Unit: Technical Assessment Unit

Public assessment report for biological products

Havrix 1440

Administrative information:

Trade name of the medicinal product:	Havrix 1440
INN (or common name) of the active substance(s):	Hepatitis A viral harvest, purified harvest and inactivated harvest
Manufacturer of the finished product	GlaxoSmithKline Biologicals S.A. Parc de la Noire Epine Rue Fleming 20 1300 Wavre Belgium
Marketing Authorization holder	GlaxoSmithKline Biologicals S.A. 89, rue de l'Institut 1330 Rixensart Belgium
Applied Indication(s):	Active immunization against Hepatitis A virus infection.
Pharmaceutical form(s) and strength(s):	Suspension for Injection 1440 EL.U per ml
Route of administration	IM injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

ATC	Anatomical Therapeutic Class
AE	Adverse Event
CI	Confidence Interval
EU	European Union
ELISA	Enzyme-Linked Immunosorbent Assay
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HAV	Hepatitis A virus

IM	Intramuscular
M-M-R™II	Measles, Mumps and Rubella Vaccine, Live
MCB	Master Cell Bank
MRC5	Medical Research Council cell strain 5 (human diploid fibroblast cell line)
Protocol 010	Phase III randomized comparative clinical study supporting the manufacturing change
rHA	Recombinant human albumin
SC	Subcutaneous
SAE	Serious Adverse Event
TCID50	Median Tissue Culture Infectious Dose
VARIVAX™	Live Attenuated Varicella Virus Vaccine
WCB	Working Cell Bank

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1. **General introduction about the product including brief description of the AI, its mode of action and indications:**
- Havrix Vaccine is used for the active immunization against Hepatitis A virus infection. The HAV vaccine is a sterile suspension containing inactivated Hepatitis A virus (HAV) adsorbed onto aluminium hydroxide. The pharmaceutical form of the vaccine is a turbid liquid suspension for injection. The HAV 1440 Adult vaccine contains 1440 EL.U. of HAV antigen per dose. The nominal volume of the vaccine in the final container is 1ml.

2. **Quality aspects:**

2.2.1 Introduction

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Havrix Adult is an inactivated hepatitis A vaccine containing purified, formaldehyde-inactivated hepatitis A virus (HM175 strain, RIT4380) propagated in human diploid MRC-5 cells. The vaccine antigen is manufactured using a well-established cell culture process followed by purification and viral inactivation. The quality assessment focused on the manufacture and control of the drug substance and drug product, including the manufacturing process, control of materials, specifications, analytical methods, stability, and container closure system.

2.2.2 Drug Substance (Active ingredient)

- **General information**

- The active ingredient of GlaxoSmithKline (GSK) Biologicals Havrix 1440 vaccine is Hepatitis A viral harvest, purified harvest and inactivated harvest.
- The production cell line is Human diploid cells, strain MRC-5 initiated from foetal lung tissue.
- The bulk vaccine is a clear colorless liquid free from foreign particles.
- Biological, physico-chemical, biochemical, immunological characterization of Hepatitis A viral particles is mentioned in the MA file.
- European pharmacopoeia name of Drug Substance (monograph no. 1107): Hepatitis A viral harvest, purified harvest and inactivated harvest.

- **Manufacture, process controls and characterization:**

Manufacturer:
<u>Manufacturing & testing of the drug substance (active ingredient):</u>
GlaxoSmithKline Biologicals S.A.89, rue de l'Institut, 1330 Rixensart, Belgium.

Description of Manufacturing Process and Process Controls.
Production of the Hepatitis A bulk can be divided into the following stages:
- Cell substrate preparation
- Virus inoculation
- Virus replication
- Virus harvest
- Purification
- Inactivation
- Storage
- Flow diagrams for the HAV inoculum production process and the HAV bulk antigen production process are provided in the MA file.
- A detailed description of the manufacturing process is provided in the MA file.

Control of Materials.
- MRC-5 human diploid cells are used as cell substrate for HAV replication.

- The passage history of the MCB and the flow chart for the WCB production are provided in the MA file.
- The quality control testing performed at various stages of the preparation of the vaccine bulk is provided in details in the MA file.

- **Controls of Critical Steps and Intermediates.**
  The tests conducted during the process controls and the quality control release tests which are conducted to ensure the product quality and consistency are provided in the MA file.

