(HEPATITIS A VACCINE, INACTIVATED)
VAQTA®

DESCRIPTION

VAQTA* [Hepatitis A Vaccine, Inactivated] is an inactivated whole virus vaccine derived from hepatitis A virus (HAV) 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. One milliliter of the vaccine contains approximately 50 units (U) 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).

VAQTA is a sterile suspension for intramuscular injection.

VAQTA is supplied in two formulations:

Pediatric/Adolescent Formulation (12 Months Through 18 Years of Age): each 0.5 mL dose contains approximately 25U of hepatitis A virus antigen 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.

Adult Formulation (19 Years of Age and Older): each 1 mL dose contains approximately 50U of hepatitis A virus antigen 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.

CLINICAL PHARMACOLOGY

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.[1]

Protection from hepatitis A disease has been shown to be related to the presence of antibody. Protection after vaccination with VAQTA has been associated with the onset of seroconversion (≥10 mIU/mL of hepatitis A antibody, measured by a modification of the HAVAB** radioimmunoassay [RIA][2]) and with an anamnestic antibody response following booster vaccination with VAQTA.

Efficacy of VAQTA

A very high degree of protection has been demonstrated after a single dose of VAQTA in children and adolescents.[3] The protective efficacy, immunogenicity and safety 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). Each child received an intramuscular dose of VAQTA (~25U) or placebo. Among those individuals who were initially seronegative (by modified HAVAB), 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.

* Registered trademark of MERCK & CO., Inc.

** Trademark of Abbott Laboratories

Because of the long incubation period of the disease (approximately 20 to 50 days, or longer in children[4]), the primary endpoint was based on clinically confirmed cases*** 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 ($p<0.001$). A secondary endpoint was pre-defined as the number of clinically confirmed cases of hepatitis A ≥30 days after vaccination. With this secondary endpoint, 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.† 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. To date, 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.[5]

Although cases of imported infection have occurred, the study community has remained free of outbreaks, evidence for the effectiveness of VAQTA for use in community outbreak control. In contrast, three nearby sister communities to Monroe have continued to experience outbreaks.[3, 6]

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 highly immunogenic in all age groups.

In initially seronegative children 12 through 23 months of age, who received VAQTA with or without other vaccines, 96% (n=471; 95% CI: 93.7%, 97.5%) seroconverted post dose 1 with a Geometric Mean Titer (GMT) of 48 mIU/mL (95% CI: 44.7, 51.6); and 100% (n=343; 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) were seropositive after the second dose of VAQTA. This rate was similar to the expected rate of 99% in 2 to 3 year old children.

In combined clinical studies in children and adolescents 2 through 18 years of age, 97% (n=1230; 95% CI: 96%, 98%) and 100% (n=1057; 95% CI: 99.5%, 100%) of subjects seroconverted after the first and second doses with a GMT of 43 mIU/mL (95% CI: 40, 45) and 10,077 mIU/mL (95% CI: 9394, 10,810), respectively.

In combined clinical studies in adults 19 years of age and older who received VAQTA (50 U/1.0 mL) 95% (n=1411; 95% CI: 94%, 96%) and 99.9% (n=1244; 95% CI: 99.4%, 100%) of subjects seroconverted with a GMT of 37 mIU/mL (95% CI: 35, 38) and 6013 mIU/mL (95% CI: 5592, 6467), respectively, after the first and second doses. Furthermore, at 2 weeks post-vaccination, 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.

Persistence

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 up to 6 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 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 and 1191 mIU/mL (n=47) at 5 to 6 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 and 1500 mIU/mL (n=53) at 5 to 6 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 up to 6 years in adults. 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

*** 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.

† 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.

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.

Immune memory was demonstrated by an anamnestic response in individuals who received either a ~25U/0.5 mL (Table 1—Monroe Efficacy Study) or a ~50U/1.0 mL (adult clinical study) booster dose 6 to 18 months after the primary dose.

Table 1
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.

In a clinical study involving healthy adults who received two doses (~50U) of VAQTA, 4 weeks after the booster dose was administered at 6, 12, and 18 months after the first dose, 100% of 1201 subjects, 98% of 91 subjects, and 100% of 84 subjects were seropositive, 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 (95% CI: 3589, 6679), and 6043 (95% CI: 4687, 7793), respectively.

