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 ----------
- 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 1.0-mL primary dose administered intramuscularly, and a 1.0-mL booster dose administered intramuscularly 6 to 18 months later. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------
Sterile suspension supplied in four presentations:
- 0.5-mL pediatric dose in single-dose vials and prefilled syringes. (3, 11, 16)
- 1.0-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 allergic or hypersensitivity reactions (*e.g.*, anaphylaxis) after a previous dose of any hepatitis A vaccine or with an anaphylactic reaction to neomycin. (4, 6.2, 11)

---------- WARNINGS AND PRECAUTIONS ----------
- Use caution when administering VAQTA to individuals with latex allergies. (5.2)

---------- ADVERSE REACTIONS ----------
The most common local adverse reactions and systemic adverse events reported in different clinical trials across different age groups were:
- Children — 12 through 23 months of age: injection-site pain/tenderness (6.8%-42.1%) and fever (12.3%-18.5%)
- Children/Adolescents — 2 through 18 years of age: injection-site pain (18.7%) and headache (2.3%)
- Adults — 19 years of age and older: injection-site pain, tenderness, or soreness (67.0%) and headache (16.1%) (6.1)

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

----------DRUG INTERACTIONS----------
- VAQTA may be given concomitantly with measles, mumps, rubella, varicella, and pneumococcal 7-valent conjugate vaccines. (6.1, 7.1, 14.7)
- VAQTA may be given to adults concomitantly with typhoid Vi polysaccharide and yellow fever vaccines. (6.1, 7.1, 14.7)
- VAQTA may be administered concomitantly with immune globulin. (7.2, 14.5)

---------- USE IN SPECIFIC POPULATIONS ----------
- Safety and effectiveness of VAQTA have not been established in children less than 12 months of age, pregnant women, and nursing mothers. (8.1, 8.3, 8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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.

Prefilled Syringe Use

The following are instructions for using the prefilled single-dose syringes:

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[1] Registered trademark of MERCK & CO., Inc.

[2] Registered trademark of GlaxoSmithKline

- Shake well before use.
- Attach the needle by twisting in a clockwise direction until the needle fits securely on the syringe.
- Administer the entire dose as per standard protocol as stated above under DOSAGE AND ADMINISTRATION.
- Dispose of the syringe and needle in approved sharps container.

3 DOSAGE FORMS AND STRENGTHS

Sterile suspension available in four presentations:

- 0.5-mL pediatric dose in single-dose vials and prefilled syringes
- 1.0-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 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

Have appropriate medical treatment and supervision available to manage possible immediate-type hypersensitivity reactions, such as anaphylaxis, should an acute reaction occur.

5.2 Hypersensitivity to Latex

Use caution when vaccinating latex-sensitive individuals since the vial stopper and the syringe plunger stopper contain dry natural latex rubber that may cause allergic reactions.

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 Drug Interactions (7.3) and Use in Specific Populations (8.6)]*.

6 ADVERSE REACTIONS

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 most common local adverse reactions and systemic adverse events reported in different clinical trials across different age groups were:

- Children — 12 through 23 months of age: injection-site pain/tenderness (6.8%-42.1%) and fever (12.3%-18.5%)
- Children/Adolescents — 2 through 18 years of age: injection-site pain (18.7%) and headache (2.3%)
- Adults — 19 years and older: injection-site pain, tenderness, or soreness (67.0%) and headache (16.1%) (6.1)

6.1 Clinical Trials Experience

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.

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, Oral	12.3% (29/236) (8.4%, 17.2%)	14.6% (99/679) (12.0%, 17.5%)
≥102.0°F, 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.

[3] Registered trademark of Sanofi Pasteur, Inc.

[4] Registered trademark of Wyeth Pharmaceuticals, Inc.

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) (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)

Body System	**VAQTA administered alone (N=1453)**	**VAQTA + ProQuad (N=347)**
Adverse Event	Rate (n/total n)	
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*		
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 and T≥102.2°F, 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 and then vaccinated with 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 who received VAQTA with or without ProQuad and pneumococcal 7-valent conjugate vaccine 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.

