WHO PRODUCT INFORMATION

NAME OF THE MEDICINAL PRODUCT

Havrix 1440 Adult suspension for injection
Havrix 720 Junior suspension for injection
Hepatitis A (inactivated) vaccine (adsorbed)

QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (1 ml) of Havrix 1440 Adult contains:

Hepatitis A virus (inactivated)[1,2]	1440 ELISA Units
[1]Produced on human diploid (MRC-5) cells	
[2]Adsorbed on aluminium hydroxide, hydrated	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, hydrated	0.25 milligrams Al^{3+}

Excipients: Amino acids for injections, disodium phosphate, monopotassium phosphate, polysorbate 20, potassium chloride, sodium chloride, water for injections.

Neomycin sulphate is present as a residue from the manufacturing process.
Havrix is a turbid liquid suspension. Upon storage, a fine white deposit with a clear colourless supernatant can be observed.

CLINICAL PARTICULARS

Therapeutic 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.

In areas of low to 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.

Persons at increased risk due to their sexual behaviour. Homosexuals, persons with multiple sexual partners.

Haemophiliacs.

Abusers of Injectable Drugs.

Contacts of Infected Persons. Since virus shedding of 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. For example American Indians, Eskimos, recognised community-wide HAV epidemics.

Subjects with chronic liver disease or who are at risk of developing chronic liver disease (e.g. Hepatitis B and Hepatitis C chronic carriers and alcohol abusers). Hepatitis A tends to compromise the outcome of the chronic liver disease.

In areas of intermediate to high prevalence of hepatitis A (e.g. 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

Posology

- **Primary vaccination**

- Adults and adolescents 16 years of age and above

A single dose of Havrix 1440 Adult (1 ml suspension) is used for primary immunisation.

- Children and adolescents from 1 year up to and including 15 years of age*

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

*It is acceptable for adolescents up to and including 18 years of age to receive a single dose of Havrix 720 Junior.

- **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 the primary dose (see Pharmacodynamic properties).

Method 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 Qualitative and Quantitative Composition), or to subjects having shown signs of hypersensitivity after previous administration of Havrix.

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.

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.

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.

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.

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.

Undesirable effects

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 trial data

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

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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

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).

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 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 17 years allows prediction that at least 95% (95% CI: 88% - 99%) and 90% (95% CI: 82% - 95%) 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-wide hepatitis A 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.

PHARMACEUTICAL PARTICULARS

Incompatibilities

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

Shelf life

The expiry date is indicated on the label and packaging.

Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze; discard if vaccine has been frozen.
Store in the original package in order to protect from light.
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.

Nature and contents of container

- Havrix 1440 Adult: 1 ml of suspension in a vial (type I glass) for 1 dose with a stopper (butyl rubber) - pack sizes of 1, 10, 25 and 100.
- Havrix 720 Junior: 0.5 ml of suspension in a vial (type I glass) for 1 dose with a stopper (butyl rubber) - pack sizes of 1, 10, 25 and 100.

Not all pack sizes may be marketed.

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 should be well shaken to obtain a slightly opaque white suspension. Discard the vaccine if the content appears otherwise.

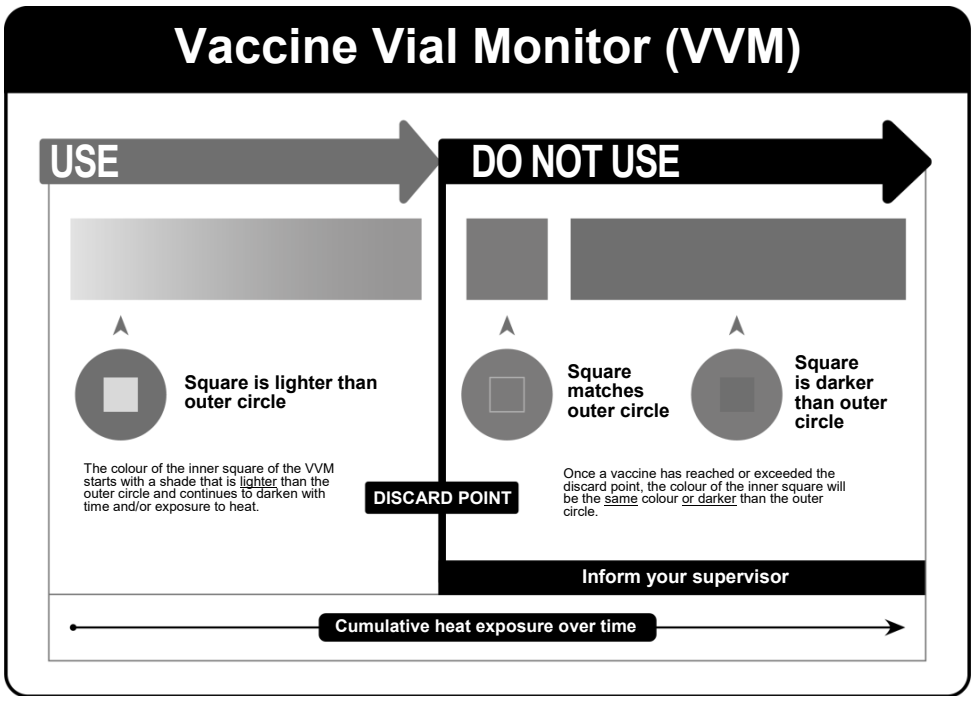
Any unused product or waste material should be disposed of in accordance with local requirements.

Vaccine Vial Monitor (see VVM infographic at the end of the leaflet)

The Vaccine Vial Monitor (VVM) is part of the label used for all Havrix batches supplied by GlaxoSmithKline Biologicals. The colour dot that appears on the label of the vial is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the inner square. Its colour will change progressively. As long as the colour of this square is lighter than the colour of the outer circle, then the vaccine can be used. As soon as the colour of the inner square is the same colour as the outer circle or of a darker colour than the outer circle, then the vial should be discarded.

It is absolutely critical to ensure that the storage conditions specified above (in particular the cold chain) are complied with. GlaxoSmithKline Biologicals will assume no liability in the event Havrix has not been stored in compliance with the storage instructions.



For further information, please contact the manufacturer.

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