

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

VAQTA[®] (Hepatitis A Vaccine, Inactivated)
Suspension for Intramuscular Injection
Initial U.S. Approval: 1996

INDICATIONS AND USAGE

VAQTA is a vaccine indicated for the prevention of disease caused by hepatitis A virus (HAV) in persons 12 months of age and older. The primary dose should be given at least 2 weeks prior to expected exposure to HAV. (1.1)

DOSAGE AND ADMINISTRATION

- For intramuscular administration only. (2)
- Children/Adolescents: vaccination consists of a 0.5-mL primary dose administered intramuscularly, and a 0.5-mL booster dose administered intramuscularly 6 to 18 months later. (2.1)
- Adults: vaccination consists of a 1-mL primary dose administered intramuscularly, and a 1-mL booster dose administered intramuscularly 6 to 18 months later. (2.1)

DOSAGE FORMS AND STRENGTHS

Suspension supplied in four presentations:

- 0.5-mL pediatric dose in single-dose vials and prefilled syringes. (3, 11, 16)
- 1-mL adult dose in single-dose vials and prefilled syringes. (3, 11, 16)

CONTRAINDICATIONS

Do not administer VAQTA to individuals with a history of immediate and/or severe allergic or hypersensitivity reactions (e.g., anaphylaxis) after a previous dose of any hepatitis A vaccine or with an anaphylactic reaction to neomycin. (4, 11)

WARNINGS AND PRECAUTIONS

- Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine. (5.1)
- The vial stopper and the syringe plunger stopper and tip cap contain dry natural latex rubber that may cause allergic reactions in latex-sensitive individuals. (5.2)

ADVERSE REACTIONS

The most common local adverse reactions and systemic adverse events ($\geq 15\%$) reported in different clinical trials across different age groups when VAQTA was administered alone or concomitantly were:

- Children — 12 through 23 months of age: injection-site pain/tenderness (37.0%), injection-site erythema (21.2%), fever (16.4% when administered alone, and 27.0% when administered concomitantly) (6.1)
- Children/Adolescents — 2 through 18 years of age: injection-site pain (18.7%) (6.1)
- Adults — 19 years of age and older: injection-site pain, tenderness, or soreness (67.0%), injection-site warmth (18.2%) and headache (16.1%) (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal studies have been conducted. Use only if clearly indicated. (8.1)
- Safety and effectiveness of VAQTA have not been established in children less than 12 months of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Indications and Use

VAQTA[®] [Hepatitis A Vaccine, Inactivated] is indicated for the prevention of disease caused by hepatitis A virus (HAV) in persons 12 months of age and older. The primary dose should be given at least 2 weeks prior to expected exposure to HAV.

2 DOSAGE AND ADMINISTRATION

FOR INTRAMUSCULAR ADMINISTRATION ONLY.

2.1 Dosage and Schedule

Children/Adolescents (12 months through 18 years of age): The vaccination schedule consists of a primary 0.5-mL dose administered intramuscularly, and a 0.5-mL booster dose administered intramuscularly 6 to 18 months later.

Adults (19 years of age and older): The vaccination schedule consists of a primary 1-mL dose administered intramuscularly, and a 1-mL booster dose administered intramuscularly 6 to 18 months later.

Booster Immunization Following Another Manufacturer's Hepatitis A Vaccine: A booster dose of VAQTA may be given at 6 to 12 months following a primary dose of HAVRIX [see *Clinical Studies (14.6)*].

2.2 Preparation and Administration

Shake the single-dose vial or single-dose prefilled syringe well to obtain a slightly opaque, white suspension before withdrawal and use. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard if the suspension does not appear homogenous or if extraneous particulate matter remains or discoloration is observed.

For single-dose vials, withdraw and administer entire dose of VAQTA intramuscularly using a sterile needle and syringe.

For single-dose prefilled syringes, securely attach a needle by twisting in a clockwise direction and administer dose of VAQTA intramuscularly.

For adults, adolescents, and children older than 2 years of age, the deltoid muscle is the preferred site for intramuscular injection. For children 12 through 23 months of age, the anterolateral area of the thigh is the preferred site for intramuscular injection.

3 DOSAGE FORMS AND STRENGTHS

Suspension for injection available in four presentations:

- 0.5-mL pediatric dose in single-dose vials and prefilled syringes
- 1-mL adult dose in single-dose vials and prefilled syringes

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

4 CONTRAINDICATIONS

Do not administer VAQTA to individuals with a history of immediate and/or severe allergic or hypersensitivity reactions (e.g., anaphylaxis) after a previous dose of any hepatitis A vaccine, or to individuals who have had an anaphylactic reaction to any component of VAQTA, including neomycin [see *Description (11)*].

5 WARNINGS AND PRECAUTIONS

5.1 Prevention and Management of Allergic Vaccine Reactions

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

5.2 Hypersensitivity to Latex

The vial stopper and the syringe plunger stopper and tip cap contain dry natural latex rubber that may cause allergic reactions in latex-sensitive individuals [see *How Supplied/Storage and Handling (16)*].

5.3 Altered Immunocompetence

Immunocompromised persons, including individuals receiving immunosuppressive therapy, may have a diminished immune response to VAQTA and may not be protected against HAV infection after vaccination [see *Use in Specific Populations (8.6)*].

5.4 Limitations of Vaccine Effectiveness

Hepatitis A virus has a relatively long incubation period (approximately 20 to 50 days). VAQTA may not prevent hepatitis A infection in individuals who have an unrecognized hepatitis A infection at the time of vaccination. Vaccination with VAQTA may not result in a protective response in all susceptible vaccinees.

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 VAQTA has been evaluated in over 10,000 subjects 1 year to 85 years of age. Subjects were given one or two doses of the vaccine. The second (booster dose) was given 6 months or more after the first dose.

The most common local adverse reactions and systemic adverse events ($\geq 15\%$) reported in different clinical trials across different age groups when VAQTA was administered alone or concomitantly were:

- Children — 12 through 23 months of age: injection-site pain/tenderness (37.0%), injection-site erythema (21.2%), fever (16.4% when administered alone, and 27.0% when administered concomitantly).
- Children/Adolescents — 2 through 18 years of age: injection-site pain (18.7%)
- Adults — 19 years of age and older: injection-site pain, tenderness, or soreness (67.0%), injection-site warmth (18.2%) and headache (16.1%)

Allergic Reactions

Local and/or systemic allergic reactions that occurred in <1% of over 10,000 children/adolescents or adults in clinical trials regardless of causality included: injection-site pruritus and/or rash; bronchial constriction; asthma; wheezing; edema/swelling; rash; generalized erythema; urticaria; pruritus; eye irritation/itching; dermatitis [see *Contraindications (4)* and *Warnings and Precautions (5.1)*].

