VAQTA® 25 U / 0.5 ML
VAQTA® 50 U / ML
Hepatitis A virus antigen, Inactivated
Suspension for Intramuscular injection only

1 THERAPEUTIC INDICATIONS

1.1 Indications and Use

VAQTA[1] [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.

VAQTA may be administered along with immune globulin (IG) at a separate site with a separate syringe for post-exposure prophylaxis *[see Clinical Studies (14.5)]*.

1.2 Limitations of Use

VAQTA will not prevent hepatitis caused by infectious agents other than hepatitis A virus. Because of the long incubation period (approximately 20 to 50 days) for hepatitis A, it is possible for unrecognized hepatitis A infection to be present at the time the vaccine is given. The vaccine may not prevent hepatitis A in such individuals.

Vaccination with VAQTA may not result in a protective response in all susceptible vaccinees.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage and Schedule

Children/Adolescents (12 months through 18 years of age): Vaccination 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*): Vaccination consists of a primary 1.0-mL dose administered intramuscularly, and a 1.0-mL booster dose administered intramuscularly 6 to 18 months later.

Interchangeability of the Booster Dose: A booster dose of VAQTA may be given at 6 to 12 months following the primary dose of another inactivated hepatitis A vaccine (*i.e.,* HAVRIX[2]) *[see Clinical Studies (14.6)].*

2.2 Method of Administration

For intramuscular use only.

- Shake well to obtain a slightly opaque, white suspension before withdrawal and use.
- Thoroughly agitate to maintain suspension of the vaccine.
- Discard if the suspension does not appear homogenous or if extraneous particulate matter remains or discoloration is observed.

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.

Single-Dose Vial Use

- Withdraw dose of vaccine from the single-dose vial using a sterile needle and syringe.

3 DOSAGE FORMS AND STRENGTHS

Suspension for injection available in two presentations:

- 0.5-mL pediatric dose in single-dose vials
- 1.0-mL adult dose in single-dose vials

[1] Registered trademark of Merck Sharp & Dohme Corp., a subsidiary of **Merck & Co., Inc.**

[2] Registered trademark of GlaxoSmithKline

[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 contains 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.

5.5 Sodium content

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

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 (≥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%), 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

In two open-label clinical trials involving 706 healthy children 12 through 23 months of age who received one or two 25U doses of VAQTA, subjects were monitored for local adverse reactions and fever for 5 days and systemic adverse events for 14 days after each vaccination by diary cards. In one trial, 89 children were enrolled and received VAQTA alone. In the other trial, children were randomized to receive the first dose of VAQTA with or without M-M-R II®[1] (Measles, Mumps, and Rubella Virus Vaccine, Live) and VARIVAX®[1] (Varicella Virus Vaccine Live) (N=617) and the second dose of VAQTA with or without Tripedia[3] (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) (DTaP) and optionally either ORIMUNE[4] (Poliovirus vaccine live oral trivalent) (OPV) or IPOL[3] (Poliovirus Vaccine Inactivated) (IPV) (N=555). The race distribution of the study subjects who received at least one dose of VAQTA in these studies was as follows: 62.2% Caucasian; 15.3% Hispanic-American; 12.4% African-American; 6.1% Native American; 3.0% other; 0.7% Oriental, 0.1% Asian; and 0.1% Indian. The distribution of subjects by gender was 53.2% male and 46.8% female. Listed below are the solicited local adverse reactions and systemic adverse events (with 95% Confidence Interval (CI)) (Table 1) and unsolicited local adverse reactions and systemic adverse events (Table 2) reported at ≥1.0% in children who received one or two doses of VAQTA alone and for subjects who received VAQTA concomitantly with other vaccines.

Table 1
Incidences of Solicited Local Adverse Reactions and Systemic Adverse Events in Healthy Infants 12 through 23 Months of Age Occurring at ≥1% After Any Dose

Adverse Event	**VAQTA administered alone (N=241)**	**VAQTA + vaccines administered concomitantly* (N=706)**
	Rate (n/total n) (95% CI)	
Injection-site†		
Pain/tenderness/soreness	6.8% (16/236) (3.9%, 10.8%)	8.6% (59/683) (6.6%, 11.0%)
Swelling	4.2% (10/236) (2.1%, 7.7%)	5.1% (35/683) (3.6%, 7.1%)
Erythema	3.8% (9/236) (1.8%, 7.1%)	5.9% (40/683) (4.2%, 7.9%)
Warmth	2.5% (6/236) (0.9%, 5.5%)	3.2% (22/683) (2.0%, 4.8%)
Systemic‡		
Fever§		
≥100.4°F (≥38.0°C), Oral	12.3% (29/236) (8.4%, 17.2%)	14.6% (99/679) (12.0%, 17.5%)
≥102.0°F (≥38.8°C), Oral	3.4% (8/236) (1.5%, 6.6%)	4.9% (33/679) (3.4%, 6.8%)
Abnormal	1.7% (4/236) (0.5%, 4.3%)	0.9% (6/679) (0.3%, 1.9%)
Rash (measles-like, rubella-like, varicella-like)	0.0% (0/236) (0.0%, 1.5%)	1.8% (12/683) (0.9%, 3.1%)

