PRODUCT INFORMATION

VAQTA®
(Hepatitis A Vaccine, Inactivated)

DESCRIPTION

VAQTA® (Hepatitis A Vaccine, Inactivated) is an inactivated whole virus vaccine derived from hepatitis A virus grown in cell culture in human MRC-5 diploid fibroblasts and has been shown to induce antibody to hepatitis A virus protein. 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, formalin inactivated, and then adsorbed onto aluminium hydroxide. One millilitre 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 µg of non-viral protein, less than 4×10^{-6} µg of DNA, less than 10^{-4} µg of bovine albumin and less than 0.8 µg of formaldehyde. Other process chemical residuals (including neomycin) are less than 10 parts per billion (ppb).

The manufacture of this product includes exposure to bovine related materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

VAQTA is supplied in two formulations:

Paediatric/Adolescent Formulation: Each 0.5 mL dose contains approximately 25 U of hepatitis A virus protein as the active ingredient and approximately 0.225 mg of aluminium provided as aluminium hydroxide, 35 µg of borax as a pH stabiliser, in 0.9% sodium chloride.

Adult Formulation: Each 1 mL dose contains approximately 50 U of hepatitis A virus protein as the active ingredient and approximately 0.45 mg of aluminium provided as aluminium hydroxide, 70 µg of borax as a pH stabiliser, in 0.9% sodium chloride.

PHARMACOLOGY

<u>Clinical Trials</u>

Clinical trials have been conducted worldwide with several formulations of the vaccine in 3159 children 12 to 23 months of age and 8361 healthy individuals ranging from 2 to 85 years of age.

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 ($\geq$ 10 mIU/mL of hepatitis A antibody) and with an anamnestic antibody response following booster vaccination with VAQTA.

Immunogenicity

In a clinical study, 96% of 471 children ~ 12 months of age seroconverted with a geometric mean titre of 48 mIU/mL within 6 weeks after the primary ~ 25 U intramuscular dose of VAQTA. After each dose of VAQTA, the hepatitis A antibody titres were comparable between children who were initially seropositive to hepatitis A and children who were initially seronegative to hepatitis A. These data suggest that maternal antibody to hepatitis A in children ~ 12 months of age does not affect the immune response to VAQTA.

In another study of children 12 through 15 months of age at entry, who received two ~ 25 U intramuscular doses of VAQTA 6 months apart with or without other vaccines, 100% (n=182; 95% CI: 98.0%, 100%) were seropositive within 4 weeks after the second dose of VAQTA given with other vaccines for both doses, and 99.4% (n=159, 95% CI: 96.5%, 100%) were seropositive within 4 weeks after a second dose of VAQTA only.

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, 96% of 1039 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 receive 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

The protective efficacy, immunogenicity, and safety of VAQTA were evaluated in a randomised, 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 modification of the HAVAB** radioimmunoassay [RIA]),

** Trademark of Abbott Laboratories

seroconversion was achieved in > 99% of vaccine recipients within 4 weeks after vaccination. The onset of seroconversion following a single dose of VAQTA was shown to parallel the onset of protection against clinical hepatitis A disease.

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

No studies of the efficacy of VAQTA in children < 2 years of age were performed. Use in this group is supported by immunogenicity data alone. The presence of hepatitis A antibody has been used as a correlate of protection, and similarity of the immune response has been established between ~ 12-month-old children and 2- to 3-year-old children.

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 most children and adolescents who participated in the Monroe Efficacy Study

Follow up surveillance, in over 880 vaccine recipients, for up to 9 years after termination of the study showed that VAQTA continued to confer complete protection against clinical hepatitis A disease despite a small number of documented cases in the community among non-vaccinated individuals visiting or residing there. To date, no cases of hepatitis A disease ≥ 50 days after vaccination have occurred in those vaccinees from the Monroe Efficacy Study monitored for up to 9 years.

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 an 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 a study 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. There are no data on persistence of antibody in children who commenced vaccination at 12 to 23 months of age.

*** 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 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 (n=171). After an initial decline over 2 to 3 years, the GMTs appeared to plateau and were stable at the last assessment 6 years after the initial dosing.