Children — 12 through 23 Months of Age

Across five clinical trials, 4374 children 12 to 23 months of age received one or two 25U doses of VAQTA, including 3885 children who received 2 doses of VAQTA and 1250 children who received VAQTA concomitantly with one or more other vaccines, including Measles, Mumps, and Rubella Virus Vaccine, Live (M-M-R II[®]), Varicella Vaccine, Live (VARIVAX[®]), Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine, Adsorbed (Tripedia or INFANRIX), Measles, Mumps, Rubella, and Varicella Vaccine, Live (ProQuad[®]), Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM₁₉₇, Prevnar), or

Haemophilus B Conjugate Vaccine (Meningococcal Protein Conjugate, PedvaxHIB®). Overall, the race distribution of study subjects was as follows: 64.7% Caucasian; 15.7% Hispanic-American; 12.3% Black; 4.8% other; 1.4% Asian; and 1.1% Native American. The distribution of subjects by gender was 51.8% male and 48.2% female.

In an open-label clinical trial, 653 children 12 to 23 months of age were randomized to receive a first dose of VAQTA with ProQuad and Prevnar concomitantly (N=330) or a first dose of ProQuad and pneumococcal 7-valent conjugate vaccine concomitantly, followed by a first dose of VAQTA 6 weeks later (N=323). Approximately 6 months later, subjects received either the second doses of ProQuad and VAQTA concomitantly or the second doses of ProQuad and VAQTA separately. The race distribution of the study subjects was as follows: 60.3% Caucasian; 21.6% African-American; 9.5% Hispanic-American; 7.2% other; 1.1% Asian; and 0.3% Native American. The distribution of subjects by gender was 50.7% male and 49.3% female.

Table 1 presents rates of solicited local reactions at the VAQTA injection site and rates of elevated temperatures ($\geq 100.4^{\circ}\text{F}$ and $\geq 102.2^{\circ}\text{F}$) that occurred within 5 days following each dose of VAQTA and elevated temperatures $>98.6^{\circ}\text{F}$ for a total of 14 days after vaccination; occurrences of these events were recorded daily on diary cards. Table 2 presents rates of unsolicited systemic adverse events that occurred within 14 days at $\geq 5\%$ in any group following each dose of VAQTA.

Table 1: Incidences of Solicited Local Adverse Reactions at the VAQTA Injection Site and Elevated Temperatures Following Each Dose of VAQTA in Healthy Children 12-23 Months of Age Receiving VAQTA Alone or Concomitantly With ProQuad and PREVNAR*

Adverse reaction: Days 1-5 unless noted	Dose 1		Dose 2	
	VAQTA alone	VAQTA + ProQuad + Prevnar concomitantly	VAQTA alone	VAQTA + ProQuad concomitantly
Injection site adverse reactions	N=274	N=311	N=251	N=263
Injection site erythema	11.7%	9.6%	12.7%	9.5%
Injection site pain/tenderness	15.3%	20.9%	20.3%	17.5%
Injection site swelling	9.5%	6.8%	7.6%	6.1%
Temperature $> 98.6^{\circ}\text{F}$ or feverish (Days 1-14)	12.4%	35.7%	10.8%	10.3%
	N=243	N=285	N=221	N=237
Temperature $\geq 100.4^{\circ}\text{F}$	10.3%	16.8%	10%	4.2%
Temperature $\geq 102.2^{\circ}\text{F}$	2.1%	3.5%	2.3%	2.5%

*Pneumococcal 7-valent Conjugate Vaccine
N=number of subjects for whom data are available.

Table 2: Incidences of Unsolicited Systemic Adverse Events $\geq 5\%$ in Any Group Following Each Dose of VAQTA in Healthy Children 12-23 Months of Age Receiving VAQTA Alone or Concomitantly With ProQuad and PREVNAR*

Adverse Event: Days 1-14	Dose 1		Dose 2	
	VAQTA alone	VAQTA + ProQuad + PREVNAR concomitantly	VAQTA alone	VAQTA + ProQuad concomitantly
	N=274	N=311	N=251	N=263
General Disorders and Administration Site Conditions				
Irritability	3.6%	6.1%	2.8%	2.7%
Infections and Infestations				
Upper respiratory tract infection	3.3%	6.1%	4.8%	5.7%
Skin and Subcutaneous Tissue Disorders				
Dermatitis diaper	1.1%	6.1%	2.4%	3.4%

*Pneumococcal 7-valent Conjugate Vaccine

In Stage I of an open, multicenter, randomized study, children 15 months of age were randomized to receive the first dose of VAQTA alone (N=151) or concomitantly with PedvaxHIB and INFANRIX (N=155); another group of children 15 months of age were randomized to receive the first dose of VAQTA alone (N=152) or concomitantly with PedvaxHIB (N=159). All groups received the second dose of VAQTA alone at least 6 months following the first dose. The race distribution of Stage I study subjects was: 63.9% Caucasian; 17.5% Hispanic-American; 14.7% Black; 2.6% other; and 1.3% Asian. The distribution of subjects by gender was 54.0% male and 46.0% female. In Stage II of this study, an additional 654

children 12-17 months of age received the first dose of VAQTA alone followed by the second dose of VAQTA 6 months later. The race distribution of Stage II of the study subjects was: 66.1% Caucasian; 10.6% Hispanic-American; 16.8% Black; 4.7% other; and 1.5% Asian. The distribution of subjects by gender was 51.2% male and 48.8% female.

Table 3 presents rates of solicited local reactions at the VAQTA injection-site and rates of elevated temperatures ($\geq 100.4^{\circ}\text{F}$ and $\geq 102.2^{\circ}\text{F}$) that occurred within 5 days following each dose of VAQTA and elevated temperatures $>98.6^{\circ}\text{F}$ for a total of 14 days following each dose of VAQTA. Occurrences of these events were recorded daily on diary cards. Table 4 presents rates of unsolicited systemic adverse events that occurred within 14 days at $\geq 5\%$ following each dose of VAQTA.

Table 3: Incidences of Solicited Local Adverse Reactions at the VAQTA Injection Site and Elevated Temperatures Following Each Dose of VAQTA in Healthy Children 12-23 Months of Age Receiving VAQTA Alone or Concomitantly with PedvaxHIB With or Without INFANRIX (Stage I) and those Receiving VAQTA Alone at Both Doses (Stage II)

Adverse Reaction: Days 1-5 unless noted	Stage I			Stage II	
	Dose 1 VAQTA alone	VAQTA + PedvaxHIB and Infanrix or VAQTA + PedvaxHIB concomitantly	Dose 2 VAQTA alone	Dose 1 VAQTA alone	Dose 2 VAQTA alone
Injection site adverse reactions	N=256	N=302	N=503	N=647	N=599
Injection site erythema	18.0%	19.9%	21.5%	11.7%	16.2%
Injection site pain/tenderness	21.9%	36.4%	27.4%	20.1%	22.9%
Injection site swelling	10.2%	14.2%	10.1%	7.1%	7.0%
Temperature $> 98.6^{\circ}\text{F}$ or feverish (Days 1- 14)	10.2%	17.2%	10.7%	10.0%	8.2%
	N=234	N=290	N=473	N=631	N=591
Temperature \geq 100.4 $^{\circ}\text{F}$	9.0%	16.9%	9.1%	9.4%	8.6%
Temperature ≥ 102.2 $^{\circ}\text{F}$	3.8%	3.1%	3.2%	2.9%	2.4%

N= number of subjects for whom data is available

Table 4: Incidences of Unsolicited Systemic Adverse Events $\geq 5\%$ in Any Group Following Each Dose of VAQTA in Healthy Children 12-23 Months of Age Receiving VAQTA Alone or Concomitantly with PedvaxHIB With or Without INFANRIX (Stage I) and Those Receiving VAQTA Alone at Both Doses (Stage II)