N=Number of subjects enrolled/randomized.
n=Number of subjects in each category.
*VAQTA administered alone or concomitantly with M-M-R II and VARIVAX at Dose 1. VAQTA administered alone or concomitantly with DTaP and poliovirus vaccine optionally at Dose 2.
†Adverse Reactions at the injection site (VAQTA) Days 1-5 after vaccination
‡Systemic Adverse Events reported Days 1-14 after vaccination, regardless of causality.
§Monitored Days 1-5 after vaccination.

Table 2
Incidences of Unsolicited Local Adverse Reactions and Systemic Adverse Events in Healthy Infants 12 through 23 Months of Age Occurring at ≥1%

Body system Adverse Event	**VAQTA administered alone (N=241)**	**VAQTA + vaccines administered concomitantly* (N=706)**
	Rate (n/total n)	

[3] Registered trademark of Sanofi Pasteur, Inc.

[4] Registered trademark of Wyeth Pharmaceuticals, Inc.

	(95% CI)	
Eye disorders†		
Conjunctivitis	0.4% (1/236) (0.0%, 2.3%)	1.3% (9/683) (0.6%, 2.5%)
Respiratory, thoracic and mediastinal disorders†		
Rhinorrhea	3.7% (9/236) (1.8%, 7.1%)	5.7% (39/683) (4.1%, 7.7%)
Cough	3.7% (9/236) (1.8%, 7.1%)	5.1% (35/683) (3.6%, 7.1%)
Asthma	1.2% (3/236) (0.3%, 3.7%)	0.7% (5/683) (0.2%, 1.7%)
Respiratory congestion	0.4% (1/236) (0.0%, 2.3%)	1.6% (11/683) (0.8%, 2.9%)
Nasal congestion	0.4% (1/236) (0.0%, 2.3%)	1.2% (8/683) (0.5%, 2.3%)
Laryngotracheobronchitis	0.4% (1/236) (0.0%, 2.3%)	1.2% (8/683) (0.5%, 2.3%)
Gastrointestinal disorders†		
Diarrhea	3.3% (8/236) (1.5%, 6.6%)	5.9% (40/683) (4.2%, 7.9%)
Vomiting	2.9% (7/236) (1.2%, 6.0%)	4.0% (27/683) (2.6%, 5.7%)
Skin and subcutaneous tissue disorders†		
Rash	1.7% (4/236) (0.5%, 4.3%)	4.5% (31/683) (3.1%, 6.4%)
Metabolism and nutrition disorders†		
Anorexia	1.7% (4/236) (0.5%, 4.3%)	1.2% (8/683) (0.5%, 2.3%)
Infections and infestations†		
Upper respiratory infection	10.0% (24/236) (6.6%, 14.8%)	10.1% (69/683) (8.0%, 12.6%)
Otitis Media	4.1% (10/236) (2.1%, 7.7%)	7.6% (52/683) (5.7%, 9.9%)
Otitis	0.8% (2/236) (0.1%, 3.0%)	1.8% (12/683) (0.9%, 3.1%)
Viral exanthema	0.4% (1/236) (0.0%, 2.3%)	1.0% (7/683) (0.4%, 2.1%)
General disorders and administration site conditions†		
Irritability	7.1% (17/236) (4.3%, 11.3%)	10.8% (74/683) (8.6%, 13.4%)
Injection-site ecchymosis‡	0.0% (0/236) (0.0%, 1.6%)	1.0% (7/683) (0.4%, 2.2%)
Psychiatric disorders†		
Insomnia	1.7% (4/236) (0.5%, 4.3%)	0.7% (5/683) (0.2%, 1.7%)
Crying	1.2% (3/236) (0.3%, 3.7%)	1.8% (12/683) (0.9%, 3.1%)

N=Number of subjects enrolled/randomized.
n=Number of subjects in each category.
*VAQTA administered alone or concomitantly with M-M-R II and VARIVAX at Dose 1. VAQTA administered alone or concomitantly with DTaP and poliovirus vaccine optionally at Dose 2.
†Systemic Adverse Events reported Days 1-14 after vaccination, regardless of causality.
‡Adverse Reactions at the injection site (VAQTA) Days 1-5 after vaccination.