Tables 5 and 6 present injection-site adverse reactions (Days 1 to 5 postvaccination with VAQTA) and systemic adverse events (Days 1 to 14 postvaccination with VAQTA) observed among recipients of VAQTA concomitantly with ProQuad and pneumococcal 7-valent conjugate vaccine and VAQTA administered separately from ProQuad and pneumococcal 7-valent conjugate vaccine at a rate of at least 1% following any dose of VAQTA. Among all subjects, fever (>98.6°F or feverish) was the most common systemic adverse event, and injection-site pain/tenderness was the most common injection-site adverse reaction.

In the 14 days after vaccination with any dose of VAQTA, the rate of fever (>98.6°F or feverish) was increased in subjects who received VAQTA with ProQuad and pneumococcal 7-valent conjugate vaccine as compared to VAQTA alone {risk difference (20.0% [95% CI: 13.0, 26.8]) and relative risk (2.10 [95% CI: 1.59, 2.79] in post-hoc analysis)}. A difference in rates of fever was noted after Dose 1 of VAQTA with ProQuad and pneumococcal 7-valent conjugate vaccine, but not after Dose 2 of VAQTA with ProQuad. The rates of fever ≥100.4°F and ≥102.2°F in the five days after vaccination were similar in both treatment groups (Table 6).

In the 28 days after vaccination, the administration of Dose 1 of VAQTA with Dose 1 of ProQuad and Dose 4 of pneumococcal 7-valent conjugate vaccine does not increase incidence rates of fever (>98.6°F or feverish) as compared to when ProQuad is administered with pneumococcal 7-valent conjugate vaccine alone {38.6% and 42.7%, respectively; relative risk (0.9 [95% CI: 0.75, 1.09])} in post-hoc

analysis). Similarly, the administration of Dose 2 of VAQTA with Dose 2 of ProQuad does not increase incidence rates of fever (>98.6°F or feverish) as compared to when Dose 2 of ProQuad is administered alone {17.4% and 17.0%, respectively; relative risk (1.02 [95% CI: 0.70, 1.51])}.

Table 5
Incidences of Unsolicited and Solicited Local Adverse Reactions Occurring at ≥1% at the Injection Site for VAQTA in Healthy Infants 12 through 23 Months of Age Receiving VAQTA Alone or Concomitantly With ProQuad and PCV7*

Adverse Reaction	VAQTA alone (N=323)	VAQTA with ProQuad + PCV7 (N=330)
	Rate (n/total n)	
Injection-site erythema†	17.8% (51/286)	13.3% (44/330)
Injection-site pain/tenderness†	25.5% (73/286)	25.8% (85/330)
Injection-site swelling†	13.3% (38/286)	9.7% (32/330)
Injection-site bruising†,‡	2.4% (7/286)	1.8% (6/330)
Injection-site rash †,‡	0.3% (1/286)	1.2% (4/330)

N=Number of subjects enrolled/randomized.
n=Number of subjects in each category.
* PCV7 = Pneumococcal 7-valent conjugate.
† Adverse Reactions at the injection site (VAQTA) Days 1-5 after vaccination.
‡ Unsolicited Reaction.