Adverse Event: Days 1-14	Stage I			Stage II	
	Dose 1 VAQTA alone	VAQTA + PedvaxHIB and Infanrix or VAQTA + PedvaxHIB concomitantly	Dose 2 VAQTA alone	Dose 1 VAQTA alone	Dose 2 VAQTA alone
	N=256	N=302	N=503	N=647	N=599
Gastrointestinal Disorders					
Diarrhea	3.9%	8.3%	3.8%	4.6%	3.8%
Teething	3.1%	2.3%	1.4%	5.7%	4.3%
General Disorders and Administration Site Conditions					
Irritability	6.3%	9.6%	4.0%	8.8%	6.5%
Infections and Infestations					
Upper respiratory tract infection	2.3%	3.3%	3.0%	4.9%	5.2%
Respiratory, Thoracic and Mediastinal Disorders					
Rhinorrhea	2.0%	4.0%	3.8%	6.2%	3.8%

Data presented in Tables 1 through 4 on solicited local reactions, and solicited and unsolicited systemic adverse events with incidence $\geq 5\%$ following each dose of VAQTA are representative of other clinical trials of VAQTA in children 12 through 23 months of age. Across the five studies conducted in children 12-23 months of age, $\geq 39.9\%$ of subjects experienced local adverse reactions and $\geq 55.7\%$ of subjects

experienced systemic adverse events. The majority of local and systemic adverse events were mild to moderate in intensity.

The following additional unsolicited local adverse reactions and systemic adverse events were observed at a common frequency of $\geq 1\%$ to $< 10\%$ in any individual clinical study. This listing includes only the adverse reactions not reported elsewhere in the label. These local adverse reactions and systemic adverse events occurred among recipients of VAQTA alone or VAQTA given concomitantly within 14 days following any dose of VAQTA across four clinical studies.

Eye disorders: Conjunctivitis

Gastrointestinal disorders: Constipation; vomiting

General disorders and administration site conditions: Injection-site bruising; injection-site ecchymosis

Infections and infestations: Otitis media; nasopharyngitis; rhinitis; viral infection; croup; pharyngitis streptococcal; laryngotracheobronchitis; viral exanthema; gastroenteritis viral; roseola

Metabolism and nutrition disorders: Anorexia

Psychiatric disorders: Insomnia; crying

Respiratory, thoracic and mediastinal disorders: Cough; nasal congestion; respiratory congestion

Skin and subcutaneous tissue disorders: Rash vesicular; measles-like/rubella-like rash; varicella-like rash; rash morbilliform

Serious Adverse Events (Children 12 through 23 Months of Age): Across the five studies conducted in subjects 12-23 months of age, 0.7% (32/4374) of subjects reported a serious adverse event following any dose of VAQTA, and 0.1% (5/4374) of subjects reported a serious adverse event judged to be vaccine related by the study investigator. The serious adverse events were collected over the period defined in each protocol (14, 28, or 42 days). Vaccine-related serious adverse events which occurred following any dose of VAQTA with or without concomitant vaccines included febrile seizure (0.05%), dehydration (0.02%), gastroenteritis (0.02%), and cellulitis (0.02%).

Children/Adolescents — 2 Years through 18 Years of Age

In 11 clinical trials, 2615 healthy children 2 years through 18 years of age received at least one dose of VAQTA. These studies included administration of VAQTA in varying doses and regimens (1377 children received one or more 25U doses). The race distribution of the study subjects who received at least one dose of VAQTA in these studies was as follows: 84.7% Caucasian; 10.6% American Indian; 2.3% African-American; 1.5% Hispanic-American; 0.6% other; 0.2% Oriental. The distribution of subjects by gender was 51.2% male and 48.8% female.

In a double-blind, placebo-controlled efficacy trial (i.e. The Monroe Efficacy Study), 1037 healthy children and adolescents 2 through 16 years of age were randomized to receive a primary dose of 25U of VAQTA and a booster dose of VAQTA 6, 12, or 18 months later, or placebo (alum diluent). All study subjects were Caucasian: 51.5% were male and 48.5% were female. Subjects were followed days 1 to 5 postvaccination for fever and local adverse reactions and days 1 to 14 for systemic adverse events. The most common adverse events/reactions were injection-site reactions, reported by 6.4% of subjects. Table 5 summarizes local adverse reactions and systemic adverse events reported in $\geq 1\%$ of subjects. There were no significant differences in the rates of any adverse events or adverse reactions between vaccine and placebo recipients after Dose 1.

Table 5: Local Adverse Reactions and Systemic Adverse Events (≥1%) in Healthy Children and Adolescents from the Monroe Efficacy Study

Adverse Event	VAQTA (N=519)		Placebo (Alum Diluent) ^{*,†,‡} (N=518) Rate (Percent)
	Dose 1 [*] Rate (Percent)	Booster Rate (Percent)	
Injection Site [§]	n=515	n=475	n=510
Pain	6.4%	3.4%	6.3%
Tenderness	4.9%	1.7%	6.1%
Erythema	1.9%	0.8%	1.8%
Swelling	1.7%	1.5%	1.6%
Warmth	1.7%	0.6%	1.6%
Systemic [¶]	n=519	n=475	n=518
Abdominal pain	1.2%	1.1%	1.0%
Pharyngitis	1.2%	0%	0.8%
Headache	0.4%	0.8%	1.0%

N=Number of subjects enrolled/randomized.

Percent=percentage of subjects for whom data are available with adverse event

n=number of subjects for whom adverse events available

* No statistically significant differences between the two groups.

† Second injection of placebo not administered because code for the trial was broken.

‡ Placebo (Alum diluent) = amorphous aluminum hydroxyphosphate sulfate.

§ Adverse Reactions at the injection site (VAQTA) Days 1-5 after vaccination with VAQTA

¶ Systemic adverse events reported Days 1-15 after vaccination, regardless of causality.

Adults — 19 Years of Age and Older

In an open-label clinical trial, 240 healthy adults 18 to 54 years of age were randomized to receive either VAQTA (50U/1-mL) with Typhim Vi (Typhoid Vi polysaccharide vaccine) and YF-Vax (yellow fever vaccine) concomitantly (N=80), typhoid Vi polysaccharide and yellow fever vaccines concomitantly (N=80), or VAQTA alone (N=80). Approximately 6 months later, subjects who received VAQTA were administered a second dose of VAQTA. The race distribution of the study subjects who received VAQTA with or without typhoid Vi polysaccharide and yellow fever vaccine was as follows: 78.3% Caucasian; 14.2% Oriental; 3.3% other; 2.1% African-American; 1.7% Indian; 0.4% Hispanic-American. The distribution of subjects by gender was 40.8% male and 59.2% female. Subjects were monitored for local adverse reactions and fever for 5 days and systemic adverse events for 14 days after each vaccination. In the 14 days after the first dose of VAQTA, the proportion of subjects with adverse events was similar between recipients of VAQTA given concomitantly with typhoid Vi polysaccharide and yellow fever vaccines compared to recipients of typhoid Vi polysaccharide and yellow fever vaccines without VAQTA. Table 6 summarizes solicited local adverse reactions and Table 7 summarizes unsolicited systemic adverse events reported in ≥5% in adults who received one or two doses of VAQTA alone and for subjects who received VAQTA concomitantly with typhoid Vi polysaccharide and yellow fever vaccines. There were no solicited systemic complaints reported at a rate ≥5%. Fever ≥101°F occurred in 1.3% of subjects in each group.