  Process Validation
  - The process validation and evaluation performed on the drug substance manufacturing process is provided in the MA file to demonstrate that the process consistently yields a product which reliably meets specifications.

- **Manufacturing Process Development.**
  - The production process of Inactivated Hepatitis A bulk evolved and changes were introduced. These changes consist of:
  - Change in cell bank
  - Change in working seed
  - Scale-up of antigen production
  - Use of irradiated serum and trypsin

- **Characterization.**
  The characterization comprised the Characterization and identification of viral particles, and Determination of HAV immunogenicity and antigenicity before and after inactivation.

- **Specification**
  The specifications tests of Hepatitis A (MRC5) bulk, Hepatitis A (MRC5) purified bulk and Inactivated Hepatitis A (MRC5) bulk are according to the Ph. Eur.

- **Analytical Procedures.**
  Details of the test methods are provided in the MA file.

- **Batch analysis.**
  Batch analysis data are provided for Hepatitis A virus harvest, Hepatitis A virus purified bulk and Inactivated Hepatitis A virus bulk.

- **Reference Standards or Materials.**

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An in-house inactivated HAV bulk lot, representative of the commercial manufacturing process serves as reference standard for testing of Hepatitis A virus (HAV) antigen content on HAV bulk.

- **Container closure system**

The harvests and purified and inactivated bulks are stored in High Density Polyethylene (HDPE) containers.

- **Stability of drug substance**

- Recommended storage conditions: -45°C.
- The proposed shelf-life is 24 months for the harvest and 24 or 42 months for the purified bulk.

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**

- The HAV vaccine is a sterile suspension containing inactivated Hepatitis A virus (HAV) adsorbed onto aluminium hydroxide. The pharmaceutical form of the vaccine is a turbid liquid suspension for injection.
- The HAV 1440 Adult vaccine contains 1440 EL.U. of HAV antigen per dose. The nominal volume of the vaccine in the final container is 1ml.
- The active substance is Hepatitis A virus antigen (HAV), HM175 strain. The excipients include aluminum hydroxide, amino acids for injection, disodium phosphate anhydrous, monopotassium phosphate, sodium chloride, potassium chloride, polysorbate 20 and water for injection.

- Pharmaceutical Development including brief description on Components of drug product.

- The HAV 1440 Adult vaccine contains 1440 EL.U. of HAV antigen per dose. The nominal volume of the vaccine in the final container is 1ml.
- The initial compositions of the current HAV vaccines were identical to the first HAV vaccines in all aspects except the quantity of active ingredient per vaccine dose.
- Later, the composition of the current HAV vaccine has been changed - 2-phenoxyethanol (2PE), initially added during the adsorption/formulation step as preservative (final concentration 5 mg/ml) to prevent the microbial contamination, was removed from the vaccine composition (formulation).

- Formulation Development

HAV vaccine formulation development was performed with the first HAV vaccine. This consisted of change to the formulation buffer, change to the method for determination of HAV antigen content and aluminum content.

- Manufacturing Process Development

The principles and equipment for preservative-free manufacturing process of HAV vaccine are the same as those applied for the production of preservative containing HAV vaccine. The preservative-free vaccine formulation was validated through successful production and testing of six HAV final container vaccine lots, for which the batch analyses data and stability data are provided.

- Microbiological Attributes.
The preservative-free Hepatitis A vaccine is manufactured according to the GMP rules. This vaccine cannot be terminally sterilised because the active ingredient is a biological product that cannot be autoclaved and because the active ingredient is adsorbed and cannot undergo a sterile filtration. However, the manufacture of the active ingredients is carried out under conditions that ensure that the inactivated HAV bulk is sterile.

- Compatibility.
The compatibility between the vaccine components and the container closure system has been validated by stability studies.

Manufacture of the drug product:
- Description of manufacturing process and process controls along with manufacturers and responsibilities
Manufacturer:
Formulation of the Hepatitis A vaccine, Filling of the Hepatitis A vaccine in vials & syringes, Packaging and labelling and Quality Control testing are performed at:

GlaxoSmithKline Biologicals S.A.Parc de la Noire Epine, Rue Fleming 20, 1300 Wavre, Belgium.
A flow diagram of the vaccine formulation process is provided in the MA file.

