PRODUCT CIRCULAR

VAQTA®
[Hepatitis A Vaccine, Purified Inactivated, MSD]

I. THERAPEUTIC CLASS

VAQTA is an inactivated whole virus vaccine which has been shown to induce antibody to hepatitis A virus protein.

II. INDICATIONS

VAQTA is indicated for active pre-exposure prophylaxis against disease caused by HAV. VAQTA is recommended for healthy individuals from 12 months of age and older who are at risk of contracting or spreading infection or who are at risk of life-threatening disease if infected (e.g., hepatitis C with diagnosed liver disease, adults with Human Immunodeficiency Virus [HIV]).

III. DOSAGE AND ADMINISTRATION

DO NOT INJECT INTRAVASCULARLY OR INTRADERMALLY

VAQTA is for intramuscular injection. 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.

Adults with Bleeding Disorders
For individuals with bleeding disorders who are at risk of hemorrhage following intramuscular injection (e.g., hemophiliacs), this vaccine can be administered subcutaneously (See PRECAUTIONS).

The vaccination series consists of one primary dose and one booster dose given according to the following schedule:

Children/Adolescents – 12 Months Through 17 Years of Age

Individuals 12 months through 17 years of age should receive a single 0.5 mL (~25 U) dose of vaccine at elected date and a booster dose of 0.5 mL (~25 U) 6 to 18 months later.

Adults

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

Adults With Human Immunodeficiency Virus (HIV)

HIV-infected adults should receive a single 1.0 mL (~50 U) dose of vaccine at elected date and a booster dose of 1.0 mL (~50 U) 6 months later.

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.

Use With Other Vaccines

VAQTA may be given concomitantly with yellow fever, typhoid, measles, mumps, rubella, varicella, pneumococcal 7-valent conjugate, diphtheria toxoid, tetanus toxoid, acellular pertussis, and *Haemophilus influenzae* b vaccines. Data on concomitant use with other vaccines are limited. (See DRUG INTERACTIONS, *Use With Other Vaccines*.)

Separate injection sites and syringes should be used for concomitant administration of injectable vaccines.

Known or Presumed Exposure to HAV/Travel to Endemic Areas

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 (see DRUG INTERACTIONS).

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.

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.

IV. CLINICAL PHARMACOLOGY

IVa. Clinical Studies

Clinical trials conducted worldwide with several formulations of the vaccine in 4374 children 12 through 23 months of age and 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. Protection after vaccination with VAQTA was associated with the onset of seroconversion (≥ 10 mIU/mL of hepatitis A antibody, measured by a modification of the HAVAB[**] radioimmunoassay [RIA]) and with an anamnestic antibody response following booster vaccination with VAQTA.

In a post-marketing safety 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. Safety was monitored by reviewing medical records that tracked emergency room and outpatient visits, hospitalizations and deaths. There was no serious, vaccine-related, adverse event identified among the 42,110 individuals in this study. There was no nonserious, vaccine-related, adverse event resulting in outpatient visits, with the exception of diarrhea/gastroenteritis in adults at a rate of 0.5%. There was no vaccine-related, adverse event identified that had not been reported in earlier clinical trials with VAQTA.

Immunogenicity

Children – 12 Through 23 Months of Age

[**] Trademark of Abbott Laboratories.

In a clinical trial, children 12 through 23 months of age were randomized to receive the first dose of VAQTA with or without M-M-R II and VARIVAX (N=617) and the second dose of VAQTA with or without Tripedia and optionally either oral poliovirus vaccine or IPOL (N=555). The race distribution of study subjects who received at least one dose of VAQTA was as follows: 56.7% Caucasian; 17.5% Hispanic-American; 14.3% African-American; 7.0% Native American; 3.4% other; 0.8% Oriental; 0.2% Asian; and 0.2% Indian. The distribution of subjects by gender was 53.6% male and 46.4% female. In the analysis population, there were 471 initially seronegative children 12 through 23 months of age, who received the first dose of VAQTA with (N=237) or without (N=234) M-M-R II and VARIVAX of whom 96% (95% CI: 93.7%, 97.5%) seroconverted (defined as having an anti-HAV titer ≥ 10 mIU/mL) post dose 1 with an anti-HAV GMT of 48 mIU/mL (95% CI: 44.7, 51.6). There were 343 children in the analysis population who received the second dose of VAQTA with (N=168) or without (N=175) Tripedia and optional oral poliovirus vaccine or IPOL of whom 100% (95% CI: 99.3%, 100%) seroconverted post dose 2 with an anti-HAV GMT of 6920 mIU/mL (95% CI: 6136, 7801). Of children who received only VAQTA at both visits, 100% (n=97) seroconverted after the second dose of VAQTA.

