SUMMARY OF PRODUCT CHARACTERISTICS

Havrix Adults Vaccine

1. NAME OF THE MEDICINAL PRODUCT

Havrix Adults Vaccine
Suspension for Injection.
Hepatitis A (inactivated) vaccine (adsorbed).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One dose (1.0 ml) contains:
Hepatitis A virus (inactivated)[1,2] 1440 ELISA Units

[1] Produced on human diploid (MRC-5) cells
[2]Adsorbed on aluminium hydroxide, hydrated Total: 0.50 milligrams Al^{3+}

Havrix Adults Vaccine may contain traces of neomycin B sulphate, which is used during the manufacturing process (see section 4.3).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in a prefilled syringe
Slightly opaque white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Active immunisation with hepatitis A vaccine is recommended for non-immune adult and adolescent (16 years of age and above) travellers to high risk areas, (Africa, Asia, Central and South America, the Middle East, possibly Southern and Eastern Europe).

Other high risk non-immune groups may be considered for immunisation.

- Those with recent close contact with infected individual
- Child care workers
- Staff and residents at institutions for persons with mental handicap
- Persons with haemophilia and recipients of plasma-derived clotting factors
- Patients with chronic liver disease especially if visiting a high-risk area
- Health care workers
- Food handlers
- Sewage workers
- Prison officers
- Those with renal failure prior to dialysis
- Military and diplomatic personnel
- Intravenous drug abusers
- Homosexuals
- Persons with multiple sexual partners

It is also indicated for use during outbreaks of hepatitis A infection.

If there is a history of jaundice, age over 50 years or residence in high risk areas, then screening for immunity to hepatitis A is advised before immunisation. If the blood test confirms immuity to hepatitis A, immunisation is not needed.

4.2 Posology and method of administration

Posology

Primary Vaccination

Primary immunisation consists of a single dose of Havrix Adults Vaccine.

Havrix Adults confers protection against hepatitis A within two to three weeks (See Section 5.1, Pharmacodynamic Effects).

If exposure to a high risk of contracting hepatitis A is expected before completion of primary immunisation or if protection is needed less than two weeks before departure, concomitant administration of immune serum globulin might be considered. In this case, the hepatitis A vaccine should be given at a different site.

Serological data indicate that there should be continuing protection against Hepatitis A for up to 5 years after the first dose in subjects who responded to the initial vaccination.

Booster Vaccination

After primary vaccination with Havrix Adults Vaccine, 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 effects).

Clinical data demonstrate that anti-HAV antibodies persist for at least 10 years in vaccinees who receive the complete vaccination course (i.e. 2 doses of Havrix Adults Vaccine; See Section 5.1, Pharmacodynamic effects)

Havrix Adults is not recommended in persons under 16 years of age.

Method of administration

Havrix Adults is for intramuscular use only and must not be given intravascularly. The vaccine should be administered into the deltoid region and not in the gluteal region.

Exceptionally the vaccine may be administered subcutaneously in patients with thrombocytopenia or bleeding disorders. Firm pressure should be applied to the injection site (without rubbing) for at least two minutes. However, this route of administration may result in suboptimal response to the vaccine.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 to or neomycin.
Hypersensitivity after previous administration of hepatitis A vaccine.

Havrix contains traces of neomycin. The vaccine should not be used in subjects with known hypersensitivity to neomycin.

The administration of Havrix Adults should be postponed in subjects suffering from acute severe febrile illness.

4.4 Special warnings and special precautions for use

As with all vaccinations, appropriate medication (e.g. adrenaline) should be readily available for immediate use in case of anaphylaxis.

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.

It is possible that subjects may be in the incubation period of hepatitis A infection at the time of immunisation. It is not known whether Havrix Adults 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 the primary immunisation and such patients may therefore require administration of additional doses of vaccine.

This medicine contains potassium, less than 1 mmol (39 mg) per 1 ml dose, i.e. essentially ‘potassium- free’. This medicinal product contains less than 1 mmol sodium (23 mg) per 1 ml dose, that is to say essentially ‘sodium- free’.

