Unit: Technical Assessment Unit

Public assessment report for biological products

(Trade name of the product)

Administrative information:

Trade name of the medicinal product:	Havrix Junior 720
INN (or common name) of the active substance(s):	HAV antigen 720 Elisa units (E.L.U) adsorbed on Aluminium hydroxide AL 0.25mg
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 SA, 89, rue de l'Institut, B-1330 Rixensart – Belgium.
Applied Indication(s):	Indicated for active immunization against disease caused by hepatitis A virus (HAV).
Pharmaceutical form(s) and strength(s):	Suspension for injection
Route of administration	Suspension for intramuscular injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

GSK	**GlaxoSmithKline**
FDA	**Food and Drug Administration, USA**
ELISA	**Enzyme-linked immunosorbent assay**
HAV	**Hepatitis A virus**
EL. U	**ELISA Units**
QC	**Quality Control**
HDPE	**Hight Density Polyethylene**
IHA	**Inactivated Hepatitis A**

Table of contents

3. non-clinical aspects……
4. Clinical aspects……..

1. **General introduction about the product including brief description of the AI, its mode of action and indications.**

- Havrix vaccine is a sterile suspension for injection composed of inactivated Hepatitis A virus (HAV) adsorbed onto aluminium hydroxide. The pharmaceutical form of the vaccine is a turbid liquid suspension for injection.
- The vaccine is a monodose preparation presented in 1.25 ml pre-filled glass syringes for injection with rubber closures.
- The composition and manufacturing process havrix 1440 and havrix 720 are identical for both presentations except the volume of vaccine final bulk distributed in final containers. Thus Havrix 720 Junior contains exactly one half of the adult vaccine for each component

2. **Quality aspects:**

2.2.1 Introduction

As mentioned above in the general introduction.

2.2.2 Drug Substance (Active ingredient)

- **General information**

The mature infectious HAV virion is a 27 nm icosahedral particle consisting of 60 copies each of four structural proteins. Three polypeptides (VP1, VP2, VP3) have been unequivocally identified as part of the capsid. A fourth polypeptide of only 17 amino acid length (VP4) has been predicted from the nucleotide sequence of the virus but has never been identified in virions.

Manufacture, process controls and characterization:

Manufacturer:

GlaxoSmithKline Biologicals S.A. Parc de la Noire Epine, Rue Fleming 20, 1300 **Wavre, Belgium.**	Manufacturer of HAV drug substance
GlaxoSmithKline Biologicals S.A. Parc de la Noire Epine, Rue Fleming 20, 1300 **Wavre, Belgium.**	HAV drug substance testing

- **Description of Manufacturing Process and Process Controls.**

- Hepatitis A vaccine is produced using classical cell culture methods and well-known purification techniques. Hepatitis A virus (HAV), strain HM175 was adapted to replicate on human diploid cells, strain MRC-5.

- **Control of Materials.**

All the raw materials (and their analytical references) used in the manufacture of HAVantigen bulks and Specific safety evaluation for biologically sourced materials are well described in MA file.

- **Controls of Critical Steps and Intermediates.**

Quality-control (QC) release tests: GSK Biologicals performs QC-release tests on the intermediates isolated during the manufacturing process, on the drug substances and on the drug product. The specifications are described in detail in respective GSK Biologicals Monographs. Specifications are registered via the product-registration file and changes are submitted to authorities.

All the control tests on each step are convenient and well provided in MA file

- **Process Validation**

- The demonstration of process consistency for at least 3 consecutive batches that must show compliance with the pre-established quality standards
- Critical parameters for each stage of HAV manufacturing process are listed.
- The consistency of the cell culture and virus replication process and purification process has been demonstrated on six consecutive commercial batches.
- The consistency of the inactivation process has been demonstrated on three consecutive commercial batches

- **Manufacturing Process Development.**

Since the vaccine registration, 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.

- **Characterization.**

Elucidation of Structure and other Characteristics

Biological, physico-chemical, biochemical and immunological characterization of Hepatitis A antigen have been carried out during the development of HAV vaccine.

Impurities

Residual non-viral proteins in the HAV vaccine originate from MRC-5 cells and from FBS. Protein and DNA derived from these MRC-5 cells are not considered as impurities that require complete elimination.

