For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

HAVRIX 1440 (ADULT) / 720 (JUNIOR)

Inactivated Hepatitis A Vaccine (Adsorbed) IP

1. NAME OF THE MEDICINAL PRODUCT

Inactivated Hepatitis A Vaccine (Adsorbed) IP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

HAVRIX 1440:

Each dose (1.0 mL) contains:
Hepatitis A virus antigen (HAV)[HM 175 strain , propagated in MRC_5 human diploid cells] ……. 1440 ELISA units
Aluminium (as adjuvant) …….. 0.5 mg [as hydrated Aluminium Oxide IP]

HAVRIX 720:

Each dose (0.5 mL) contains:
Hepatitis A virus antigen (HAV)[HM 175 strain, propagated in MRC_5 human diploid cells] …… 720 ELISA units
Aluminium (as adjuvant) …… 0.25 mg [as hydrated Aluminium Oxide IP] .

3. PHARMACEUTICAL FORM

Suspension for injection

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For active immunisation against infections caused by hepatitis A virus (HAV) for Children and Adolescents (from 1 year up to and including 18 years of age) and adults (from age 19 years and onwards). The booster dose may be given at any time between 6 months and 5 years, but preferably between 6 and12 months after the primary dose.

4.2. Posology and method of 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 *section 5.1 Pharmacodynamic Properties*).

Method of Administration

HAVRIX must be injected intramuscularly only. It is recommended to inject the vaccine in the deltoid region in adults and in children. The deltoid muscle is not yet sufficiently developed in very young children, so the vaccine should be administered in the anterolateral part of the thigh. The injection must not be administered in the gluteal region subcutaneously or intradermally because the antibody response might be sub-optimal.

However, the vaccine should be administered subcutaneously in patients suffering from thrombocytopoenia or subject to serious haemorrhage (e.g. haemophiliacs) because bleeding could occur after intramuscular administration in such persons. Strong pressure should be exercised at the site of the injection (without rubbing) for at least 2 minutes.

The vaccine may never be administered intravascularly.

4.3. Contraindications

HAVRIX may not be administered to persons with a known hypersensitivity to a component of the vaccine (see *Section 2 Qualitative and Quantitative Composition* and *Section 6.1 List of Excipients)*, or to those who have shown signs of hypersensitivity during a previous administration of *HAVRIX*.

4.4. Special warnings and precautions for use

As in the case of other vaccines, *HAVRIX* will not be administered to patients with an acute febrile illness. A common infection does not constitute a contra-indication, however.

People may already be in the incubation period of hepatitis A at the time of vaccination. In such circumstances, it is not certain that *HAVRIX* will prevent hepatitis A.

In patients undergoing haemodialysis and in subjects with a deficient immune system, the anti-HAV (hepatitis A virus) may remain insufficient after a primo-vaccination; in such patients, additional doses of the vaccine may have to be administered to attain an adequate antibody count.

HAVRIX may contain traces of neomycin. The vaccine will have to be used with caution in patients with a known hypersensitivity to this antibiotic.

As with every product administered parenterally, it is recommended to prepare an appropriate medical treatment for immediate use, if an anaphylactic reaction were to occur after the administration of the vaccine. For this reason, the vaccinated persons should remain under medical supervision for half an hour after vaccination.

Syncope (fainting) can occur after any vaccination, or even before with adolescents in particular, as a psychogenic reaction to injection. This can be accompanied by several neurological signs such as a transient disturbance in vision, paraesthesia and tonic clonic movements of the limbs during the recovery phase. It is important that caution be set up to avoid injuries in the event of fainting.

HAVRIX may be administered with persons who are HIV positive.

Vaccination is not justified in subjects with anti-hepatitis A IgG.

This vaccine contains less than 1 mmol of sodium (23 mg) per dose, it is therefore essentially 'sodium-free'.

This vaccine contains potassium, less than 1 mmol (39 mg) per dose, it is therefore essentially 'potassium-free'.

4.5. Interaction with other medicinal products and other forms of interaction

As *HAVRIX* is an inactivated vaccine, it can be administered simultaneously with other inactivated vaccines without any apparent interference with the immune response. When the simultaneous administration of other vaccines or immunoglobulins is deemed necessary, they must be injected with different syringes at different injection sites.

HAVRIX may not be mixed with other vaccines in the same syringe.

HAVRIX can be administered simultaneously with vaccines against typhoid fever, yellow fever, tetanus and with MMR (Measles, Mumps, and Rubella) or MMRV (Measles, Mumps, Rubella and Varicella) vaccine.

In case of concomitant administration, separate syringes and different injection sites must be used.

Concomitant administration of *HAVRIX* and serum immunoglobulins does not alter the protective effect of the *HAVRIX* vaccine.

4.6. Pregnancy and lactation

Pregnancy

The effect of the inactivated hepatitis A virus antigen on foetal development has not been evaluated. However, like all inactivated viral vaccines, the risks for the foetus are considered negligible.

