

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Havrix Junior Monodose Vaccine. Hepatitis A (inactivated) vaccine (absorbed). Suspension for injection in a pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (0.5ml) contains:

Hepatitis A virus (inactivated)^{1,2} 720 ELISA Units

¹Produced on human diploid (MRC-5) cells

²Adsorbed on aluminium hydroxide, hydrated Total: 0.25 milligrams Al³⁺

The vaccine may contain traces of neomycin and formaldehyde which are used during the manufacturing process (see section 4.3).

Excipients with known effect:

Havrix Junior Monodose contains 83 micrograms of phenylalanine and 25 micrograms of polysorbate 20 per dose (see section 4.4).

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Suspension for injection in pre-filled syringe.

Turbid liquid suspension. Upon storage, a fine white deposit with a clear colourless supernatant can be observed.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Havrix is indicated for active immunisation against hepatitis A virus (HAV) infection in children, adolescents and adults:

- Havrix Junior Monodose: individuals aged 1 to 15 years included. It can also be used for adolescents aged up to and including 18 years.
- Havrix Monodose: individuals aged 16 years and above.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Primary vaccination

Havrix Junior Monodose (0.5 ml suspension)

A single dose of Havrix Junior Monodose is used for immunisation of children and adolescents aged 1 to 15 years included.

It could also be acceptable to use a single dose of Havrix Junior Monodose for immunisation of adolescents aged 16 to 18 years included, if necessary (see section 5.1).

Havrix Monodose (1.0 ml suspension)

A single dose of Havrix Monodose is used for immunisation of adults and adolescents 16 years of age and above.

For optimal antibody response, primary immunisation should be given at least 2, preferably 4 weeks prior to expected exposure to hepatitis A virus (see section 5.1).

Booster vaccination

After primary vaccination with either Havrix Junior Monodose or Havrix Monodose, a booster dose is recommended in order to ensure long-term protection. This booster dose should preferably be given between 6 months and 12 months after primary vaccination, however, it can be administered for up to 5 years after primary vaccination. (see section 5.1).

Interchangeability

Havrix is interchangeable with other inactivated hepatitis A vaccines.

Elderly population

There are limited data with inactivated hepatitis A vaccines in elderly individuals.

Paediatric population

The safety and efficacy of Havrix Junior Monodose in children less than 1 year of age have not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Method of administration

Havrix Junior Monodose (0.5 ml suspension) should be administered intramuscularly in the deltoid region in children and adolescents and in the antero-lateral part of the thigh in young children if the deltoid muscle is not yet sufficiently developed (see section 6.6).

Havrix Monodose (1.0 ml suspension) should be administered intramuscularly in the deltoid region in adolescents and adults (see section 6.6).

With any administration site, firm pressure should be applied to the injection site (without rubbing) for at least two minutes post injection.

Havrix should not be administered in the gluteal region.

Havrix should under no circumstances be administered intravascularly.

Havrix should not be administered subcutaneously or intradermally (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to neomycin or to formaldehyde.

Hypersensitivity after previous administration of any hepatitis A vaccine.

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.

General recommendations

As with other vaccines, the administration of Havrix should be postponed in individuals suffering from acute severe febrile illness. The presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination.

Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

Havrix will not prevent hepatitis infection caused by other agents such as hepatitis B virus, hepatitis C virus, hepatitis E virus or other pathogens known to infect the liver.

Individuals may be in the incubation period of a hepatitis A infection at the time of vaccination. It is not known whether Havrix will prevent hepatitis A in such cases.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

The immune response to Havrix could be impaired in immunocompromised individuals. Those individuals always require administration of a 2-dose vaccination schedule.

Havrix should be administered with caution to individuals with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to them. Exceptionally and if in accordance with official recommendations, the vaccine may be administered subcutaneously to these individuals. However, this route of administration may lead to suboptimal anti-HAV antibody response. With both routes of administration, firm pressure should be applied to the injection site (without rubbing) for at least two minutes post injection.