Post Exposure Prophylaxis

While a study evaluating VAQTA alone in a post-exposure setting has not been conducted, the concurrent use of VAQTA (~50U) and immune globulin (IG, 0.06 mL/kg) was evaluated in a clinical study involving healthy adults 18 to 39 years of age. Table 2 provides seroconversion rates and GMT 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 2
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

† Undetectable is defined as <10mIU/mL.

*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).

N/A = Not Applicable

Interchangeability of the Booster Dose

A 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. When VAQTA was given as a booster dose following HAVRIX, the vaccine produced an adequate immune response (see Table 3). (See DOSAGE AND ADMINISTRATION, *Interchangeability of the Booster Dose*.)

Table 3
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.

Immune Response to Concomitantly Administered Vaccines

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 or without M-M-R* II (Measles, Mumps, and Rubella Vaccine, Live) and VARIVAX* (Varicella Virus Vaccine Live [Oka/Merck]) at 12 months of age. Rates of seroprotection to hepatitis A were similar among 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 immune response to VARIVAX are insufficient to adequately assess the immunogenicity of VARIVAX when administered concomitantly with VAQTA. In this same study, immune responses were evaluated in 183 subjects who were administered VAQTA with and without DTaP (TRIPEDIA§) at 18 months of age. Rates of seroprotection to hepatitis A were similar among the two groups who received VAQTA with or without DTaP. Data are insufficient to assess the immune response of DTaP when administered with VAQTA. Data are insufficient to assess the immune response to VAQTA and polio vaccine following concomitant administration of the vaccines. There are no data to assess the concomitant use of Haemophilus b conjugate vaccine and Prevnar§§ with VAQTA. (See DOSAGE AND ADMINISTRATION, *Use With Other Vaccines*.)

A controlled clinical study was conducted with 240 healthy adults, 18 to 54 years of age, who were randomized to receive either VAQTA, typhoid and yellow fever vaccines concomitantly at separate injection sites, or VAQTA alone. The seropositivity rate for hepatitis A when VAQTA, typhoid and yellow fever vaccines were administered concomitantly was generally similar to when VAQTA was given alone. The antibody response rates for typhoid and yellow fever were adequate when typhoid and yellow fever vaccines were administered concomitantly with and without VAQTA. The GMTs for hepatitis A when VAQTA, typhoid 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 DOSAGE AND ADMINISTRATION, *Use With Other Vaccines*.)

INDICATIONS AND USAGE

VAQTA is indicated for active immunization against disease caused by hepatitis A virus in persons 12 months of age and older. Primary immunization should be given at least 2 weeks prior to expected exposure to HAV.

†† Registered trademark of GlaxoSmithKline
§Registered trademark of Sanofi Pasteur, Inc.
§§Registered trademark of Wyeth Pharmaceuticals, Inc.

The Advisory Committee on Immunization Practices (ACIP) has issued recommendations for hepatitis A vaccination for persons who are at increased risk for infection and for any person wishing to obtain immunity.[7] Please consult the Centers for Disease Control and Prevention for updates to those recommendations (www.cdc.gov).

If passive protection against hepatitis A is required either following exposure to hepatitis A virus or in persons in need of combined immediate and long-term protection, VAQTA may be administered along with immune globulin at a separate site with a separate syringe.

Revaccination

See DOSAGE AND ADMINISTRATION, *DOSAGE.*

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine is a contraindication (see DESCRIPTION).

Hepatitis A vaccine should not be administered to persons with a history of a severe reaction to a prior dose of hepatitis A vaccine or to a vaccine component.8

WARNINGS

The vial stopper and the syringe plunger stopper contain dry natural latex rubber that may cause allergic reactions in latex sensitive individuals.

Individuals who develop symptoms suggestive of hypersensitivity after an injection of hepatitis A vaccine should not receive further injections of the vaccine (see CONTRAINDICATIONS).

As with any vaccine, if administered to immunocompromised persons, including individuals receiving immunosuppressive therapy, the expected immune response may not be obtained.

PRECAUTIONS

General

Epinephrine injection (1:1000) and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

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.