Table 6: Incidences of Solicited Local Adverse Reactions in Healthy Adults ≥19 Years of Age Occurring at ≥5% After Any Dose

Adverse Event	VAQTA administered alone (N=80)	VAQTA + ViCPS* and Yellow Fever vaccines administered concomitantly [†] (N=80)
	Rate (Percent)	
Injection-site[‡]		
Pain/tenderness/soreness	78.8%	70.3%
Warmth	23.7%	23.7%
Swelling	16.2%	8.8%
Erythema	17.5%	6.3%

N=Number of subjects enrolled/randomized.

Percent=percentage of subjects with adverse event.

*ViCPS=Typhoid Vi polysaccharide vaccine.

†VAQTA administered concomitantly with typhoid Vi polysaccharide (ViCPS) and yellow fever vaccines.

‡ Adverse Reactions at the injection site (VAQTA) Days 1-5 after vaccination

Table 7: Incidences of Unsolicited Systemic Adverse Events in Adults ≥19 Years of Age Occurring at ≥5% After Any Dose

Body System Adverse Event	VAQTA administered alone (N=80)	VAQTA + ViCPS* and Yellow Fever vaccines administered concomitantly† (N=80)
	Rate (Percent)	
General disorders and administration site reactions‡		
Asthenia/fatigue	7.5%	11.3%
Chills	1.3%	7.5%
Gastrointestinal disorders‡		
Nausea	7.5%	12.5%
Musculoskeletal and connective tissue disorders‡		
Myalgia	5.0%	10.0%
Arm pain	0.0%	6.3%
Nervous system disorders‡		
Headache	23.8%	26.3%
Infections and infestations‡		
Upper respiratory infection	7.5%	3.8%
Pharyngitis	2.5%	6.3%

N=Number of subjects enrolled/randomized with data available.

Percent=percentage of subjects with adverse event for whom data are available.

*ViCPS=Typhoid Vi polysaccharide vaccine.

†VAQTA administered concomitantly with typhoid Vi polysaccharide (ViCPS) and yellow fever vaccines.

‡Systemic Adverse Events reported Days 1-15 after vaccination, regardless of causality.

In four clinical trials involving 1645 healthy adults 19 years of age and older who received one or more 50U doses of hepatitis A vaccine, subjects were followed for fever and local adverse reactions 1 to 5 days postvaccination and for systemic adverse events 1 to 14 days postvaccination. One single-blind study evaluated doses of VAQTA with varying amounts of viral antigen and/or alum content in healthy adults ≥170 pounds and ≥30 years of age (N=210 adults administered 50U/1-mL dose). One open-label study evaluated VAQTA given with immune globulin (IG) or alone (N=164 adults who received VAQTA alone). A third study was single-blind and evaluated 3 different lots of VAQTA (N=1112). The fourth study that was also single-blind evaluated doses of VAQTA with varying amounts of viral antigen in healthy adults ≥170 pounds and ≥30 years of age (N=159 adults administered the 50U/1-mL dose). Overall, the race distribution of the study subjects who received at least one dose of VAQTA was as follows: 94.2% Caucasian; 2.2% Black; 1.5% Hispanic; 1.5% Oriental; 0.4% other; 0.2% American Indian. 47.6% of subjects were male and 52.4% were female. The most common adverse event/reaction was injection-site pain/soreness/tenderness reported by 67.0% of subjects. Of all reported injection-site reactions 99.8% were mild (*i.e.*, easily tolerated with no medical intervention) or moderate (*i.e.*, minimally interfered with usual activity possibly requiring little medical intervention). Listed below in Table 8 are the local adverse reactions and systemic adverse events reported by ≥5% of subjects, in decreasing order of frequency within each body system.

Table 8: Incidences of Local Adverse Reactions and Systemic Adverse Events ≥5% in Adults 19 Years of Age and Older

Body System Adverse Events	VAQTA (Any Dose) (N=1645) Rate (n/total n)
Nervous system disorders*	
Headache	n=1641 16.1%
General disorders and administration site reactions†	
Injection-site	n=1640 67.0%

pain/tenderness/soreness	
Injection-site warmth	18.2%
Injection-site swelling	14.7%
Injection-site erythema	13.7%

N=Number of subjects enrolled/randomized.

n=Number of subjects in each category with data available.

Percent=percentage of subjects for whom data are available with adverse event.

*Systemic Adverse Events reported Days 1 to 14 after vaccination, regardless of causality.

†Adverse Reactions at the injection site (VAQTA) and measured fever Days 1 to 5 after vaccination.

The following additional unsolicited systemic adverse events were observed among recipients of VAQTA that occurred within 14 days at a common frequency of $\geq 1\%$ to $< 10\%$ following any dose not reported elsewhere in the label. These adverse reactions have been reported across 4 clinical studies.

Musculoskeletal and connective tissue disorders: Back pain; stiffness

Reproductive system and breast disorders: Menstruation disorders

6.2 Post-Marketing Experience

The following additional adverse events have been reported with use of the marketed vaccine. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to a vaccine exposure.

Blood and lymphatic disorders: Thrombocytopenia.

Nervous system disorders: Guillain-Barré syndrome; cerebellar ataxia; encephalitis.

Post-Marketing Observational Safety Study

In a post-marketing, 60-day safety surveillance study, conducted at a large health maintenance organization in the United States, a total of 42,110 individuals ≥ 2 years of age received 1 or 2 doses of VAQTA (13,735 children/adolescents and 28,375 adult subjects). Safety was passively monitored by electronic search of the automated medical records database for emergency room and outpatient visits, hospitalizations, and deaths. Medical charts were reviewed when an event was considered to be possibly vaccine-related by the investigator. None of the serious adverse events identified were assessed as being related to vaccine by the investigator. Diarrhea/gastroenteritis, resulting in outpatient visits, was determined by the investigator to be the only vaccine-related nonserious adverse reaction in the study. There was no vaccine-related adverse reaction identified that had not been reported in earlier clinical trials with VAQTA.

7 DRUG INTERACTIONS

7.1 Use with Other Vaccines

Do not mix VAQTA with any other vaccine in the same syringe or vial. Use separate injection sites and syringes for each vaccine. Please refer to package inserts of coadministered vaccines.

In clinical trials in children, VAQTA was concomitantly administered with one or more of the following US licensed vaccines: Measles, Mumps, and Rubella Virus Vaccine, Live; Varicella Vaccine, Live; Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine, Adsorbed; Measles, Mumps, Rubella, and Varicella Vaccine, Live; Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM₁₉₇); and Haemophilus B Conjugate Vaccine (Meningococcal Protein Conjugate). Safety and immunogenicity were similar for concomitantly administered vaccines compared to separately administered vaccines.