Excipients

Havrix Junior Monodose contains 83 micrograms phenylalanine in each dose.

Havrix Monodose contains 166 micrograms phenylalanine in each dose.

Phenylalanine may be harmful for individuals with phenylketonuria (PKU).

Havrix Junior Monodose contains 25 micrograms of polysorbate 20 in each dose.

Havrix Monodose contains 50 micrograms of polysorbate 20 in each dose.

Polysorbates may cause allergic reactions.

This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

This vaccine contains potassium less than 1 mmol (39 mg) per dose, i.e. essentially "potassium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Since Havrix is an inactivated vaccine, its concomitant use with other inactivated vaccines is unlikely to result in interference with the immune responses.

Havrix can be given concomitantly with any of the following vaccines: typhoid, yellow fever, cholera (injectable), tetanus or with monovalent and combination vaccines comprised of measles, mumps, rubella and varicella.

Havrix can be administered simultaneously with immunoglobulins. Seroconversion rates remain unchanged, although antibody titres may be lower than after Havrix administration alone.

When concomitant administration of injectable vaccines or of immunoglobulins is considered necessary, the products must be given with different syringes and needles and at different injection sites.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women (between 300-1 000 pregnancy outcomes) indicates no malformative or foeto/ neonatal toxicity.

Animal studies do not indicate reproductive toxicity (see section 5.3).

The use of Havrix may be considered during pregnancy, if necessary.

Breast-feeding

It is unknown whether Havrix is excreted in human milk. Although the risk can be considered as negligible, Havrix should be used during breast-feeding only when clearly needed.

Fertility

There are no data on the effects of Havrix on human fertility. Effects on human fertility have not been evaluated in animal studies.

4.7 Effects on ability to drive and use machines

Havrix has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common local undesirable effect, both in children and adults, are pain and redness at the injection site. The most common general undesirable effects are, in children, irritability and in adults, fatigue and headache.

Tabulated list of adverse reactions

Clinical trial data

The safety profile presented in table below is based on data from 5331 subjects including 1664 children (up to 18 years of age) vaccinated with Havrix Junior Monodose and 3667 adults (from 16 years of age) vaccinated with Havrix Monodose, in clinical trials (total vaccinated cohort). A total of 3193 doses of Havrix Junior Monodose and 7131 doses of Havrix Monodose were administered during clinical trials. A total number of 3971 doses of Havrix Monodose were administered concomitantly with Engerix-B in 2064 adult subjects.

Adverse reactions reported are listed according to the following frequency:

Very common ($\geq 1/10$)
 Common ($\geq 1/100$ to $< 1/10$)
 Uncommon ($\geq 1/1\ 000$ to $< 1/100$)
 Rare ($\geq 1/10\ 000$ to $< 1/1\ 000$)
 Very rare ($< 1/10\ 000$)

Within each frequency grouping the adverse reactions are presented in the order of decreasing seriousness.

System organ class	Frequency	Adverse reactions
Infections and infestations	Uncommon	Upper respiratory tract infection ⁽²⁾ , rhinitis
Metabolism and nutrition disorders	Common	Appetite lost
Psychiatric disorders	Very common	Irritability ⁽¹⁾
Nervous system disorders	Very common	Headache ⁽³⁾
	Common	Drowsiness ⁽²⁾
	Uncommon	Dizziness ⁽²⁾
	Rare	Hypoaesthesia ⁽²⁾ , paraesthesia ⁽²⁾
Gastrointestinal disorders	Common	Gastrointestinal signs and symptoms ^{(2) (5)} , diarrhoea ⁽⁴⁾ , nausea
	Uncommon	Vomiting
Skin and subcutaneous tissue disorders	Uncommon	Rash ⁽¹⁾
	Rare	Pruritus ⁽²⁾
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia ⁽²⁾ , musculoskeletal stiffness ⁽²⁾
General disorders and administration site conditions	Very common	Injection site pain and injection site erythema, fatigue ⁽²⁾
	Common	Malaise, fever (≥ 37.5 C), injection site reaction (such as injection site induration ⁽⁴⁾ and injection site swelling)
	Uncommon	Influenza like illness ⁽²⁾
	Rare	Chills ⁽²⁾

