NEW ZEALAND DATA SHEET

1. PRODUCT NAME

HAVRIX 1440: 1440 EU/mL inactivated hepatitis A virus (HM 175 hepatitis A virus strain) vaccine, suspension for injection.

HAVRIX JUNIOR: 720 EU/0.5 mL inactivated hepatitis A virus (HM 175 hepatitis A virus strain) vaccine, suspension for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (1.0 mL) of HAVRIX 1440 contains:

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

One dose (0.5 mL) of HAVRIX JUNIOR contains:

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

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 HAV infection in subjects at risk of exposure to HAV.

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.

In areas of low and intermediate prevalence of hepatitis A, immunisation with HAVRIX is particularly recommended in subjects who are, or will be, at increased risk of infection, such as:

Travellers:

Persons travelling to areas where the prevalence of hepatitis A is high. These areas include Africa, Asia, 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. Active immunisation is indicated for these individuals.

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, nursing, medical and paramedical personnel in hospitals and institutions, especially gastroenterology and paediatric units, sewage workers, food handlers, among others.

Homosexual men:

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

Abusers of injectable drugs; Persons with multiple sexual partners:

Epidemiological evidence suggests that IV drug abuse and multiple sexual partners are risk factors for hepatitis A infection.

Contacts of infected persons:

Since virus shedding from infected persons may occur for a prolonged period, active immunisation of close contacts is recommended.

Persons who require protection as part of hepatitis A outbreak control or because of regionally elevated morbidity

Specific population groups known to have a higher incidence of hepatitis A:

eg. American Indians, Eskimos, recognised community-wide HAV epidemics.

Subjects with chronic liver disease or who are at risk of developing chronic liver disease:

(eg. Hepatitis B and Hepatitis C chronic carriers and alcohol abusers).
Hepatitis A tends to compromise the outcome of chronic liver disease.

In areas of high prevalence of hepatitis A (eg. Africa, Asia, the Mediterranean basin, the Middle East, Central and South America) susceptible individuals may be considered for active immunisation.

Haemophiliacs

4.2 Dose and method of administration

Dose

Adults (16 years and older)

A single 1 mL dose of 1440 ELISA units is recommended 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. The exact duration of this protection subsequent to the booster dose is under evaluation (see Section 5.1 Pharmacodynamic properties).

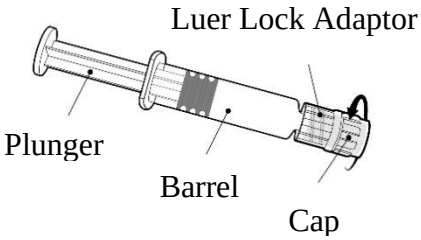
Children and adolescents (1 year up to and including 15 years)

A single 0.5 mL dose of HAVRIX JUNIOR is recommended 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 under evaluation (see Section 5.1 Pharmacodynamic properties).

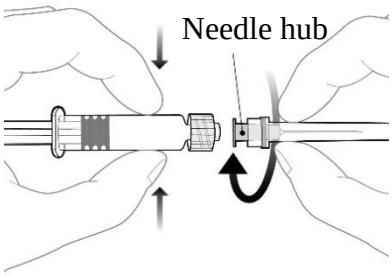
Method of administration

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.

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 in the gluteal region.

The vaccine should not be administered subcutaneously/intradermally since administration by these routes may result in less than optimal anti-HAV antibody response.

HAVRIX should under no circumstances be administered intravenously.

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. Firm pressure should be applied to the injection site (without rubbing) for at least two minutes.

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 administration of HAVRIX.

4.4 Special warnings and precautions for use

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

It is possible that subjects 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.

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

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.

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.

HAVRIX can be given to HIV-infected persons.

Seropositivity against hepatitis A is not a contraindication.

4.5 Interaction with other medicines 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.

Concomitant administration of immunoglobulins does not impact the protective effect of the vaccine.

When concomitant administration of other 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

Adequate human data on use during pregnancy and adequate animal reproduction studies are not available. However, as with all inactivated viral vaccines the risks to the foetus are considered to be negligible.

HAVRIX should be used during pregnancy only when clearly needed.

Breast-feeding

Adequate human data on use during lactation and adequate animal reproduction studies are not available. Although the risk can be considered as negligible, HAVRIX should be used during lactation only when clearly needed.

Fertility

No data available.

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 Undesirable effects

Tabulated list of adverse reactions

HAVRIX is well tolerated.

In controlled clinical studies, signs and symptoms were monitored in all subjects for four days following the administration of HAVRIX. A checklist was used for this purpose. The vaccinees were also requested to report any clinical events occurring during the study period.

The frequency of solicited adverse events was lower following the booster dose of HAVRIX. Most events reported were considered by the subjects as "mild" and did not last for more than 24 hours. The frequency of solicited adverse events following the administration of HAVRIX is not different from the frequency of solicited adverse events reported following the administration of other aluminium adsorbed purified antigen vaccines.