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

In an open, multicenter, randomized study involving 617 children 15 months of age, 306 were randomized to receive VAQTA with or without PedvaxHIB and INFANRIX, and 311 were randomized to receive VAQTA with or without PedvaxHIB. The race distribution of the study subjects was as follows: 63.9% Caucasian; 17.5% Hispanic-American; 14.7% Black; 2.6% other; and 1.3% Asian. The distribution of subjects by gender was 54.0% male and 46.0% female. The

seropositivity rate for hepatitis A antibody (defined as the percent of subjects with an anti-HAV titer ≥ 10 mIU/mL) 4 weeks post dose 2 was 100% (n=208, 95% CI: 98.2%, 100.0%) in those who received VAQTA concomitantly with PedvaxHIB and INFANRIX or concomitantly with PedvaxHIB. In those subjects who received VAQTA alone, the seropositivity rate for hepatitis A antibody was 100% (n=183, 95% CI: 98.0%, 100.0%), regardless of baseline hepatitis A serostatus. Overall, the anti-HAV GMT in the concomitant groups was 3616.5 mIU/mL (95% CI: 3084.5, 4240.2). The anti-HAV GMT in the nonconcomitant groups was 4712.6 mIU/mL (95% CI: 3996.8, 5556.8). Comparable responses were observed in both the initially seronegative and seropositive subjects.

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

Children/Adolescents – 2 Through 17 Years of Age

In combined clinical studies, 97% of 1214 children and adolescents 2 to 17 years of age seroconverted within 4 weeks after a single ~25 U intramuscular dose of VAQTA. Similarly, 95% of 1428 adults ≥ 18 years of age seroconverted within 4 weeks after a single ~50 U intramuscular dose of VAQTA. Immune memory was later demonstrated by an anamnestic antibody response in individuals who received a booster dose (see ***Persistence***).

While a study evaluating VAQTA alone in a post-exposure setting has not been conducted, the concurrent use of VAQTA (~50 U) 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 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 After Vaccination With VAQTA Plus IG, VAQTA Alone, and IG Alone

	VAQTA plus IG	VAQTA	IG
Weeks	Seroconversion Rate		
4	100% (n=129)	96% (n=135)	87% (n=30)
24	92% (n=125)	*97% (n=132)	0% (n=28)
28	100% (n=114)	100% (n=128)	N/A

* Seroconversion rate in the vaccine alone group significantly higher than that in the vaccine plus IG group (p=0.05).
N/A = Not Applicable

Efficacy

A very high degree of protection has been demonstrated after a single dose of VAQTA in children and adolescents. 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 to 16 years of age in a U.S. community with recurrent outbreaks of hepatitis A (The Monroe Efficacy Study). Each child received a single intramuscular dose of VAQTA (approximately 25 U) or placebo. Among those individuals who were initially seronegative (measured by a modification of the HAVAB** radioimmunoassay [RIA]), seroconversion was achieved in >99% of vaccine recipients within 4 weeks after vaccination. The onset of seroconversion following a single dose of VAQTA was shown to parallel the onset of protection against clinical hepatitis A disease.

Because of the long incubation period of the disease (approximately 20 to 50 days, or longer in children), the analysis of protective efficacy was based on cases*** of clinically confirmed 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 ($p<0.001$). Twenty-eight cases of clinically confirmed hepatitis 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 most vaccinees 6, 12, or 18 months after the primary dose.

** Trademark of Abbott Laboratories

*** 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.

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 ~25 U dose in 90% of a cohort of children and adolescents (n=39) who participated in The Monroe Efficacy Study; 95% of this cohort‡ demonstrated an anamnestic antibody response 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 9 years.

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.

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

In studies of healthy children (≥ 2 years of age) and adolescents who received two doses (~25 U) of VAQTA at 0 and 6 to 18 months, the hepatitis A antibody response to date has been shown to persist for at least 10 years. The GMTs declined over the first 5 to 6 years, but appeared to plateau through 10 years.

In studies of healthy adults who received two doses (~50 U) of VAQTA at 0 and 6 months, the hepatitis A antibody response to date has been shown to persist at least 6 years. After an initial decline over 2 years, the GMTs appeared to plateau during the 2- to 6-year period.