⁽¹⁾ only with Havrix Junior Monodose

⁽²⁾ only with Havrix Monodose

⁽³⁾ reported with a frequency of common with Havrix Junior Monodose

⁽⁴⁾ reported with a frequency of uncommon with Havrix Junior Monodose

⁽⁵⁾ gastrointestinal = including nausea, vomiting, diarrhoea (symptoms not separately recorded)

Post-marketing data

The following additional adverse reactions have been identified during post-marketing surveillance with both Havrix Junior Monodose and Havrix Monodose.

System organ class	Frequency	Adverse reactions
Immune system disorders	Rare	Anaphylaxis, allergic reactions including anaphylactoid reactions and serum sickness like reaction
Nervous system disorders	Rare	Convulsions
Vascular disorders	Rare	Vasculitis
Skin and subcutaneous tissue disorders	Rare	Angioneurotic oedema, erythema multiforme, urticaria
Musculoskeletal and connective tissue disorders	Rare	Arthralgia

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

Cases of overdose have been reported during post-marketing surveillance. Adverse events reported following overdosage were similar to those reported with normal vaccine administration.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hepatitis A vaccines, ATC code J07BC02

Mechanism of action

Havrix confers immunisation against HAV by stimulating specific immune responses evidenced by the induction of antibodies against HAV.

Pharmacodynamic effects

The immunogenicity of Havrix was assessed in 39 studies in more than 6 000 subjects including adults, adolescents and children.

Immune response

In clinical studies, 99% of vaccinees seroconverted 30 days after the primary dose.

In a subset of adult clinical studies where the kinetics of the immune response were studied, early and rapid seroconversion was demonstrated following administration of the primary dose of Havrix Monodose in 79% of vaccinees at day 13, 86.3% at day 15, 95.2% at day 17 and 100% at day 19.

Limited data are available from clinical studies involving infants below 1 year of age. In those studies, Havrix Junior Monodose was administered at 2, 4 and 6 months of age or as 2 doses given 6 months apart from 4 to 6 months of age. Humoral antibodies against HAV were detected in most vaccinees one month following the administration of the last vaccine dose; infants with pre-existing antibodies of maternal origin had a markedly diminished response compared to initially seronegative infants (see section 4.2).

In clinical studies involving children 1-18 years of age, specific humoral antibodies against HAV were detected in more than 93% of vaccinees at day 15 and 99 % of vaccinees one month following administration of the primary dose of Havrix Junior Monodose.

In clinical studies in which adolescents 16-18 years of age received Havrix Junior Monodose, humoral antibodies against HAV were detected in more than 94% of vaccinees at day 15 and in 100% of vaccinees one month following administration of the primary dose of Havrix Junior Monodose.

Immune response in patients with chronic liver disease

In two clinical trials, 300 subjects with chronic liver disease (chronic hepatitis B, chronic hepatitis C or other) were vaccinated with 2 doses of Havrix Monodose given at an interval of 6 months. The vaccine provided detectable antibody titres in at least 95% of the vaccinees, one month after the second dose.

Persistence of the immune response

In order to ensure long-term protection, a booster dose should be given between 6 and 12 months after the primary dose of Havrix Junior Monodose or Havrix Monodose. In clinical trials, all vaccinees were seropositive one month after the booster dose.

However, if the booster dose has not been given between 6 and 12 months after the primary dose, the administration of this booster dose can be given up to 5 years after the primary dose. In a comparative trial in adults, a booster dose given up to 5 years after the primary dose has been shown to induce similar antibody levels as a booster dose given between 6 and 12 months after the primary dose.