As with other intramuscular injections, VAQTA should not be given to individuals with bleeding disorders such as hemophilia or thrombocytopenia, or to persons on anticoagulant therapy unless the potential benefits clearly outweigh the risk of administration. If the decision is made to administer VAQTA to such persons, it should be given with caution with steps taken to avoid the risk of hematoma following the injection.[8]

As with any vaccine, vaccination with VAQTA may not result in a protective response in all susceptible vaccinees.

An acute infection or febrile illness may be reason for delaying use of VAQTA except when, in the opinion of the physician, withholding the vaccine entails a greater risk.

Information for Vaccine Recipients and Parents or Guardians

Patients, parents or guardians should be informed by the healthcare provider of the potential benefits and risks of the vaccine. It is important that the vaccine recipient, parent or guardian be questioned concerning occurrence of any symptoms and/or signs of an adverse reaction after a previous dose of hepatitis A vaccine. The healthcare provider should inform the patients, parents or guardians about the potential for adverse events that have been temporally associated with administration of VAQTA. The patient, or parent or guardian accompanying the recipient, should be told to report severe or unusual adverse events to the physician or clinic where the vaccine was administered.

The patient, parent or guardian should be given the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/nip). 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.org.[8]

Drug Interactions

VAQTA should not be mixed with any other vaccine in the same syringe or vial.

If VAQTA is administered to a person receiving immunosuppressive therapy, or who has an immunodeficiency disorder, an adequate immunologic response may not be obtained.[9]

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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.

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.

Pediatric Use

The safety of VAQTA has been evaluated in 706 children 12 through 23 months of age, and 2615 children/adolescents 2 through 18 years of age. (See ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION.)

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

Geriatric Use

Of the total number of adults in clinical studies of VAQTA, conducted pre- and post-licensure, 68 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. In a large post-marketing safety study in 42,110 individuals, ≥2 years of age, 4769 were 65 years of age or older, 1073 of whom were 75 years of age or older. There were no adverse experiences judged by the investigator to be vaccine related in the geriatric study population. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

ADVERSE REACTIONS

The safety of VAQTA has been evaluated in over 10,000 subjects ages 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. As with any vaccine, there is the possibility that use of VAQTA in very large populations might reveal adverse experiences not observed in clinical trials.

Clinical Studies

Children —12 Through 23 Months of Age

In combined clinical trials involving 706 healthy children 12 through 23 months of age who received one or more ~25U dose, subjects were monitored for local adverse events and fever for 5 days after each vaccination and systemic adverse events for 14 days after each vaccination by diary cards. Some of these children received VAQTA in combination with other routinely recommended pediatric vaccines. Listed below are the complaints (with 95% CI) for all solicited events and for unsolicited events reported at ≥1.0% without regard to causality in decreasing order of frequency within each body system.

Table 4
All Incidences of Solicited Local and Systemic Complaints in Healthy Infants 12 to 23 Months of Age

Reaction	VAQTA	
	Dose 1	Booster
	Adverse event rate (n/total n) (95% CI)	
Injection-Site Complaints		
Pain/Tenderness/Soreness	3.5% (24/682) (2.3%, 5.2%)	3.1% (19/622) (1.9%, 4.9%)
Erythema	1.3% (9/682) (0.6%, 2.6%)	1.6% (10/622) (0.8%, 3.0%)
Swelling	1.6% (11/682) (0.8%, 2.9%)	1.3% (8/622) (0.6%, 2.6%)
Warmth	0.9% (6/682) (0.4%, 2.0%)	0.8% (5/622) (0.3%, 2.0%)
Systemic Complaints		
Rash, Measles-like/Rubella-like	1.0% (7/683) (0.4%, 2.2%)	-
Rash, Varicella-like	0.9% (6/683) (0.3%, 2.0%)	-
Fever ≥100.4°F, oral	9.1% (62/678) (7.1%, 11.6%)	11.3% (69/611) (9.0%, 14.1%)
Fever ≥102°F, oral	3.8% (26/678) (2.5%, 5.6%)	3.1% (19/611) (1.9%, 4.9%)

Unsolicited adverse events ≥1% (95% CI)

