1. NAME OF THE MEDICINAL PRODUCT

Havrix 720 Junior
Havrix 1440

Suspension for injection in a pre-filled syringe
Suspension for injection in a vial
Hepatitis A antigen (inactivated) vaccine (adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Havrix 720 Junior:
One dose (0.5 mL) contains:
Hepatitis A virus antigen (inactivated)[1,2] 720 ELISA Units

Havrix 1440:
One dose (1.0 mL) contains:
Hepatitis A virus antigen (inactivated)[1,2] 1440 ELISA Units

[1] Produced on human diploid (MRC-5) cells
[2]Adsorbed on aluminium (as aluminium hydroxide) Total Havrix 720: 0.25 milligrams Al^{3+}
Total Havrix 1440: 0.50 milligrams Al^{3+}

Havrix vaccine may contain traces of neomycin B sulfate, which is used during the manufacturing process (see section 4.3).

Excipient(s) with known effect:
Havrix 720 Junior: This vaccine contains phenylalanine 83 micrograms per dose (see section 4.4).
Havrix 1440: This vaccine contains phenylalanine 166 micrograms per dose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.
Turbid liquid suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Havrix 720 Junior:
Active immunisation against HAV infection from 1 year up to and including 15 years of age.

The vaccine is particularly indicated for those at increased risk of infection or transmission. It is also indicated for use during outbreaks of hepatitis A infection.

Havrix 1440:
Active immunisation against infections caused by hepatitis A virus. The vaccine is particularly indicated for those at increased risk of infection or transmission.

4.2 Posology and method of administration

Posology
Havrix 720 Junior - Children/adolescents (1-15 years):
Primary immunisation consists of a single dose given intramuscularly. This provides anti-HAV antibodies for at least one year.

This vaccine confers protection against hepatitis A within two to four weeks.

In order to obtain more persistent immunity, for at least 10 years, a booster dose is recommended between 6 and 12 months after primary immunisation.

Booster vaccination delayed up to 3 years after the primary dose induces similar antibody levels as a booster dose administered within the recommended time interval.

Current recommendations do not support the need for further booster vaccination among immunocompetent subjects after a 2-dose vaccination course (see section 5.1).

Havrix 720 Junior can be used as a booster in subjects previously immunised with any inactivated hepatitis A vaccine.

In the event of a subject being exposed to a high risk of contracting hepatitis A within two weeks of the primary immunisation dose, human normal immunoglobulin may be given simultaneously with this vaccine at different injection sites.

Havrix 1440 - Adults (16 years and over):
Primary immunisation consists of a single dose given intramuscularly. This provides anti-HAV antibodies for at least one year.

This vaccine confers protection against hepatitis A within 2-4 weeks.

In order to obtain more persistent immunity, a booster dose is recommended between 6 and 12 months after primary immunisation.

Although a booster should be given within 6–12 months of the initial vaccination, it has been shown that immunocompetent subjects given a booster up to 3 years after the initial vaccination can develop similar antibody levels to subjects given a booster within the recommended time period. Subjects given a booster up to 5 years after initial vaccination can also show a satisfactory antibody response, but approximately 30% of individuals receiving a delayed booster have no detectable anti-HAV antibodies prior to booster dosing.

It is unnecessary to restart the primary vaccination schedule if the booster is administered within 5 years of the primary vaccination.

Current recommendations do not support the need for further booster vaccination among immunocompetent subjects after a 2-dose vaccination course (see section 5.1).

The results described above should be considered to apply only to immunocompetent adults.

Havrix 1440 can be used as a booster in subjects previously immunised with any inactivated hepatitis A vaccine.

In the event of a subject being exposed to a high risk of contracting hepatitis A within 2 weeks of the primary immunisation dose, human normal immunoglobulin may be given simultaneously with this vaccine at different injection sites.

Method of administration
The vaccine should be injected intramuscularly in the deltoid region or into the antero-lateral part of the thigh in young children. The vaccine should not be administered in the gluteal region.

The vaccine should never be administered intravascularly.

The vaccine should not be administered subcutaneously/intradermally since administration by these routes may result in a less than optimal anti-HAV antibody response. In subjects with a bleeding disorder who are at risk of haemorrhage following intramuscular injection (e.g. haemophiliacs), this vaccine may be administered by deep subcutaneous injection as per local guidance. Firm pressure should be applied to the injection site (without rubbing) for at least two minutes.