Of the local solicited adverse events the most frequently reported was injection site soreness (less than 0.5% reported as severe) which resolved spontaneously. Other local solicited adverse events reported were mild redness and swelling, with a frequency of about 4% of all vaccinations.

The systemic adverse events reported by vaccinees were essentially mild, most did not last for more than 24 hours and included headache, malaise, vomiting, fever, nausea, and loss of appetite. These events were reported with a frequency varying between 0.8% and 12.8% of vaccinations. All events resolved.

The nature of the signs and symptoms observed in children is similar to that of adults, however, these have been reported less frequently.

The safety profile presented below is based on data from more than 5300 subjects.

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

Clinical trials

Infections and infestations
Uncommon: upper respiratory tract infection, rhinitis

Metabolism and nutrition disorders
Common: appetite lost

Psychiatric disorders
Very common: irritability

Nervous system disorders
Very common: headache
Common: drowsiness
Uncommon: dizziness
Rare: hypoaesthesia, paraesthesia

Gastrointestinal disorders
Common: gastrointestinal symptoms (such as diarrhoea, nausea, vomiting)

Skin and subcutaneous tissue disorders
Uncommon: rash
Rare: pruritus

Musculoskeletal and connective tissue disorders
Uncommon: myalgia, musculoskeletal stiffness

General disorders and administration site conditions
Very common: pain and redness at the injection site, fatigue
Common: malaise, fever (≥37.5°C), injection site reaction (such as swelling or induration)
Uncommon: influenza like illness
Rare: chills

Post-marketing surveillance data

Very rarely fatigue, diarrhoea, myalgia, arthralgia, allergic reactions, including anaphylactoid reactions, and convulsions have been reported.

Immune system disorders
Anaphylaxis, allergic reactions including mimicking serum sickness

Vascular disorders
Vasculitis

Skin and subcutaneous tissue disorders
Angioneurotic oedema, urticaria, erythema multiforme

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic 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

Immune response

In clinical studies, 99% of vaccinees seroconverted 30 days after the first dose. In a subset of clinical studies where the kinetics of the immune response were studied, early and rapid seroconversion was demonstrated following administration of a single dose of HAVRIX in 79% of vaccinees at day 13, 86.3% at day 15, 95.2% at day 17 and 100% at day 19, which is shorter than the average incubation period of hepatitis A (4 weeks) (see Section 5.3 Preclinical safety data).

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 1440 Adult or HAVRIX JUNIOR (720 EU/0.5 mL). In clinical trials, virtually, 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 delayed up to 5 years. In a comparative trial, 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 titers following 2 doses of HAVRIX given 6 to 12 months apart has been evaluated.

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	97.69 %	94.22 %	100 %
30	96.53 %	92.49 %	99.42 %
35	94.22 %	89.02 %	98.93 %
40	92.49 %	86.11 %	97.84 %
Predictions for HAV-123			
25	97.22 %	93.52 %	100 %
30	95.37 %	88.89 %	99.07 %
35	92.59 %	86.09 %	97.22 %
40	90.74 %	82.38 %	95.37 %

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-wide outbreaks (Alaska, Slovakia, USA, UK, Israel and Italy). These studies demonstrated that vaccination with HAVRIX led to termination of the outbreaks. A vaccine coverage of 80% led to termination of the outbreaks 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 immunisation programme was implemented for children in their second year of life:

- 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 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. 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

Animal toxicology and/or pharmacology

Appropriate safety tests have been performed.

In an experiment in 8 non-human primates, the animals were exposed to a heterologous hepatitis A strain and vaccinated 2 days after exposure. This post exposure vaccination resulted in protection of all animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The vaccine preparation also contains neomycin sulphate (trace amounts), polysorbate 20 and amino acid supplement in a phosphate buffered saline solution.

6.2 Incompatibilities

HAVRIX should not be mixed with other vaccines or immunoglobulins in the same syringe.

6.3 Shelf life

3 years.

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

6.4 Special precautions for storage

Vaccine should be stored at +2 °C to +8 °C.
Do not freeze; discard if vaccine has been frozen.

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 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.
- 1 mL of suspension in a vial (type I glass) with a stopper (butyl rubber).

Monodose vials or prefilled syringes in packs of one

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.

- 0.5 mL of suspension in a vial (type I glass) with a stopper (butyl rubber).

Monodose vials or prefilled syringes in packs of one.

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

The content, upon storage, may present a fine white deposit with a clear colourless supernatant.

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 of HAVRIX, the vial/syringe should be well shaken to obtain a slightly opaque white suspension. Discard the vaccine if the content appears otherwise.

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

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

GlaxoSmithKline NZ Ltd
Private Bag 106600
Downtown
Auckland 1143
NEW ZEALAND

ph (09) 367 2900
fax (09) 367 2910

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 24 Feb 1994

10. DATE OF REVISION OF THE TEXT

1 March 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: 8.0