(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: 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: 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. While the course of the disease is generally benign and does not result in chronic hepatitis, infection with hepatitis A virus remains an important cause of morbidity and occasional fulminant hepatitis and death.[1]

Hepatitis A is transmitted most often by the fecal-oral route, with infection occurring primarily within private households. Common-source outbreaks due to contaminated food and water supplies have occurred following consumption of certain foods such as raw shellfish, and uncooked foods prepared by an infected food-handler or otherwise contaminated prior to ingestion (salads, sandwiches, frozen raspberries, etc.). Bloodborne transmission, while uncommon, is possible via blood transfusion, contaminated blood products, or from needles shared with an infected viremic individual. Sexual transmission has also been reported.[1-14,16]

The disease burden due to hepatitis A in the United States has been estimated to be approximately 143,000 infections per year, of which 75,800 result in clinical hepatitis A disease, 11,400 hospitalizations, and 80 deaths due to fulminant hepatitis. Worldwide, it has been estimated that 1.4 million cases are reported annually.[2] The clinical manifestations of hepatitis A infection often pass unrecognized in children ≤2 years of age whereas overt hepatitis A develops in the majority of infected older children and adults. Symptoms and signs of hepatitis A infection

are similar to those associated with other types of viral hepatitis and include anorexia, nausea, fever/chills, jaundice, dark urine, light-colored stools, abdominal pain, malaise, and fatigue.[1]

Clinical Trials

Clinical trials conducted worldwide with several formulations of the vaccine in 9421 healthy individuals ranging from 2 to 85 years of age have demonstrated that VAQTA is highly immunogenic and generally well tolerated.

Protection from hepatitis A disease has been shown to be related to the presence of antibody; an anamnestic antibody response occurs in healthy individuals with a history of infection who are subsequently re-exposed to hepatitis A virus.[3] Similarly, 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][15]) and with an anamnestic antibody response following booster vaccination with VAQTA.

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 (13,735 children/adolescent 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. (See ADVERSE REACTIONS, *Post-marketing Safety Study*.)

Immunology

In combined clinical studies, 97% of 1230 healthy children and adolescents 2 through 18 years of age seroconverted with a geometric mean titer (GMT) of 43 mIU/mL within 4 weeks after a single ~25U/0.5 mL intramuscular dose of VAQTA. Similarly, 95% of 1411 adults ≥19 years of age seroconverted with a GMT of 37 mIU/mL within 4 weeks after a single ~50U/1.0 mL intramuscular dose of VAQTA. Furthermore, at 2 weeks post-vaccination, 69% (n=744) of adults seroconverted with a GMT of 16 mIU/mL after a single dose of VAQTA.[18] Immune memory was demonstrated by an anamnestic antibody response in individuals who received either a ~25U/0.5 mL or ~50U/1.0 mL booster dose (see *Persistence*).

A ~50U/1.0 mL intramuscular dose of VAQTA also was evaluated at four weeks post primary dose in healthy adolescents (18 years of age); 94% of 17 adolescents seroconverted with a GMT of 40 mIU/mL. In individuals 18 years of age, the GMT following a ~50U/1.0 mL booster dose was greater than the GMT following a ~25U/0.5 mL booster dose. Both doses were immunogenic and were generally well tolerated. (See DOSAGE AND ADMINISTRATION.)

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 1 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 1
Seroconversion Rates (%) and Geometric Mean Titers (GMT) after Vaccination with VAQTA plus IG, VAQTA Alone, and IG Alone

** Trademark of Abbott Laboratories

	VAQTA plus IG	VAQTA	IG
Weeks	Seroconversion Rate GMT (mIU/mL)		
4	100% 42 (n=129)	96% 38 (n=135)	87% 19 (n=30)
24	92% 83 (n=125)	97%* 137* (n=132)	0% Undetectable† (n=28)
28	100% 4872 (n=114)	100% 6498 (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

Efficacy

A very high degree of protection has been demonstrated after a single dose of VAQTA in children and adolescents.[19] 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.

Because of the long incubation period of the disease (approximately 20 to 50 days, or longer in children[22]), 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. 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.

Persistence

The total duration of the protective effect of VAQTA in healthy vaccinees is unknown at present. However, seropositivity was shown to persist up to 18 months after a single ~25U dose in a cohort of 35 out of 39 children and adolescents who participated in The Monroe Efficacy Study; 95% of this cohort responded anamnestically following a booster at 18 months. 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 6 years.[23]

The effectiveness of VAQTA for use in community outbreak control has been demonstrated by the fact that, although cases of imported infection have occurred, the study community has remained free of outbreaks. In contrast, three nearby sister communities to Monroe have continued to experience outbreaks.[18-20]

*** 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.

In adults, seropositivity has been shown to persist up to 18 months after a single ~50U dose. Persistence of immunologic memory was demonstrated with an anamnestic antibody response to a booster dose of ~25U given 6 to 18 months after the primary dose in children and adolescents (Table 2), and to a booster dose of ~50U given 6 to 18 months after the primary dose to adults (Table 3).