The vaccine should not be used in pregnant women unless genuinely necessary.

Lactation

The effect on breastfeeding infants of administration of *HAVRIX* to the mother has not been evaluated in clinical studies. The risk-benefit balance of administering *HAVRIX* to breastfeeding women should be carefully evaluated by caregivers.

4.7. Effects on ability to drive and use machines

It is very unlikely that the vaccine would have any effect on the ability to drive and use machines.

4.8. Undesirable effects

Clinical Trials

The safety profile presented below is based on data collected in 5343 subjects, including 1676 children, vaccinated with *HAVRIX* in clinical trials (total vaccinated cohort). A total of 3193 doses of *HAVRIX* Junior 720 and 7131 doses of *HAVRIX* 1440 were administered in clinical studies. A total of 3971 doses of *HAVRIX* was administered concomitantly with *ENGERIX B* to 2064 adult subjects.

Frequencies, per dose, are defined as follows:

Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥1/1000 to < 1/100
Rare: ≥1/10000 to < 1/1000
Very rare: < 1/10000

Undesirable effects reported with HAVRIX Junior 720

<u>Infections and infestations</u>

Uncommon: rhinitis

<u>Metabolism and nutrition disorders</u>

Common: loss of appetite

<u>Psychiatric disorders</u>

Very common: irritability

Nervous system disorders

Common: drowsiness, headaches
Very rare: neuritis, including Guillain-Barré syndrome and transverse myelitis.

Gastrointestinal disorders

Common: nausea
Uncommon: diarrhoea, vomiting

Skin and subcutaneous tissue disorders

Uncommon: rash

General disorders and administrative site conditions

Very common: pain and redness at injection site
Common: swelling, malaise, fever (> 37.5°C)
Uncommon: reaction at the injection site (induration)

Undesirable effects reported with HAVRIX 1440

Infections and infestations

Uncommon: upper respiratory tract infection, rhinitis

Metabolism and nutrition disorders

Common: loss of appetite

Nervous system disorders

Very common: headaches
Uncommon: dizziness
Rare: hypoaesthesia, paraesthesia
Very rare: neuritis, including Guiliain-Barré syndrome and transverse myelitis.

Gastrointestinal disorders:

Common: gastrointestinal syndromes, diarrhoea, nausea
Uncommon: vomiting

Skin and subcutaneous tissue disorders

Rare: pruritis

Musculoskeletal and systemic disorders:

Uncommon: myalgia, musculoskeletal stiffness

General disorders and administrative site conditions

Very common: pain and redness at injection site, fatigue
Common: swelling, malaise, fever (>37.5°C), reaction at the injection site (induration)
Uncommon: influenza like illness
Rare: shivering

Post-marketing surveillance

Immune system disorders

Anaphylactic reactions, allergic reactions, including anaphylactoid reactions and serum sickness like disease.

Nervous system disorders

Convulsions

Vascular disorders

Vasculitis

Skin and subcutaneous tissue disorders

Angioneurotic oedema, urticaria, erythema multiforme

Musculoskeletal and connective tissue disorders

Arthralgia

4.9. Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: hepatitis A vaccine, ATC code: J07 B C 02.

HAVRIX protects against infection caused by the hepatitis A virus (HAV) by inducing the production of specific (anti-HAV) antibodies against this virus.

Immune response

Clinical studies have shown that specific humoral anti-HAV antibodies are obtained in 99% of the vaccinated subjects, 30 days after the first vaccine dose.

In clinical studies where the kinetic curve of the immuno response was examined, a rapid and immediate seroconversion was shown after the administration of a single dose of *HAVRIX* in 79% of the vaccinated subjects on the 13th day, in 86.3% on the 15th day, in 95.2% on the 17th day, and in 100% on the 19th day, which is shorter than the average incubation period of the illness (4 weeks).

Persistence of the immune response

For a long term protection, a booster dose must be administered between 6 and 12 months after the first dose of *HAVRIX* 1440 or *HAVRIX* 720 Junior. During clinical trials, all the vaccinated subjects were virtually seropositive one month after the booster dose.

However, if the booster dose was not administered between 6 and 12 months after the first dose, it can be administered up to 5 years at the latest. In a comparative test, a booster dose administered 5 years after the first dose confers similar antibody titres to those conferred by a booster dose administered 6 to 12 months after the first dose.

The long-term persistency of antibodies against hepatitis A after 2 doses of *HAVRIX* administered between intervals of 6 and 12 months has been evaluated.

Data available after 17 years allow the prediction that at least 95% (95% CI: 88%- 99%) and 90% (95% CI: 82%-95%) of subjects will remain seropositive (> 15mIU/mL) 30 years and 40 years respectively after vaccination.

Current data do not justify the need for a booster vaccination in immunocompetent subjects after a vaccination scheme with 2 doses.