- Control of critical steps and intermediates
In-process controls performed during vaccine formulation are described in the MA file.

- Process validation and / or evaluation.
Each lot of final bulk and each lot of final container HAV vaccine is tested per specifications provided in the MA file. Compliance with the product specifications and consistency data retrospectively validate production process. Batch analysis results indicate the consistency and the compliance with the QC release requirements.

- **Product specification:**

- Excipients comply with the European Pharmacopoeia.

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- Analytical procedures are explained in the MA file.
- No excipient of human or animal origin and no novel excipient is used for the preparation of HAV vaccine.
- The specifications for the routine Quality control release of Hepatitis A virus (HAV) vaccine, at final bulk and final container levels, are described in the MA file.
- Analytical procedures and validation of analytical procedures are explained in the MA file.

- **Reference Standards or Materials.**
  An in-house inactivated HAV bulk lot, representative of the commercial manufacturing process serves as reference standard for testing of Hepatitis A potency in final container vaccine.

- **Container closure system.**
  - During filling operations, syringe barrels are sealed with plunger stoppers. During packaging operations, a plunger rod is screwed into the upper end of the plunger stopper and a backstop device is added on the syringe round flange. The syringes are then blistered and packed in boxes. Needles for injection might also be provided.
  - For each container closure system component, a detailed description and the corresponding specifications are provided.

- **Stability of the drug product.**
  Based on available stability data:
  Approved Shelf Life: 36 months
  Aapproved Storage Conditions: 2-8º

- **Adventitious agents:**
  The HAV harvests are tested for the following adventitious agents:
  - Bacteria, mycoplasma and fungi
  - Tests for adventitious agents on cell culture
  - Tests on animals for extraneous agents

3. Non-clinical aspect

➢ **HAVRIX® 1440** is an inactivated hepatitis A virus vaccine. None of the components of the vaccine is infectious, presented as a suspension for injection. Havrix™ is indicated for active immunization against hepatitis A. Havrix™ 1440 Adult is for recipients 16 years and older.

➢ **Pharmacology:** Pharmacological testing of HAV vaccine consisted of: **1)** an evaluation of the effect of inactivation of the vaccine on immunogenicity in mice. It should be noted that exposure to a formaldehyde concentration of 250 µg/ml at 37°C for an extended period of 15 days has no effect

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on the immunogenicity. This confirms the stable nature of the HAV capsid antigens. **2)** Two protection studies in chimpanzees. From both studies, it can be concluded that anti-HAV antibodies originating from the vaccination of chimpanzees with inactivated HAV can induce passive immunoprophylaxis against IV challenge with virulent HAV. Protection is demonstrated by virologic, biochemical, histologic and serologic criteria. **3)** Efficacy studies on chimpanzees and marmosets. The results obtained from the chimpanzee study show that vaccination at 1 or 3 days following oral infection with a heterologous wild-type strain can modify the course of infection. Passive transfer of antibodies to HAV effectively prevents hepatitis A when given after exposure but does not provide lasting protection from infection. The suboptimal immune response elicited by the low vaccine dose in the pre-exposure group was sufficient to induce complete protection against oral challenge with heterologous HAV in all marmosets. In the post-exposure group, the 360 EL.U. was the dose of vaccine that resulted in partial protection, whereas the 1440-EL.U. was the dose of vaccine elicited complete protection against disease and virus excretion. **4)** Safety pharmacology was assessed as a part of the protection studies performed. The results show that the vaccinated animals remained in good health throughout the entire observation period.

- **Pharmacokinetics:** PK studies are not required for vaccines according to the Note for Guidance on preclinical pharmacological and toxicological testing of vaccines (CHMP/SWP/465/95) and the WHO guideline on nonclinical testing of vaccines.
- **Toxicology:** All the HAV vaccines were registered in Europe before the EMEA Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines (CPMP/SWP/465/95) came into force in June 1998. Furthermore, none of the active ingredients or excipients in the HAV vaccines are novel. Consequently, no GLP toxicity studies have been performed with the HAV vaccines. However, a GLP reproductive toxicity study in Sprague Dawley rats was conducted with GSK's HAV and hepatitis B combination vaccine, Twinrix® (HAB). In conclusion, IM administration of HAB vaccine to naive and primed (30 days pre-mating) female rats on gestation days 6, 8, 11 and 15 was not associated with maternal toxicity. No adverse or treatment-related effects on pre- or post-natal development of the fetuses/pups up to weaning on postnatal day 25 were observed.
- **Overall conclusion:** The nonclinical evaluations performed in different animal species have shown that the Havrix® vaccine is safe and induce the appropriate immunological protection.