LOCALIZED INJECTION-SITE REACTIONS
Ecchymosis 1.0% (0.4%, 2.2%).
DIGESTIVE SYSTEM
Diarrhea 5.9% (4.3%, 8.0%); vomiting 4.0% (2.7%, 5.8%); anorexia 1.2% (0.6%, 2.4%).
NERVOUS SYSTEM/PSYCHIATRIC
Irritability 10.8% (8.6%, 13.4%); crying 1.8% (1.0%, 3.2%).
RESPIRATORY SYSTEM
Upper respiratory infection 10.1% (8.0%, 12.7%); rhinorrhea 5.7% (4.1%, 7.8%); cough 5.1% (3.6%, 7.1%); respiratory congestion 1.6% (0.8%, 2.9%); nasal congestion 1.2% (0.6%, 2.4%); laryngotracheobronchitis 1.2% (0.6%, 2.4%).
SKIN AND SKIN APPENDAGES
Rash 4.5% (3.1%, 6.4%); viral exanthema 1.0% (0.4%, 2.2%).
SPECIAL SENSES – Ear
Otitis media 7.6% (5.8%, 9.9%); otitis: 1.8% (1.0%, 3.2%).
SPECIAL SENSES – Eye
Conjunctivitis 1.3% (0.6%, 2.6%).

Serious Adverse Events: There were 7 children who experienced 9 seizures during the entire study period. Seizures were reported between 9 days and 81 days following the administration of VAQTA. Some subjects had received concomitant or nonconcomitant immunization with M-M-R II and VARIVAX. None of the events were considered to be related to VAQTA by the investigator. Other serious events that occurred during the study included bronchiolitis, dehydration, RLL (Right Lower Lobe) pneumonia, asthma, and asthma exacerbation, which were also considered by the investigator to be unrelated to VAQTA. These events occurred 9 days to 46 days following the administration of VAQTA. Some subjects received concomitant or nonconcomitant immunization with M-M-R II, and VARIVAX or TRIPEDIA, and/or oral or inactivated polio vaccine.

Children/Adolescents — 2 Through 18 Years of Age
Safety Data Gathered from Monroe Efficacy Study

In The Monroe Efficacy Study, 1037 healthy children and adolescents, 2 through 16 years of age, received a primary dose of ~25U of hepatitis A vaccine and a booster 6, 12, or 18 months later, or placebo. Subjects were followed during a 5-day period for fever and local complaints and during a 14-day

period for systemic complaints. Injection-site complaints, generally mild and transient[3], were the most frequently reported complaints. Table 5 summarizes the local and systemic complaints (≥1%) reported in this study, without regard to causality. There were no significant differences in the rates of any complaints between vaccine and placebo recipients after Dose 1.

Table 5
Local and Systemic Complaints (≥1%) in Healthy Children and Adolescents From the Monroe Efficacy Study

Reaction	VAQTA Dose 1*	VAQTA Booster	Placebo*,†
Injection-Site Complaints			
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 Complaints			
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)

* No statistically significant differences between the two groups.
† Second injection of placebo not administered because code for the trial was broken.

Children/Adolescents — 2 Through 18 Years of Age - Combined Clinical Trials

In combined clinical trials (including Monroe Efficacy Study participants) involving 2615 healthy children (≥2 years of age) and adolescents who received one or more ~25U doses of hepatitis A vaccine, subjects were followed for fever and local complaints during a 5-day period postvaccination and systemic complaints during a 14-day period postvaccination. Injection-site complaints, generally mild and transient, were the most frequently reported complaints. Listed below are the complaints reported by ≥1% of subjects, without regard to causality, in decreasing order of frequency within each body system.

LOCALIZED INJECTION-SITE REACTIONS

Pain (18.7%); tenderness (16.9%); warmth (8.6%); erythema (7.5%); swelling (7.3%); ecchymosis (1.3%).

BODY AS A WHOLE

Fever (≥102°F, Oral) (3.1%); abdominal pain (1.6%).

DIGESTIVE SYSTEM

Diarrhea (1.0%); vomiting (1.0%).

NERVOUS SYSTEM/PSYCHIATRIC

Headache (2.3%).

RESPIRATORY SYSTEM

Pharyngitis (1.5%); upper respiratory infection (1.1%); cough (1.0%).

