Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

VAQTA Adult 50 U/1 ml, suspension for injection in a prefilled syringe. Hepatitis A vaccine, inactivated, adsorbed. For adults

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (1mL) contains:

Hepatitis A virus (strain CR 326F) (inactivated) [1, 2] .....50 U [3]

1 Produced on human diploid (MRC–5) fibroblast cells.
2 Adsorbed on amorphous aluminium hydroxyphosphate sulphate (0.45 mg Al^{3+}).
3 Units measured according to the in-house method of the manufacturer-Merck Sharp & Dohme LLC

This vaccine may contain traces of neomycin and formaldehyde, which are used during the manufacturing process. See sections 4.3 and 4.4.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension for injection in a prefilled syringe.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

VAQTA 50 U/1 mL is indicated for active pre-exposure prophylaxis against disease caused by hepatitis A virus. VAQTA 50 U/1 mL is recommended for healthy adults 18 years 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., those with Human Immunodeficiency Virus [HIV] or hepatitis C with diagnosed liver disease).

The use of VAQTA should be based on official recommendations.

For optimal antibody response, primary immunization should be given at least 2, preferably 4 weeks prior to expected exposure to hepatitis A virus.

VAQTA will not prevent hepatitis caused by infectious agents other than hepatitis A virus.

4.2 Posology and method of administration

Posology

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

Primary dose:
Adults 18 years of age and older should receive a single 1.0 mL (50 U) dose of vaccine at an elected date.

Booster dose:
Adults 18 years of age and older who received a primary dose should receive a booster dose of 1.0 mL (50 U) 6 to 18 months after the first dose.

Hepatitis A virus (HAV) antibodies persist for at least 6 years after the second dose (i.e. booster). Based on mathematic modeling duration of antibody persistence is predicted for at least 25 years (see section 5.1).

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. (See section 5.1.)

Adults with HIV
HIV-infected adults should receive a single dose of 1.0 mL (50 U) at elected date followed by a booster dose of 1.0 mL (50 U) 6 months later.

Paediatric population
There is a paediatric formulation available for children and adolescents. For details please refer to the Summary of Product Characteristics of VAQTA 25 U/0.5 mL.

Method of administration

VAQTA should be injected INTRAMUSCULARLY in the deltoid region. The vaccine should not be administered intradermally since administration by this route may result in a less than optimal response.

For individuals with bleeding disorders who are at risk of haemorrhage following intramuscular injection (e.g., haemophiliacs), this vaccine may be administered subcutaneously (see section 5.1).

Precautions to be taken before handling or administering the medicinal product
For instructions on preparation of the medicinal product before administration, see section 6.6.

4.3 Contraindications

History of hypersensitivity to the active substances, to any of the excipients listed in section 6.1, to neomycin or to formaldehyde (which may be present as trace residues, see sections 2 and 4.4).
Vaccination should be delayed in subjects with current severe febrile infections.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Individuals who develop symptoms suggestive of hypersensitivity after an injection of VAQTA should not receive further injections of the vaccine. This vaccine may contain traces of neomycin and formaldehyde which are used during the manufacturing process (see sections 2 and 4.3).

VAQTA must not be administered into a blood vessel.

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

Qualitative testing for antibodies to hepatitis A prior to immunization should be considered based on the probability of previous hepatitis A virus infection in patients who grew up in areas of high endemicity, and/or with a history of jaundice.

VAQTA does not cause immediate protection against hepatitis A, and there may be a period of 2 to 4 weeks before antibody becomes detectable.

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

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.

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

Excipient(s) with known effect:
This medicinal product contains less than 1mmol (23mg) sodium per dose and is considered to be essentially sodium free.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Known or presumed exposure to HAV/Travel to endemic areas
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), in countries where IG is available VAQTA may be administered concomitantly with IG using separate sites and syringes. Although the antibody titer obtained is likely to be lower than when the vaccine is given alone. The clinical relevance of this observation has not been established.

Use with other vaccines
VAQTA may be given concomitantly at separate injection sites with yellow fever and polysaccharide typhoid vaccines (see section 5.1). Though data in subjects 18 years of age and older are not available, studies in children 12 through 23 months of age have shown that VAQTA may be administered concomitantly with measles, mumps, rubella, varicella, pneumococcal 7-valent conjugate, and inactivated polio vaccines. Immunogenicity data are insufficient to support concomitant administration of VAQTA with DTaP (Diphtheria, Tetanus and acellular Pertussis).

Interaction studies other than with yellow fever and polysaccharide typhoid vaccines are not yet available; however, interactions with other vaccines are not anticipated when vaccines are administered at different injection sites. When concurrent administration is necessary, VAQTA must not be mixed with other vaccines in the same syringe, and other vaccines should be administered at different sites.

4.6 Fertility, pregnancy and lactation

Pregnancy
It is not known whether VAQTA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. VAQTA is not recommended in pregnancy unless there is a high risk of hepatitis A infection, and the attending physician judges that the possible benefits of vaccination outweigh the risks to the fetus.

