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HAVRIX™ 1440

HAVRIX™ 720 Junior Monodose

TITLE

Hepatitis A (inactivated) vaccine (adsorbed).

SCOPE

Hepatitis A (inactivated) vaccine (adsorbed).

Tradename

Havrix 1440
Havrix 720 Junior Monodose

Formulations and strengths

HAVRIX™, hepatitis A virus vaccine is a sterile suspension containing formaldehyde-inactivated hepatitis A virus (HM175 hepatitis A virus strain) adsorbed onto aluminium hydroxide.

The virus is propagated in MRC_5 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 Adult is standardised to ensure a viral antigen content of not less than 1440 ELISA Units (El.U.) of viral antigens, in a 1.0 ml dose volume.

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

Excipients

Aluminium hydroxide
Amino acid Supplement
Disodium phosphate
Monopotassium phosphate
Sodium chloride
Potassium chloride
Polysorbate 20
Water for injections

Residues

Neomycin sulphate (Havrix 720: less than 10 ng and Havrix 1440: less than 20 ng)
Formaldehyde

CLINICAL INFORMATION

Indications

HAVRIX™ is indicated for active immunisation against hepatitis A virus (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.

Dosage and administration

Posology

- ***Primary vaccination***

- Adults 19 years of age and above

A single dose of HAVRIX™ 1440 Adult (1.0 ml suspension) is used for primary immunisation.

- Children and adolescents from 1 year up to and including 18 years of age.

A single dose of HAVRIX™ 720 Junior (0.5 ml suspension) is used for primary immunisation.

- ***Booster vaccination***

After primary vaccination with either Havrix 1440 Adult or Havrix 720 Junior, a booster dose is recommended in order to ensure long term protection. This booster dose should be given at any time between 6 months and 5 years, but preferably between 6 and 12 months after primary dose. (see Pharmacodynamic effects).

- ***Route of administration***

HAVRIX™ is for **intramuscular** administration. The vaccine should be injected in the deltoid region in adults and children, in the antero-lateral part of the thigh in young children.

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 a less than optimal anti-HAV antibody response.

Havrix should under no circumstances be administered intravascularly.

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 (see *Formulations, Excipients* and *Residues*), or to subjects having shown signs of hypersensitivity after previous administration of HAVRIX™.
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 contra-indication for vaccination

Warnings and precautions

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 should always be readily available for treatment in case of a rare anaphylactic event following the administration of the vaccine. For this reason, the vaccinee should remain under medical supervision for 30 minutes after vaccination.

HAVRIX™ can be given to HIV-infected persons.

Seropositivity against hepatitis A is not a contra-indication.

Interactions

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 if immunoglobulins is considered necessary, the products must be given with different syringes and needles and at different injection sites.

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

Lactation
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.

Ability to perform tasks that require judgment, motor or cognitive skills

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

Adverse reactions

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

Frequencies per dose are defined as follows:
Very common: ≥ 10%
Common: ≥ 1% and < 10%
Uncommon: ≥ 0.1% and < 1%
Rare: ≥ 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 (≥37.5°C), injection site reaction (such as induration)
Uncommon: influenza like illness
Rare: chills

- **Post-marketing surveillance**

Immune system disorders
Anaphylaxis, allergic reactions including anaphylactoid reactions and mimicking serum sickness

Nervous system disorders
Convulsions

Vascular disorders
Vasculitis

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

Musculoskeletal and connective tissue disorders
Arthralgia

Overdosage

Cases of overdose have been reported during post-marketing surveillance. Adverse events reported following overdosage were similar to those reported with normal vaccine administration.

Clinical Pharmacology

Pharmacodynamics

ATC code

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

Pharmacodynamics effects

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

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 also non-clinical information)

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.

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 720 Junior. 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 10 years allows prediction that at least 97% of subjects will remain seropositive (>20 mIU/ml) 25 years after vaccination.

Current data do not support the need for further booster vaccination among immunocompetent subjects after a 2 dose vaccination course.

Pharmacokinetics

Evaluation of pharmacokinetic properties is not required for vaccines.

Clinical Studies

See section "*Pharmacodynamic effects*".

NON-CLINICAL INFORMATION

Animal toxicology and/or pharmacology

Appropriate safety tests have been performed.
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.

PHARMACEUTICAL INFORMATION

Shelf-life

The expiry date of the vaccine is indicated on the label and packaging.
When stored under prescribed conditions of temperatures between +2º C and +8º C, the shelf-life is three years.

Storage

Vaccines should be stored at +2º C to +8º C.

Do not freeze; discard if vaccine has been frozen.

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

Nature and contents of container

The contents, 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 Pharmacopaeia requirements.

Incompatibilities

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

Use and 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.

Manufacturer

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Licence Holder And Importer

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Licence Number

Havrix 1440	101-61-28393
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