In clinical trials in adults, VAQTA was concomitantly administered with typhoid Vi polysaccharide and yellow fever vaccines [see *Adverse Reactions (6.1) and Clinical Studies (14.2, 14.7)*]. Safety and immunogenicity were similar for concomitantly administered vaccines compared to separately administered vaccines.

7.2 Use with Immune Globulin

VAQTA may be administered concomitantly with Immune Globulin, human, using separate sites and syringes. The recommended vaccination regimen for VAQTA should be followed. Consult the manufacturer's product circular for the appropriate dosage of Immune Globulin. A booster dose of VAQTA should be administered at the appropriate time as outlined in the recommended regimen for VAQTA [see *Clinical Studies (14.5)*].

7.3 Immunosuppressive Therapy

If VAQTA is administered to a person receiving immunosuppressive therapy, an adequate immunologic response may not be obtained.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

The safety of VAQTA has been evaluated in 4374 children 12 through 23 months of age, and 2615 children/adolescents 2 through 18 years of age who received at least one 25U dose of VAQTA [see *Adverse Reactions (6) and Dosage and Administration (2)*].

Safety and effectiveness in infants below 12 months of age have not been established.

8.5 Geriatric Use

In the post-marketing observational safety study which included 42,110 persons who received VAQTA [see *Adverse Reactions (6.2)*], 4769 persons were 65 years of age or older and 1073 persons were 75 years of age or older. There were no adverse events judged by the investigator to be vaccine-related in the geriatric study population. In other clinical studies, 68 subjects 65 years of age or older were vaccinated with VAQTA, 10 of whom were 75 years of age or older. No overall differences in safety and immunogenicity were observed between these subjects and younger subjects; however, greater sensitivity of some older individuals cannot be ruled out. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

8.6 Immunocompromised Individuals

Immunocompromised persons may have a diminished immune response to VAQTA and may not be protected against HAV infection.

11 DESCRIPTION

VAQTA is an inactivated whole virus vaccine derived from hepatitis A virus grown in cell culture in human MRC-5 diploid fibroblasts. It contains inactivated virus of a strain which was originally derived by further serial passage of a proven attenuated strain. The virus is grown, harvested, purified by a combination of physical and high performance liquid chromatographic techniques developed at the Merck Research Laboratories, formalin inactivated, and then adsorbed onto amorphous aluminum hydroxyphosphate sulfate.

VAQTA is a sterile suspension for intramuscular injection. One milliliter of the vaccine contains approximately 50U of hepatitis A virus antigen, which is purified and formulated without a preservative. Within the limits of current assay variability, the 50U dose of VAQTA contains less than 0.1 mcg of non-viral protein, less than 4×10^{-6} mcg of DNA, less than 10^{-4} mcg of bovine albumin, and less than 0.8 mcg of formaldehyde. Other process chemical residuals are less than 10 parts per billion (ppb), including neomycin.

Each 0.5-mL pediatric dose contains 25U of hepatitis A virus antigen and adsorbed onto approximately 0.225 mg of aluminum provided as amorphous aluminum hydroxyphosphate sulfate, and 35 mcg of sodium borate as a pH stabilizer, in 0.9% sodium chloride.

Each 1-mL adult dose contains 50U of hepatitis A virus antigen and adsorbed onto approximately 0.45 mg of aluminum provided as amorphous aluminum hydroxyphosphate sulfate, and 70 mcg of sodium borate as a pH stabilizer, in 0.9% sodium chloride.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

VAQTA has been shown to elicit antibodies to hepatitis A as measured by ELISA.

Protection from hepatitis A disease has been shown to be related to the presence of antibody. However, the lowest titer needed to confer protection has not been determined.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

VAQTA has not been evaluated for its carcinogenic or mutagenic potential, or its potential to impair fertility.

14 CLINICAL STUDIES

14.1 Efficacy of VAQTA: The Monroe Clinical Study

The immunogenicity and protective efficacy of VAQTA were evaluated in a randomized, double-blind, placebo-controlled study involving 1037 susceptible healthy children and adolescents 2 through 16 years of age in a U.S. community with recurrent outbreaks of hepatitis A (The Monroe Efficacy Study). All of these children were Caucasian, and there were 51.5% male and 48.5% female. Each child received an intramuscular dose of VAQTA (25U) (N=519) or placebo (alum diluent) (N=518). Among those individuals who were initially seronegative (measured by a modification of the HAVAB radioimmunoassay [RIA]), seroconversion was achieved in >99% of vaccine recipients within 4 weeks after vaccination. The onset of seroconversion following a single dose of VAQTA was shown to parallel the onset of protection against clinical hepatitis A disease.

Because of the long incubation period of the disease (approximately 20 to 50 days, or longer in children), clinical efficacy was based on confirmed cases¹ of hepatitis A occurring ≥ 50 days after vaccination in order to exclude any children incubating the infection before vaccination. In subjects who were initially seronegative, the protective efficacy of a single dose of VAQTA was observed to be 100% with 21 cases of clinically confirmed hepatitis A occurring in the placebo group and none in the vaccine group ($p < 0.001$).

The number of clinically confirmed cases of hepatitis A ≥ 30 days after vaccination were also compared. In this analysis, 28 cases of clinically confirmed hepatitis A occurred in the placebo group while none occurred in the vaccine group ≥ 30 days after vaccination. In addition, it was observed in this trial that no cases of clinically confirmed hepatitis A occurred in the vaccine group after day 16.² Following demonstration of protection with a single dose and termination of the study, a booster dose was administered to a subset of vaccinees 6, 12, or 18 months after the primary dose.

No cases of clinically confirmed hepatitis A disease ≥ 50 days after vaccination have occurred in those vaccinees from The Monroe Efficacy Study monitored for up to 9 years.

14.2 Other Clinical Studies

The efficacy of VAQTA in other age groups was based upon immunogenicity measured 4 to 6 weeks following vaccination. VAQTA was found to be immunogenic in all age groups.

¹The clinical case definition included all of the following occurring at the same time: 1) one or more typical clinical signs or symptoms of hepatitis A (e.g., jaundice, malaise, fever $\geq 38.3^{\circ}\text{C}$); 2) elevation of hepatitis A IgM antibody (HAVAB-M); 3) elevation of alanine transferase (ALT) ≥ 2 times the upper limit of normal.

²One vaccinee did not meet the pre-defined criteria for clinically confirmed hepatitis A but did have positive hepatitis A IgM and borderline liver enzyme (ALT) elevations on days 34, 50, and 58 after vaccination with mild clinical symptoms observed on days 49 and 50.