Breastfeeding
It is not known whether VAQTA is excreted in human milk and the effect on breast-fed infants following administration of VAQTA to mothers has not been studied. Hence, VAQTA should be used with caution in women who are breast-feeding.

Fertility
VAQTA has not been evaluated in fertility studies.

Animal reproduction studies have not been conducted with VAQTA.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, VAQTA is expected to have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

In clinical trials with 1,529 healthy adults who received one or more doses of hepatitis A vaccine, subjects were followed for elevated temperature and local reactions during a 5-day period postvaccination and systemic adverse events including fever during a 14-day period postvaccination. Injection-site reactions, generally mild and transient, were the most frequently reported adverse events.

Post-marketing safety study
In a post-marketing safety study, a total of 29,587 individuals ≥18 years of age received 1 or 2 doses of VAQTA. There was no serious vaccine-related adverse event identified. There was no non serious vaccine-related adverse event resulting in outpatient visits, with the exception of diarrhea/gastroenteritis in adults at a rate of 0.5%.

Tabulated summary of adverse reactions

The table presents adverse reactions reported as vaccine related observed in clinical trials, and in a post-authorisation safety study and adverse reactions spontaneously reported after use of the marketed vaccine.

Adverse reactions are ranked under headings of frequency using the following convention:
[Very Common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Not Known (cannot be estimated from the available data)].

System Organ Class	Frequency	Adverse reactions
Infections and infestations	Uncommon	Pharyngitis, Upper respiratory infection
	Rare	Bronchitis, Infectious gastroenteritis
Blood and lymphatic system disorders	Uncommon	Lymphadenopathy
	Not Known	Thrombocytopenia[2]

Metabolism and nutrition disorders	Rare	Anorexia
Psychiatric disorders	Rare	Apathy, Insomnia
Nervous system disorders	Common	Headache
	Uncommon	Dizziness, Paresthesia
	Rare	Somnolence, Migraine, Tremor
	Not Known	Guillain-Barré syndrome[2]
Eye disorders	Rare	Itching eye, Photophobia, Tearing
Ear and labyrinth disorders	Uncommon	Ear pain
	Rare	Vertigo
Vascular disorders	Uncommon	Hot flashes
Respiratory, thoracic and mediastinal disorders	Uncommon	Respiratory congestion, Nasal congestion, Cough
	Rare	Pharyngeal edema, Sinus disorder
Gastrointestinal disorders	Uncommon	Nausea, Diarrhea/ Gastroenteritis[1], Flatulence, Vomiting
	Rare	Dry mouth, Mouth ulcer
Skin and subcutaneous tissue disorders	Uncommon	Pruritus, Urticaria, Erythema
	Rare	Night sweats, Rash, Skin disorder
Musculoskeletal and connective tissue disorders	Common	Arm pain (in the injected arm)
	Uncommon	Myalgia, Stiffness, Shoulder pain, Musculoskeletal pain, Back pain, Arthralgia, Leg pain, Neck pain, Muscle weakness
	Rare	Muscle cramp, Elbow pain, Hip pain, Jaw pain, Spasm
Reproductive system and breast disorders	Rare	Menstruation disorder
General disorders and administrative site conditions	Very Common	Injection-site tenderness, Pain, Warmth, Swelling, Erythema
	Common	Asthenia/Fatigue, Fever (≥38.3°C, Oral) Injection-site ecchymosis, Pain/Soreness
	Uncommon	Injection-site pruritus, Stiffness/Tightness, Pain, Injection-site hematoma, Chills, Abdominal pain, Malaise, Injection-site induration and numbness, Cold sensation, Flu-like illness
	Rare	Injection-site burning, Induration (≤2.5 centimeters), Muscle twitching, Rash, Abdominal distention, Chest pain, Flank pain, Irritability

[1] Post-authorisation safety study
[2] Spontaneous reporting after use of marketed vaccine

Description of selected adverse reactions

As with all vaccines, allergic reactions, in rare cases leading to shock, may occur (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

There are no data with regard to overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: viral vaccines, hepatitis A, inactivated, whole virus
ATC code: J07BC02

VAQTA contains inactivated virus of a strain which was originally derived by further serial passage of a proven attenuated strain. The virus is grown, harvested, highly purified, formalin inactivated, and then adsorbed onto amorphous aluminum hydroxyphosphate sulfate. 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 x 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).

Mechanism of action
Hepatitis A vaccine elicits circulating neutralising antibodies to Hepatitis A virus sufficient to confer protection against the virus.

Clinical efficacy and safety
Clinical studies showed seroconversion rates were 95% in adults within 4 weeks after the recommended primary dose. In a sub-set of these individuals ≥60 years of age, data indicate that 88% (n=64) seroconverted by week 4 after the primary dose.

