Unit: Technical Assessment Unit

Public assessment report for biological products

Twinrix Adult

Administrative information:

Trade name of the medicinal product:	Twinrix Adult
INN (or common name) of the active substance(s):	1 dose (1 ml) contains: Hepatitis A virus antigen (HM 175 strain) 720 ELISA Units r-DNA Hepatitis B virus surface antigen (HBsAg) 20 mcg
Manufacturer of the finished product	1- GlaxoSmithKline Biologicals S.A. Parc de la Noire Epine Avenue Fleming, 20 1300 Wavre, Belgium. 2- GlaxoSmithKline Biologicals Branch of SmithKline Beecham Pharma GmbH & Co. KG Zirkusstrasse 40 01069 Dresden, Germany
Marketing Authorization holder	GlaxoSmithKline Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart - Belgium.
Applied Indication(s):	Twinrix Adult is indicated for use in non-immune adults and adolescents 16 years of age and above who are at risk of both hepatitis A and hepatitis B infection.
Pharmaceutical form(s) and strength(s):	Suspension for injection
Route of administration	Intramuscular injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

HBsAg	**Hepatitis B virus surface antigen**
HAV	**Hepatitis A virus antigen**
HBV	**Hepatitis B virus**
MS	**Master Seed**
ELISA	**Enzyme linked Immunosorbent Assay**
QS	**Quality Control**
RABS	**Restricted Access Barrier Systems**
DNA	**Deoxyribonucleic Acid**
HDPE	**High Density Polyethylene**
VHP	**Vaporized Hydrogen Peroxide**
FDA	**Food and Drug Authority**
WHO	**World Health Organization**
GMP	**Good Manufacturing Practices**
US	**United State**
OD	**Optical Density**

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1. **General introduction about the product including brief description of the AI, its mode of action and indications**.
   Twinrix Adult is a vaccine, which is available as a suspension for injection. It contains inactivated (killed) hepatitis A viruses and parts of the hepatitis B virus as active substances. It is available in a 1 ml vial and in a 1 ml prefilled syringe.

2. <u>Quality aspects:</u>

2.1 Introduction

As mentioned in the general introduction

2.2 Drug Substance (Active ingredient)

- **General information**
  Biological, physico-chemical, biochemical and immunological characterization of Hepatitis A antigen is addressed in the MA file
  - **Manufacture, process controls and characterization:**
    The name and address of manufacturers involved in the manufacture and testing of HAV drug substance and HBV drug substance and a brief description of the responsibilities are provided below.

Manufacturer(s)	Responsibilities
GlaxoSmithKline Biologicals S.A. Parc de la Noire Epine Avenue Fleming, 20 1300 Wavre Belgium	Manufacturer of HAV drug substance HAV drug substance testing
GlaxoSmithKline Biologicals S.A. 89, rue de l'Institut 1330 Rixensart Belgium	Manufacturer of HBV drug substance
GlaxoSmithKline Biologicals S.A. Parc de la Noire Epine Avenue Fleming, 20 1300 Wavre Belgium	HBV drug substance testing

- **Description of Manufacturing Process and Process Controls.**
  The detailed manufacturing process is mentioned in the MA file along with flow diagram highlighting the process steps with their IPC
  The steps of each process are described in details.
  - **Reference Standards or Materials.**

The information provided regarding reference standards was sufficient, with the applicant submitting testing & specifications

- **Stability of drug substance**

  Recommended storage condition: +2°C to +8°C for 6 months

2. 3 Drug product:

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

  HAV-HBV Adult vaccine is a vaccine combining purified inactivated hepatitis A virus (HAV) and recombinant DNA hepatitis B surface antigen (HBsAg). The HAV-HBV Adult vaccine is presented as a 1.0 mL monodose. The pharmaceutical form of the HAV-HBV vaccine is a turbid liquid suspension for injection.

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

  Container closure system includes:

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

- **Manufacture of the drug product:**

  - Description of manufacturing process and process controls along with manufacturers and responsibilities.

Manufacturer(s)	Responsibilities
GlaxoSmithKline Biologicals S.A. Parc de la Noire Epine Rue Fleming 20 1300 Wavre Belgium GlaxoSmithKline Biologicals Branch of SmithKline Beecham Pharma GmbH & Co. KG Zirkusstrasse 40 01069 Dresden Germany	Manufacturer(s) Filling in syringes

- **Product specification:**

  -Specifications proposed for release and shelf-life testing of the finished product comply with current ICH guidelines Q6B /USP/Eur.Ph.
  -The provided Certificates of Analysis (COAs) comply with the stated specifications.
  - Justification of the drug product specifications at the release and during stability studies are provided.

  - **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 after antigen desorption from the aluminium adjuvant. The same reference standard is used for testing of antigen content in the HAV drug substance.
    HBV
    The reference material is stored at +2 - +8°C.
  - **Container closure system.**
    The HBV purified bulks are stored in single-use and ready-to-use sterile bags equipped with aseptic connectors and are irradiated by the supplier. PE bags from two different suppliers can be used for the storage of the HBV purified bulk.
  - **Stability of the drug product.**
    approved Shelf Life: 12 months
    approved Storage Conditions: 2-8 °.

3. Clinical aspect:

➢ **Clinical Overview**

The clinical development program supporting the proposed updates for Twinrix™ included studies evaluating accelerated vaccination schedules and long-term persistence of immune responses following primary vaccination.
The clinical evidence comprised:

- One pivotal immunogenicity and safety study (HAB-049) evaluating an accelerated vaccination schedule (0, 7, 21 days and Month 12) in healthy adults.
- Two long-term follow-up studies (HAB-028 and HAB-032) assessing persistence of hepatitis A and hepatitis B antibodies up to 60 months following vaccination with Twinrix™ Adult.
- One long-term follow-up study (HAB-039) evaluating antibody persistence up to 48 months following vaccination with Twinrix™ Junior.
- Supporting long-term persistence studies with the monovalent comparator vaccines Engerix-B™ (HBV-006) and Havrix™ (HAV-058).

