1 NAME OF THE MEDICINAL PRODUCT

Havrix 720 Junior
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

One dose (0.5 ml) contains:
Hepatitis A virus antigen[1] 720 ELISA Units

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

Havrix 720 Junior vaccine may contain traces of neomycin B sulfate, which is used during the manufacturing process (see section 4.3).

Excipient(s) with known effect:
This vaccine contains phenylalanine 83 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

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.

4.2 Posology and method of administration

Posology

Havrix 720 Junior vaccine should be injected intramuscularly in the deltoid muscle. The vaccine should never be administered intravenously.

Dosage:

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.

Method of administration

The vaccine should be injected intramuscularly in the deltoid muscle.
The vaccine should never be administered intravenously.

4.3 Contraindications

Hypersensitivity to the active substance, to any of the excipients listed in section 6.1, or to neomycin (present at traces).

4.4 Special warnings and precautions for use

Immunisation should be postponed in subjects suffering from an acute severe febrile illness. The presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

As for all vaccines, appropriate medication e.g.epinephrine (adrenaline) should be readily available for immediate use in case of anaphylaxis.
It is possible that subjects may be in the incubation period of a hepatitis A infection at the time of immunisation. It is not known whether Havrix 720 Junior will prevent hepatitis A in such cases.

In haemodialysis patients and in subjects with an impaired immune system, adequate anti-HAV antibody titres may not be obtained after the primary immunisation and such patients may therefore require administration of additional doses of vaccine.

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.

Excipients

This vaccine contains 83 micrograms of phenylalanine in each dose. Phenylalanine may be harmful to patients that have phenylketonuria (PKU).

This medicine contains potassium, less than 1 mmol (39 mg) per 0.5 ml dose, i.e. essentially 'potassium- free'.

This medicinal product contains less than 1 mmol sodium (23 mg) per 0.5 ml dose, that is to say essentially 'sodium- free'.

4.5 Interaction with other medicinal products and other forms of interaction

Simultaneous administration of Havrix with normal immunoglobulin does not influence the seroconversion rate to Havrix, however, it may result in a lower antibody titre. A similar effect could be observed with Havrix 720 Junior.

Preliminary data on the concomitant administration of Havrix, at a dose of 720 ELISA units/ml, with recombinant hepatitis B virus vaccine suggests that there is no interference in the immune response to either antigen. Havrix 720 Junior can be given concomitantly with monovalent and combination vaccines comprised of measles, mumps, rubella and varicella. When concomitant administration is considered necessary the vaccines must be given at different injection sites.

Havrix 720 Junior must not be mixed with other vaccines in the same syringe.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of this vaccine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. The use of this vaccine may be considered during pregnancy, if necessary.

Breast-feeding

It is unknown whether this vaccine is excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

No fertility data are available.

4.7 Effects on ability to drive and use machines

No studies of the effects of Havrix 720 Junior on the ability to drive and use machines have been performed. However, some of the effects mentioned under section 4.8 "Undesirable effects" may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

The safety profile presented below is based on data from more than 5300 subjects that participated in clinical trials, plus reactions observed through post-marketing surveillance. It should be noted that it was not possible to calculate the frequency of reactions from the post-marketing data, therefore the frequency is noted as "Not known".

The most frequently reported reactions are pain and redness at site of injection (Havrix 1440 has reports in over 50% of doses, Havrix 720 Junior has reports in 18.2% of doses overall). Swelling at the site of injection was the next most frequently reported reactions.

Frequencies per dose are defined as follows:

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 data available

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness

* refers to adverse reaction reported only for Havrix 1440 (1ml adult dose)
** refers to adverse reactions reported only for Havrix 720 Junior (0.5ml children's dose)
# this adverse reaction was identified through post-marketing surveillance but was not observed in randomised controlled clinical trials. The frequency category of rare was estimated from a statistical calculation based on the total number of paediatric patients exposed to Havrix in randomised controlled clinical trials (n=4574).

