**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 ml) contains:
Hepatitis A virus antigen (HAV)[HM 175 strain, propagated in MRC5 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 MRC5 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**

HAVRIX is indicated for active immunisation against infections caused by hepatitis A virus (HAV).

**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 thrombocytopenia 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 tonicoclonic 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.

**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.

Concomitant administration of vaccines against typhoid fever, yellow fever or tetanus does not interfere with the immune response of HAVRIX vaccine.

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 was 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, < 1/10
Uncommon: ≥1/1000, < 1/100
Rare: ≥1/10000, < 1/1000
Very rare: < 1/10000

Undesirable effects reported with HAVRIX Junior 720

Infections and infestations

Uncommon: rhinitis

Metabolism and nutrition disorders

Common: loss of appetite

Psychiatric disorders

Very common: irritability

Nervous system disorders

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

Gastrointestinal disorders:

Common: gastrointestinal syndromes, diarrhoea, nausea
Very common: vomiting

Skin and subcutaneous tissue disorders

Rare: pruritis

Musculoskeletal and connective tissue disorders:

Very rare: 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 pseudo-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

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, code ATC: 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.

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).
The efficacy of *HAVRIX* in interrupting an epidemic of hepatitis A was studied in large populations (Alaska, Slovakia, USA, UK, Israel and Italy). These studies showed that vaccination with *HAVRIX* was efficacious. A vaccine coverage of 80% led to termination of the outbreaks within 4 to 8 weeks.

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.

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, monopotassium phosphate, polysorbate 20, potassium chloride, sodium chloride, water for preparation 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 a refrigerator (between +2°C and +8°C).
Do not freeze; destroy the vaccine if it 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.

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.
HAVRIX 720 JUNIOR: 0.5 ml in vial OR in prefilled glass syringe

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

Not all the presentations may be marketed in India.

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.

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)

Not applicable

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 5th February, 1998

| Manufactured by: | Imported, Labelled & Packed by: | For further information please contact:
| GlaxoSmithKline Biologicals s.a. Rue de l’Institut, 89 B-1330 Rixensart, Belgium. | GlaxoSmithKline Asia Pvt Ltd., Plot No. A-10/1, Additional M.I.D.C., Ambad-Pathardi Block, Nashik-422010, India | GlaxoSmithKline Pharmaceuticals Limited, Registered office: Dr. Annie Besant Road, Worli Mumbai 400 030, India |

HAVRIX is a registered trademark of GlaxoSmithKline

Version HAX/PI/IN/2015/01 dated 23-July-2015

Aligned to SPC dated 21 June 2013 (adapted from GDS 11/ IPI 07 dated 26 March 2012)