Table 6
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 and PCV7*

Body System Adverse Event†	VAQTA alone (N=323)	VAQTA with ProQuad + PCV7 (N=330)
	Rate (n/total n)	
Eye disorders‡		
Conjunctivitis	1.4% (4/286)	0.9% (3/330)
Gastrointestinal disorders‡		
Diarrhea	2.8% (8/286)	4.8% (16/330)
Vomiting	2.1% (6/286)	3.0% (10/330)
General disorders and administration site conditions‡		
Irritability	5.9% (17/286)	7.3% (24/330)
Fever ≥102.2°F (≥39.0°C) (Days 1-5 postvaccination)§	3.9% (10/257)	5.5% (16/293)
Fever ≥100.4°F (≥38.0°C) (Days 1-5 postvaccination)§	16.7% (43/257)	18.1% (53/293)
Fever >98.6°F or feverish (Days 1-14 postvaccination)¶	18.5% (53/286)	38.2% (126/330)
Infections and infestations‡		
Croup infectious	1.4% (4/286)	0.9% (3/330)
Ear infection	0.3% (1/286)	1.8% (6/330)
Gastroenteritis	1.0% (3/286)	0.9% (3/330)
Gastroenteritis viral	1.0% (3/286)	0.6% (2/330)
Nasopharyngitis	2.4% (7/286)	3.6% (12/330)
Otitis media	5.9% (17/286)	7.6% (25/330)
Otitis media acute	1.0% (3/286)	0.6% (2/330)
Pharyngitis	1.0% (3/286)	0.9% (3/330)
Pharyngitis streptococcal	1.0% (3/286)	0.6% (2/330)
Rhinitis	2.4% (7/286)	2.1% (7/330)
Roseola	0.3% (1/286)	1.5% (5/330)
Upper respiratory tract infection	6.6% (19/286)	10.3% (34/330)
Viral infection	0.3% (1/286)	2.7% (9/330)
Respiratory, thoracic and mediastinal disorders‡		
Cough	3.1% (9/286)	4.5% (15/330)
Nasal congestion	1.0% (3/286)	2.1% (7/330)
Rhinorrhea	3.1% (9/286)	4.8% (16/330)
Skin and subcutaneous tissue disorders‡		
Dermatitis diaper	3.1% (9/286)	7.9% (26/330)
Rash	1.4% (4/286)	3.0% (10/330)
Rash morbilliform	0.3% (1/286)	2.4% (8/330)
Rash vesicular	0.7% (2/286)	1.2% (4/330)

N=Number of subjects enrolled/randomized.
n=Number of subjects in each category.

	VAQTA alone (N=323)	VAQTA with ProQuad + PCV7 (N=330)
*PCV7 = Pneumococcal 7-valent conjugate. †Following administration of VAQTA either with or without other vaccines. ‡Systemic Adverse Events reported Days 1-14 after vaccination, regardless of causality. §T≥100.4°F and T≥102.2°F, recorded Days 1-5 after vaccination ¶Risk difference (20.0% [95% CI: 13.0, 26.8]) and relative risk (2.10 [95% CI: 1.59, 2.79]) in post-hoc analysis.		

Children/Adolescents — 2 through 18 Years of Age

The Monroe Efficacy Study

The Monroe Efficacy Study was a double-blind, randomized, placebo-controlled study of the protective efficacy, safety, and immunogenicity of VAQTA in 1037 healthy children and adolescents, 2 through 16 years of age, who were initially seronegative for hepatitis A. Placebo control was alum diluent. These children were randomized to receive a primary dose of 25U of hepatitis A vaccine and a booster 6, 12, or 18 months later, or placebo (alum diluent). All of these children were Caucasian and there were 51.5% males and 48.5% females. In this blinded study, 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 the local adverse reactions and systemic adverse events (≥1%) reported in this study. 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)
	Dose 1* Rate (n/total n)	Booster Rate (n/total n)	Rate (n/total n)
Injection-site§			
Pain	6.4% (33/515)	3.4% (16/475)	6.3% (32/510)
Tenderness	4.9% (25/515)	1.7% (8/475)	6.1% (31/510)
Erythema	1.9% (10/515)	0.8% (4/475)	1.8% (9/510)
Swelling	1.7% (9/515)	1.5% (7/475)	1.6% (8/510)
Warmth	1.7% (9/515)	0.6% (3/475)	1.6% (8/510)
Systemic¶			
Abdominal pain	1.2% (6/519)	1.1% (5/475)	1.0% (5/518)
Pharyngitis	1.2% (6/519)	0% (0/475)	0.8% (4/518)
Headache	0.4% (2/519)	0.8% (4/475)	1.0% (5/518)

N=Number of subjects enrolled/randomized.
n=Number of subjects in each category.
* 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.

Combined Clinical Trials

In eleven randomized clinical trials (including Monroe Efficacy Study participants) involving 2615 healthy children (≥2 years of age) and adolescents who received at least one dose of hepatitis A vaccine, subjects were followed for fever and local adverse reactions days 1 to 5 and for systemic adverse events 1 to 14 days postvaccination. These studies 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: 84.7% 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. The most common adverse events/reactions were injection-site reactions reported by 24.3% of subjects. Of all reported injection-site reactions, 99.4% 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 ≥1% of subjects, in decreasing order of frequency within each body system.