Follow-up of subjects in a study in children and adolescents (2 to 16 years of age) indicated:

- For subjects who received VAQTA at 0 and 6 months, 100% (175/175) of subjects remained seropositive (≥ 10 mIU anti-HAV/mL) with a GMT of 819 mIU/mL at 2.5 to 3.5 years, 100% (174/174) of subjects remained seropositive with a GMT of 505 mIU/mL at 5 to 6 years, and 100% (114/114) of subjects remained seropositive with a GMT of 574 mIU/mL at 10 years post vaccination.
- For subjects who received VAQTA at 0 and 12 months, 100% (49/49) of subjects remained seropositive with a GMT of 2224 mIU/mL at 2.5 to 3.5 years, 100% (47/47) remained seropositive with a GMT of 1191 mIU/mL at 5 to 6 years, and 100% (36/36) remained seropositive with a GMT of 1005 mIU/mL at 10 years post vaccination.
- For subjects who received VAQTA at 0 and 18 months, 100% (53/53) of subjects remained seropositive with a GMT of 2501 mIU/mL at 2.5 and 3.5 years, 100% (56/56) of subjects remained seropositive with a GMT of 1614 mIU/mL at 5 to 6 years, and 100% (41/41) remained seropositive with a GMT of 1507 mIU/mL at 10 years post vaccination

Follow-up of subjects in a study in adults (18-41 years of age) who received VAQTA at 0 and 6 months indicated:

- 100% (378/378) subjects remained seropositive with a GMT of 1734 mIU/mL at 1 year postvaccination,
- 99.2% (252/254) of subjects remained seropositive with a GMT of 687 mIU/mL at 2 to 3 years postvaccination,
- 99.1% (219/221) of subjects remained seropositive with a GMT of 605 mIU/mL at 4 years postvaccination, and
- 99.4% (170/171) of subjects remained seropositive with a GMT of 684 mIU/mL at 6 years post vaccination.

Follow-up of subjects in a study in children and adolescents (2 to 17 years of age) who received VAQTA at 0 and 6 months indicated:

- 99.7% (307/308) subjects remained seropositive with a GMT of 2424 mIU/mL at 1 year postvaccination,
- 99.6% (275/276) of subjects remained seropositive with a GMT of 1022 mIU/mL at 2 to 3 years postvaccination,
- 100% (267/267) of subjects remained seropositive with a GMT of 881 mIU/mL at 4 years postvaccination, and
- 100% (220/220) of subjects remained seropositive with a GMT of 927 mIU/mL at 6 years post vaccination.

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 modeling 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 of 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$^{\Sigma}$ (hepatitis A vaccine, inactivated) given at 6 or 12 months following an initial dose of HAVRIX$^{\Sigma}$. When VAQTA was given as a booster dose following HAVRIX$^{\Sigma}$, 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$^{\Sigma}$ Seropositivity Rate, Booster Response Rate† and Geometric Mean Titre at 4 Weeks Postbooster

First Dose	Booster Dose	Seropositivity Rate	Booster Response Rate†	Geometric Mean Titre
HAVRIX$^{\Sigma}$ 1440 EL.U.	VAQTA 50 U	99.7% (n=313)	86.1% (n=310)	3272 (n=313)
HAVRIX$^{\Sigma}$ 1440 EL.U.	HAVRIX$^{\Sigma}$ 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 titre and postbooster titre $\geq$ 100 mIU/mL.

Use With Other Vaccines

A concomitant use study was conducted among 617 healthy children who were randomised to receive VAQTA (~ 25 U) with or without M-M-R II® [Measles, Mumps, and Rubella Virus Vaccine Live] and VARIVAX® [Varicella Virus Vaccine Live (Oka/Merck)] at ~ 12 months of age, and VAQTA (~ 25 U) with or without DTaP (Diphtheria, Tetanus, and acellular Pertussis) vaccine (and an optional dose of polio vaccine) at ~ 18 months of age. In this study, the concomitant administration of VAQTA with other vaccines at separate injection sites was generally well tolerated. The safety profile of VAQTA administered alone at ~ 12 months and ~ 18 months of age was comparable to the safety profile of VAQTA administered alone to children 2 to 16 years of age. The safety profile of the concomitant administration of VAQTA with other vaccines at ~ 12 months and ~ 18 months of age was comparable to the safety profile of VAQTA administered alone at ~ 12 months and ~ 18 months of age.

