Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

VAQTA Paediatric 25 U/0.5 mL, suspension for injection in a prefilled syringe. Hepatitis A vaccine, inactivated, adsorbed. For children and adolescents

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5mL) contains:
Hepatitis A virus (strain CR 326F) (inactivated) [1, 2] .....25 U [3]

[1] Produced on human diploid (MRC–5) fibroblast cells.
[2] Adsorbed on amorphous aluminium hydroxyphosphate sulphate (0.225 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 25 U/0.5 mL is indicated for active pre-exposure prophylaxis against diseasecaused by hepatitis A virus. VAQTA 25 U/0.5 mL is recommended for healthy individuals from 12 months of age to 17 years of age 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).

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:
Individuals 12 months through 17 years of age should receive a single 0.5 mL (25 U) dose of vaccine at an elected date.

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

Booster dose:
Individuals who received a primary dose at 12 months through 17 years of age should receive a booster dose of 0.5 mL (25 U) 6 to 18 months after the first dose.

Hepatitis A virus (HAV) antibodies persist for at least 10 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 as shown by data for adults, 18 to 83 years of age; no such data are available for VAQTA (25 U/0.5 mL) presentation.

Method of administration
VAQTA should be injected INTRAMUSCULARLY. The deltoid muscle is the preferred site for injection. The anterolateral thigh region may be used in infants if the deltoid muscle is not sufficiently developed. The vaccine should not be administered subcutaneously or intradermally since administration by these routes 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) other measures can be taken such as intramuscular administration of the vaccine after anti-haemophilia or other similar therapy, or applying pressure. This vaccine may be administered subcutaneously to these subjects.

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.

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.

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

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
Hepatitis A response has been shown to be similar when VAQTA was given alone or concomitantly with measles, mumps, rubella, varicella, pneumococcal 7-valent conjugate, inactivated polio, diphtheria toxoid, tetanus toxoid, acellular pertussis, or *Haemophilus influenzae* b vaccine. Responses to measles, mumps, rubella, varicella, pneumococcal 7-valent conjugate, inactivated polio, diphtheria toxoid, tetanus toxoid, acellular pertussis, and *Haemophilus influenzae* b were not affected by concomitant administration with VAQTA. Studies in adults 18 to 54 years of age have shown that VAQTA may be administered concomitantly with yellow fever and polysaccharide typhoid vaccines.

VAQTA must not be mixed with other vaccines in the same syringe. When concurrent administration is necessary, different injection sites and separate syringes must be used for each vaccine.

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.

Breast-feeding
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

Children 12 months through 23 months of age
In 5 combined clinical trials, 4,374 children 12 through 23 months of age received one or two 25U doses of VAQTA. Out of the 4,374 children who received VAQTA, 3,885 (88.8%) children received 2 doses of VAQTA and 1,250 (28.6%) children received 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 including fever during a 14-day period postvaccination.

In three of the five protocols which specifically prompted for injection-site erythema, pain/tenderness, and swelling daily for Day 1 through Day 5 postvaccination, the most frequently reported injection-site adverse reaction after any dose of VAQTA was injection-site pain/tenderness.

The most common systemic adverse events among recipients of VAQTA alone were fever and irritability. The data from the five protocols were combined as similar methods for collecting systemic adverse events were used.

Children/adolescents (2 years through 17 years of Age)
In clinical trials with 2,595 healthy children (≥2 years of age) and adolescents 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.
Adverse reactions reported as vaccine related are listed below in decreasing order of frequency within each system organ classification.

Post-marketing safety study
In a post-marketing safety study, a total of 12,523 individuals 2 through 17 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.

Tabulated summary of adverse reactions
The tables below present 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)]
Children 12 months through 23 months of age

System Organ Class	Frequency	Adverse Reactions
Blood and lymphatic system disorders	Not Known	Thrombocytopenia[1]
Immune system disorders	Rare	Multiple allergies
Metabolism and nutrition disorders	Uncommon	Decreased appetite,Anorexia
	Rare	Dehydration
Psychiatric disorders	Uncommon	Insomnia, Restlessness
	Rare	Agitation, Nervousness, Phobia, Screaming, Sleep disorder
Nervous system disorders	Uncommon	Somnolence, Crying, Lethargy, Hypersomnia, Poor quality sleep
	Rare	Dizziness, Headache, Ataxia
	Not Known	Guillain-Barré syndrome[1]
Eye disorders	Rare	Eyelid margin crusting
Respiratory, thoracic and mediastinal disorders	Uncommon	Rhinorrhea, Cough, Nasal congestion
	Rare	Respiratory tract congestion, Sneezing, Asthma, Allergic rhinitis, Oropharyngeal pain
Gastrointestinal disorders	Common	Diarrhea
	Uncommon	Vomiting
	Rare	Flatulence, Abdominal distension, Upper abdominal pain, Faeces discolored, Frequent bowel movements, Nausea, Stomach discomfort, Constipation, Eructation, Infantile spitting up
Skin and subcutaneous tissue disorders	Uncommon	Rash, Dermatitis diaper
	Rare	Urticaria, Cold sweat, Eczema, Generalized erythema, Papular rash, Blister, Erythema, Generalized rash, Heat rash, Hyperhidrosis, Skin warm
Musculoskeletal, connective tissue disorders	Rare	Synovitis
General disorders and administrative site conditions	Very Common	Injection-site pain/tenderness, Injection-site erythema
	Common	Injection-site swelling, Fever, Irritability, Injection-site warmth, Injection-site bruising
	Uncommon	Injection-site hematoma, Injection-site nodule, Malaise, Injection-site rash,
	Rare	Pain, Injection-site haemorrhage, Injection-site

		pruritus, Discomfort, Fatigue, Gait disturbance, Injection-site discoloration, Injection-site papule, Injection-site urticaria, Feeling hot