Serious Adverse Events: Subjects in an open-label study were randomized to receive VAQTA (Dose 1) alone (N=308) or VAQTA concomitantly with M-M-R II and VARIVAX (N=309). Seven children experienced a total of 9 seizures between 9 days and 81 days following the administration of the vaccines. None of the events was considered to be related to VAQTA by the investigator. Other serious events that occurred during the study included bronchiolitis (N=1), dehydration (N=2), RLL (Right Lower Lobe) pneumonia and asthma (N=1), and asthma exacerbation (N=1), which occurred 9 days to 46 days following the administration of VAQTA and were also considered by the investigator to be unrelated to VAQTA.

In an open-label clinical trial of 1800 subjects, 699 healthy children 12 to 23 months of age were randomized to receive two doses of VAQTA (N=352) or two doses of VAQTA concomitantly with two doses of ProQuad[1] (Measles, Mumps, Rubella and Varicella Virus Vaccine Live) (N=347) at least 6 months apart. An additional 1101 subjects received two doses of VAQTA alone at least 6 months apart (non-randomized), resulting in 1453 subjects receiving two doses of VAQTA alone (1101 non-randomized and 352 randomized) and 347 subjects receiving two doses of VAQTA concomitantly with ProQuad (all randomized). The race distribution of the study subjects who received VAQTA with or without ProQuad was as follows: 66.4% Caucasian; 19.7% Hispanic-American; 6.7% African-American; 5.0% other; 2.1% Asian; and 0.1%

Native American. The distribution of subjects by gender was 51.2% male and 48.8% female. Tables 3 and 4 present injection-site adverse reactions and fever ≥100.4°F (≥38.0°C) and ≥102.2°F (≥39.0°C) (Days 1 to 5 postvaccination) and systemic adverse events, including fever or feverish >98.6°F (>37.0°C) (Days 1 to 14 postvaccination) observed among recipients of VAQTA alone or concomitantly with ProQuad at a rate of at least 1% following any dose of VAQTA. Among all subjects, fever (>98.6°F (>37.0°C) or feverish) was the most common systemic adverse event and injection-site pain/tenderness was the most common injection-site adverse reaction. Based on a post-hoc analysis, the rate of fever (>98.6°F (>37.0°C) or feverish) after any dose of VAQTA was increased in subjects who received VAQTA with ProQuad as compared to VAQTA alone in the 14 days after vaccination {risk difference (11.8% [95% CI: 6.8, 17.2]) and relative risk (1.72 [95% CI: 1.40, 2.12])}. The difference in rate of fever (>98.6°F (>37.0°C) or feverish) was higher after Dose 1 (11.5%) as compared to Dose 2 (4.0%). The rates of fever ≥100.4°F (≥38.0°C) and ≥102.2°F (≥39.0°C) in the 5 days after any dose of VAQTA were similar in both treatment groups.

Table 3
Incidences of Unsolicited and Solicited Local Adverse Reactions at the Injection Site for VAQTA Occurring at ≥1% in Healthy Infants 12 through 23 Months of Age After Any Dose of VAQTA Alone or Concomitantly With ProQuad

Adverse Reaction	VAQTA administered alone (N=1453)	VAQTA + ProQuad (N=347)
	Rate (n/total n)	
Injection-site erythema*	21.2% (300/1415)	17.7% (59/334)
Injection-site pain/tenderness*	42.1% (596/1415)	35.9% (120/334)
Injection-site swelling*	12.6% (178/1415)	13.5% (45/334)
Injection-site bruising*,†	2.6% (37/1415)	3.0% (10/334)

N=Number of subjects enrolled/randomized.
n=Number of subjects in each category.
*Adverse Reactions at the injection site (VAQTA) Days 1-5 after vaccination
†Unsolicited Reaction.