LABORATORY FINDINGS

Very few laboratory abnormalities were reported and included isolated reports of elevated liver function tests, eosinophilia, and increased urine protein.

Adults — 19 Years of Age and Older

In combined clinical trials involving 1512 healthy adults who received one or more ~50U doses of hepatitis A vaccine, subjects were followed for fever and local complaints during a 5-day period postvaccination and systemic complaints during a 14-day period postvaccination. Injection-site complaints, generally mild and transient, were the most frequently reported complaints. Listed below are the complaints reported by ≥1% of subjects, without regard to causality, in decreasing order of frequency within each body system.

LOCALIZED INJECTION-SITE REACTIONS

Tenderness (52.7%); pain (51.1%); warmth (17.4%); swelling (13.8%); erythema (13.1%); ecchymosis (1.5%); pain/soreness (1.2%).

BODY AS A WHOLE

Asthenia/fatigue (3.9%); fever (2.7%); abdominal pain (1.3%).

DIGESTIVE SYSTEM

Diarrhea (2.5%); nausea (2.3%).

MUSCULOSKELETAL SYSTEM
Myalgia (1.9%); arm pain (1.3%); back pain (1.1%); stiffness (1.0%).
NERVOUS SYSTEM/PSYCHIATRIC
Headache (16.0%).
RESPIRATORY SYSTEM
Pharyngitis (2.7%); upper respiratory infection (2.7%); nasal congestion (1.1%).
UROGENITAL SYSTEM
Menstruation disorder (1.1%).
Allergic Reactions

Local and/or systemic allergic reactions that occurred in <1% of 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 and WARNINGS.)

Marketed Experience

The following additional adverse reactions have been reported with use of the marketed vaccine.
HEMIC AND LYMPHATIC SYSTEM
Very rarely, thrombocytopenia.
NERVOUS SYSTEM
Very rarely, Guillain-Barré syndrome, cerebellar ataxia, encephalitis.
Post-marketing 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[10] (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 event 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 event in the study. There was no vaccine-related adverse event identified that had not been reported in earlier clinical trials with VAQTA.

DOSAGE AND ADMINISTRATION

Do not inject intravascularly, intradermally, or subcutaneously.

VAQTA is for intramuscular injection. The *deltoid muscle* is the preferred site for intramuscular injection.
DOSAGE

The vaccination regimen consists of one primary dose and one booster dose for healthy children, adolescents, and adults, as follows:

Children/Adolescents

Individuals 12 months through 18 years of age should receive a single 0.5 mL (~25U) dose of vaccine at elected date and a booster dose of 0.5 mL (~25U) 6 to 18 months later.

Adults

Adults 19 years of age and older should receive a single 1.0 mL (~50U) dose of vaccine at elected date and a booster dose of 1.0 mL (~50U) 6 to 18 months later.

For all age groups, a booster dose is recommended anytime between 6 and 18 months after the administration of the primary dose in order to elicit a high antibody titer.
Interchangeability of the Booster Dose

A booster dose of VAQTA may be given at 6 to 12 months following the initial dose of other inactivated hepatitis A vaccines (e.g., HAVRIX). (See CLINICAL PHARMACOLOGY, *Interchangeability of Booster Dose*.)

Use With Other Vaccines

VAQTA may be given concomitantly with typhoid and yellow fever vaccines. The GMTs for hepatitis A when VAQTA, typhoid, 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. VAQTA may be given concomitantly with M-M-R II. Data on concomitant use with other vaccines are limited. Separate injection sites and syringes should be used for concomitant administration of injectable vaccines. (See CLINICAL PHARMACOLOGY, *Use With Other Vaccines*.)

Use With Immune Globulin

VAQTA may be administered concomitantly with immune globulin (IG) using separate sites and syringes. The vaccination regimen for VAQTA should be followed as stated above. 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 above.

ADMINISTRATION

Known or Presumed Exposure to HAV/Travel to Endemic Areas

For individuals requiring either post-exposure prophylaxis or combined immediate and longer term protection (e.g., travelers departing on short notice to endemic areas), VAQTA may be administered concomitantly with IG using separate sites and syringes (see CLINICAL PHARMACOLOGY).