The hepatitis A response rates after each dose of VAQTA when VAQTA was given alone or concomitantly with M-M-R II and VARIVAX or DTaP and an optional dose of polio vaccine were similar. The hepatitis A response rates also were similar to predefined historical rates seen in 2- to 3-year-old children administered VAQTA alone. When VAQTA was administered concomitantly with M-M-R II and VARIVAX, the measles, mumps, and rubella response rates were similar to the historical rates for M-M-R II. VAQTA may be given concomitantly at separate injection sites with M-M-R II. Immunogenicity data are insufficient to support concomitant administration of VAQTA with DTaP. The immune responses to polio vaccine co-administered with VAQTA are not available (See DOSAGE AND ADMINISTRATION, *Use With Other Vaccines*.).

$^{\Sigma}$ Trademark of GlaxoSmithKline, Philadelphia, PA, U.S.A

In a clinical trial involving 653 healthy children 12 to 15 months of age, 330 were randomised to receive VAQTA (~ 25 U), ProQuad [Measles, Mumps, Rubella and Varicella (Oka/Merck) Virus Vaccine Live, MSD], and Prevenar (Pneumococcal 7-valent Conjugate Vaccine) concomitantly, and 323 were randomised to receive ProQuad and Prevenar concomitantly followed by VAQTA 6 weeks later. The seropositivity rate after 2 doses of VAQTA given concomitantly with ProQuad and Prevenar was 100% [95% CI: 98.0%, 100.0%] and for VAQTA given without ProQuad and Prevenar was 99.4% [95% CI: 96.5%, 100.0%]. Hepatitis A response was similar among the two groups who received VAQTA with or without ProQuad and Prevenar. Seroconversion rates and antibody titers for varicella and *S. pneumoniae* types 4, 6B, 9V, 14, 18C, 19F, and 23F were similar between the groups at 6 weeks post-vaccination.

For the varicella component of ProQuad, in subjects with baseline antibody titres < 1.25 gpELISA units/mL, the observed seroprotection rate per protocol population (the population with a titre ≥ 5 gpELISA units/mL) was reported as 93.3% (95% CI: [89.2%, 96.2%]) when VAQTA was given concomitantly with ProQuad and Prevnar, compared with 98.3% (95% CI: [95.6%, 99.5%]) when ProQuad and Prevnar were given concomitantly followed by VAQTA 6 weeks later.

In a clinical trial involving 1800 healthy children 12 to 23 months of age, 1453 received two ~ 25 U intramuscular doses of VAQTA, and 347 were randomised to receive two ~ 25 U intramuscular doses of VAQTA concomitantly with 2 doses of ProQuad at least 6 months apart. Rates of solicited injection-site reactions (pain/tenderness, erythema, swelling) were higher than prior experience with VAQTA in 12- to 23-month-old children. Among all subjects, fever [> 98.6˚F (> 37˚C) or feverish] was the most common systemic adverse event and injection-site pain/tenderness was the most common injection-site reaction.

A controlled clinical study was conducted with 240 healthy adults, 18 to 54 years of age, who were randomised 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.

The immune response to polio vaccine, haemophilus influenzae type b (HIB) conjugate vaccine, and meningococcal polysaccharide vaccine co-administered with VAQTA are not available (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 was100%, and the GMT was 1564 mIU/mL. The SPR and GMT measured 4 weeks after the first dose and the GMT after the second dose were lower than has historically been seen after intramuscular injection. At 24 weeks after the first dose, prior to the booster dose, the SPR was similar to that seen after intramuscular injection. Patients receiving VAQTA by subcutaneous injection should be advised that protection from infection is not reliably achieved until 24 weeks after the first dose. Subcutaneous injection was associated with a 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 $\geq$ 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.

INDICATIONS

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

Individuals who are or will be at increased risk of infection include:

- Travellers to areas of intermediate or high endemicity for hepatitis A.
- Persons for whom Hepatitis A is an occupational hazard.