4.5 Interaction with other medicinal products and other forms of Interaction

The concomitant administration of Havrix with normal immunoglobulin does not influence the seroconversation rate but may result in a relatively lower HAV antibody titre than when the vaccine is given alone. Havrix and immunoglobulins should be administered at separate injection sites.
Preliminary data on the concomitant administration of Havrix, with recombinant hepatitis B virus vaccine suggests that there is no interference in the immune response to either antigen.
Interference with immune response is unlikely to occur when Havrix Adults is administered with other inactivated or live vaccines.
Havrix Adults can be given concomitantly with monovalent and combination vaccines comprised of measles, mumps, rubella and varicella.
When concomitant administration is considered necessary the vaccines must be given at different injection sites.
Havrix Adults must not be mixed with other vaccines in the same syringe.

4.6 Fertility, pregnancy and lactation

Pregnancy
The effect of Havrix Adults on foetal development has not been assessed. However, as with all inactivated viral vaccines the risks to the foetus are considered to be negligible. Havrix Adults should be used during pregnancy only when clearly needed.

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Breast-feeding
The effect on breast-fed infants of the administration of Havrix Adults to their mothers has not been evaluated in clinical studies. Havrix Adults should therefore be used with caution in breast-feeding women.

Fertility
No fertility data are available.

4.7 Effects on ability to drive and use machines

Havrix has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

In controlled clinical studies, the most commonly reported reactions after administration of Havrix Adults were irritability, headache, pain and redness at the injection site and fatigue.

The safety profile presented below is based on data from more than 5300 subjects.
Frequencies per dose are defined as follows:
Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1,000 to < 1/100
Rare: ≥1/10,000 to < 1/1,000
Very rare: < 1/10,000

- 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 and 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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to Pharmaceutical Services, Ministry of Health, CY-1475, www.moh.gov.cy/phs Fax: + 357 22608649.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Hepatitis A vaccine, 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 was 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. In clinical trials, virtually all vaccinees were seropositive one month after the booster dose.

Long term persistence of hepatitis A antibody titres has been evaluated following 2 doses of Havrix given 6 to 12 months apart to healthy immunocompetent subjects aged 17 to 40 years. 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.
Current data do not support the need for further booster vaccination among immunocompetent subjects after a 2-dose vaccination course.

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 outbreaks. These studies indicated that administration of a single dose of Havrix contributed to termination of the outbreaks. In one study, vaccine coverage in excess of 80% was followed by termination of the outbreak 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 immunization 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.

5.2 Pharmacokinetic properties

Not applicable to vaccine products.

5.3 Preclinical safety data

Not applicable to vaccine products.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 20, amino acids for injection, disodium phosphate anhydrous, monopotassium phosphate, sodium chloride, potassium chloride, and water for injections. For adsorbent, see section 2.

6.2 Incompatibilities

Not applicable.

6.3 Shelf- life

36 months.

6.4 Special precautions for storage

Store at 2°C-8°C in a refrigerator. Store in the original package in order to protect from light. Do not freeze. 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.

6.5 Nature and contents of container

Colourless glass vials (Type I, Ph Eur) with grey butyl rubber stoppers and aluminium overcaps fitted with avocado coloured flip-off tops containing 1 ml of suspension in packs of one.
1 ml of suspension in prefilled syringe (type I glass) with a plunger stopper (rubber butyl) with or without needles - pack size of 1.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

The vaccine should be inspected visually for any foreign particulate matter and/or variation of physical aspect prior to administration. Before use, the product should be well shaken to obtain a slightly opaque white suspension. Discard if the contents of the syringe appear otherwise.

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals S.A.
Rue de l'Institut 89
1330 Rixensart
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

16694

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05.08.96
Date of latest renewal: 21.03.12

10. DATE OF REVISION OF THE TEXT

12 August 2020