Specification

Inactivated Hepatitis A (MRC5) bulk :

Assays involved in control of drug substance are performed according to approved control procedures that describe the main steps in a procedure. The specification for each test is stated in MA File

- **Analytical Procedures.**

Analytical procedures for all test methods employed for the testing of Single harvest, Purified bulk and inactivated bulk are described in the MA file

Tests were performed according to the Ph. Eur

- **Batch analysis.**

The compilation of relevant batch analysis data shows that wherever the production is done, the obtained process performance is very similar. This confirms that the production of inactivated HAV antigen bulk is consistent.
-All the quality control results obtained from these batches comply with the release specifications.

- **Reference Standards or Materials.**

The standard lot is stored at -70°C.
QC release testing of the inactivated hepatitis A bulk reference is provided in MA file

- **Container closure system**

- The harvests and purified and inactivated bulks are stored in High Density Polyethylene (HDPE) containers, as other bulk vaccines manufactured by the Company.
- The compatibility between bulk vaccine and primary container/closure materials is demonstrated through stability studies.

- **Stability of drug substance**

Based on available stability data
Approved shelf life:6 months
Approved storage conditions: (storage at +2°C to +8°C for 6 months)

2.2.3 Drug product:

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

Description:
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.
- HAV 720 Pediatric (also called Junior) vaccine contains 720 EL.U. of HAV antigen per dose. The nominal volume of the vaccine in the final container is 0.5 ml

The vaccine is presented as monodose preparation in 1.25 ml pre-filled glass syringes for injection with rubber closures.

- Pharmaceutical Development including brief description on

-Components of drug product.
-The final HAV vaccine formulation contains not less than 1440 EL.U. of inactivated Hepatitis A virus, strain HM175, per ml (which means that 1 dose (1 ml) of HAV 1440 Adult vaccine contains not less than 1440 EL.U. and 1 dose (0.5 ml) of HAV 720 Paediatric vaccine contains not less than 720 EL.U. of HAV antigen).

- Overages
In order to guarantee declared HAV antigen content and taking into account of the variation inherent in the ELISA test, a calculated overage of 10% is applied for HAV active ingredient.

- Physicochemical and Biological Properties

- The HAV vaccine is indicated for active immunisation against Hepatitis A virus infection.
- The HAV vaccine is a turbid liquid suspension containing inactivated HAV bulk adsorbed on aluminium hydroxide adjuvant.
- The HAV vaccine is formulated using phosphate buffer salt solution to maintain the isotonicity and the pH at 7.0 □ 0.2.

- Container closure system and their compatibility.

The prefilled syringes used as container-closure system for the HAV vaccine includes plunger stoppers and tip caps manufactured from grey butyl rubber formulations FM457 (plunger stoppers) and FM27 (tip caps).

- Microbiological Attributes.

- The preservative-free Hepatitis A vaccine is manufactured according to the GMP rules.
- This vaccine cannot be terminally sterilized 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.

1- GlaxoSmithKline Biologicals S.A. Parc de la Noire Epine, Rue Fleming 20, 1300 **Wavre, Belgium** (Formulation and Filling activities).

2- GlaxoSmithKline Biologicals Branch of SmithKline Beecham Pharma GmbH & Co. KG. Zirkusstrasse 40, 01069 **Dresden, Germany** (Filling activities).

- **Reference Standards or Materials.**

. The validation and batch analysis data concerning reference standard, as well as details of the validation of future reference standard lots are described.

- **Container closure system.**

Pre-filled syringe (Type I glass) with a plunger stopper (butyl rubber) **FM 457** with a rubber tip cap **FM 30**

A syringe barrel, 1.25 mL, with a Luer Lock closure system, a large cut flange and a styrene butadiene rubber tip cap (FM30 formulation). The syringe barrel is supplied by both Becton Dickinson (BD) and Schott.

- A plunger stopper (FM457 formulation) and a plunger rod.

For container closure system for HAV final container vaccine, the nature and size of containers, closures and caps are illustrated in the M.A file.