  Employees of child day-care centres

  Certain institutional workers (e.g. caretakers for the intellectually disabled)

  Health workers and teachers in remote Aboriginal and Torres Strait Islander communities

  Nursing staff and other health care workers in contact with patients in paediatric wards and infectious disease wards

  Sewerage workers
- Recipients of blood products
- Individuals with chronic liver disease and those who have had a liver transplant.
- Homosexually active males.
- Human Immunodeficiency Virus (HIV)-Infected Adults

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine.

PRECAUTIONS

General

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 unrecognised 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 adrenaline, should be available for immediate use should an anaphylactic or anaphylactoid reaction occur.

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.

VAQTA should be administered with caution to people with bleeding disorders who are at risk of haemorrhage following intramuscular injection

VAQTA may be administered subcutaneously when clinically appropriate (e.g. people with bleeding disorders who are at risk of haemorrhage), although the kinetics of seroconversion are slower for the first subcutaneous dose of VAQTA compared with historical data for intramuscular administration.

Carcinogenicity, mutagenicity and impairment of fertility

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

Use in Pregnancy (Category B2)

Animal reproduction studies have not been conducted with VAQTA. It is also not known whether VAQTA can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. VAQTA should be given to a pregnant woman only if clearly needed.

Use in Lactation

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.

Paediatric Use

VAQTA has been shown to be generally well-tolerated and highly immunogenic in individuals 12 months to 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.

Interactions with Other Drugs

Use With Immune Globulin

For subjects requiring post exposure prophylaxis or combined immediate and longer term protection (eg. travellers departing on short notice to endemic areas), VAQTA may be administered concomitantly with IG using separate sites and syringes. Results from one clinical trial in adults support this regimen (see PHARMACOLOGY, Immunogenicity).

Use with Other Vaccines

VAQTA may be given concomitantly with yellow fever, typhoid, measles, mumps, rubella, varicella and pneumococcal 7-valent conjugate vaccines (see Pharmacology, Use with other vaccines and Adverse Reactions).

Immunogenicity data are insufficient to support concomitant administration of VAQTA with DTaP. Data on concomitant use with other vaccines are limited (see PHARMACOLOGY, Use with Other Vaccines).

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

The Advisory Committee on Immunisation 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 simultaneously with hepatitis A vaccine without affecting either vaccine's immunogenicity or increasing the frequency of adverse events.

Effects on Ability to Drive and Operate Machinery

There were no specific data. However, asthenia/fatigue, and headache have been reported following administration of VAQTA.

ADVERSE REACTIONS

Clinical Trials

In combined clinical trials, VAQTA was administered to 3159 children 12 to 23 months of age, and 8361 healthy children, adolescents and adults and was generally well tolerated.

The Monroe Efficacy Study

In The Monroe Efficacy Study, 1037 healthy children and adolescents 2 to 16 years of age received either a primary dose of ~ 25 U 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, were the most frequently reported complaints. Table 3 summarises the local and systemic complaints (≥ 1%) reported in this study, without regard to causality. There were no significant differences in the rates of any complaint between vaccine and placebo recipients after Dose 1.

Table 3

Local and Systemic Complaints (≥ 1%)
Healthy Children and Adolescents from
The Monroe Efficacy Study

Reaction	VAQTA		Placebo*#
	Dose 1*	Booster	
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 difference between the two groups.

\# Second injection of placebo not administered because code for the trial was broken

Children – 12 Months to 23 Months of Age
In combined clinical trials involving 706 healthy children ,12 to 23 months of age, who received one or more ~ 25 U doses of hepatitis A vaccine with or without other paediatric vaccines, subjects were followed for fever and local complaints during a 5-day period post-vaccination and systemic complaints during a 14-day period post-vaccination. Irritability and upper respiratory infection were the most frequently reported complaints. Localised injection-site complaints were generally mild and transient. Table 4 summarises the local and systemic complaints (≥ 1%) reported in these studies, without regard to causality, in decreasing order of frequency, within each body system.

