AUSTRALIAN PRODUCT INFORMATION

HAVRIX 1440 AND HAVRIX JUNIOR (inactivated Hepatitis A virus vaccine) suspension for injection

1 NAME OF THE MEDICINE

Inactivated Hepatitis A virus vaccine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

HAVRIX, hepatitis A vaccine, is a sterile suspension containing formaldehyde - inactivated hepatitis A virus (HM 175 hepatitis A virus strain) adsorbed onto aluminium hydroxide hydrate.

The virus is propagated in MRC5 human diploid cells. Before viral extraction, the cells are extensively washed to remove culture medium constituents. A virus suspension is then obtained by lysis of the cells followed by purification using ultrafiltration techniques and gel chromatography. The virus is then inactivated with formalin. Residual formaldehyde in the vaccine should be not more than 0.01%.

One dose (1.0 mL) of HAVRIX 1440 Adult contains:

Hepatitis A virus (inactivated)[1,2]	1440 ELISA Units
1Produced on human diploid (MRC-5) cells	
2Adsorbed on aluminium hydroxide hydrate	Total: 0.50 milligrams Al^{3+}

One dose (0.5 mL) of HAVRIX 720 Junior contains:

Hepatitis A virus (inactivated)[1,2]	720 ELISA Units
[1]Produced on human diploid (MRC-5) cells	
[2]Adsorbed on aluminium hydroxide hydrate	Total : 0.25 milligrams Al^{3+}

The manufacture of this product includes exposure to bovine derived materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

HAVRIX meets the World Health Organization requirements for biological substances.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Suspension for injection.

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 susceptible subjects at risk of exposure to HAV. HAVRIX JUNIOR is indicated in subjects aged 2 to 15 years and HAVRIX 1440 is indicated in subjects aged 16 years and older.

In areas of low prevalence of hepatitis A, immunisation with HAVRIX is particularly recommended in the following subjects:

Travellers: Persons travelling to areas of intermediate or high endemicity for hepatitis A. These areas include Africa, Asia, India, the Pacific Islands, the Mediterranean basin, the Middle East, Central and South America.

Armed Forces: Armed forces personnel who travel to higher endemicity areas or to areas where hygiene is poor, have an increased risk of HAV infection.

Persons for whom hepatitis A is an occupational hazard or for whom there is an increased risk of transmission. These include:

- employees in day-care centres particularly in situations where children have not been toilet trained
- teachers and other close contacts of the intellectually disabled
- staff and residents of residential facilities for the intellectually disabled
- health workers and teachers in remote Aboriginal and Torres Strait Islander communities
- nursing staff and other healthcare workers in contact with patients in paediatric wards, infectious diseases wards, emergency rooms and intensive care units
- sewerage workers
- food handlers, since food hygiene procedures and food processing methods are not always adequate to protect from contamination from food handlers.

Homosexual men: Increased incidence of hepatitis A infection among homosexual males suggests that the disease may be sexually transmitted in this group.

Contacts of infected persons: Since virus shedding from infected persons may occur for a prolonged period, active immunisation of close contacts is recommended. The use of vaccine in outbreak control has been shown to be more effective than the use of immunoglobulin.

Specific population groups known to have a higher incidence of hepatitis A: eg. Australian aboriginals, recognised community-wide HAV epidemics.

Individuals with chronic liver disease and recipients of liver transplants, as hepatitis A infections is likely to be more severe in these groups. Many injecting drug users will have pre-existing liver disease from hepatitis B or hepatitis C infection.

Recipients of blood products, such as Factor VIII eg. haemophiliacs.

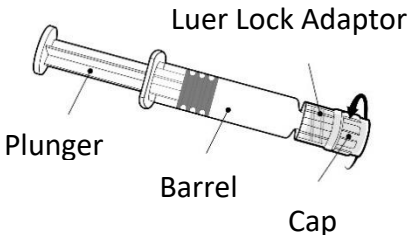
HAVRIX will not prevent hepatitis infection caused by other agents such as hepatitis B virus, hepatitis C virus, hepatitis D virus, hepatitis E or other pathogens known to infect the liver.

4.2 DOSE AND METHOD OF ADMINISTRATION

HAVRIX is administered by intramuscular injection. THE VACCINE SHOULD NEVER BE ADMINISTERED INTRAVENOUSLY.