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‡ Two children had post-booster titers of 6724 mIU/mL and 105,281 mIU/mL (their pre-booster titers were 4959 mIU/mL and 43,029 mIU/mL, respectively). These titers did not meet the criteria for an anamnestic antibody response as defined by the study protocol (≥ 10-fold rise from pre-booster titer to post-booster titer and post-booster titer ≥ 100 mIU/mL). This suggests an anamnestic response following exposure to wild-type virus sometime after the primary but before the booster dose.

Data available from long-term studies show persistence of antibodies up to 10 years in subjects who received 2 doses of VAQTA. Although the total duration of the protective effect of VAQTA in healthy, immunocompetent subjects is unknown, mathematical modelling using persistence data from subjects up to 41 years of age projects that at least 99% of subjects should remain seropositive (≥ 10 mIU anti-HAV/mL) for 25 years or possibly longer.

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

Table 2

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.

* Trademark of GlaxoSmithKline

Use With Other Vaccines

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

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

Clinical Studies of VAQTA with ProQuad and Prevnar

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

Clinical Studies of VAQTA with INFANRIX and PedvaxHIB

In the clinical trial of concomitant administration of VAQTA with INFANRIX and PedvaxHIB in children 15 months of age, described in Section IVa, when the first dose of VAQTA was administered concomitantly with either INFANRIX and PedvaxHIB or PedvaxHIB, there was no interference in immune response to hepatitis A as measured by seropositivity rates after dose 2 of VAQTA compared to administration of both doses of VAQTA alone. When dose 1 of VAQTA was administered concomitantly with either PedvaxHIB and INFANRIX or PedvaxHIB, there was no interference in immune response to *Haemophilus influenzae* b (as measured by the proportion of subjects who attained an anti-polyribosylribitol phosphate antibody titer >1.0 mcg/mL at 4 weeks after vaccination), compared to subjects receiving either PedvaxHIB and INFANRIX or PedvaxHIB. When VAQTA was administered concomitantly with INFANRIX and PedvaxHIB, there was no interference in immune responses at 4 weeks after vaccination to the pertussis antigens (PT, FHA, or pertactin, as measured by GMTs) and no interference in immune responses to diphtheria toxoid or tetanus toxoid (as measured by the proportion of subjects achieving an antibody titer >0.1 IU/mL) compared to administration of INFANRIX and PedvaxHIB.

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

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

Subcutaneous Administration

In a clinical study with 114 healthy seronegative adults who received subcutaneous administration of VAQTA (~50 U), at 4 weeks following the first dose, the seropositivity rate (SPR) was 78%, and the GMT was 21 mIU/mL. At 24 weeks following the first dose and just prior to the second subcutaneous injection, the SPR was 95%, and the GMT was 153 mIU/mL. At 4 weeks following the second subcutaneous injection, the SPR was 100%, and the GMT was

1564 mIU/mL. The kinetics of seropositivity were slower for the first subcutaneous dose of VAQTA compared with historical data for intramuscular administration. At 24 weeks following the first subcutaneous dose, the SPR was similar to the historical data at 4 weeks after the initial intramuscular dose. However, at 4 weeks following the second subcutaneous dose, the SPR was similar to the historical data 4 weeks after the second dose with intramuscular administration. Subcutaneous administration of VAQTA was generally well tolerated.

Patients receiving VAQTA by subcutaneous injection should be advised that protection from injection is not reliably achieved until 24 weeks after the first dose. Subcutaneous injection was associated with higher rate of local adverse events than intramuscular injection.

Administration in HIV-Infected Adults

In a clinical study with 180 adults, 60 HIV-positive and 90 HIV-negative adults received VAQTA (~50 U) and 30 HIV-positive adults received placebo. At 4 weeks following the first dose of VAQTA, the SPR was 61% for HIV-positive adults and 90% for HIV-negative adults. At 28 weeks following the first dose (4 weeks following the second dose) of VAQTA, the SPRs were satisfactory for all groups: 94% (GMT of 1060 mIU/mL) in HIV-positive and 100% (GMT of 3602 mIU/mL) in HIV-negative adults. Furthermore, in the HIV-positive group receiving VAQTA, the SPR was 100% (GMT of 1959 mIU/mL) in subjects with CD4 cell counts ≥ 300 cell/mm^3; however, the SPR was 87% (GMT of 517 mIU/mL) in subjects with CD4 cell counts <300 cell/mm^3. The kinetics of the immune response were slower in the HIV-positive group compared with the HIV-negative group. In HIV-positive adults, administration of VAQTA did not appear to adversely affect the CD4 cell counts and HIV RNA burden.