Table 2
Children/Adolescents
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.

Table 3
Adults
Seroconversion Rates (%) and Geometric Mean Titers (GMT) for a Cohort of Vaccinees at the Time of the Booster (~50U) and 4 Weeks Later

Months Following Initial ~50U Dose	Cohort* (n=1201) 0 and 6 Months	Cohort* (n=91) 0 and 12 Months	Cohort* (n=84) 0 and 18 Months
	Seroconversion Rate GMT (mIU/mL) (95% CI)		
6	98% 139 (129, 149)	—	—
7	100% 5987 (5561, 6445)	—	—
12	—	93% 107 (78, 146)	—
13	—	98% 4896 (3589, 6679)	—
18	—	—	96% 120 (88, 164)
19	—	—	100% 6043 (4687, 7793)

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

In a clinical study involving healthy children 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 studies of healthy adults who received two doses (~50U) of VAQTA at 0 and 6 months, the hepatitis A antibody response to date has been shown to persist up to 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.

Studies in healthy children, adolescents and adults are ongoing to evaluate longer-term antibody persistence and the need, if any, for additional booster doses.

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 4) and was generally well tolerated. (See DOSAGE AND ADMINISTRATION, *Interchangeability of the Booster Dose*.)

Table 4
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.

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, 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. The concomitant administration of these three vaccines at separate injection sites was generally well tolerated. (See INDICATIONS AND USAGE, *Use With Other Vaccines* and DOSAGE AND ADMINISTRATION, *Use With Other Vaccines*.)

INDICATIONS AND USAGE

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

Individuals who are or will be at increased risk of infection by HAV include:[2-14,16,17]

TRAVELERS

Persons traveling to areas of higher endemicity for hepatitis A. These areas include, but are not limited to, Africa, Asia (except Japan), the Mediterranean basin, Eastern Europe, the Middle East, Central and South America, Mexico, and parts of the Caribbean. Current CDC (Centers for Disease Control and Prevention) advisories should be consulted with regard to specific locales.

MILITARY PERSONNEL

PEOPLE LIVING IN, OR RELOCATING TO, AREAS OF HIGH ENDEMICITY

CERTAIN ETHNIC AND GEOGRAPHIC POPULATIONS THAT EXPERIENCE CYCLIC HEPATITIS A EPIDEMICS SUCH AS:

Native peoples of Alaska and the Americas.

OTHERS

Persons engaging in high-risk sexual activity (such as homosexually active males); users of illicit injectable drugs; residents of a community experiencing an outbreak of hepatitis A.

‡Registered trademark of Smithkline Beecham

Hemophiliacs and other recipients of therapeutic blood products (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Persons who test positive for hepatitis C virus and have diagnosed liver disease.[24]

Although the epidemiology of hepatitis A does not permit the identification of other specific populations at high risk of disease, outbreaks of hepatitis A or exposure to hepatitis A virus have been described in a variety of populations in which VAQTA may be useful:

— Certain institutional workers (e.g., caretakers for the developmentally challenged)
— Employees of child day-care centers
— Laboratory workers who handle live hepatitis A virus
— Handlers of primate animals that may be harboring HAV

PEOPLE EXPOSED TO HEPATITIS A

For those requiring both immediate and long-term protection, VAQTA may be administered concomitantly with IG.

Revaccination

See DOSAGE AND ADMINISTRATION, *DOSAGE.*

Use With Other Vaccines

VAQTA may be given concomitantly at separate injection sites 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. (See CLINICAL PHARMACOLOGY, *Use With Other Vaccines* and DOSAGE AND ADMINISTRATION, *Use With Other Vaccines*.)

The Advisory Committee on Immunization Practices has stated that limited data from studies conducted among adults indicate that simultaneous administration of hepatitis A vaccine with diphtheria, poliovirus (oral and inactivated), tetanus, oral typhoid, cholera, Japanese encephalitis, rabies, or yellow fever vaccine does not decrease the immune response to either vaccine or increase the frequency of reported adverse events. Studies indicate that hepatitis B vaccine can be administered with VAQTA without affecting immunogenicity or increasing the frequency of adverse events.[25]

Use With Immune Globulin

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 and DOSAGE AND ADMINISTRATION).

VAQTA IS NOT RECOMMENDED FOR USE IN INFANTS YOUNGER THAN 2 YEARS OF AGE SINCE DATA ON USE IN THIS AGE GROUP ARE NOT CURRENTLY AVAILABLE.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine.

WARNINGS

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

If VAQTA is used in individuals with malignancies or those receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

PRECAUTIONS

General

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 any vaccine, adequate treatment provisions, including epinephrine, should be available for immediate use should an anaphylactic or anaphylactoid reaction occur.

VAQTA should be administered with caution to people with bleeding disorders who are at risk of hemorrhage following intramuscular injection (see DOSAGE AND ADMINISTRATION).

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.

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

VAQTA has been shown to be generally well tolerated and highly immunogenic in individuals 2 through 18 years of age. See DOSAGE AND ADMINISTRATION for the recommended dosage schedule.