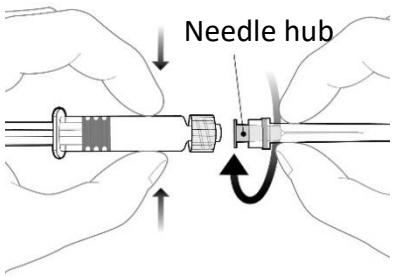
Each dose consists of ready-to-use sterile suspension. The vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspect prior to administration. Before use of HAVRIX, the syringe should be well shaken to obtain a slight opaque white suspension. Discard if the contents of the syringe appear 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.

The pre-filled syringe is for use in a single patient only. Any unused product or waste material should be disposed of in accordance with local requirements..

Adults (16 years and older)

A single dose of HAVRIX 1440 (1 mL) is used for primary immunisation.

To prolong the protective effect, a single booster dose of HAVRIX 1440 is recommended at any time between 6 and 12 months after the primary dose. Long term persistence of serum antibodies after vaccination with HAVRIX is under evaluation. Data available after five years show persistence of antibodies which is consistent with a projected 20 years persistence (based on mathematical calculations). Further measurement of antibody titres are needed to confirm these mathematical projections.

Children and adolescents (aged 2 years up to and including 15 years)

A single dose of HAVRIX JUNIOR (0.5 mL) is used for primary immunisation.

To prolong the protective effect, a single booster dose of HAVRIX JUNIOR is recommended at any time between 6 and 12 months after the primary dose. The exact duration of this protection subsequent to the booster dose is unknown.

HAVRIX should be injected intramuscularly into the deltoid region of the upper arm in adults and older children or the antero-lateral aspect of the thigh in infants. The vaccine should not be administered intramuscularly in the gluteal region or subcutaneously/intradermally since administration by these routes may result in a less than optimal anti-HAV antibody response.

4.3 CONTRAINDICATIONS

HAVRIX should not be administered to subjects with known hypersensitivity to any component of the vaccine, or to subjects having shown signs of hypersensitivity after previous HAVRIX administration.

As with other vaccines, the administration of HAVRIX should be postponed in subjects with severe febrile illness. The presence of a minor infection, however is not a contraindication.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

HAVRIX should never be administered intravenously.

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

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

The antibody response to HAVRIX may be impaired in subjects whose immune system is compromised by either disease or drugs.

HAVRIX should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.

It is possible that the subjects may be in the incubation period of hepatitis A infection at the time of immunisation. It is not known whether HAVRIX will prevent hepatitis A in such cases.

Use in the elderly

Clinical experience with HAVRIX 1440 in the elderly is also limited.

Paediatric use

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No data are available concerning concomitant administration of ISG with HAVRIX 1440 or HAVRIX JUNIOR. Clinical experience with HAVRIX 720 ELISA suggests that the concomitant administration of ISG with the first dose of HAVRIX does not influence the seroconversion rate, but may result in a relatively lower anti-HAV antibody titre than when the primary course of vaccine is given alone. HAVRIX and ISG should be administered at separate injection sites.

Since HAVRIX is an inactivated vaccine its concomitant use with other inactivated vaccines is unlikely to result in interference with immune response. 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.

Clinical experience of the concomitant administration of HAVRIX 720 ELISA units and the recombinant hepatitis B virus vaccine (Engerix-B) suggests no interference in the respective immune responses to each of the antigens. When given concomitantly, HAVRIX and Engerix-B should be administered in separate syringes at separate sites.

If another vaccine needs to be administered concurrently, the vaccines must be administered using separate syringes at separate sites.

HAVRIX must not be mixed with other vaccines.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

(Pregnancy Category B2)

Adequate human data on use during pregnancy and adequate animal reproduction studies are not available. Although there is no convincing evidence of risk to the foetus from immunisation of pregnant women using inactivated virus vaccines, HAVRIX should be used during pregnancy only when clearly needed.