The following are the ACIP and American Academy of Family Physicians (AAFP) recommendations for all intramuscular injections: “For administration of VAQTA for children and adolescents (persons ≥12 months to 18 years), the deltoid muscle can be used if the muscle mass is adequate. The needle size can range from 22 to 25 gauge and from 7/8 to 1 ¼ inches, on the basis of the size of the muscle. For toddlers, the anterolateral thigh can be used, but the needle should be longer, usually 1 inch.

For adults (persons aged >18 years) the deltoid muscle is recommended for routine intramuscular vaccinations. The anterolateral thigh can be used. The suggested needle size is 1 – 1 ½ inches and 22-25 gauge.”[8]

The vaccine should be used as supplied; no reconstitution is necessary.

Shake well before withdrawal and use. Thorough agitation is necessary to maintain suspension of the vaccine. Discard if the suspension does not appear homogenous.

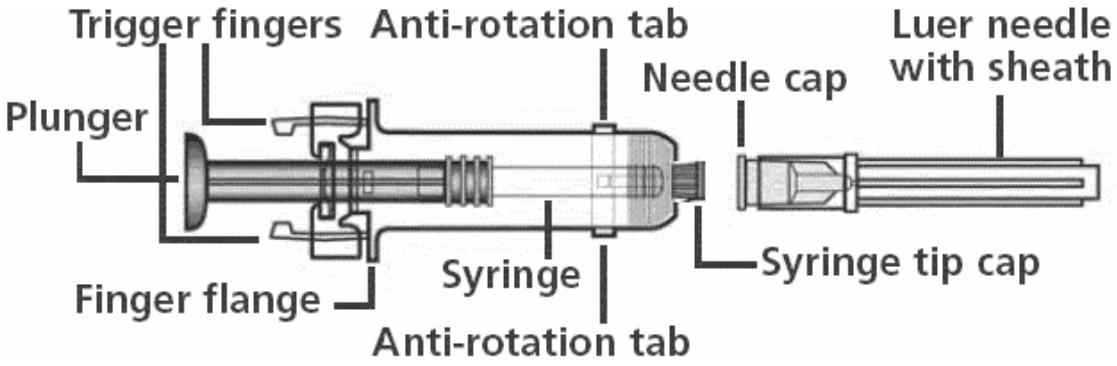
Parenteral drug products should be inspected visually for extraneous particulate matter and discoloration prior to administration whenever solution and container permit. After thorough agitation, VAQTA is a slightly opaque, white suspension.

A separate sterile syringe and sterile disposable needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another. Needles should be disposed of properly and should not be recapped.

Prefilled Syringe Use with and without Needle Guard (Safety) Device

Prefilled Syringe with Needle Guard (Safety) Device

Instructions for using the prefilled single-dose syringes preassembled with needle guard device



NOTE: Please use the enclosed needle for administration. If a different needle is chosen, it should fit securely on the syringe and be no longer than 1 inch to ensure proper functioning of the needle guard device. Two detachable labels are provided which can be removed after the needle is guarded.

At any of the following steps, avoid contact with the Trigger Fingers to keep from activating the safety device prematurely.

Remove Syringe Tip Cap and Needle Cap. Attach Luer Needle by pressing both Anti-Rotation Tabs to secure syringe and by twisting the Luer Needle in a clockwise direction until secured to the syringe. **Remove Needle Sheath. Administer injection** per standard protocol as stated above under DOSAGE AND ADMINISTRATION. Depress the Plunger while grasping the Finger Flange **until the entire dose has been given**. The Needle Guard Device will **NOT** activate to cover and protect the needle unless the **ENTIRE** dose has been given. While the Plunger is still depressed, remove needle from the vaccine recipient. Slowly release the Plunger and allow syringe to move up until the entire needle is guarded. For documentation of vaccination, remove detachable labels by pulling slowly on them. **Dispose in approved sharps container.**

Prefilled Syringe without Needle Guard (Safety) Device

This package does not contain a needle guard (safety device) or a needle. 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.

HOW SUPPLIED

PEDIATRIC/ADOLESCENT FORMULATION

Vials

No. 4831 — VAQTA for pediatric/adolescent use is supplied as 25U/0.5 mL of hepatitis A virus protein in a 0.5 mL single-dose vial, **NDC** 0006-4831-00.