[1] Spontaneous reporting after use of marketed vaccine

Children/adolescents (2 years through 17 years of age)

System Organ Class	**Frequency**	**Adverse Events**
Blood and lymphatic system disorders	Not Known	Thrombocytopenia[1]
Metabolism and nutrition disorders	Rare	Anorexia
Psychiatric disorders	Uncommon	Irritability
	Rare	Nervousness
Nervous system disorders	Common	Headache
	Uncommon	Dizziness
	Rare	Somnolence, Paraesthesia
	Not Known	Guillain-Barré syndrome[1]
Ear and labyrinth disorders	Rare	Ear pain
Vascular disorders	Rare	Flushing
Respiratory, thoracic and mediastinal disorders	Rare	Nasal congestion, Cough; Rhinorrhea
Gastrointestinal disorders	Uncommon	Abdominal pain, Vomiting, Diarrhea, Nausea
Skin and subcutaneous tissue disorders	Uncommon	Rash, Pruritus
	Rare	Urticaria, Sweating
Musculoskeletal, connective tissue disorders	Uncommon	Arm pain (in the injected limb), Arthralgia, Myalgia
	Rare	Stiffness
General disorders and administrative site conditions	Very Common	Injection-site pain and Tenderness
	Common	Injection-site warmth, Erythema and Swelling, Fever, Injection-site ecchymosis
	Uncommon	Asthenia/fatigue, Injection-site pruritus and Pain/soreness
	Rare	Injection-site induration, Flu-like illness, Chest pain, Pain, Warm sensation, Injection-site scab, Stiffness/tightness and Stinging

[1] 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 aluminium hydroxyphosphate sulfate.

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

Efficacy of VAQTA: The Monroe Clinical Study

Clinical studies showed that the seroconversion rate in children approximately 12 months of age was 96% within 6 weeks after the recommended primary dose and that the seroconversion rate was 97% in children (≥ 2 years of age) and adolescents within 4 weeks after the recommended primary dose. The onset of seroconversion following a single dose of VAQTA was shown to parallel the onset of protection against clinical hepatitis A disease. Protective efficacy has been demonstrated after a single dose of VAQTA in 1,037 children and adolescents 2 to 16 years of age in a US community with recurrent outbreaks of hepatitis A (The Monroe Efficacy Study). Seroconversion was achieved in more than 99% of vaccine recipients within 4 weeks of the vaccination. The pre-exposure protective efficacy of a single dose of VAQTA was observed to be 100% beginning 2 weeks after vaccination. A booster dose was administered to most vaccinees 6, 12, or 18 months after the primary dose. The effectiveness of VAQTA for use in this community has been demonstrated by the fact that after 9 years, since the trial ended, there has been no case of hepatitis A disease in any vaccinee.

Persistence of immunologic memory was demonstrated with an anamnestic antibody response to a booster dose given 6 to 18 months after the primary dose in children (≥2years of age) and adolescents. To date, no cases of clinically confirmed hepatitis A disease ≥ 50 days after vaccination have occurred in these vaccinees from the Monroe Efficacy Study monitored for up to 9 years.

Immunogenicity studies in children 12 through 23 months of age

In three combined clinical studies that assessed immunogenicity, 1,022 initially seronegative subjects received 2 doses of VAQTA alone or concomitantly with other vaccines (combined diphtheria toxoid-tetanus toxoid-acellular pertussis and/or *Haemophilus influenzae* b and/or combined measles-mumps-rubella-varicella and/or combined measles-mumps-rubella and/or varicella and/or pneumococcal 7-valent conjugate vaccine). Seroconversion was achieved in 99.9% of initially seronegative subjects. No significant differences were observed when vaccines were given individually or concomitantly.

Use in children with maternal antibody to hepatitis A

In a concomitant use study, children received VAQTA (25U) at approximately 12 months and approximately 18 months of age with or without other pediatric vaccines. After each dose of VAQTA (25 U), the hepatitis A antibody titers 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 approximately 12 months of age does not affect the immune response to VAQTA.

Antibody persistence

In studies of healthy children (≥2 years of age) and adolescents who received an initial 25 U dose of VAQTA at Day 0 and a subsequent 25 U dose 6 to 18 months later, the hepatitis A antibody response to date has been shown to persist for at least 10 years. The GMTs tend to decline over time. The geometric mean titers (GMTs) declined over the first 5 to 6 years, but appeared to plateau through 10 years.

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.

Post-marketing safety study

In a post-marketing safety study, conducted at a large health maintenance organization in the United States, a total of 12,523 individuals 2 through 17 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 12,523 individuals in this study. There was no nonserious, vaccine-related, adverse event resulting in outpatient visits. 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

0.5 mL suspension in a pre-filled syringe (type I glass) with plunger-stopper (bromobutyl), with attached needle.

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

Pack size of 1 pre-filled 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

PA1286/056/001

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10 DATE OF REVISION OF THE TEXT

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