Use in lactation

Adequate human data on use during lactation and adequate animal reproduction studies are not available. HAVRIX should therefore be used with caution in breast feeding women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The vaccine is unlikely to produce an effect on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

Solicited and unsolicited events occurring during clinical trials are listed below. The safety profile presented below is based on data from more than 5300 subjects. Events are listed within body systems and categorised by frequency according to the following definitions:

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

Local reactions at injection site:

Very common: soreness, redness

Common: induration, swelling

Body as a whole:

Very common: headache, fatigue

Common: fever (>37.5°C), malaise

Uncommon: influenza like illness

Rare: chills

Dermatologic:

Uncommon: rash

Rare: pruritis

Respiratory:

Uncommon: pharyngitis, other upper respiratory tract infections, rhinitis

Gastrointestinal:

Common: nausea, diarrhoea, vomiting, appetite lost

Uncommon: abdominal pain

Musculoskeletal:

Uncommon: myalgia, musculoskeletal stiffness

Haematologic:

Rare: lymphadenopathy

Central nervous system

Very common: irritability

Common: drowsiness

Uncommon: dizziness.

Rare: hypoaesthesia, paraesthesia.

When ISG was given concurrently with HAVRIX 720 ELISA units, the incidence but not severity of the adverse events were higher, this being largely due to more reports of local adverse events.

Post Marketing Data

Since marketing of the product, elevations of serum liver enzymes (usually transient) have been reported rarely. However a causal relationship with the vaccine has not been established. Neurological manifestations occurring in temporal association have been reported extremely rarely with the vaccine and include transverse myelitis, Guillain-Barre syndrome and neuralgic amyotrophy. No causal relationship has been established.

Very rarely, allergic reactions including anaphylactic reactions, and convulsions have been reported.

Anaphylaxis and mimicking serum sickness, vasculitis, angioneurotic oedema, urticaria, erythema multiforme, arthralgia have also been reported.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

HAVRIX confers immunity against hepatitis A virus (HAV) infection by inducing the production of specific anti-HAV antibodies in normal healthy individuals.

The mean titre of anti-HAV antibodies induced by HAVRIX is higher than that observed after passive immunisation using specific HAV immune serum globulins (ISG). Vaccine-induced anti-HAV antibodies have been shown to be qualitatively indistinguishable from those of the specific HAV ISG.

A booster dose may be administered at any time between 6 and 12 months after the primary dose, to induce a rise in antibody titres. Long term persistence of serum antibodies has been predicted using mathematical modelling of data obtained after vaccination of adults (17-40 years age) with HAVRIX 1440.

Data available after 17 years allows prediction that at least 95% and 90% of subjects will remain seropositive (≥15 mIU/mL) 30 and 40 years after vaccination, respectively (see Table 1).

Table 1: Predicted proportion of subjects with anti-HAV level ≥15 mIU/mL and 95% confidence intervals for studies HAV-112 and HAV-123.

Year	≥15 mIU/mL	95% CI	
		LL	UL
Predictions for HAV-112			
25	97.7 %	94.2 %	100 %
30	96.5 %	92.5 %	99.4 %
35	94.2%	89.0 %	98.9 %
40	92.5 %	86.1 %	97.8 %
Predictions for HAV-123			
25	97.2 %	93.5 %	100 %
30	95.4 %	88.9 %	99.1 %
35	92.6 %	86.1 %	97.2 %
40	90.7 %	82.4 %	95.4 %

Clinical trials

Immunogenicity in adults: In clinical studies involving over 400 subjects, 16 to 50 years of age, specific humoral antibodies against HAV were elicited in 88% of vaccinees after 15 days and in approximately 99% of vaccinees 1 month after the administration of a single dose of HAVRIX 1440 ELISA units. GMTs of seroconverters ranged from 264 to 339 IU/L at day 15 and increased to a range of 335 to 637 IU/L at 1 month following vaccination. In two clinical trials in which a booster dose was given 6 months following the initial dose, 100% of vaccinees were seropositive 1 month after the booster dose, with GMTs ranging from 3318 to 5925 IU/L.

Immunogenicity in children: In clinical studies involving subjects 2 to 19 years of age (N=314), specific humoral antibodies against HAV were elicited in 93% of vaccinees after 15 days and in approximately 99% of vaccinees 1 month after the administration of a single dose of HAVRIX JUNIOR. The GMTs 1 month after the initial dose ranged from 194 to 305 IU/L. One month following the booster dose at month 6, all subjects were seropositive with GMTs ranging from 2495 to 3644 IU/L.

In one additional study in which the booster dose was delayed until 1 year following the initial dose, 95.2% of all subjects were seropositive just prior to administration of the booster dose. One month later, all subjects were seropositive with GMTs of 2657 IU/L.