The efficacy of *HAVRIX* in preventing an HAV infection among persons in contact with the patients was evaluated in a blind clinical trial. Although no control group was given immunoglobulins (IG), this study suggests that *HAVRIX* is efficacious in preventing infection after exposure and that the vaccine may be recommended to people around patients in primary cases of HAV infection when immunoglobulins cannot be administered.

HAVRIX is well tolerated in seropositive and seronegative subjects.

Primates exposed to the virulent heterologous strain of hepatitis A were vaccinated 2 days after exposure. This post-exposure vaccination provided total protection to the animals.

Efficacy of *HAVRIX* in controlling epidemics
The efficacy of *HAVRIX* was evaluated in different communities affected by hepatitis A epidemics (Alaska, Slovakia, USA, UK, Israel and Italy). These studies showed that vaccination with *HAVRIX* was effective. 80% vaccine cover resulted in controlling the epidemic in 4 to 8 weeks.

Impact of mass vaccination on the incidence of the disease

A reduction in the incidence of hepatitis A was observed in countries where a vaccination programme providing for two doses of *HAVRIX* had been started for children in the second year of life.

— In Israel, two retrospective studies carried out on the basis of databases revealed an 88% and 95% reduction in the incidence of hepatitis A in the general population 5 and 8 years respectively after the launch of the vaccination programme. The data from the national surveillance programme also revealed a reduction of 95% in the incidence of hepatitis A compared with the time before vaccination was carried out.

— In Panama, a retrospective study carried out on the basis of a database revealed a 90% reduction in the incidence of hepatitis A reported in the population vaccinated, as well as a reduction of 87% in the general population, 3 years after the launch of the vaccination programme. In paediatric hospitals in Panama City, not a single confirmed case of acute infection with hepatitis A virus was diagnosed 4 years after the launch of the vaccination programme.

— The reduction in the incidence of hepatitis A observed in the general population (vaccinated and not vaccinated) in the two countries show collective immunity.

5.2. Pharmacokinetic properties

An evaluation of pharmacokinetic properties is not required for vaccines.

5.3. Preclinical safety data

Pre-clinical data reveal no special hazard for humans based on general safety studies.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Aluminium (as Aluminium Hydroxide), amino acids for injections, disodium phosphate anhydrous, monopotassium phosphate, polysorbate 20, potassium chloride, sodium chloride, water for injections.

6.2. Incompatibilities

This vaccine must not be mixed with other vaccines in the same syringe.

6.3. Shelf life

36 months

The expiry date is indicated on the label and packaging.

6.4. Special precautions for storage

Store in the original pack away from light.

Store in a refrigerator (between +2°C and +8°C).

Do not freeze; destroy the vaccine if it has been frozen.
The stability data indicate that *HAVRIX* is stable at temperatures not exceeding 25°C for 3 days. These data are intended as a guide for health professionals only if there is a temporary departure from the recommended temperature.

Keep out of reach of children.

6.5. Nature and contents of container

HAVRIX is presented in a glass vial or prefilled glass syringe.

Presentations:

HAVRIX 1440 ADULT: 1.0 mL in vial OR in prefilled glass syringe (type I glass) with a plunger stopper (butyl rubber) and with a rubber tip cap.
HAVRIX 720 JUNIOR: 0.5 mL in vial OR in prefilled glass syringe (type I glass) with a plunger stopper (rubber) and with a rubber tip cap.

All presentations may not be marketed in the country.

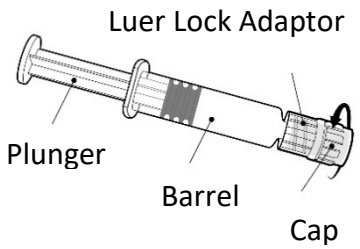
6.6. Special precautions for disposal and other handling

The vaccines must be examined visually, like all products administered parenterally, to verify that there are no foreign particles or abnormal colouration.

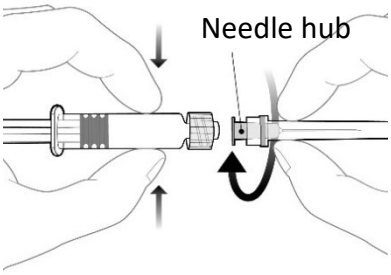
At rest, the content shows a slight whitish deposit with a colourless clear liquid above it.

The vaccine must be shaken well before use in order to obtain a white, slightly opaque suspension. If the appearance of the content is different, the product may not be used.

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.

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Pharmaceuticals Limited,
Registered office:
Dr. Annie Besant Road, Worli
Mumbai 400 030, India.

8. MARKETING AUTHORISATION NUMBER(S)

12-7/94-DC

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 5th February, 1998.

For further information please contact:
GlaxoSmithKline Pharmaceuticals Limited
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Dr. Annie Besant Road, Worli
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