4. Clinical aspect:

- **Clinical Overview**

The clinical development program for Havrix Adult (1440 EL.U.), an inactivated hepatitis A vaccine, was designed to establish its immunogenicity, clinical effectiveness, safety, manufacturing

consistency, long-term antibody persistence, and compatibility with concomitantly administered adult vaccines.

Havrix Adult is a formaldehyde-inactivated whole hepatitis A virus vaccine adsorbed onto aluminium hydroxide and is indicated for active immunization against hepatitis A in individuals ≥16 years of age.

The adult clinical development program comprised randomized controlled clinical studies conducted between 1989 and 2010 in healthy seronegative adults, together with studies in selected adult populations, including individuals with chronic renal disease and chronic hepatitis C infection. The program evaluated:

- Primary immunization using the licensed two-dose schedule (0 and 6–12 months).
- Long-term antibody persistence and immune memory.
- Manufacturing lot consistency.
- Comparability of modified and approved manufacturing processes.
- Immunogenicity in selected high-risk adult populations.
- Concomitant administration with hepatitis B and typhoid vaccines.
- Population effectiveness during hepatitis A outbreaks.

Most pivotal studies were randomized, controlled, and double-blind whenever feasible. Immunogenicity was assessed using anti-HAV antibody seropositivity rates and geometric mean concentrations (GMCs), while safety evaluations included solicited and unsolicited adverse events, serious adverse events (SAEs), and laboratory assessments.

Overall, the adult clinical development program demonstrated rapid induction of protective antibody responses, durable immune persistence, robust booster responses indicative of immune memory, consistent manufacturing performance, and a favorable safety profile.

➢ **Clinical Efficacy**

Clinical efficacy of Havrix Adult 1440 EL.U. is supported by validated immunological surrogate endpoints, comparative clinical studies, real-world effectiveness data, and extensive post-marketing experience.

Across randomized adult studies (including HAV-096, HAV-099, HAV-101, HAV-104, HAV-106, HAV-107, HAV-112, HAV-123, HAV-168, and HAV-185), administration according to the licensed two-dose schedule induced rapid seroconversion and sustained antibody persistence. Following completion of the vaccination schedule, virtually all vaccinated adults became seropositive, while booster vaccination produced strong anamnestic responses consistent with durable protection.

Lot consistency studies demonstrated equivalent immune responses across manufacturing lots, while study HAV-168 confirmed comparable clinical performance between vaccines produced using the approved and modified manufacturing processes.

Comparative study HAV-189 demonstrated universal seropositivity after completion of vaccination compared with another licensed hepatitis A vaccine (Vaqta®), although antibody concentrations were quantitatively higher in the comparator group.
Co-administration studies (TypHA-006, HAB-061, and HAB-121) demonstrated that concomitant administration with hepatitis B or typhoid vaccines did not compromise immune responses.
The Alaska outbreak intervention program involving approximately 4,930 vaccinated individuals provided direct evidence of effectiveness, demonstrating a marked reduction in symptomatic hepatitis A following vaccination, particularly in communities achieving vaccination coverage above 70%.
Collectively, these data demonstrate rapid onset of protection, durable immunity, and effective prevention of hepatitis A disease following the recommended two-dose schedule.

- **Clinical Immunogenicity**

Immunogenicity was extensively evaluated in healthy adults and selected adult high-risk populations.
Following a single dose of Havrix Adult 1440 EL.U., seropositivity generally exceeded 80–95% within two weeks and approached 100% one month after vaccination, with anti-HAV GMCs typically ranging from approximately 350 to 830 mIU/mL.
Before booster vaccination, 85–98% of adults remained seropositive at 6–12 months. Administration of the booster dose elicited a strong anamnestic response, increasing GMCs approximately 14- to 29-fold and confirming durable immune memory.
Lot consistency studies demonstrated highly comparable antibody responses among manufacturing lots, while study HAV-168 confirmed equivalent immunogenicity between vaccines produced using the approved and modified manufacturing processes.
Studies in adults with chronic renal disease and chronic hepatitis C infection demonstrated satisfactory immune responses, although seroconversion occurred more slowly than in healthy adults.
Co-administration with hepatitis B vaccine and typhoid vaccine did not adversely affect immune responses to either Havrix or the concomitantly administered vaccines.
Overall, the available evidence demonstrates that Havrix Adult induces rapid, robust, and persistent anti-HAV antibody responses with durable immune memory and consistent performance across manufacturing lots and vaccination schedules.