Table 4
Incidences of Unsolicited and Solicited Systemic Adverse Events by Body System Occurring at ≥1% in Healthy Infants 12 through 23 Months of Age After Any Dose of VAQTA Alone or Concomitantly With ProQuad

Body System Adverse Event	VAQTA administered alone (N=1453)	VAQTA + ProQuad (N=347)
	Rate (n/total n)	
Eye disorders*		
Conjunctivitis	0.9% (13/1415)	1.5% (5/334)
Gastrointestinal disorders*		
Constipation	1.1% (15/1415)	0.3% (1/334)
Diarrhea	10.1% (143/1415)	6.9% (23/334)
Vomiting	6.4% (90/1415)	4.8% (16/334)
General disorders and administration site conditions*		
Irritability	11.2% (158/1415)	10.8% (36/334)
Fever ≥102.2°F (≥39.0°C) (Days 1-5 postvaccination)†	4.0% (56/1383)	4.1% (13/320)
Fever ≥100.4°F (≥38.0°C) (Days 1-5 postvaccination)†	16.3% (226/1383)	15.9% (51/320)
Fever >98.6°F or feverish (>37.0°C) (Days 1-14 postvaccination)‡	16.3% (231/1415)	28.1% (94/334)
Infections and infestations*		
Ear infection	1.1% (15/1415)	0.0% (0/334)
Gastroenteritis	1.1% (16/1415)	0.6% (2/334)
Gastroenteritis viral	0.8% (11/1415)	1.8% (6/334)
Nasopharyngitis	4.7% (66/1415)	4.8% (16/334)
Otitis media	4.0% (56/1415)	3.3% (11/334)
Rhinitis	3.2% (45/1415)	0.3% (1/334)
Upper respiratory tract infection	6.6% (93/1415)	9.0% (30/334)
Viral infection	1.1% (16/1415)	0.9% (3/334)
Metabolism and nutrition disorders*		
Anorexia	1.1% (15/1415)	0.9% (3/334)
Respiratory, thoracic and mediastinal disorders*		

Body System Adverse Event	**VAQTA administered alone (N=1453)** Rate (n/total n)	**VAQTA + ProQuad (N=347)**
Cough	7.8% (111/1415)	6.0% (20/334)
Nasal congestion	2.6% (37/1415)	2.1% (7/334)
Rhinorrhea	7.6% (107/1415)	6.6% (22/334)
Skin and subcutaneous tissue disorders*		
Dermatitis diaper	1.7% (24/1415)	5.7% (19/334)
Rash	2.0% (29/1415)	5.7% (19/334)
Rash morbilliform	0.0% (0/1415)	4.8% (16/334)

N=Number of subjects enrolled/randomized.
n=Number of subjects in each category.
*Systemic Adverse Events reported Days 1-14 after vaccination, regardless of causality.
†T≥100.4°F (≥38.0°C) and T≥102.2°F (≥39.0°C), recorded Days 1-5 after vaccination.
‡Risk Difference (11.8% [95% CI: 6.8, 17.2]) and relative risk (1.72 [95% CI: 1.40, 2.12]) in post-hoc analysis.

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[4] (Pneumococcal 7-valent Conjugate Vaccine) 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 5 presents rates of solicited local reactions at the VAQTA injection site and rates of elevated temperatures (≥100.4°F (≥38.0°C) and ≥102.2°F (≥39.0°C)) that occurred within 5 days following each dose of VAQTA and elevated temperatures >98.6°F (>37.0°C) for a total of 14 days after vaccination; occurrences of these events were recorded daily on diary cards. Table 6 presents rates of unsolicited systemic adverse events that occurred within 14 days at ≥5% in any group following each dose of VAQTA.

Table 5
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 PCV7*

	Dose 1		**Dose 2**	
Adverse reaction: Days 1-5 unless noted	**VAQTA alone**	**VAQTA + ProQuad + PCV7 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°F or feverish (>37.0°C) (Days 1-14)	12.4%	35.7%	10.8%	10.3%
	N=243	N=285	N=221	N=237
Temperature ≥ 100.4°F (≥38.0°C)	10.3%	16.8%	10%	4.2%
Temperature ≥ 102.2 °F (≥39.0°C)	2.1%	3.5%	2.3%	2.5%

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

Table 6
Incidences of Unsolicited Systemic Adverse Events ≥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 PCV7*

	Dose 1		**Dose 2**	
Adverse Event: Days 1-14	**VAQTA alone**	**VAQTA + ProQuad + PCV7 concomitantly**	**VAQTA alone**	**VAQTA + ProQuad concomitantly**

	Dose 1		Dose 2	
	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

Data presented in Tables 5 through 6 on solicited local reactions, and solicited and unsolicited systemic adverse events with incidence ≥5% following each dose of VAQTA are representative of other clinical trials of VAQTA in children 12 through 23 months of age.

The following additional unsolicited local adverse reactions and systemic adverse events were observed at a common frequency of ≥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

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 7 summarizes local adverse reactions and systemic adverse events reported in ≥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 7
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/1.0 mL) with Typhim Vi[3] (Typhoid Vi polysaccharide vaccine) and YF-Vax[3] (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 8 summarizes solicited local adverse reactions and Table 9 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 (≥38.3°C) occurred in 1.3% of subjects in each group.