Table 8
Incidences of Local Adverse Reactions and Systemic Adverse Events ≥1% in Healthy Children and Adolescents 2 through 18 Years of Age

Body System Adverse Event	**VAQTA Alone (N=2615)**	**Placebo (Alum Diluent)* (N=542)**
	Rate (n/total n) 95% CI	
Respiratory, thoracic, and mediastinal disorders†		
Pharyngitis	1.5% (40/2609) (1.1%, 2.1%)	0.9% (5/542) (0.3%, 2.1%)
Upper respiratory infection	1.1% (29/2609) (0.8%, 1.6%)	0.0% (0/542) (0.0%, 0.7%)
Cough	1.0% (26/2609) (0.7%, 1.5%)	0.0% (0/542) (0.0%, 0.7%)
Gastrointestinal disorders†		
Abdominal pain	1.6% (42/2609) (1.2%, 2.2%)	0.9% (5/542) (0.3%, 2.1%)
Diarrhea	1.0% (26/2609) (0.7%, 1.5%)	0.0% (0/542) (0.0%, 0.7%)
Vomiting	1.0% (27/2609) (0.7%, 1.5%)	0.2% (1/542) (0.0%, 1.0%)
Nervous system disorders†		
Headache	2.3% (60/2609) (1.8%, 3.0%)	1.1% (6/542) (0.4%, 2.4%)
General disorders and administration site reactions†,‡		
Injection-site pain	18.7% (488/2608) (17.2%, 20.3%)	6.4% (34/534) (4.5%, 8.8%)
Injection-site tenderness	16.9% (441/2608) (15.5%, 18.4%)	6.6% (35/534) (4.6%, 9.0%)
Injection-site warmth	8.6% (223/2608) (7.5%, 9.7%)	1.7% (9/534) (0.8%, 3.2%)
Injection-site erythema	7.5% (195/2608) (6.5%, 8.6%)	1.7% (9/534) (0.8%, 3.2%)
Injection-site swelling	7.3% (190/2608) (6.3%, 8.4%)	1.7% (9/534) (0.8%, 3.2%)
Fever (≥102°F, oral)†	1.1% (28/2591) (0.7%, 1.6%)	0.9% (5/542) (0.3%, 2.1%)
Injection-site ecchymosis	1.3% (35/2608) (0.9%, 1.9%)	0.4% (2/534) (0.1%, 1.4%)

N=Number of subjects enrolled/randomized.
n=Number of subjects in each category.
*Placebo (Alum diluent) = amorphous aluminum hydroxyphosphate sulfate. Data represent adverse events following a single dose of placebo, since they were subsequently unblinded and received vaccine.
†Systemic Adverse Events reported Days 1 to 14 after vaccination, regardless of causality.
‡Adverse Reactions at the injection site (VAQTA) and measured fevers Days 1 to 5 after vaccination

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® (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 was given with or without typhoid Vi polysaccharide and yellow fever vaccines, the proportion of subjects with adverse events was similar between recipients of

VAQTA concomitantly with typhoid Vi polysaccharide and yellow fever vaccines compared to recipients of typhoid Vi polysaccharide and yellow fever vaccines, but higher compared to recipients of VAQTA alone. Listed below are the solicited local adverse reactions and systemic adverse events (Table 9) and unsolicited systemic adverse events (Table 10) reported at ≥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.

Table 9
Incidences of Solicited Local Adverse Reactions and Systemic Adverse Events 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 (n/total n)	
***Injection-site*‡**		
Pain/tenderness/soreness	78.8% (63/80)	70.3% (56/80)
Warmth	23.7% (19/80)	23.7% (19/80)
Swelling	16.2% (13/80)	8.8% (7/80)
Erythema	17.5% (14/80)	6.3% (5/80)
***Systemic*§**		
N=Number of subjects enrolled/randomized. n=Number of subjects in each category. *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 §There were no solicited systemic complaints ≥5%. Fever (≥101°F, Oral) was reported at 1.3% (1/80) in both groups.		