- **Stability of the drug product.**

Stability Summary and Conclusion: illustrated in the M.A. file with conclusion.
- the storage of the final container for up to 36 months at +2°C/+8°C;
- the storage of the final bulk in high density polyethylene (HDPE) containers for up to 12 months at +2°C/+8°C;
- temperature excursions outside of the recommended temperature range, during transport or during storage, due to equipment failures or power outages

Adventitious agents

3. **Non –clinical aspect:**

- **HAVRIX® junior 720** is an inactivated hepatitis A virus vaccine. None of the components of the vaccine is infectious, presented as a suspension for injection. It is indicated for active immunization against hepatitis A virus (HAV) infection in subjects at risk of exposure to HAV aged 1 to 15 years included. It is acceptable to administer Havrix Junior to adolescents up to and including 18 years of age.
- **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 □g/ml at 37°C for an extended period of 15 days has no effect 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:**

The benefit of vaccination with Havrix has been extensively demonstrated in adults and children through numerous clinical trials conducted in different regions of the world. It is also supported by many years on the market and a large post-marketing exposure.

Clinical Efficacy (Immunogenicity):

The hepatitis A vaccine was highly immunogenic in all age groups, and virtually all subjects developed protective concentrations of antibodies one month after a single dose of vaccine. Kinetics studies have shown that the single-dose primary vaccination induces a rapid response that confers protection against hepatitis A within two to four weeks. This is well within the incubation period of the virus, which is of approximately 28 days, and the vaccine can be expected to afford rapid protection when needed in particular for travelers.

WHO specifically notes that inactivated hepatitis A vaccines can be co-administered with other routine childhood vaccines including measles, mumps and rubella vaccines. The results of study HAV-231 demonstrating that the responses to Havrix, MMRII and Varivax were not impaired by their co-administration. In two other studies conducted in a similar population, Havrix co-administered with MMR/V vaccines resulted in high anti-HAV seropositivity rates and GMCs that were comparable to those observed when Havrix was administered alone in HAV-231. The results of the studies also indicate that the MMR/V response is not expected to be impacted by co-administration with Havrix. All three studies evaluated immunogenicity post-dose, and there was no evidence of interference on the immune response at this time point.

The Havrix vaccine schedule requires administration of two doses. Post-dose 2 results from study HAV-231 showed robust responses to the second dose in all study groups. The results from study HAV-231 suggest that the immune response after completion of the primary course of Havrix is similar when the first Havrix dose is given alone or co-administered with MMR +V vaccines.

Clinical Safety:

The tolerability and safety of Havrix was established in the numerous clinical trials conducted since onset of its development. Soreness at the injection site and fever were the most frequent local and general symptoms. Pain was the most frequently reported solicited local symptom Irritability was the most frequently reported solicited general

symptom, the vaccine displayed a low reactogenicity and was safe in all age groups and populations in which it was studied. These included certain risk groups such as patients suffering from hemophilia, chronic liver disease, HIV positive subjects, liver or renal transplant recipients, patients suffering from end stage renal disease and undergoing dialysis. who may require additional doses of the vaccine.

SAEs were assessed as possibly related to vaccination with havrix 720 by the investigator: reported febrile convulsion, autism (the investigator's assessment stated that the event was temporally related; however, a causal relationship of this event to study vaccination, could not be confirmed nor excluded), complex febrile convulsion, grade 2 idiopathic thrombocytopenic purpura and grade 3 lymphadenitis. All events were resolved.

Reactogenicity and safety of Havrix when co-administered with MMR/V vaccines is consistent with the known safety profile of Havrix as reported in the PI. No new or unexpected safety concerns were identified in any of the studies, and no change to the PI is proposed on the basis of these results.

Concomitant administration of Havrix with measles, mumps, rubella and/or varicella vaccines could help reduce the number of vaccination visits required to complete the recommended childhood vaccination series in countries where hepatitis A vaccination is recommended.

Overall conclusion:

Havrix 720 Junior vaccine clinical data revealed that the vaccine is well-tolerated, safe and immunogenic when injected intramuscularly to children and adolescents from 1 year up to and including 18 years of age: as a single dose of HAVRIX 720 Junior (0.5 mL suspension) is used for primary immunization and a booster dose is recommended at any time between 6 and 12 months after a single dose of HAVRIX 720 Junior in order to ensure long-term protection. Also, the data revealed a favorable benefit-risk ratio for coadministration of Havrix with measles, mumps, rubella and varicella vaccines.

5. **General Conclusion and Recommendations if any:**