Table 8
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 9
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/1.0 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/1.0 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 10 are the local adverse reactions and systemic adverse events reported by ≥5% of subjects, in decreasing order of frequency within each body system.

Table 10
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*	n=1641
Headache	16.1%
***General disorders and administration site reactions**†*	n=1640
Injection-site pain/tenderness/soreness	67.0%
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 ≥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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il /

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; Measles, Mumps, Rubella, and Varicella Vaccine, Live; Pneumococcal 7-valent Conjugate Vaccine. 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.

Data on concomitant use of VAQTA with other vaccines such as combination diphtheria toxoid, tetanus toxoid and acellular pertussis vaccine and poliovirus vaccine are insufficient to support coadministration with VAQTA *[see Clinical Studies (14.7)]*.

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

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes.

There are no adequate and well-controlled studies designed to evaluate VAQTA in pregnant women. Available post-approval data do not suggest an increased risk of miscarriage or major birth defects in women who received VAQTA during pregnancy.

Developmental toxicity studies have not been conducted with VAQTA in animals.

Data

Human Data

Post-approval adverse reactions 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.

In prospectively reported spontaneous post-approval reports from 1995 to 2018, 36 women with a known pregnancy outcome were exposed to VAQTA during pregnancy following the last menstrual period. After excluding induced abortions (n=4) and those with exposure in the third trimester (n=2), there were 30 pregnancies with known outcomes with exposures in the first or second trimester. Miscarriage was reported for 3 of 30 (10%) pregnancies. Major birth defects were reported for 1 of 27 (3.7%) live born infants. The rates of miscarriage and major birth defects were consistent with estimated background rates.

8.2 Lactation

Risk Summary

It is not known whether VAQTA is excreted in human milk. Data are not available to assess the effects of VAQTA on the breastfed infant or on milk production/excretion.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VAQTA and any potential adverse effects on the breastfed child from VAQTA or from the underlying maternal condition. For preventive vaccines the underlying condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use

The safety of VAQTA has been evaluated in 3159 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 x 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, 4.5 mg sodium chloride, and 35 mcg of sodium borate, water for injection.

Each 1.0-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, 9 mg sodium chloride, and 70 mcg of sodium borate, water for injection.

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. *[See Use in Specific Populations (8).]*

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[5] radioimmunoassay [RIA]),

[5] Trademark of Abbott Laboratories

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 cases[6] 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.[7] 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.

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 DTaP and optionally either oral or inactivated poliovirus vaccine (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) DTaP and optional oral or inactivated poliovirus vaccine 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.

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[6] The 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 ≥38.3°C); 2) elevation of hepatitis A IgM antibody (HAVAB-M); 3) elevation of alanine transferase (ALT) ≥2 times the upper limit of normal.

[7] One 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/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/1.0 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/1.0 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/1.0 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 11.

Table 11
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/1.0 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 12 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 12
Seroconversion Rates (%) and Geometric Mean Titers (GMT) After Vaccination with VAQTA Plus IG, VAQTA Alone, and IG Alone

	VAQTA plus IG	VAQTA	IG
Weeks	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 (Hepatitis A vaccine, inactivated) 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 13) *[see Dosage and Administration (2.1)].*

Table 13
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 DTaP

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 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 Pneumococcal 7-valent Conjugate Vaccine

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 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.

There are no data to assess concomitant use of *Haemophilus influenzae* type b conjugate vaccine with VAQTA *[see Drug Interactions (7.1)].*

16 HOW SUPPLIED/STORAGE AND HANDLING

VAQTA is available in single-dose vials.

Pediatric/Adolescent Formulations

25U/0.5 mL in single-dose vials

0.5 mL suspension in a vial (type I glass) and rubber stopper. Pack sizes: carton box of 1 or 10 vials.

Adult Formulations

50U/mL in single-dose vials

1.0-mL suspension in a vial (type I glass) and rubber stopper. Pack sizes: carton box of 1 or 10 vials.

Not all pack sizes may be marketed.

Shelf life

The expiry date of the product is indicated on the packaging materials.

Store vaccine at 2-8°C.
DO NOT FREEZE since freezing destroys potency.

License Holder

Merck, Sharp & Dohme (Israel-1996) Company Ltd., P.O. Box 7121 Petah-Tikva 49170.

Manufacturer

Merck Sharp & Dohme B.V., Haarlem, Holland

Registration numbers

VAQTA 25U/0.5ML: 134-51-29739
VAQTA 50U/ML: 134-52-29740

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