- **Clinical Safety**

The safety of Havrix Adult 1440 EL.U. was evaluated in more than 9,000 vaccinated adults, including healthy volunteers, special adult populations, and participants in large field effectiveness studies.
Overall, Havrix was well tolerated, with most adverse events being mild to moderate, transient, and self-limiting.

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Injection-site soreness was the most frequently reported local adverse reaction, occurring after approximately 35–73% of administered doses. Redness and swelling occurred less frequently and were generally mild, while Grade 3 local reactions were uncommon.

The most frequently reported systemic adverse reactions were headache, fatigue, and malaise. Fever, nausea, vomiting, myalgia, dizziness, and gastrointestinal symptoms occurred infrequently and generally resolved without intervention.

Unsolicited adverse events consisted mainly of mild conditions such as fatigue, dizziness, myalgia, diarrhea, upper respiratory tract infections, influenza-like illness, injection-site hematoma, pruritus, and transient laboratory abnormalities. Occasional elevations in liver enzymes were not considered clinically significant or vaccine-related.

Serious adverse events were rare. Reported events, including isolated cases of Guillain–Barré syndrome, dengue infection, and hospitalization for low back pain, were generally assessed as unrelated or unlikely to be related to vaccination. No consistent vaccine-related safety signal was identified.

Comparable safety profiles were demonstrated across manufacturing lots, manufacturing processes, comparative vaccine studies, and co-administration studies. The Alaska field program further confirmed the favorable safety profile under routine clinical use.

Overall, the accumulated evidence demonstrates that Havrix Adult has a well-established and favorable safety profile consistent with that expected for an inactivated viral vaccine.

- **Benefit-Risk Analysis**

The overall benefit–risk profile of Havrix Adult 1440 EL.U. is considered highly favorable.

Hepatitis A remains an important cause of acute viral hepatitis worldwide, particularly among travelers and adults at increased occupational or environmental risk. In the absence of specific antiviral therapy, vaccination remains the primary preventive strategy.

Clinical studies demonstrated that Havrix Adult induces rapid and durable immune responses following the licensed two-dose schedule, with consistently high seropositivity rates, long-term antibody persistence, and robust immune memory. Clinical effectiveness was confirmed by the Alaska outbreak intervention study, which demonstrated a substantial reduction in hepatitis A incidence following vaccination.

The vaccine showed consistent immunogenicity across manufacturing lots, comparable performance following manufacturing process modifications, and preserved immune responses during concomitant administration with hepatitis B and typhoid vaccines.

The safety profile was favorable, characterized predominantly by mild, transient local and systemic reactions, while serious vaccine-related adverse events were not identified.

Overall, the demonstrated protection against hepatitis A clearly outweighs the limited and predictable risks associated with vaccination, supporting a positive benefit–risk balance for Havrix Adult.

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- **Overall Conclusion**

The clinical development program provides comprehensive evidence supporting the efficacy, immunogenicity, safety, and long-term effectiveness of Havrix Adult (1440 EL.U.).
Randomized clinical studies consistently demonstrated rapid seroconversion, sustained antibody persistence, and strong booster responses indicative of durable immune memory. Immunogenicity was maintained across manufacturing lots, manufacturing processes, and during concomitant administration with hepatitis B and typhoid vaccines.
The vaccine exhibited a favorable and well-characterized safety profile, with predominantly mild, transient adverse reactions and no clinically significant vaccine-related safety concerns.
Overall, the totality of clinical evidence supports that Havrix Adult (1440 EL.U.) is a safe, highly immunogenic, and clinically effective vaccine for the prevention of hepatitis A in adults and supports its continued use according to the approved prescribing information.

5. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.