(Twinrix Adult)

Across the clinical development program, more than 1,200 subjects were enrolled. The studies evaluated the durability of immune responses, the immunogenicity of an accelerated vaccination schedule, and the safety profile of the combined hepatitis A and hepatitis B vaccine.

- **Clinical Efficacy**

The clinical studies demonstrated that Twinrix™ induced immune responses against both hepatitis A virus (HAV) and hepatitis B virus (HBV).
In Study HAB-049, the accelerated schedule (0, 7, 21 days and Month 12) provided rapid protection against both hepatitis A and hepatitis B. One week after the third vaccine dose (Month 1), all vaccine recipients were seropositive for anti-HAV antibodies and 82% achieved seroprotective anti-HBs antibody levels.
Prior to administration of the fourth dose at Month 12, seroprotection against hepatitis B increased to 94%, while hepatitis A seropositivity remained above 96%. One month after the fourth dose, all evaluated subjects achieved seropositivity for hepatitis A antibodies and seroprotective levels of hepatitis B antibodies.
The immune responses elicited by Twinrix™ were comparable to those achieved with concomitant administration of the corresponding monovalent hepatitis A and hepatitis B vaccines.
Long-term follow-up studies demonstrated persistence of protective immune responses for at least 60 months following completion of the standard primary vaccination schedule.

- **Clinical Immunogenicity**

Accelerated Schedule (Study HAB-049)
The accelerated schedule induced robust antibody responses against both vaccine antigens.
Key findings included:

Time Point	Anti-HAV Response	Anti-HBs Response
Month 1 (1 week after Dose 3)	100% seropositive	82% seroprotected
Month 12 (pre-booster)	96.2% seropositive	94% seroprotected
Month 13 (1 month after Dose 4)	100% seropositive	100% seroprotected

High geometric mean antibody titres (GMTs) were observed following completion of the vaccination schedule, indicating strong immune stimulation and immune memory.
Long-Term Antibody Persistence
Studies HAB-028 and HAB-032 demonstrated persistence of anti-HAV and anti-HBs antibodies up to 60 months after initiation of the standard Twinrix™ Adult vaccination schedule.
The kinetics of antibody decline were consistent with those observed following administration of the monovalent vaccines Havrix™ and Engerix-B™, indicating comparable long-term immunological behaviour.
Supporting studies with the monovalent vaccines demonstrated persistence of antibody responses for up to:

- 60 months for hepatitis B vaccine (Engerix-B™)
- 96 months for hepatitis A vaccine (Havrix™)

(Twinrix Adult)

The available evidence supports durable immune protection and the presence of immunological memory following primary vaccination.

- **Clinical Safety**

The safety profile of Twinrix™ was evaluated primarily in Study HAB-049 and supported by long-term follow-up studies.
The vaccine was generally well tolerated.

Solicited Adverse Events

The most commonly reported local adverse event was:

- Injection-site soreness

The most commonly reported general adverse event was:

- Fatigue

Most solicited adverse events were mild to moderate in intensity and transient in nature.
The incidence, type, and severity of solicited local and general adverse events were comparable between the Twinrix™ group and the group receiving concomitant administration of the monovalent hepatitis A and hepatitis B vaccines.
The frequency of solicited adverse events generally decreased following subsequent vaccine doses.

Serious Adverse Events

Eight serious adverse events (SAEs) were reported in the accelerated schedule study.
Of these:

- Three SAEs occurring in one Twinrix™ recipient were considered related to vaccination.
- The affected subject recovered completely without sequelae.
- All remaining SAEs were assessed as unrelated to vaccination.

No new or unexpected safety concerns were identified during long-term follow-up.

- **Benefit-Risk Analysis**

The available clinical data demonstrate that Twinrix™ provides effective immunization against both hepatitis A and hepatitis B infections.
The accelerated vaccination schedule offers an important public health benefit by providing rapid immune protection in individuals requiring vaccination within a limited timeframe, such as travellers to areas with increased endemicity of hepatitis A and/or hepatitis B.
The immunogenicity of the accelerated schedule was shown to be comparable to that achieved with the corresponding monovalent vaccines. Long-term follow-up data demonstrated persistence of antibodies for at least five years following completion of the primary vaccination series, with antibody decline patterns similar to those observed with the monovalent hepatitis A and hepatitis B vaccines.
The safety profile was consistent with the established safety profiles of the individual vaccine components and no new safety concerns were identified.
Overall, the clinical benefits associated with prevention of hepatitis A and hepatitis B infection outweigh the identified risks.

- **Overall Conclusion**

The clinical development program demonstrated that Twinrix™ is immunogenic, well tolerated, and capable of inducing protective immune responses against both hepatitis A and hepatitis B.
The accelerated vaccination schedule (0, 7, 21 days and Month 12) provided rapid and robust immune responses, with antibody levels comparable to those achieved following administration of the corresponding monovalent vaccines. Long-term follow-up studies confirmed persistence of antibodies for up to 60 months after vaccination, supporting durable protection.
The overall safety profile was acceptable and consistent with previous experience with hepatitis A and hepatitis B vaccines.
Based on the totality of clinical evidence, the benefit-risk balance of Twinrix™ remains favorable for active immunization against hepatitis A and hepatitis B in the indicated populations.

4. General Conclusion and Recommendations if any:

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

https://www.ema.europa.eu/en/documents/overview/twinrix-adult-epar-summary-public_en.pdf