No. 4831 — VAQTA for pediatric/adolescent use is supplied as 25U/0.5 mL of hepatitis A virus protein in a 0.5 mL single-dose vial, in a box of 10 single-dose vials, **NDC** 0006-4831-41.

Syringes

No. 4095 — VAQTA for pediatric/adolescent use is supplied as 25U/0.5 mL of hepatitis A virus protein in a 0.5 mL single-dose prefilled Luer Lock syringe, preassembled with UltraSafe Passive®[§§§]delivery system in a box of 6 single-dose prefilled syringes. Six one-inch 23 gauge needles are provided separately in the package, **NDC** 0006-4095-06.

No. 4095 — VAQTA for pediatric/adolescent use is supplied as 25U/0.5 mL of hepatitis A virus protein in a carton of 6 0.5 mL prefilled single-dose Luer Lock syringes with tip caps, **NDC** 0006-4095-09.

ADULT FORMULATION

Vials

No. 4841 — VAQTA for adult use is supplied as 50U/1 mL of hepatitis A virus protein in a 1 mL single-dose vial, **NDC** 0006-4841-00.

No. 4841 — VAQTA for adult use is supplied as 50U/1 mL of hepatitis A virus protein in a 1 mL single-dose vial, in a box of 10 single-dose vials, **NDC** 0006-4841-41.

Syringes

No. 4096— VAQTA for adult use is supplied as 50U/1 mL of hepatitis A virus protein in a 1 mL single-dose prefilled Luer Lock syringe, preassembled with UltraSafe Passive® delivery system. A one-inch 23 gauge needle is provided separately in the package, **NDC** 0006-4096-31.

No. 4096 — VAQTA for adult use is supplied as 50U/1 mL of hepatitis A virus protein in a 1 mL single-dose prefilled Luer Lock syringe, preassembled with UltraSafe Passive® delivery system in a box of 6 single-dose, prefilled syringes. Six one-inch 23 gauge needles are provided separately in the package, **NDC** 0006-4096-06.

---

§§§ UltraSafe Passive® delivery system is a Trademark of Safety Syringes, Inc.

No. 4096— VAQTA for adult use is supplied as 50U/1 mL of hepatitis A virus protein in a carton of 6 1 mL prefilled single-dose Luer Lock syringes with tip caps, **NDC** 0006-4096-09.

Storage

Store vaccine at 2-8°C (36-46°F).

DO NOT FREEZE since freezing destroys potency.

REFERENCES

1. Lemon, S.M.: Type A viral hepatitis, new developments in an old disease, NEJM *313*(17): 1059-1067, 1985.
2. Miller, W.J., et al: Sensitive assays for hepatitis A antibodies, J Med Virol *41:* 201-204, 1993.
3. Werzberger, A., et al: A Controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children, NEJM *327*(7): 453-457, 1992.
4. Ward, R., et al: Infectious Hepatitis, Studies of Its Natural History and Prevention, NEJM *258*(9): 407-416, February 27, 1958.
5. Werzberger, A., et al: Effectiveness of hepatitis A vaccine in a former frequently affected community: 9 years' followup after the Monroe field trial of VAQTA®, Vaccine *20*: 1699-1701, 2002.
6. Werzberger, A., et al: Anatomy of a trial: a historical view of the Monroe inactivated hepatitis A protective efficacy trial, J Hepatol *18*(Suppl. 2): S46-S50, 1993.
7. Recommendations of the Advisory Committee on Immunization Practices (ACIP); Prevention of Hepatitis A Through Active or Passive Immunization, MMWR *48*(RR-12): 1-37, 1999.
8. Recommendations of the Advisory Committee on Immunization Practices (ACIP); General Recommendations on Immunization, MMWR *51*(RR-2): 1-35, 2002.
9. Recommendations of the Advisory Committee on Immunization Practices (ACIP); Prevention of Hepatitis A Through Active or Passive Immunization, MMWR *42*(RR-4): 1-18, 1993.
10. Black, S., et al: A postlicensure evaluation of the safety of inactivated hepatitis A vaccine (VAQTA®, Merck) in children and adults, Vaccine *22*: 766-772, 2004.

Manuf. and Dist. by:
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued December 2007
Printed in USA