System Organ Classes	**Frequency**	**Adverse reaction**
Infections and infestations	Uncommon	Upper respiratory tract infection* Rhinitis*
Immune system disorders	Not known	Anaphylaxis Allergic reactions including anaphylactoid reactions and mimicking serum sickness
Metabolism and nutrition disorders	Common	Appetite lost
Psychiatric disorders	Very common	Irritability**
Nervous system disorders	Very common	Headache (common with Havrix 720 Junior formulation)
	Common	Drowsiness**
	Uncommon	Dizziness*
	Rare	Hypoaesthesia Paraesthesia
	Not known	Convulsions Guillain Barre Syndrome Transverse myelitis Neuralgic amyotrophy
Vascular disorders	Not known	Vasculitis
Gastrointestinal disorders	Common	Gastrointestinal symptoms*(rare with Havrix 720 Junior formulation#) Nausea Diarrhoea (uncommon with Havrix 720 Junior formulation)

	Uncommon	Vomiting
Hepatobiliary disorders	Not known	Transient increase in liver function tests
Skin and subcutaneous tissue disorders	Uncommon	Rash**
	Rare	Pruritus
	Not known	Angioneurotic oedema Erythema multiforme Urticaria
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia* Musculoskeletal stiffness*
	Not known	Arthralgia
General disorders and administration site conditions	Very common	Pain and redness at the injection site Fatigue* (rare with Havrix 720 Junior formulation#)
	Common	Fever (≥37.5°C) Injection site reaction, such as swelling or induration (uncommon with Havrix 720 Junior formulation) Malaise
	Uncommon	Influenza like illness*
	Rare	Chills

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

Pharmaco-therapeutic group: Hepatitis A vaccine, ATC code J07BC02.

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

Immune response
In clinical studies involving subjects of 1 – 18 years of age, specific humoral antibodies against HAV were detected in 93% of vaccines at day 15 and 99% of vaccines one month following administration of Havrix 720 Junior.

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. In clinical trials, virtually all vaccinees were seropositive one month after the booster dose.

Long term persistence of hepatitis A antibody titres has been evaluated following 2 doses of Havrix given 6 to 12 months apart to healthy immunocompetent subjects aged 17 to 40 years . Data available after 17 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.

Efficacy of Havrix for outbreak control

The efficacy of Havrix was evaluated in different community outbreaks. .These studies indicated that administration of a single dose of Havrix contributed to termination of the outbreaks. In one study, vaccine coverage in excess of 80% was followed by termination of the outbreak within 4 to 8 weeks

Impact of mass vaccination on disease incidence

A reduction in the incidence of hepatitis A was observed in countries where a two-dose Havrix immunization programme was implemented for children in their second year of life:

- In Israel, a retrospective database study showed up to 95 % reduction in hepatitis A incidence in the general population 8 years after the implementation of the vaccination program. Data from the National Surveillance also showed a 95% reduction in hepatitis A incidence as compared to the pre-vaccination era.
- In Panama, a retrospective database study showed a 90% reduction in reported hepatitis A incidence in the vaccinated population, and 87% in the general population, 3 years after implementation of the vaccination programme.

The observed reduction in hepatitis A incidence in the general population (vaccinated and non-vaccinated) in both countries are consistent with herd immunity.

5.2 Pharmacokinetic properties

Not applicable to vaccine products.

5.3 Preclinical safety data

Not applicable to vaccine products.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Amino acids for injection (containing phenylalanine)
Disodium phosphate
Potassium chloride
Monopotassium phosphate
Polysorbate 20
Water for injections

For adsorbent, see section 2

6.2 Incompatibilities

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

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.
Store in the original pack in order to protect from light.
Do not freeze.
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 glass vials (type 1, PhEur) with butyl rubber stopper.
Pack size of 1 or 100.

0.5 ml of suspension in prefilled syringe (type I glass) with a plunger stopper and a tip cup with or without needles.
Pack size of 1 or 10 or 100.

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.

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

108-39-29109

Hav 720 DR V7