Clinical Studies (14.5)*]. Parents/guardians recorded local and general symptoms on diary cards for 4 days (Days 0 to 3) after vaccination.

Solicited local adverse events were reported as follows among children who received the first dose of HAVRIX coadministered with pneumococcal 7-valent conjugate vaccine: Pain was reported in 36% of subjects, redness in 41% of subjects, and swelling in 29% of subjects. Reported rates of these local adverse events were similar to those in children who received the first dose of pneumococcal 7-valent conjugate vaccine alone (44%, 46%, and 27%, respectively). Among children who received the first dose of HAVRIX alone, pain was reported in 28% of subjects, redness in 22% of subjects, and swelling in 7% of subjects.

Solicited general adverse events were reported as follows among children who received the first dose of HAVRIX coadministered with pneumococcal 7-valent conjugate vaccine: Irritability was reported in 35% of subjects, drowsiness in 26% of subjects, loss of appetite in 25% of subjects, and fever in 14% of subjects. Reported rates of these general adverse events were similar to those in children who received the first dose of pneumococcal 7-valent conjugate vaccine alone (41%, 32%, 25%, and 16%, respectively). Among children who received the first dose of HAVRIX alone, irritability was reported in 35% of subjects, drowsiness in 29% of subjects, loss of appetite in 26% of subjects, and fever in 9% of subjects.

## **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**

HAVRIX may be given concurrently with INFANRIX (DTaP) and Hib conjugate vaccine (PRP-T) (Sanofi Pasteur SA) [see *Adverse Reactions (6.1) and Clinical Studies (14.5)*].

HAVRIX may be given concurrently with pneumococcal 7-valent conjugate vaccine (Wyeth Pharmaceuticals Inc.) [see *Adverse Reactions (6.1) and Clinical Studies (14.5)*].

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 have been evaluated in 20,869 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 consists of 1440 EL.U. of viral antigen, adsorbed on 0.5 mg of aluminum as aluminum hydroxide.

Each 0.5-mL pediatric dose of vaccine consists of 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.

The tip cap and the rubber plunger of the needleless prefilled syringes contain dry natural latex rubber. The vial stopper is latex-free.

### **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).<sup>1</sup> 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 at 0, 1, and 12 months. 19,037 children received a primary course (doses at 0 and 1 months) of HAVRIX and 19,120 children received a primary course (doses at 0 and 1 months) of ENGERIX-B. 38,157 children entered surveillance at day 138 and were observed for an additional 8 months. Using the protocol-defined endpoint ( $\geq 2$  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).

In a study designed to interrupt an epidemic of hepatitis A among Native Americans in Alaska, vaccination with a single dose of HAVRIX (1440 EL.U./mL in adults, 720 EL.U./0.5 mL in children and adolescents) appeared to be efficacious.

### **14.2 Immunogenicity in Children and Adolescents**

#### **Immune Response to HAVRIX 720 EL.U./0.5 mL at 11 Months of Age and Older:**

In a prospective, open-label, multicenter study, 1,085 children were enrolled into 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 Hib conjugate vaccine (PRP-T) (Sanofi Pasteur SA) at month 0 and HAVRIX at month 6;

(4) Children 15 to 18 months of age who received INFANRIX coadministered with Hib conjugate vaccine (PRP-T) (Sanofi Pasteur SA) 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% black, 3% Asian, and 27% were of other racial groups. The anti-hepatitis A antibody vaccine responses and GMTs, calculated on responders for groups 1, 2, and 5 are presented in Table 1. 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 1. 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 <sup>a</sup>
15-18 months (Group 2)	200	100	98, 100	1,635 <sup>a</sup>
23-25 months (Group 5)	211	100	98, 100	1,911

Vaccine response = Seroconversion (anti-HAV  $\geq 15$  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.

<sup>a</sup> 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  $\geq 0.5$ ).

Immune Response to HAVRIX 360 EL.U. at 2 Years of Age and Older: In 6 clinical studies of subjects 2 to 18 years of age (n = 762) who received 2 doses of HAVRIX (360 EL.U.) given 1 month apart, the GMT ranged from 197 to 660 mIU/mL. Ninety-nine percent of subjects seroconverted following 2 doses. When a booster (third) dose of HAVRIX 360 EL.U. was administered 6 months following the initial dose, all subjects were seropositive 1 month following the booster 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 at 2 Years of Age and Older:** In 4 clinical studies, children and adolescents (n = 314), 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  $\geq 20$  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 a 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.

Also, HAVRIX has been found to be efficacious in a clinical study of children at high risk of HAV infection [see *Clinical Studies (14.1)*].

### **14.3 Immunogenicity in Adults**

Over 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  $\geq 20$  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**

Concomitant Administration With INFANRIX (DTaP) and Hib Conjugate Vaccine (PRP-T): In a US multicenter randomized study, 468 subjects, children 15 months of age (range 14 to 16 months) received either HAVRIX coadministered with INFANRIX (DTaP) and Hib conjugate vaccine (PRP-T) (Sanofi Pasteur SA) followed by a second dose of HAVRIX 6 to 9 months later (n = 127); INFANRIX and Hib conjugate vaccine alone followed by a first dose of HAVRIX one month later and a second dose of HAVRIX 6 to 9 months after the first (n = 132); or HAVRIX administered alone followed by a second dose of HAVRIX 6 to 9 months later (n = 135). Children had completed a primary series of diphtheria, tetanus, acellular pertussis, and Hib conjugate vaccines.