The immunogenicity of VAQTA after subcutaneous administration to HIV-infected individuals has not been assessed.

V. CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine.

VI. PRECAUTIONS

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

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

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.

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.

For individuals with bleeding disorders who are at risk following intramuscular injection (e.g., hemophiliacs), other measures can be taken such as intramuscular administration of the vaccines after anti-hemophilia therapy or similar therapy or applying pressure. This vaccine can be administered subcutaneously to these subjects, although the kinetics of seroconversion are slower for the first subcutaneous dose of VAQTA compared with historical data for intramuscular administration.

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

Any 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.

VII. PREGNANCY

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.

VIII. 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.

IX. PEDIATRIC USE

VAQTA has been shown to be generally well tolerated and highly immunogenic in individuals 12 months through 17 years of age. See DOSAGE AND ADMINISTRATION for the recommended dosage schedule.

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

X. DRUG INTERACTIONS

Use With Other Vaccines

VAQTA may be given concomitantly with yellow fever, typhoid, measles, mumps, rubella, varicella, pneumococcal 7-valent conjugate, diphtheria toxoid, tetanus toxoid, acellular pertussis, and *Haemophilus influenzae* b vaccines. Data on concomitant use with other vaccines are limited. (See DOSAGE AND ADMINISTRATION, *Use With Other Vaccines*.)

Separate injection sites and syringes should be used for concomitant administration of injectable vaccines.

The Advisory Committee on Immunization Practices, (ACIP advises the U.S. Public Health Service on vaccination policy), 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.

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.

XI. SIDE EFFECTS

Clinical Studies

Children – 12 Months Through 23 Months of Age

In 5 combined clinical trials, 4374 children 12 through 23 months of age received one or two ~25 U doses of VAQTA. Out of the 4374 children who received VAQTA, 3885 (88.8%) children received 2 doses of VAQTA, with 1250 (32.2%) of those children receiving VAQTA concomitantly with other vaccines. Children were followed for elevated temperature and injection-site adverse reactions during a 5-day period postvaccination and systemic adverse events during a 14-day period postvaccination.

The most frequently reported injection-site adverse reaction after any dose of VAQTA was injection-site pain/tenderness/soreness. The data from three of the five protocols were combined as these three studies specifically prompted for injection-site erythema, pain/tenderness/soreness, and swelling daily for Day 1 through Day 5 postvaccination whereas two protocols did not.

The most common systemic adverse events among recipients of VAQTA alone and VAQTA given concomitantly with other vaccines were pyrexia (fever >37°C or feverish) and irritability. The rates of all other systemic adverse events were comparable between recipients of VAQTA alone and VAQTA given concomitantly with other vaccines. The data from the five protocols were combined as similar methods for collecting systemic adverse events were used.

The adverse events that were observed among recipients of VAQTA alone or VAQTA given concomitantly with measles, mumps, rubella, varicella, pneumococcal 7-valent conjugate, oral or inactivated polio, diphtheria toxoid, tetanus toxoid, acellular pertussis, and *Haemophilus influenzae* b vaccines at a frequency of at least 1.0% and regardless of causality, are listed in decreasing order of frequency within each system organ class.

The frequency classifications are as follows:
Very Common (≥ 1/10); Common (≥ 1/100, <1/10)

Adverse Events in Children 12 Months Through 23 Months of Age Administered VAQTA Alone (At Both Doses)

Infections and infestations

Common: Upper respiratory infection; otitis media; nasopharyngitis; rhinitis; viral infection; croup; gastroenteritis.

Eye disorders

Common: Conjunctivitis.

Respiratory, thoracic and mediastinal disorders

Common: Rhinorrhea; cough; nasal congestion.

Gastrointestinal disorders

Common: Diarrhea; vomiting; teething.

Skin and subcutaneous tissue disorders

Common: Dermatitis diaper; rash.

General disorders and administration site conditions

Very Common: Injection-site pain/tenderness/soreness; injection-site erythema; pyrexia (fever >37°C or feverish, Days 1-14); injection-site swelling; irritability.

Common: Fever >39°C, Oral (Days 1-5); injection-site bruising; injection-site hematoma.

Adverse Events in Children 12 Months Through 23 Months of Age Administered VAQTA Concomitantly with Measles, Mumps, Rubella, Varicella, Pneumococcal 7-valent Conjugate, Oral or Inactivated Polio, Diphtheria Toxoid, Tetanus Toxoid, Acellular Pertussis, or Haemophilus Influenzae b Vaccines (At Least One Dose)

Infections and infestations

Common: Upper respiratory infection; otitis media; nasopharyngitis; viral infection; otitis; rhinitis; laryngotracheobronchitis.