Protective Efficacy: Protective efficacy with HAVRIX has been demonstrated in a double-blind, randomized controlled study in school children (age 1 to 16 years) in Thailand who were at high risk of HAV infection. A total of 40,119 children were randomized to be vaccinated with either HAVRIX 360 ELISA units or Engerix-B at 0, 1, 12 months. 19,037 children received a primary course (0, 1 months) of HAVRIX and 19,120 children received a primary course (0, 1 months) of Engerix-B. 38,157 children entered surveillance at day 138 and were observed for an additional 8 months. Using the protocol-defined endpoint (≥2 days absence from school, ALT level >45 IU/mL, and a positive result in the HAVAB-M test), 32 cases of clinical hepatitis A occurred in the control group; in the HAVRIX group, two cases were identified. These two cases were mild both in terms of biochemical and clinical indices of hepatitis A disease. Thus the calculated efficacy rate for prevention of clinical hepatitis A was 94% (95% confidence intervals 74% to 99%).

In outbreak investigations occurring in the trial, 26 clinical cases of hepatitis A (of a total of 34 occurring in the trial) occurred. No cases occurred in HAVRIX vaccinees.

Using additional virological and serological analyses post hoc, the efficacy of HAVRIX was confirmed. Up to three additional cases of very mild clinical illness may have occurred in vaccinees. Using available testing, these illnesses could neither be proven nor disproven to have been caused by HAV. By including these as cases, the calculated efficacy rate for prevention of clinical hepatitis A would be 84% (95% confidence intervals 60% to 94%).

The benefit of post-exposure vaccination has been studied in an animal model. Primates exposed to the virulent heterologous hepatitis A strain were vaccinated with either a single dose of 360 or 1440 ELISA unit vaccine 2 days after exposure. Only partial protection was observed in the animals vaccinated with the lower dose, with three of four animals developing hepatitis A. Post-exposure vaccination with 1440 ELISA units provided complete protection against disease and HAV transmission although 2 of the four animals had evidence of infection.

Impact of mass vaccination on disease incidence: A reduction in the incidence of hepatitis A was observed in two countries where a two-dose HAVRIX immunization program was implemented for children in their second year of life. The two countries had intermediate A hepatitis virus endemicity before the program:

- In Israel, two retrospective database studies showed 88% and 95% reduction in hepatitis A incidence in the general population 5 and 8 years after the implementation of the vaccination program, respectively. Data from National Surveillance also showed a 95% reduction in hepatitis A incidence as compared to the pre-vaccination period.
- 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. In paediatric hospitals in Panama City, confirmed acute hepatitis A cases were no longer diagnosed 4 years after implementation of the vaccination programme.
- The observed reductions in hepatitis A incidence in the general population (vaccinated and non-vaccinated) in both countries demonstrate herd immunity.

5.2 PHARMACOKINETIC PROPERTIES

Not relevant to vaccines

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available

Carcinogenicity

No data available

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The vaccine preparation contains aluminium hydroxide hydrate, aluminium (HAVRIX JUNIOR only), neomycin sulphate (trace amounts), polysorbate 20 and amino acid supplement in a phosphate buffered saline solution, dibasic sodium phosphate heptahydrate, monobasic potassium phosphate, sodium chloride, potassium chloride and water for injections.

6.2 INCOMPATIBILITIES

See Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

HAVRIX must be stored at +2 °C to +8 °C. DO NOT FREEZE, discard if vaccine has been frozen.

The shelf life of HAVRIX is three years from the date of manufacture at temperatures of +2 °C to +8 °C.

Stability

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 exposure to such temperatures, and are not recommendations for storage.

6.5 NATURE AND CONTENTS OF CONTAINER

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.

HAVRIX 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.

The tip cap and rubber plunger stopper of the pre-filled syringe are not made with natural rubber latex.

Not all presentations and pack sizes may be marketed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Not relevant to vaccines

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

GlaxoSmithKline Australia Pty Ltd

Level 4, 436 Johnston Street,

Abbotsford, Victoria, 3067

9 DATE OF FIRST APPROVAL

22 December 2009

10 DATE OF REVISION

19 July 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2	Updates to instructions for use
4.8	Editorial updates to adverse event information
6.5	Revision to container information

Version 9.0