Table 4

Local and Systemic Complaints (≥ 1%)
Healthy Children (12 months to 23 months) Who
Received One or More ~ 25 U Doses of Hepatitis A vaccine

Reaction	**VAQTA ~ 25 U (n=706) Percent**
Localised Injection Site Reactions	
Pain/tenderness/soreness	8.6
Erythema	5.9
Swelling	5.1
Warmth	3.2
Ecchymosis	1.0
Body as a Whole	
Fever (≥38.9^{0}C, Oral)	6.5
Digestive System	
Diarrhoea	5.9
Vomiting	4.0
Anorexia	1.2
Nervous System/Psychiatric	
Irritability	10.8
Crying	1.8
Respiratory System	
Upper respiratory infection	10.1
Rhinorrhoea	5.7
Cough	5.1
Respiratory congestion	1.6
Nasal congestion	1.2
Laryngotracheobronchitis	1.2
Skin and Skin Appendages	
Rash	4.5
Measles-like/rubella-like rash	1.0
Viral exanthema	1.0
Special Senses	
Otitis media	7.6
Otitis	1.8
Conjunctivitis	1.3

Concomitant use with ProQuad – (see Pharmacology, Use with other vaccines)
In a clinical trial involving 1800 healthy children 12 to 23 months of age, 1453 received two ~ 25 U intramuscular doses of VAQTA (including 1101 non-randomised and 352 randomised), and 347 were randomised to receive two ~ 25 U intramuscular doses of VAQTA concomitantly with 2 doses of ProQuad at least 6 months apart. Among all subjects, fever [> 98.6˚F (> 37˚C) or feverish] was the most common systemic adverse event and injection-site pain/tenderness was the most common injection-site adverse reaction.

Based on a post-hoc analysis, the rate of fever (> 98.6˚F (> 37.0˚C) or feverish) after any dose of VAQTA was increased in subjects who received VAQTA with ProQuad as compared to VAQTA alone in the 14 days after vaccination {risk difference (11.8% [95% CI: 6.8, 17.2]) and relative risk (1.72 [95% CI: 1.40, 2.12])}. The difference in rate of fever (> 98.6˚F (> 37˚C) or feverish) was higher after Dose 1 (11.5%) as compared to Dose 2 (4.0%). The rates of fever ≥ 100.4˚F (≥ 38.0˚C) and ≥ 102.2˚F (≥ 39.0˚C) in the 5 days after any dose of VAQTA were similar in both treatment groups.

Concomitant use with ProQuad and Pneumoccal 7-valent Conjugate Vaccine [Prevnar] – (see Pharmacology, Use with other vaccines)
In a clinical trial involving 653 healthy children 12 to 15 months of age, 330 were randomised to receive the first dose of VAQTA (~ 25 U), the first dose of ProQuad [Measles, Mumps, Rubella and Varicella (Oka/Merck) Virus Vaccine Live, MSD] and the fourth dose of Prevnar (Pneumococcal 7-valent Conjugate Vaccine) concomitantly on day 1; these subjects received the second doses of VAQTA and ProQUAD at week 24 or later. The remaining 232 subjects were randomised to receive their first dose of ProQuad and fourth dose of Prevnar concomitantly on day 1, followed by the first dose of VAQTA 6 weeks later; these subjects received a second dose of VAQTA at week 30 or later, and a second dose of ProQuad at week 34 or later. Subjects in both study groups received the second dose of VAQTA at least 24 weeks after their first dose. Among all subjects, fever (> 98.6ºF or feverish) was the most common systemic adverse event, and injection-site pain/tenderness was the most common injection-site adverse reaction.

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

In the 28 days after vaccination, the administration of Dose 1 of VAQTA with Dose 1 of ProQuad and Dose 4 of pneumococcal 7-valent conjugate vaccine does not increase incidence rates of fever (fever (> 98.6˚F or feverish) as compared to when ProQuad is administered with pneumococcal 7-valent conjugate vaccine alone {38.6% and 42.7%, respectively; relative risk (0.9 [95% CI: 0.75, 1.09])} in post-hoc analysis. Similarly, the administration of Dose 2 of VAQTA with Dose 2 of ProQuad does not increase incidence rates of fever (> 98.6ºF or feverish) as compared to when Dose 2 of ProQuad is administered alone {17.4% and 17.0%, respectively; relative risk (1.02 [95% CI: 0.70, 1.51])}.