Children — 12 through 23 Months of Age

In a clinical trial, children 12 through 23 months of age were randomized to receive the first dose of VAQTA with or without M-M-R II and VARIVAX (N=617) and the second dose of VAQTA with or without Tripedia and optionally either oral poliovirus vaccine (no longer licensed in the US) or IPOL (N=555). The race distribution of study subjects who received at least one dose of VAQTA was as follows: 56.7% Caucasian; 17.5% Hispanic-American; 14.3% African-American; 7.0% Native American; 3.4% other; 0.8% Oriental; 0.2% Asian; and 0.2% Indian. The distribution of subjects by gender was 53.6% male and 46.4% female. In the analysis population, there were 471 initially seronegative children 12 through 23 months of age, who received the first dose of VAQTA with (N=237) or without (N=234) M-M-R II and VARIVAX of whom 96% (95% CI: 93.7%, 97.5%) seroconverted (defined as having an anti-HAV titer ≥ 10 mIU/mL) post dose 1 with an anti-HAV geometric mean titer (GMT) of 48 mIU/mL (95% CI: 44.7, 51.6). There were 343 children in the analysis population who received the second dose of VAQTA with (N=168) or without (N=175) Tripedia and optional oral poliovirus vaccine or IPOL of whom 100% (95% CI: 99.3%, 100%) seroconverted post dose 2 with an anti-HAV GMT of 6920 mIU/mL (95% CI: 6136, 7801). Of children who received only VAQTA at both visits, 100% (n=97) seroconverted after the second dose of VAQTA.

In a clinical trial involving 653 healthy children 12 to 15 months of age, 330 were randomized to receive VAQTA, ProQuad, and pneumococcal 7-valent conjugate vaccine concomitantly, and 323 were randomized to receive ProQuad and pneumococcal 7-valent conjugate vaccine concomitantly followed by VAQTA 6 weeks later. The race distribution of the study subjects was as follows: 60.3% Caucasian; 21.6% African-American; 9.5% Hispanic-American; 7.2% other; 1.1% Asian/Pacific; and 0.3% Native American. The distribution of subjects by gender was 50.7% male and 49.3% female. In the analysis population, the seropositivity rate for hepatitis A antibody (defined as the percent of subjects with an anti-HAV titer ≥ 10 mIU/mL) was 100% (n=182; 95% CI: 98.0%, 100%) post dose 2 with an anti-HAV GMT of 4977 mIU/mL (95% CI: 4068, 6089) when VAQTA was given with ProQuad and pneumococcal 7-valent conjugate vaccine and 99.4% (n=159, 95% CI: 96.5%, 100%) post dose 2 with an anti-HAV GMT of 6123 mIU/mL (95% CI: 4826, 7770) when VAQTA alone was given. These seropositivity rates were similar whether VAQTA was administered with or without ProQuad and pneumococcal 7-valent conjugate vaccine.

In an open, multicenter, randomized study involving 617 children 15 months of age, 306 were randomized to receive VAQTA with or without PedvaxHIB and INFANRIX, and 311 were randomized to receive VAQTA with or without PedvaxHIB. The race distribution of the study subjects was as follows: 63.9% Caucasian; 17.5% Hispanic-American; 14.7% Black; 2.6% other; and 1.3% Asian. The distribution of subjects by gender was 54.0% male and 46.0% female. The seropositivity rate for hepatitis A antibody (defined as the percent of subjects with an anti-HAV titer ≥ 10 mIU/mL) 4 weeks post dose 2 was 100% (n=208, 95% CI: 98.2%, 100.0%) in those who received VAQTA concomitantly with PedvaxHIB and INFANRIX or concomitantly with PedvaxHIB. In those subjects who received VAQTA alone, the seropositivity rate for hepatitis A antibody was 100% (n=183, 95% CI: 98.0%, 100.0%), regardless of baseline hepatitis A serostatus. Overall, the anti-HAV GMT in the concomitant groups was 3616.5 mIU/mL (95% CI: 3084.5, 4240.2). The anti-HAV GMT in the nonconcomitant groups was 4712.6 mIU/mL (95% CI: 3996.8, 5556.8). Comparable responses were observed in both the initially seronegative and seropositive subjects.

In three combined clinical studies 1022 initially seronegative subjects received 2 doses of VAQTA alone or concomitantly with other vaccines. Of the seronegative subjects, 99.9% achieved an anti-HAV titer ≥ 10 mIU/mL (95% CI: 99.5%, 100%) and an anti-HAV GMT of 5392.1 mIU/mL (95% CI: 4996.5, 5819.0) 4 weeks following dose 2 of VAQTA.

Children/Adolescents — 2 Years through 18 Years of Age

Immunogenicity data were combined from eleven randomized clinical studies in children and adolescents 2 through 18 years of age who received VAQTA (25U/0.5 mL). These included administration of VAQTA in varying doses and regimens (N=404 received 25U/0.5 mL), the Monroe Efficacy Study (N=973), and comparison studies for process and formulation changes (N=1238). The race distribution of the study subjects who received at least one dose of VAQTA in these studies was as follows: 84.8% Caucasian; 10.6% American Indian; 2.3% African-American; 1.5% Hispanic-American; 0.6% other; 0.2% Oriental. The distribution of subjects by gender was 51.2% male and 48.8% female. The proportions of subjects

who seroconverted 4 weeks after the first and second doses administered 6 months apart were 97% (n=1230; 95% CI: 96%, 98%) and 100% (n=1057; 95% CI: 99.5%, 100%) of subjects with anti-HAV GMTs of 43 mIU/mL (95% CI: 40, 45) and 10,077 mIU/mL (95% CI: 9394, 10,810), respectively.

Adults — 19 Years of Age and Older

Immunogenicity data were combined from five randomized clinical studies in adults 19 years of age and older who received VAQTA (50U/1-mL). One single-blind study evaluated doses of VAQTA with varying amounts of viral antigen and/or alum content in healthy adults ≥170 pounds and ≥30 years of age (N=208 adults administered 50U/1-mL dose). One open-label study evaluated VAQTA given with immune globulin or alone (N=164 adults who received VAQTA alone). A third study was single-blind and evaluated 3 different lots of VAQTA (N=1112). The fourth study was single-blind and evaluated doses of VAQTA with varying amounts of viral antigen in healthy adults ≥170 pounds and ≥30 years of age (N=159 adults administered the 50U/1-mL dose). The fifth study was an open-label study to evaluate various regimens for time of administration of the booster dose of VAQTA (6, 12, and 18 months post dose 1, N=354). The race distribution of the study subjects who received at least one dose of VAQTA in these studies was as follows: 93.2% Caucasian; 2.5% African-American; 2.1% Hispanic-American; 1.4% Oriental; 0.5% other; 0.3% American Indian. The distribution of subjects by gender was 44.8% male and 55.2% female. The proportion of subjects who seroconverted 4 weeks after the first and second doses administered 6 months apart was 95% (n=1411; 95% CI: 94%, 96%) and 99.9% (n=1244; 95% CI: 99.4%, 100%) with GMTs of 37 mIU/mL (95% CI: 35, 38) and 6013 mIU/mL (95% CI: 5592, 6467), respectively. Furthermore, at 2 weeks postvaccination, 69.2% (n=744; 95% CI: 65.7%, 72.5%) of adults seroconverted with an anti-HAV GMT of 16 mIU/mL after a single dose of VAQTA.

14.3 Timing of Booster Dose Administration

Children/Adolescents — 2 through 18 Years of Age

In the Monroe Efficacy Study, children were administered a second dose of VAQTA (25U/0.5 mL) 6, 12, or 18 months following the initial dose. For subjects who received both doses of VAQTA, the GMTs and proportions of subjects who seroconverted 4 weeks after the booster dose administered 6, 12, and 18 months after the first dose are presented in Table 9.