Table 10
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 (n/total n)	
General disorders and administration site reactions		
Asthenia/fatigue	7.5% (6/80)	11.3% (9/80)
Chills	1.3% (1/80)	7.5% (6/80)
Gastrointestinal disorders		
Nausea	7.5% (6/80)	12.5% (10/80)
Musculoskeletal and connective tissue disorders		
Myalgia	5.0% (4/80)	10.0% (8/80)
Arm pain	0.0% (0/80)	6.3% (5/80)
Nervous system disorders		
Headache	23.8% (19/80)	26.3% (21/80)
Infections and infestations		
Upper respiratory infection	7.5% (6/80)	3.8% (3/80)
Pharyngitis	2.5% (2/80)	6.3% (5/80)
N=Number of subjects enrolled/randomized. n=Number of subjects in each category. *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.		

Combined Clinical Trials

In four randomized 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 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). The race distribution of the study subjects who received at least one dose of VAQTA in these studies was as follows: 94.2% Caucasian; 2.2% Black; 1.5% Hispanic; 1.5% Oriental; 0.4% other; 0.2% American Indian. The distribution of subjects by gender was 47.6% male and 52.4% 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 11 are the local adverse reactions and systemic adverse events reported by ≥1% of subjects, in decreasing order of frequency within each body system.

Table 11
Incidences of Local Adverse Reactions and Systemic Adverse Events ≥1% in Adults 19 Years of Age and Older

Body System Adverse Events	**VAQTA (Any Dose) (N=1645)** Rate (n/total n) (95% CI)
Nervous system disorders*	
Headache	16.1% (265/1641) (14.4%, 18.0%)
Gastrointestinal disorders*	
Abdominal pain	1.3% (22/1641) (0.8%, 2.0%)
Diarrhea	2.6% (43/1641) (1.9%, 3.5%)
Nausea	2.4% (40/1641) (1.8%, 3.3%)
Musculoskeletal and connective tissue disorders*	
Myalgia	1.9% (31/1641) (1.3%, 2.7%)
Arm pain	1.5% (25/1641) (1.0%, 2.2%)
Back pain	1.1% (18/1641) (0.7%, 1.7%)
Stiffness	1.0% (17/1641) (0.6%, 1.7%)
Infections and infestations*	
Pharyngitis	2.9% (47/1641) (2.1%, 3.8%)
Upper respiratory infection	2.7% (45/1641) (2.0%, 3.7%)
General disorders and administration site reactions†	
Injection-site pain/tenderness/soreness	67.0% (1099/1640) (64.6%, 69.3%)
Injection-site warmth	18.2% (298/1640) (16.3%, 20.1%)
Injection-site swelling	14.7% (242/1640) (13.1%, 16.6%)
Injection-site erythema	13.7% (224/1640) (12.0%, 15.4%)
Asthenia/fatigue	4.0% (67/1641) (3.2%, 5.2%)
Injection-site ecchymosis	1.3% (22/1640) (0.8%, 2.0%)
Fever (≥101°F, oral)†	1.0% (17/1626) (0.6%, 1.7%)
Reproductive system and breast disorders*	
Menstruation disorders	1.0% (17/1641) (0.6%, 1.7%)

N=Number of subjects enrolled/randomized.
n=Number of subjects in each category.
*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.

6.2 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:

Local
Injection-site pruritus and/or rash.

Systemic
Bronchial constriction; asthma; wheezing; edema/swelling; rash; generalized erythema; urticaria; pruritus; eye irritation/itching; dermatitis *[see Contraindications (4) and Warnings and Precautions (5.1)].*

6.3 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.

6.4 Post-Marketing Observational Safety Study

In a post-marketing, short-term 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 indicated. There was no serious, vaccine-related adverse reaction identified among the 42,110 vaccine recipients in this study. 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.

VAQTA may be given concomitantly with measles, mumps, rubella, varicella, and pneumococcal 7-valent conjugate vaccines *[see Adverse Reactions (6.1) and Clinical Studies (14.7)]*.

VAQTA may be given to adults concomitantly with typhoid Vi polysaccharide and yellow fever vaccines *[see Adverse Reactions (6.1) and Clinical Studies (14.7)]*.

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 IG. 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 woman who is breast-feeding.

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 a large post-marketing observational safety study in 42,110 individuals, 4769 were 65 years of age or older, of whom 1073 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 of VAQTA, conducted pre- and post-licensure, 68 subjects were vaccinated with VAQTA who were 65 years of age or older, 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 *[see Drug Interactions (7.3)].*

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 1.0-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, and 70 mcg of sodium borate as a pH stabilizer, in 0.9% sodium chloride.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Hepatitis A Disease

Hepatitis A virus is one of several hepatitis viruses that cause a systemic infection with pathology in the liver. The incubation period ranges from approximately 20 to 50 days. The course of the disease following infection ranges from asymptomatic infection to fulminant hepatitis and death.