Seropositivity to HAV was defined as anti-HAV  $\geq 15$  mIU/mL [lower limit of antibody measurement by assay]. Results of analyses of the co-primary immunogenicity endpoints are as follows: One month after the second dose of HAVRIX, the seropositivity rate (100%, 84/84) in those receiving the first dose of HAVRIX coadministered with INFANRIX and Hib conjugate vaccine was shown to be non-inferior to that achieved (100%, 88/88) in children who received HAVRIX alone (lower limit of 95% CI on the difference of HAVRIX + INFANRIX + Hib conjugate vaccine minus HAVRIX  $> -5\%$ ). One month after the second dose of HAVRIX, anti-HAV GMTs were 1,904 mIU/mL for HAVRIX coadministered with INFANRIX and Hib conjugate vaccine and 1,700 mIU/mL for HAVRIX alone (non-inferior based on the lower limit of 95% CI for the adjusted GMT ratio [HAVRIX + INFANRIX + Hib conjugate vaccine:HAVRIX]  $\geq 0.5$ ).

One month after the first dose of HAVRIX coadministered with INFANRIX and Hib conjugate vaccine, seroprotection rates ( $\geq 0.1$  mIU/mL) for diphtheria and tetanus were non-inferior to those achieved following INFANRIX and Hib conjugate vaccine alone (lower limit of

95% CI on the difference of HAVRIX + INFANRIX + Hib conjugate vaccine minus INFANRIX + Hib conjugate vaccine >-10%). For each of the pertussis antigens, vaccine response rates were non-inferior to those achieved following INFANRIX and Hib conjugate vaccine alone (antibody concentrations  $\geq 5$  EL.U./mL in subjects initially seronegative or post-vaccination antibody concentration  $\geq 2$  times the pre-vaccination antibody concentration in subjects initially seropositive; lower limit of 95% CI on the difference of HAVRIX + INFANRIX + Hib conjugate vaccine minus INFANRIX + Hib conjugate vaccine >-10%). GMTs for antibodies against each of the pertussis antigens following HAVRIX coadministered with INFANRIX and Hib conjugate vaccine were non-inferior to those following INFANRIX and Hib conjugate vaccine alone (lower limit of 95% CI for the adjusted GMT ratio [HAVRIX + INFANRIX + Hib conjugate vaccine:INFANRIX + Hib conjugate vaccine]  $\geq 0.66$ ). One month after vaccination, the anti-PRP seroprotection rate ( $\geq 1$  mcg/mL) following HAVRIX coadministered with INFANRIX and Hib conjugate vaccine (100%, 90/90) was non-inferior to that achieved following INFANRIX and Hib conjugate vaccine alone (97.5%, 79/81) (lower limit of 95% CI on the difference of HAVRIX + INFANRIX + Hib conjugate vaccine minus INFANRIX + Hib conjugate vaccine >-10%).

**Concomitant Administration With Pneumococcal 7-Valent Conjugate Vaccine:** In a US multicenter study, children 15 months of age (range 14 to 16 months) received one of 3 regimens: (Group 1) HAVRIX coadministered with pneumococcal 7-valent conjugate vaccine (Wyeth Pharmaceuticals Inc.) followed by a second dose of HAVRIX 6 to 9 months later; (Group 2) HAVRIX administered alone followed by a second dose of HAVRIX 6 to 9 months later; or (Group 3) pneumococcal 7-valent conjugate vaccine administered alone followed by a first dose of HAVRIX one month later and a second dose of HAVRIX 6 to 9 months after the first.

One month after the second dose, the anti-hepatitis A GMT of HAVRIX coadministered with pneumococcal 7-valent conjugate vaccine was non-inferior to HAVRIX given alone (Group 1 GMT = 1,518 mIU/mL; Group 2 GMT = 1,666 mIU/mL). The difference in anti-hepatitis A seropositivity rates between groups (HAVRIX coadministered with pneumococcal 7-valent conjugate vaccine minus HAVRIX alone) was marginally lower than the pre-defined non-inferiority limit of -5% (lower limit of the two-sided 95% CI -5.78%). However, in all 3 groups, the seropositivity rate ranged between 98% and 100% one month after the second dose of HAVRIX (Group 1, 93/94; Group 2, 106/106; Group 3, 113/115).

One month after vaccination, non-inferiority was demonstrated with respect to GMTs for anti-pneumococcal antibodies to all 7 serotypes after the coadministration of pneumococcal 7-valent conjugate vaccine with HAVRIX compared to pneumococcal 7-valent conjugate vaccine alone. At least 98% of subjects who received pneumococcal 7-valent conjugate vaccine coadministered with HAVRIX and those who received pneumococcal 7-valent conjugate vaccine alone were seropositive for all 7 pneumococcal serotypes.

There are limited data on the coadministration of HAVRIX with other vaccines.

## 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.
2. Centers for Disease Control and Prevention. Update: Prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. Updated Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2007;56(41):1080-1084.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

HAVRIX is available in single-dose vials and prefilled TIP-LOK syringes.

720 EL.U./0.5 mL in Single-Dose Vials and Prefilled Syringes (Preservative Free Formulation)

NDC 58160-825-11 Package of 10 Single-Dose Vials

NDC 58160-825-46 Package of 5 Prefilled Disposable TIP-LOK Syringes (packaged without needles)

NDC 58160-825-51 Package of 10 Prefilled Disposable TIP-LOK Syringes (packaged without needles)

1440 EL.U./mL in Single-Dose Vials and Prefilled Syringes (Preservative Free Formulation)

NDC 58160-826-11 Package of 10 Single-Dose Vials

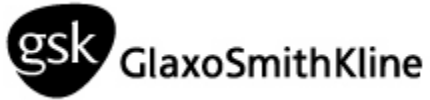
NDC 58160-826-46 Package of 5 Prefilled Disposable TIP-LOK Syringes (packaged without needles)

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 where the vaccine was administered.
- 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](http://www.cdc.gov/vaccines)).

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