Table 9: Children/Adolescents from the Monroe Efficacy Study
Seroconversion Rates (%) and Geometric Mean Titers (GMT) for Cohorts of Initially Seronegative Vaccinees at the Time of the Booster(25U) and 4 Weeks Later

Months Following Initial 25U Dose	Cohort* (n=960) 0 and 6 Months	Cohort* (n=35) 0 and 12 Months	Cohort* (n=39) 0 and 18 Months
	Seroconversion Rate GMT (mIU/mL) (95% CI)		
6	97% 107 (98, 117)	—	—
7	100% 10433 (9681, 11243)	—	—
12	—	91% 48 (33, 71)	—
13	—	100% 12308 (9337, 16226)	—
18	—	—	90% 50 (28, 89)
19	—	—	100% 9591 (7613, 12082)

* Blood samples were taken at prebooster and postbooster time points.

Adults — 19 years of age and older

Among the 5 randomized clinical studies in adults 19 years of age and older described in Section 14.2, there were additional data in which a booster dose of VAQTA (50U/1-mL) was administered 12 or 18 months after the first dose. For subjects in these studies who received both doses of VAQTA, the proportions who seroconverted 4 weeks after the booster dose administered 6, 12, and 18 months after the first dose were 100% of 1201 subjects, 98% of 91 subjects, and 100% of 84 subjects, respectively. GMTs in mIU/mL one month after the subjects received the booster dose at 6, 12, or 18 months after the

primary dose were 5987 mIU/mL (95% CI: 5561, 6445), 4896 mIU/mL (95% CI: 3589, 6679), and 6043 mIU/mL (95% CI: 4687, 7793), respectively.

14.4 Duration of Immune Response

In follow-up of subjects in The Monroe Efficacy Study, in children (≥ 2 years of age) and adolescents who received two doses (25U) of VAQTA, detectable levels of anti-HAV antibodies (≥ 10 mIU/mL) were present in 100% of subjects for at least 10 years postvaccination. In subjects who received VAQTA at 0 and 6 months, the GMT was 819 mIU/mL (n=175) at 2.5 to 3.5 years and 505 mIU/mL (n=174) at 5 to 6 years, and 574 mIU/mL (n=114) at 10 years postvaccination. In subjects who received VAQTA at 0 and 12 months, the GMT was 2224 mIU/mL (n=49) at 2.5 to 3.5 years, 1191 mIU/mL (n=47) at 5 to 6 years, and 1005 mIU/mL (n=36) at 10 years postvaccination. In subjects who received VAQTA at 0 and 18 months, the GMT was 2501 mIU/mL (n=53) at 2.5 to 3.5 years, 1614 mIU/mL (n=56) at 5 to 6 years, and 1507 mIU/mL (n=41) at 10 years postvaccination.

In adults that were administered VAQTA at 0 and 6 months, the hepatitis A antibody response to date has been shown to persist at least 6 years. Detectable levels of anti-HAV antibodies (≥ 10 mIU/mL) were present in 100% (378/378) of subjects with a GMT of 1734 mIU/mL at 1 year, 99.2% (252/254) of subjects with a GMT of 687 mIU/mL at 2 to 3 years, 99.1% (219/221) of subjects with a GMT of 605 mIU/mL at 4 years, and 99.4% (170/171) of subjects with a GMT of 684 mIU/mL at 6 years postvaccination.

The total duration of the protective effect of VAQTA in healthy vaccinees is unknown at present.

14.5 Concomitant Administration of VAQTA and Immune Globulin

The concurrent use of VAQTA (50U) and immune globulin (IG, 0.06 mL/kg) was evaluated in an open-label, randomized clinical study involving 294 healthy adults 18 to 39 years of age. Adults were randomized to receive 2 doses of VAQTA 24 weeks apart (N=129), the first dose of VAQTA concomitant with a dose of IG followed by the second dose of VAQTA alone 24 weeks later (N=135), or IG alone (N=30). The race distribution of the study subjects who received at least one dose of VAQTA or IG in this study was as follows: 92.3% Caucasian; 4.0% Hispanic-American; 3.0% African-American; 0.3% Native American; 0.3% Asian/Pacific. The distribution of subjects by gender was 28.7% male and 71.3% female. Table 10 provides seroconversion rates and GMTs at 4 and 24 weeks after the first dose in each treatment group and at one month after a booster dose of VAQTA (administered at 24 weeks) [see *Drug Interactions* (7.2)].

Table 10: Seroconversion Rates (%) and Geometric Mean Titers (GMT) After Vaccination with VAQTA Plus IG, VAQTA Alone, and IG Alone

Weeks	VAQTA plus IG	VAQTA	IG
	Seroconversion Rate GMT (mIU/mL) (95% CI)		
4	100% 42 (39, 45) (n=129)	96% 38 (33, 42) (n=135)	87% 19 (15, 23) (n=30)
24	92% 83 (65, 105) (n=125)	97%* 137* (112, 169) (n=132)	0% Undetectable [†] (n=28)
28	100% 4872 (3716, 6388) (n=114)	100% 6498 (5111, 8261) (n=128)	N/A

*The seroconversion rate and the GMT in the group receiving VAQTA alone were significantly higher than in the group receiving VAQTA plus IG (p=0.05, p<0.001, respectively).

[†]Undetectable is defined as <10mIU/mL.

N/A = Not Applicable.

14.6 Interchangeability of the Booster Dose

A randomized, double-blind clinical study in 537 healthy adults, 18 to 83 years of age, evaluated the immune response to a booster dose of VAQTA and HAVRIX given at 6 or 12 months following an initial dose of HAVRIX. Subjects were randomized to receive VAQTA (50U) as a booster dose 6 months (N=232) or 12 months (N=124) following an initial dose of HAVRIX or HAVRIX (1440 EL. U) as a booster dose 6 months (N=118) or 12 months (N=63) following an initial dose of HAVRIX. The race distribution of

the study subjects who received the booster dose of VAQTA or HAVRIX in this study was as follows: 87.2% Caucasian; 8.0% African-American; 1.9% Hispanic-American; 1.3% Oriental; 0.9% Asian; 0.4% Indian; 0.4% other. The distribution of subjects by gender was 44.9% male and 55.1% female. When VAQTA was given as a booster dose following HAVRIX, the vaccine produced an adequate immune response (see Table 11) [see *Dosage and Administration (2.1)*].

Table 11: Seropositivity Rate, Booster Response Rate* and Geometric Mean Titer 4 Weeks Following a Booster Dose of VAQTA or HAVRIX Administered 6 to 12 Months After First Dose of HAVRIX[†]

First Dose	Booster Dose	Seropositivity Rate	Booster Response Rate*	Geometric Mean Titer
HAVRIX 1440 EL.U.	VAQTA 50 U	99.7% (n=313)	86.1% (n=310)	3272 (n=313)
HAVRIX 1440 EL.U.	HAVRIX 1440 EL.U.	99.3% (n=151)	80.1% (n=151)	2423 (n=151)

*Booster Response Rate is defined as greater than or equal to a tenfold rise from prebooster to postbooster titer and postbooster titer ≥ 100 mIU/mL.

[†]Study conducted in adults 18 years of age and older.

