

DATA SHEET

Name of Medicinal Product

HAVRIX® 1440, HAVRIX® JUNIOR

inactivated hepatitis A virus (HM 175 hepatitis A virus strain)

Presentation

HAVRIX, hepatitis A virus vaccine is a sterile suspension containing formaldehyde-inactivated hepatitis A virus (HM175 hepatitis A virus strain) adsorbed onto aluminium hydroxide. Each dose contains not more than 10ng of neomycin sulphate.

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 inactivated with formaldehyde.

HAVRIX meets the World Health Organisation requirements for the manufacture of biological substances.

HAVRIX contains a purified sterile suspension of inactivated hepatitis A virus; the viral antigen content is determined by an ELISA test.

The dose of HAVRIX 1440 is standardised to ensure a viral antigen content of not less than 1440 ELISA Units (EI.U.) of viral antigens, in a 1.0 ml dose volume.

The dose of HAVRIX JUNIOR is standardised to ensure a viral antigen content of not less than 720 EI.U. of viral antigens, in a 0.5 ml dose volume.

Clinical Particulars

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.

Haemophiliacs

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.

Posology and method of administration**Dosage**

Adults (16 years and older): A single 1mL 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 Pharmacodynamic properties).

Children and adolescents (1 year up to and including 15 years): A single 0.5mL 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 Pharmacodynamic properties).

Method of Administration

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.

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.

Special warnings and special 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.

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.

Concomitant administration of typhoid, yellow fever, cholera (injectable) or tetanus does not interfere with HAVRIX immune response.

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.

Use during pregnancy and lactation

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 fetus are considered to be negligible. HAVRIX should be used during pregnancy only when clearly needed.

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.

Effects on ability to drive and use machines

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

Undesirable effects

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: $\geq 10\%$

Common: $\geq 1\%$ and $< 10\%$

Uncommon: $\geq 0.1\%$ and $< 1\%$

Rare: $\geq 0.01\%$ and $< 0.1\%$

Very rare: $< 0.01\%$

- **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: swelling, malaise, fever ($\geq 37.5^{\circ}\text{C}$), injection site reaction (such as 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

Overdose

Not applicable.

Pharmacological Properties

Pharmacodynamic properties

HAVRIX protects against hepatitis A by inducing specific anti-HAV antibodies.

In clinical studies involving subjects of 16- 50 years of age, specific humoral antibodies against HAV were detected in more than 88 % of vaccinees at day 15 and 99 % at month 1 following administration of a single dose of HAVRIX 1440.

In clinical studies involving subjects of 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 HAVRIX Junior.

In a study designed to interrupt an epidemic of hepatitis A in Alaska, nearly 5000 persons were vaccinated with one dose of HAVRIX (1440 or Junior according to the age of the vaccinee). 92% of tested recipients developed measurable anti-HAV responses. A vaccine coverage of 80% led to termination of the outbreaks.

Long term persistence of serum antibodies to hepatitis A virus after vaccination with HAVRIX is under evaluation. Nevertheless, data available after 5 years show persistence of antibodies which is consistent with a projected persistence of at least 20 years.

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

Pharmacokinetic properties

Not relevant to vaccines.

Preclinical safety data

Appropriate safety tests have been performed.

Pharmaceutical Particulars

Incompatibilities

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

Shelf life

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

Special precautions for storage

Vaccine should be stored at +2°C to +8°C.

Do not freeze; discard if vaccine has been frozen.

Additional information on the stability:

The following experimental data give an indication of the stability of the vaccine and are not recommendations for storage: HAVRIX has been kept at +37 °C for 3 weeks without a significant loss of potency.

Nature and content of container

The content, upon storage, may present a fine white deposit with a clear colourless supernatant. HAVRIX is presented in a monodose glass vial or prefilled glass syringe.

The vials are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements.

Instructions for use and handling and disposal (if appropriate)

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.

Medicine Classification

Prescription Only Medicine.

Package Quantities

HAVRIX 1440: Monodose vials and prefilled syringes in packs of one.

HAVRIX JUNIOR: Monodose vials and prefilled syringes in packs of one.

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