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 50 U given 6 to 18 months after the primary dose to adults. The data regarding the subjects more than 60 years of age are limited.
Antibody persistence
In studies of healthy adults (18 to 41 years of age) who received an initial 50 U dose of VAQTA at Day 0 and a subsequent 50 U dose 6 months later, the hepatitis A antibody response to date has been shown to persist to at least 6 years. After an initial decline over 2 years, the GMTs appeared to plateau during the 2 to 6 year period.

Data available from long-term studies up to 10 years on the persistence of HAV antibodies after 2 doses of VAQTA in healthy, immunocompetent subjects up to 41 years of age allows prediction that based on mathematical modeling at least 99% of subjects will remain seropositive (≥10 mIU anti-HAV/ml) at least 25 years after vaccination.

Based on this analysis, an additional vaccination following complete primary immunisation with 2 doses appears to be unnecessary. However, decisions regarding additional vaccination should be based on risk-benefit for the individual.

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 a comparable licensed inactivated hepatitis A vaccine given at 6 or 12 months following initial dose of the comparator vaccine. When VAQTA was given as a booster dose in this case it produced an equivalent immune response and was generally well tolerated. (See section 4.2.)

Concomitant use with immunoglobulin
Concurrent administration to healthy adults (18 to 39 years of age) of 50 U/1.0 mL of VAQTA with immunoglobulin (IG, 0.06 mL/kg) was evaluated in a clinical study. The seroconversion rate at week 24 in the vaccine alone group (97%) was higher than in the vaccine plus IG group (92% p = 0.050) but rose to 100% in both groups one month post booster.

Concomitant 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, yellow fever and polysaccharide typhoid vaccines concomitantly at separate injection sites or
- yellow fever and polysaccharide typhoid vaccines concomitantly at separate injection sites or
- VAQTA alone.

The seropositivity rate (SPR) for hepatitis A when VAQTA, yellow fever and polysaccharide typhoid vaccines were administered concomitantly was generally similar to when VAQTA was given alone. However the GMTs for hepatitis A were reduced when the three vaccines were administered concomitantly. Clinically, this reduction in GMTs may be less relevant compared to the benefits of concomitant administration. The antibody response rates for yellow fever and typhoid were equivalent when yellow fever and polysaccharide 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 addition of VAQTA to the standard practice of administering yellow fever and typhoid vaccines does not increase the rates of injection site and systemic adverse reactions. (See section 4.2.)

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 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 1,564 mIU/mL; the GMT was 2,287 mIU/mL in subjects less than 30 years of age compared with a GMT of 1,122 mIU/mL in subjects 30 years of age and older. 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.

Administration in HIV-infected adults
In a clinical study with 180 adults, 60 HIV-positive (20 to 45 years of age) and 90 HIV-negative adults (21 to 53 years of age) received VAQTA (50 U) and 30 HIV-positive adults (22 to 45 years of age) 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 1,060 mIU/mL) in HIV-positive and 100% (GMT of 3,602 mIU/mL) in HIV-negative adults. Furthermore, in the HIV-positive group receiving VAQTA, the SPR was 100% (GMT of 1,959 mIU/mL) in subjects with CD4 cell counts ≥300 cell/mm≥ ; however, the SPR was 87% (GMT of 517 mIU/mL) in subjects with CD4 cell counts <300 cell/mm≥ . Three HIV-positive adults with CD4 cell counts <100 cells/mm≥ did not seroconvert after receipt of 2 doses of vaccine. The kinetics of the immune response were slower in the HIV-positive group compared with the HIV-negative group. There was an increased rate of local and systemic adverse effects reported in HIV-positive versus HIV-negative adults. In HIV-positive adults, administration of VAQTA did not appear to adversely affect the CD4 cell counts and HIV RNA burden.

Post-marketing safety study
In a post-marketing safety study, conducted at a large health maintenance organization in the United States, a total of 29,587 individuals ≥18 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 29,587 individuals in this study. There was no non-serious, 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.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

No preclinical safety testing was performed using the vaccine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium borate
Sodium chloride
Water for injections
For adjuvant and for information regarding residual components in trace quantities, see sections 2, 4.3 and 4.4.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C)

DO NOT FREEZE since freezing destroys potency.

6.5 Nature and contents of container

1 mL suspension in a pre-filled syringe (type I glass) with plunger-stopper (chlorobutyl isoprene blend or bromobutyl).

1 mL suspension in a pre-filled syringe (type I glass) with plunger-stopper (chlorobutyl isoprene blend or bromobutyl), without needle, with a tip-cap (chlorobutyl isoprene blend or bromobutyl isoprene blend), with 0, 1 or 2 separate needles.

Pack sizes: Pack of 1 syringe.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

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

Shake well before use. Thorough agitation is necessary to maintain suspension of the vaccine. For syringe without attached needle, hold the syringe barrel and attach the needle by twisting in clockwise direction until the needle fits securely on the syringe.

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ireland (Human Health) Limited
Red Oak North
South County Business Park
Leopardstown

Dublin 18
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1286/056/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th December 1996

Date of last renewal: 21st December 2005

10 DATE OF REVISION OF THE TEXT

December 2022