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 of the administered product should be clearly recorded. It is recommended to record the batch number as well.

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 720 Junior contains 83 micrograms phenylalanine in each dose.
Havrix 1440 Adult contains 166 micrograms phenylalanine in each dose.
Phenylalanine may be harmful for individuals with phenylketonuria (PKU).

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

This vaccine contains less than 1 mmol potassium (39 mg) per dose, that is to say 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 effects, 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 the table below is based on data from 5 331 subjects including 1 664 children (up to 18 years of age) vaccinated with Havrix 720 Junior and 3 667 adults (from 16 years of age) vaccinated with Havrix 1440 Adult, in clinical trials (total vaccinated cohort). A total of 3 193 doses of Havrix 720 Junior and 7 131 doses of Havrix 1440 Adult were administered during clinical trials. A total number of 3 971 doses of Havrix 1440 Adult were administered concomitantly with Engerix-B in 2 064 adult subjects.

Adverse reactions reported are listed according to the following frequency:
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)

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 [(1)]
	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 720 Junior
[2] only with Havrix 1440 Adult
[3] reported with a frequency of common with Havrix 720 Junior
[4] reported with a frequency of uncommon with Havrix 720 Junior
[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 720 Junior and Havrix 1440 Adult.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/
Additionally, you should also report to GSK Israel (il.safety@gsk.com).

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 1440 Adult in 79% of vaccinees at day 13, 86.3% at day 15, 95.2% at day 17 and 100% at day 19.

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 720 Junior.

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 1440 Adult 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 720 Junior or Havrix 1440 Adult. In clinical trials, all vaccinees were seropositive one month after the booster dose.

Long-term persistence of hepatitis A antibody titres following 2 doses of Havrix 1440 Adult 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 720 Junior 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 $1/5^{th}$ of the human dose of HAB (200 µL 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

Sodium chloride
Amino acids for injection (containing phenylalanine)

Disodium phosphate anhydrous
Aluminium hydroxide
Potassium chloride
Monopotassium phosphate
Polysorbate 20
Water for injection

6.2 Incompatibilities

This vaccine should not be mixed with other vaccines.

6.3 Shelf life

The expiry date of the vaccine is indicated on the label and packaging.

6.4 Special precautions for storage

Store at 2°C - 8°C in a refrigerator.
Do not freeze.
Store in the original pack 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

Havrix 720 Junior:
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 or 0.5 mL of suspension in a vial (type I glass) with a stopper (butyl rubber) with or without needles.

Pack size:
Pre-filled syringe: 1 or 10 or 100
Vial: 1 or 100

Havrix 1440:
1 mL of suspension in a pre-filled syringe (type I glass) with a plunger stopper (butyl rubber) and with a rubber tip cap or 1 mL of suspension in a vial (type I glass) with stopper (butyl rubber) with or without needles.
Pack size of 1.

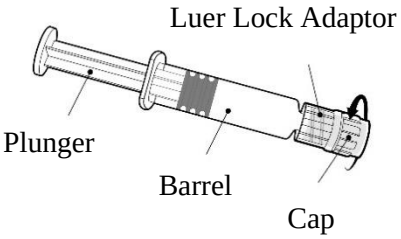
The tip cap and rubber plunger stopper of the pre-filled syringe and the stopper of the vial are made with synthetic rubber.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

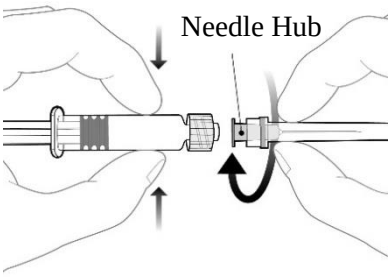
The vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspect prior to administration. Before use, the vaccine should be well shaken to obtain a slightly opaque, white suspension. Discard the vaccine if the content appears otherwise.

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. MANUFACTURER

GlaxoSmithKline Biologicals S.A., Rixensart, Belgium.

8. LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.

9. LICENSE NUMBER

Havrix 720 junior: 108-39-29109
Havrix 1440: 101-61-28393

Revised in November 2024.

Hav DR v10