Safety and effectiveness in infants below 2 years 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

VAQTA is generally well tolerated; adverse reactions usually are mild and transient.

Clinical Studies

In combined clinical trials, 16,252 doses of VAQTA were administered to 9181 healthy children, adolescents, and adults. VAQTA was generally well tolerated.

No serious vaccine-related adverse experiences were observed during clinical trials.

The Monroe Efficacy Study

In this 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 observed 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[19], 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

In combined clinical trials (including Monroe Efficacy Study participants) involving 2615 healthy children and adolescents who received one or more ~25U doses of hepatitis A vaccine, fever and local complaints were observed during a 5-day period following vaccination and systemic complaints during a 14-day period following vaccination. Injection-site complaints, generally mild and transient, were the most frequently reported complaints. Listed below are the complaints (≥1%) reported, 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, fever and local complaints were observed during a 5-day period following vaccination and systemic complaints during a 14-day period following vaccination. Injection-site complaints, generally mild and transient, were the most frequently reported complaints. Listed below are the complaints (≥1%) reported, 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.)

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.
Marketed Experience

The following additional adverse reactions have been reported with use of the marketed vaccine.
NERVOUS SYSTEM
Very rarely, Guillain-Barré syndrome, cerebellar ataxia.
Post-marketing Safety Study
In a post-marketing safety study, a total of 42,110 people ≥2 years of age received 1 or 2 doses of VAQTA. There was no serious, vaccine-related adverse event identified among the 42,110 vaccine recipients in this study. There was no vaccine-related adverse event identified that had not been reported in earlier clinical trials with VAQTA. Diarrhea/gastroenteritis, resulting in outpatient visits (in adults), was determined by the investigator to be the only vaccine-related, nonserious adverse event in the study. VAQTA was generally well tolerated in this study. (See CLINICAL PHARMACOLOGY, *Post-marketing Safety Study*.)

DOSAGE AND ADMINISTRATION

Do not inject intravenously, 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:

Pediatric/Adolescent

Individuals 2 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.

A 1.0 mL (~50U) dose also was evaluated in individuals 18 years of age and was found to be immunogenic and generally well tolerated. (See CLINICAL PHARMACOLOGY, *Immunology*.)

Adult

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. 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* and INDICATIONS AND USAGE, *Use With Other Vaccines*.)

Use With Immune Globulin

VAQTA may be administered concomitantly with 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 and DOSAGE AND ADMINISTRATION, *Use With Immune Globulin*).

Injection must be accomplished with a needle long enough to ensure intramuscular deposition of the vaccine. The Advisory Committee on Immunization Practices (ACIP) has recommended that "For all intramuscular injections, the needle should be long enough to reach the muscle mass and prevent vaccine from seeping into subcutaneous tissue, but not so long as to endanger underlying neurovascular structures or bone." For toddlers and older children they further state that "...the deltoid may be used if the muscle mass is adequate. The needle size can range from 22 to 25 gauge and from 5/8 to 1¼ inches, based on the size of the muscle...the anterolateral thigh may be used, but the needle should be longer — generally ranging from 7/8 to 1¼ inches". For adults they state that "...the deltoid is recommended for routine intramuscular vaccination among adults...The suggested needle size is 1 to 1½ inches and 20 to 25 gauge."[21]

For individuals with bleeding disorders who are at risk of hemorrhage following intramuscular injection, the ACIP recommends that when any intramuscular vaccine is indicated for such patients, "...it should be administered intramuscularly if, in the opinion of a physician familiar with the patient's bleeding risk, the vaccine can be administered with reasonable safety by this route. If the patient receives antihemophilia or other similar therapy, intramuscular vaccination can be scheduled shortly after such therapy is administered. A fine needle (≤23 gauge) can be used for the vaccination and firm pressure applied to the site (without rubbing) for at least two minutes. The patient or family should be instructed concerning the risk of hematoma from the injection."[21]

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.

It is important to use a separate sterile syringe and needle for each individual to prevent transmission of infectious agents from one person to another.

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 5 single-dose vials, **NDC** 0006-4831-38.

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. 4845 — 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 syringe, with a 5/8 inch needle, **NDC** 0006-4845-00.

No. 4845 — 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 syringe, with a 5/8 inch needle, in a box of 5 single-dose prefilled syringes, with 5/8 inch needles, **NDC** 0006-4845-38.

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 5 single-dose vials, **NDC** 0006-4841-38.

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. 4844 — VAQTA for adult use is supplied as 50U/1 mL of hepatitis A virus protein in a 1 mL single-dose prefilled syringe, with a one inch needle, **NDC** 0006-4844-00.

No. 4844 — VAQTA for adult use is supplied as 50U/1 mL of hepatitis A virus protein in a 1 mL single-dose prefilled syringe, with a one inch needle, in a box of 5 single-dose, prefilled syringes, with one inch needles, **NDC** 0006-4844-38.

Storage

Store vaccine at 2-8°C (36-46°F).

DO NOT FREEZE since freezing destroys potency.

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