Long-term persistence of hepatitis A antibody titres following 2 doses of Havrix Monodose given 6 to 12 months apart has been evaluated. In two clinical trials in adults, 96.7% and 100% of vaccinees were still seropositive at year 17.5 (study HAV-112) and year 17 (study HAV-123), respectively. Data available up to 17 and 17.5 years allow prediction that at least 95% and 90% of subjects will remain seropositive (≥ 15 mIU/ml) 30 and 40 years after vaccination, respectively.

Current data do not support the need for further booster vaccination among immunocompetent subjects after a 2-dose vaccination course.

It can be expected that the duration of protection in children following 2 doses of Havrix Junior Monodose is comparable with the above predicted duration of protection in adults.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

No special hazard for humans was observed from protection studies in chimpanzees.

A reproductive toxicity study in rats has been conducted with another hepatitis A and hepatitis B combination vaccine (HAB). This combination vaccine has the same active ingredient as Havrix. Rats were administered intramuscularly with 1/5th of the human dose of HAB (200 μ L intramuscular injection containing 144 ELISA Units of Hepatitis A virus (inactivated), 4 micrograms Hepatitis B surface antigen and 0.09 mg aluminium as aluminium salts). It was not associated with maternal toxicity and no adverse or vaccine-related effects on pre- or post-natal development of the foetuses/pups were observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Amino acids for injections (containing phenylalanine)
Disodium phosphate
Monopotassium phosphate
Polysorbate 20 (E432)
Potassium chloride
Sodium chloride

Water for injections.

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 to 8°C).

Do not freeze. Discard if vaccine has been frozen.

Store in the original package in order to protect from light.

Stability data indicate that Havrix is stable at temperatures up to 25°C for 3 days. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

6.5 Nature and contents of container

- 0.5 ml of suspension in a pre-filled syringe (type I glass) with a plunger stopper (butyl rubber) and with a rubber tip cap.
- Pack sizes of 1, 5, 10 and 25, with or without needles.

The tip cap and rubber plunger stopper of the pre-filled syringe are made with synthetic rubber.

Not all pack sizes may be marketed.

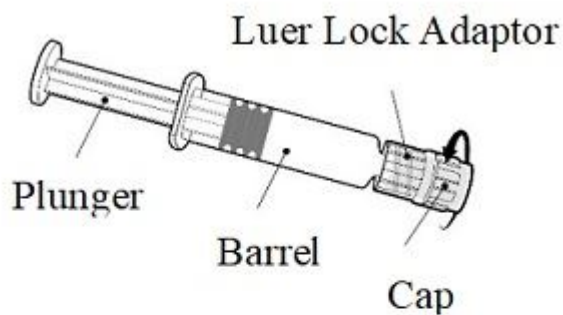
6.6 Special precautions for disposal and other handling

Havrix is a turbid liquid suspension. During storage, a fine white deposit with a colourless supernatant may form

The vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspect prior to administration. Before use of Havrix, the pre-filled syringe should be well shaken to obtain a slightly opaque white suspension.

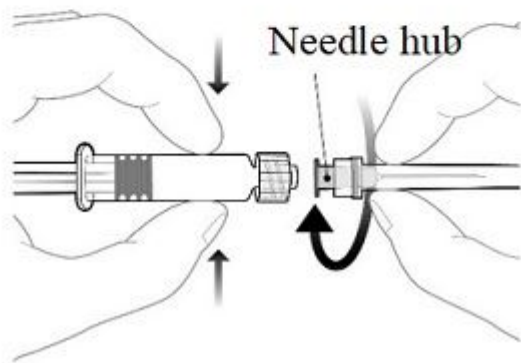
Discard the vaccine if the content appears otherwise.

Instructions for the pre-filled syringe



Hold the syringe by the barrel, not by the plunger.

Unscrew the syringe cap by twisting it anticlockwise.



To attach the needle, connect the hub to the Luer Lock Adaptor and rotate a quarter turn clockwise until you feel it lock.

Do not pull the syringe plunger out of the barrel. If it happens, do not administer the vaccine.

Disposal

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

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1077/026/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 October 1998

Date of last renewal: 01 October 2008

10 DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of: Health Products Regulatory Authority