14.7 Immune Response to Concomitantly Administered Vaccines

Clinical Studies of VAQTA with M-M-R II, VARIVAX, and Tripedia

In the clinical trial in which children 12 months of age received the first dose of VAQTA concomitantly with M-M-R II and VARIVAX described in Section 14.2, rates of seroprotection to hepatitis A were similar between the two groups who received VAQTA with or without M-M-R II and VARIVAX. Measles, mumps, and rubella immune responses were tested in 241 subjects, 263 subjects, and 270 subjects, respectively. Seropositivity rates were 98.8% [95% CI: 96.4%, 99.7%] for measles, 99.6% [95% CI: 97.9%, 100%] for mumps, and 100% [95% CI: 98.6%, 100%] for rubella, which were similar to observed historical rates (seropositivity rates 99% for all three antigens, with lower bound of the 95% CI >89%) following vaccination with a first dose of M-M-R II in this age group. Data from this study were insufficient to adequately assess the immune response to VARIVAX administered concomitantly with VAQTA. In this same study, the second dose of VAQTA at 18 months of age was given with or without Tripedia (DTaP). Seropositivity rates for diphtheria and tetanus were similar to those in historical controls. However, data from this study were insufficient to assess the pertussis response of DTaP when administered with VAQTA. Rates of seroprotection to hepatitis A were similar between the two groups who received VAQTA with or without M-M-R II and VARIVAX, and between the two groups who received VAQTA with or without DTaP.

Clinical Studies of VAQTA with ProQuad and Prevnar

In the clinical trial of concomitant use of VAQTA with ProQuad and pneumococcal 7-valent conjugate vaccine in children 12 to 15 months of age described in Section 14.2, the antibody GMTs for *S. pneumoniae* types 4, 6B, 9V, 14, 18C, 19F, and 23F 6 weeks after vaccination with pneumococcal 7-valent conjugate vaccine administered concomitantly with ProQuad and VAQTA were non-inferior as compared to GMTs observed in the group given pneumococcal 7-valent conjugate vaccine with ProQuad alone (the lower bounds of the 95% CI around the fold-difference for the 7 serotypes excluded 0.5). For the varicella component of ProQuad, in subjects with baseline antibody titers <1.25 gpELISA units/mL, the proportion with a titer ≥ 5 gpELISA units/mL 6 weeks after their first dose of ProQuad was non-inferior (defined as -10 percentage point change) when ProQuad was administered with VAQTA and pneumococcal 7-valent conjugate vaccine as compared to the proportion with a titer ≥ 5 gpELISA units/mL when ProQuad was administered with pneumococcal 7-valent conjugate vaccine alone (difference in seroprotection rate -5.1% [95% CI: -9.3, -1.4%]). Hepatitis A responses were similar when compared between the two groups who received VAQTA with or without ProQuad and pneumococcal 7-valent conjugate vaccine. Seroconversion rates and antibody titers for varicella and *S. pneumoniae* types 4, 6B, 9V, 14, 18C, 19F, and 23F were similar between groups at 6 weeks postvaccination.

Clinical Studies of VAQTA with INFANRIX and PedvaxHIB

In the clinical trial of concomitant administration of VAQTA with INFANRIX and PedvaxHIB in children 15 months of age, described in Section 14.2, when the first dose of VAQTA was administered concomitantly

with either INFANRIX and PedvaxHIB or PedvaxHIB, there was no interference in immune response to hepatitis A as measured by seropositivity rates after dose 2 of VAQTA compared to administration of both doses of VAQTA alone. When dose 1 of VAQTA was administered concomitantly with either PedvaxHIB and INFANRIX or PedvaxHIB, there was no interference in immune response to *Haemophilus influenzae b* (as measured by the proportion of subjects who attained an anti-polyribosylribitol phosphate antibody titer >1.0 mcg/mL at 4 weeks after vaccination), compared to subjects receiving either PedvaxHIB and INFANRIX or PedvaxHIB. When VAQTA was administered concomitantly with INFANRIX and PedvaxHIB, there was no interference in immune responses at 4 weeks after vaccination to the pertussis antigens (PT, FHA, or pertactin, as measured by GMTs) and no interference in immune responses to diphtheria toxoid or tetanus toxoid (as measured by the proportion of subjects achieving an antibody titer >0.1 IU/mL) compared to administration of INFANRIX and PedvaxHIB.

Clinical Studies of VAQTA with Typhoid Vi Polysaccharide Vaccine and Yellow Fever Vaccine, Live Attenuated

In the clinical trial of concomitant use of VAQTA with typhoid Vi polysaccharide and yellow fever vaccines in adults 18-54 years of age described in Section 6.1, the antibody response rates for typhoid Vi polysaccharide and yellow fever were adequate when typhoid Vi polysaccharide and yellow fever vaccines were administered concomitantly with (N=80) and nonconcomitantly without VAQTA (N=80). The seropositivity rate for hepatitis A when VAQTA, typhoid Vi polysaccharide, and yellow fever vaccines were administered concomitantly was generally similar to when VAQTA was given alone [see *Drug Interactions (7.1)*].

Data are insufficient to assess the immune response to VAQTA and poliovirus vaccine when administered concomitantly.

16 HOW SUPPLIED/STORAGE AND HANDLING

VAQTA is available in single-dose vials and prefilled Luer-Lok[®] syringes.

Pediatric/Adolescent Formulations

25U/0.5 mL in single-dose vials and prefilled Luer-Lok[®] syringes.

NDC 0006-4831-41 – box of ten 0.5-mL single dose vials.

NDC 0006-4095-02 – carton of ten 0.5-mL prefilled single-dose Luer-Lok[®] syringes with tip caps.

NDC 0006-4095-09 – carton of six 0.5-mL prefilled single-dose Luer-Lok[®] syringes with tip caps.

Adult Formulations

50U/1-mL in single-dose vials and prefilled Luer-Lok[®] syringes.

NDC 0006-4841-00 – 1-mL single dose vial.

NDC 0006-4841-41 – box of ten 1-mL single dose vials.

NDC 0006-4096-02 – carton of ten 1-mL prefilled single-dose Luer-Lok[®] syringes with tip caps.

NDC 0006-4096-09 – carton of six 1-mL prefilled single-dose Luer-Lok[®] syringes with tip caps.

Store vaccine at 2-8°C (36-46°F).

DO NOT FREEZE since freezing destroys potency.

17 PATIENT COUNSELING INFORMATION

Information for Vaccine Recipients and Parents or Guardians

- Inform the patient, parent or guardian of the potential benefits and risks of the vaccine.
- Question the vaccine recipient, parent, or guardian about the occurrence of any symptoms and/or signs of an adverse reaction after a previous dose of hepatitis A vaccine.
- Inform the patient, parent, or guardian about the potential for adverse events that have been temporally associated with administration of VAQTA.

- Tell the patient, parent, or guardian accompanying the recipient, to report adverse events to the physician or clinic where the vaccine was administered.
- Prior to vaccination, give the patient, parent, or guardian the Vaccine Information Statements which are required by the National Childhood Vaccine Injury Act of 1986. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).
- Tell the patient, parent, or guardian that the United States Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986. The VAERS toll-free number is 1-800-822-7967. Reporting forms may also be obtained at the VAERS website at (www.vaers.hhs.gov).

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