Metabolism and nutrition disorders

Common: Decreased appetite.

Nervous system disorders

Common: Crying.

Eye disorders

Common: Conjunctivitis.

Respiratory, thoracic and mediastinal disorders

Common: Rhinorrhea; cough; nasal congestion; respiratory congestion.

Gastrointestinal disorders

Common: Diarrhea; vomiting.

Skin and subcutaneous tissue disorders

Common: Rash; dermatitis diaper; measles-like/rubella-like rash.

General disorders and administration site conditions

Very Common: Injection-site pain/tenderness/soreness; pyrexia (fever >37°C or feverish, Days 1-14); injection-site erythema; injection-site swelling; irritability.

Common: Fever ≥ 39°C Oral (Days 1-5); injection-site bruising.

Children/Adolescents - 2 Through 17 Years of Age

In combined clinical trials involving 2595 healthy children (≥ 2 years of age) and adolescents (including the Monroe Efficacy Study, a placebo-controlled study of 1037 participants) who received one or more ~25 U doses of hepatitis A vaccine, subjects were followed for fever and local complaints were observed 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 (generally mild and transient)

Pain (18.7%); tenderness (16.8%); warmth (8.6%); erythema (7.5%); swelling (7.3%); ecchymosis (1.3%).

BODY AS A WHOLE

Fever (≥ 38.9°C, 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 - 18 Years of Age and Older

In combined clinical trials involving 1529 healthy adults who received one or more ~50 U 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 (generally mild and transient)

Tenderness (52.6%); pain (51.1%); warmth (17.3%); swelling (13.6%); erythema (12.9%); ecchymosis (1.5%); pain/soreness (1.2%).

BODY AS A WHOLE

Asthenia/fatigue (3.9%); fever (≥ 38.3°C, Oral) (2.6%); abdominal pain (1.3%).

DIGESTIVE SYSTEM

Diarrhea (2.4%); nausea (2.3%).

MUSCULOSKELETAL SYSTEM

Myalgia (2.0%); arm pain (1.3%); back pain (1.1%); stiffness (1.0%).

NERVOUS SYSTEM/PSYCHIATRIC

Headache (16.1%).

RESPIRATORY SYSTEM

Pharyngitis (2.7%); upper respiratory infection (2.8%); nasal congestion (1.1%).

UROGENITAL SYSTEM

Menstruation disorder (1.1%).

Local and/or systemic hypersensitivity reactions occurred in <1% of children, adolescents, or adults in clinical trials and included the following regardless of causality: pruritus, urticaria, and rash.

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.

Post-marketing Safety Study

In a post-marketing safety study, a total of 42,110 individuals ≥ 2 years of age received 1 or 2 doses of VAQTA. There was no serious, vaccine-related, adverse event identified. There was no nonserious, vaccine-related, adverse event resulting in outpatient visits, with the exception of diarrhea/gastroenteritis in adults at a rate of 0.5%.

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, encephalitis.

HEMIC AND LYMPHATIC SYSTEM

Very rarely, thrombocytopenia.

XII. OVERDOSAGE

There are no data with regard to overdose.

XIII. CHEMISTRY

VAQTA [Hepatitis A Vaccine, Purified Inactivated] is a highly purified 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. One milliliter of the vaccine contains approximately 50 units (U) of hepatitis A antigen, which is highly purified and is formulated without a preservative. Within the limits of current assay variability, the 50 U 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 (including neomycin) are less than 10 parts per billion (ppb).

XIV. COMPOSITION

XIVa. Active Ingredients

VAQTA is a sterile suspension for intramuscular injection. For individuals with bleeding disorders who are at risk of hemorrhage following intramuscular injection see DOSAGE AND ADMINISTRATION.

VAQTA is supplied in two formulations:

Pediatric/Adolescent Formulation: each 0.5 mL dose contains approximately 25 U of hepatitis A virus protein as the active ingredient.

Adult Formulation: each 1 mL dose contains approximately 50 U of hepatitis A virus protein as the active ingredient.

XIVb. Inactive Ingredients

Pediatric/Adolescent Formulation: each 0.5 mL dose contains 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 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.

XV. AVAILABILITY

Pediatric/Adolescent Formulation:

VAQTA Single Dose Vial (25 U/0.5 mL)

Adult Formulation:

VAQTA Single Dose Vial (50 U/1 mL)

XVI. STORAGE

Please refer to outer carton for storage conditions.

Product Owner:
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