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[5] 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 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.

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[5] Trademark of Abbott Laboratories

[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.

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 one study children 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 the study subjects who received at least one dose of VAQTA in this study 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 a titer ≥10 mIU/mL) post dose 1 with a 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 a 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. This rate was similar to the expected rate of 99% in 2- to 3-year-old children.

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 a titer ≥10 mIU/mL) was 100% (n=182; 95% CI: 98.0%, 100%) post dose 2 with a 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 a GMT of 6123 mIU/mL (95% CI: 4826, 7770) when VAQTA alone was given. These seropositivity rates were similar whether VAQTA was given with or without ProQuad and pneumococcal 7-valent conjugate vaccine.

Children/Adolescents — 2 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 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 a 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 in these studies 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 12.

Table 12
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 Post-Exposure Prophylaxis

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 13 provides seroconversion rates and geometric mean titers (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).

Table 13
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 14) *[see Dosage and Administration (2.1)].*

Table 14
VAQTA versus HAVRIX
Seropositivity Rate, Booster Response Rate* and Geometric Mean Titer at 4 Weeks Postbooster

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.

14.7 Immune Response to Concomitantly Administered Vaccines

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

Concomitant administration of routinely administered recommended childhood vaccines with VAQTA was assessed in a study of 617 children. In this study, the immune response to VAQTA (25U) was assessed in 471 children randomized to receive VAQTA with (N=237) or without M-M-R II and VARIVAX (N=234) at 12 months of age. The race distribution of the study subjects who received at least one dose of VAQTA in these studies 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. 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 98.8% [95% CI: 96.4%, 99.7%], 99.6% [95% CI: 97.9%, 100%], and 100% [95% CI: 98.6%, 100%], respectively, which were similar to historical rates observed following vaccination with a first dose of M-M-R II in this age group. Data on the varicella immune response were insufficient to adequately assess its immunogenicity when VARIVAX was administered concomitantly with VAQTA. In this same study, immune responses were evaluated in 183 subjects who were administered VAQTA with (N=86) and without DTaP (N=97) at 18 months of age. Rates of seroprotection to hepatitis A were similar between the two groups who received VAQTA with or without DTaP. However, data are insufficient to assess the immune response of DTaP when administered with VAQTA.

Clinical Studies of VAQTA with ProQuad and Pneumococcal 7-valent Conjugate Vaccine

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. The 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 an open-label clinical trial, 240 healthy adults 18 to 54 years of age were randomized to receive either VAQTA with typhoid Vi polysaccharide and yellow fever vaccines 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 booster dose. 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. 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. 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 and without VAQTA. The GMTs for hepatitis A when VAQTA, typhoid Vi polysaccharide, and yellow fever vaccines were administered concomitantly were reduced when compared to VAQTA alone. Following receipt of the booster dose of VAQTA, the GMTs for hepatitis A in these two groups were observed to be comparable *[see Drug Interactions (7.1)].*

Data are insufficient to assess the immune response to VAQTA and poliovirus vaccine following concomitant administration of the vaccines.

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 and prefilled Luer Lock syringes.

Pediatric/Adolescent Formulations

25U/0.5 mL in single-dose vials and prefilled Luer Lock syringes.
NDC 0006-4831-41 – box of ten 0.5-mL single dose vials.
NDC 0006-4095-09 – carton of six 0.5-mL prefilled single-dose Luer Lock syringes with tip caps.

Adult Formulations

50U/1.0 mL in single-dose vials and prefilled Luer Lock syringes.
NDC 0006-4841-00 – 1.0-mL single dose vial.
NDC 0006-4841-41 – box of ten 1.0-mL single dose vials.
NDC 0006-4096-09 – carton of six 1.0-mL prefilled single-dose Luer Lock syringes with tip caps.

Store vaccine at 2-8°C (36-46°F).
DO NOT FREEZE since freezing destroys potency.

17 PATIENT COUNSELING INFORMATION

17.1 Instructions

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 severe or unusual 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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