Havrix™

Version number: GDS012/IPI08

Havrix™

Havrix™ 1440 Adult/720 Junior

Inactivated hepatitis A vaccine

QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (1.0 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+}

Turbid liquid suspension. Upon storage, a fine white deposit with a clear colourless supernatant can be observed.

PHARMACEUTICAL FORM

Suspension for injection.

CLINICAL PARTICULARS

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 (HB) and Hepatitis C (HC) chronic carriers and alcohol abusers).

In areas of intermediate to 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.

Dosage and Administration

- **Posology**

Primary vaccination

- Adults from age 19 years and onwards

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 the primary dose (see *Pharmacodynamics*).

- **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* and *List of excipients)*, or to subjects having shown signs of hypersensitivity after previous administration of **Havrix™**.

Warnings and Precautions

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.

Interactions

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 immunoglobulines 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.

Effects on Ability to Drive and Use Machines

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%

System Organ Class	Frequency	Adverse reactions
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 data		
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	

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

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

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) (see also *Pre-clinical 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™ 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 titres 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 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 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.

Pre-clinical Safety Data

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 PARTICULARS

List of Excipients

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

Neomycin sulphate is present as residual from the manufacturing process.

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

Store in the original package in order to protect from light.

Havrix™ 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.

Nature and Contents of Container

Havrix™ is presented in a glass vial or pre-filled glass syringe.

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

Not all presentations are available in every country.

Instructions for Use/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.

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