Children/Adolescents - 2 to 17 Years of Age

In combined clinical trials (including Monroe Efficacy Study participants) involving 2595 healthy children (≥ 2 years of age) and adolescents who received one or more ~ 25 U doses of hepatitis A vaccine, subjects were followed for fever and local complaints during a 5-day period post-vaccination and systemic complaints during a 14-day period post-vaccination. Injection-site complaints, generally mild and transient, were the most frequently reported complaints. Table 5 summarises the local and systemic complaints (≥ 1%) reported in these studies, without regard to causality.

Table 5

Local and Systemic Complaints (≥ 1%)
Healthy Children (2 to 17 years) and Adolescents Who
Received One or More ~ 25 U Doses of Hepatitis A vaccine

Reaction	**VAQTA ~ 25 U (n = 2595) Percent**
Localised Injection Site Reactions	
Pain	18.5
Tenderness	16.7
Warmth	8.5
Erythema	7.4
Swelling	7.2
Ecchymosis	1.3
Body as a Whole	
Fever (≥38.9^{0}C, Oral)	3.1
Abdominal Pain	1.5
Digestive System	
Diarrhoea	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 Over

In combined clinical trials involving 1315 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 post-vaccination and systemic complaints during a 14-day period post-vaccination. Injection-site complaints, generally mild and transient, were the most frequently reported complaints. Table 6 summarises the local and systemic complaints (≥ 1%) reported in these studies, without regard to causality.

Table 6

Local and Systemic Complaints (≥ 1%)
Healthy Adults Who Received One or
More ~ 50 U Doses of Hepatitis A vaccine

Reaction	VAQTA ~ 50 U (n = 1315) Percent
Localised Injection Site Reactions	
Tenderness	43.2
Pain	41.5
Warmth	11.1
Swelling	9.6
Erythema	9.4
Ecchymosis	1.3
Pain/Soreness	1.0
Body as a Whole	
Asthenia/Fatigue	3.0
Fever (≥38.3^{0}C, Oral)	1.9
Abdominal Pain	1.3
Digestive System	
Diarrhoea	2.0
Nausea	2.0
Musculoskeletal System	
Myalgia	1.7
Nervous System/Psychiatric	
Headache	11.6
Respiratory System	
Pharyngitis	2.6
Upper respiratory infection	2.4

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 diarrhoea/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.

HAEMIC AND LYMPHATIC SYSTEM
Very rarely, thrombocytopenia.

DOSAGE AND ADMINISTRATION

DO NOT INJECT INTRAVASCULARLY OR INTRADERMALLY

VAQTA is for intramuscular injection. The *deltoid muscle* is the preferred site for intramuscular injection. While intramuscular injection results in the best immune response, VAQTA may be administered subcutaneously when clinically appropriate (see Precautions).

VAQTA does not contain a preservative. The vials and prefilled syringes are for use in a single patient only and any residual vaccine must be discarded.

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

Children/Adolescents-12 months to 17 years of age

Individuals 12 months to 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 and pneumococcal 7-valent conjugate vaccines (see Pharmacology, Use with other vaccines and Adverse Reactions).

Immunogenicity data are insufficient to support concomitant administration of VAQTA with DTaP. Data on concomitant use with other vaccines are limited (See Interactions with Other Drugs: Use with Other Vaccines.).

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

Known or Presumed Exposure to Hepatitis A Virus/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 manufacturers product information for the appropriate dosage of IG. A booster dose of VAQTA should be administered at the appropriate time as outlined above (see PRECAUTIONS: Interactions with Other Drugs).

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 discolouration 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.

OVERDOSAGE

Contact the Poisons Information Centre (tel: 131126) for advice regarding the management of overdose.

STORAGE

Store the vaccine at 2-8°C. Storage above or below the recommended temperature may reduce potency.

DO NOT FREEZE since freezing destroys potency.

PRESENTATION

VAQTA is a sterile suspension for intramuscular use and is available as single dose vials and prefilled syringes of vaccine.

NAME AND ADDRESS OF THE SPONSOR

Merck Sharp & Dohme (Australia) Pty. Limited,
Level 1, Building A, 26 Talavera Road,
Macquarie Park NSW 2113

DISTRIBUTOR

bioCSL Pty Ltd.,
63 Poplar Road, Parkville, Victoria, 3052

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