Unit: Technical Assessment Unit

Public assessment report for biological products

Engerix B Adult & Paediatric

Administrative information:

Trade name of the medicinal product:	Engerix B 20 microgrammes/I ml
INN (or common name) of the active substance(s):	Hepatitis B surface antigen 20 mcg/ml
Manufacturer of the finished product	GlaxoSmithKline Biologicals S.A., 89, rue de l'Institut, B-1330 Rixensart - Belgium. GlaxoSmithKline Biologicals S.A., Pare de la Noire Epine, 20, rue Fleming, B-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 B
Pharmaceutical form(s) and strength(s):	Suspension for injection
Route of administration	Intramuscular injection Exceptionally, the vaccine may be administered subcutaneously in patients with Thrombocytopenia or in patients subject to hemorrhage.
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

HBsAg	**Hepatitis B virus surface antigen**
QC	**Quality control**
ELISA	**Enzyme-Linked ImmunoSorbent Assay**
PTFE	**Polytetrafluoroethylene**
DS	**Duran Schott**
GMP	**Good Manufacturing Practice**

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1. **General introduction about the product including brief description of the AI, its mode of action and indications.**
   Engerix™ vaccine is a composed of purified r-DNA yeast-derived Hepatitis B virus surface antigen (HBsAg) adsorbed onto aluminium hydroxide. The pharmaceutical form of the vaccine is a turbid liquid suspension for injection.
   The vaccine is presented as monodose preparation in 3 ml uncolored glass vials with flip-off caps and in 1.25 ml pre-filled glass syringes for injection with rubber closures.

2. **Quality aspects:**

2.2.1 Introduction

As mentioned in the general introduction

2.2.2 Drug Substance (Active ingredient)

- **General information**

- International non-proprietary name (INN): Hepatitis B surface antigen.
- Company or laboratory code: Company name: Hepatitis B surface antigen (HBsAg).
- Structure: The HBsAg polypeptide is composed of 226 amino-acids and has a calculated Molecular Weight of 25,403. The primary amino acid sequence is given in section 3.2.S.1.2 Structure HBV.
- **Manufacture, process controls and characterization:**
  The drug substance is manufactured at GlaxoSmithKline Biologicals S.A.
  89, rue de l'Institut
  1330 Rixensart - Belgium

- **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 IPCs
  The steps of each process are described in details.
- **Control of Materials.**
  All materials for production are purchased from qualified suppliers. All materials received with the manufacturer's Certificate of Analysis (CoA)
  - List of raw materials of Pharmacopeial and In-House Standard with relevant COAs are provided.
  - Information regarding the used cell line & cell banking is mentioned in detail in the MA file.
- **Controls of Critical Steps and Intermediates.**
  Critical process steps and critical process parameters are mentioned in the manufacturing process and process control flow chart

- The process controls selected for each critical manufacturing step and justification of the proposed acceptance criteria are provided in the MA file.

- **Process Validation**
  - All manufacturing processes have been qualified in accordance with approved protocols and evaluated in the reports
  - The process performance qualification was carried out on three consecutive batches based on factory practice and process experience using the proposed commercial process and controls.
  -The Critical Process Parameters and Critical Control Parameters of the manufacturing process were identified and validated
- **Manufacturing Process Development.**
  The developmental history of the manufacturing process is sufficiently describing the whole changes made to the DS manufacturing process with proper justification.
  - Detailed description for each step development is mentioned in the MA file.
  - Relevant information on drug substance batches manufactured during development, in relation to the change, is provided in the MA file.

- **Specification**
  The tests performed on the drug substance comply with the requirements of ICH Q6B guideline, USP, Ph. Eur, and In-house practices.
  All specifications are well described in the MA file

- **Reference Standards or Materials.**
  The information provided regarding reference standards was sufficient, with the applicant submitting testing & specifications
- **Container closure system**

The purified bulks are stored in Duran Schott (DS) type I glass bottles.
The container closure system consists of screw caps with an inner liner made of Polytetrafluoroethylene (PTFE). Only the PTFE liner is in contact with the product.
The containers and closures are sterilized by autoclaving before use.
The compatibility between purified bulk and primary container/closure material is demonstrated through stability studies

- **Stability of drug substance**

The shelf-life of the thiomersal-free HBsAg purified bulks is validated for 12 months at +2°C to +8°C.

2.2.3 Drug product:

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

The active ingredient of HBV vaccine is hepatitis B surface antigen (HBsAg) produced by recombinant technology. HBsAg is produced in transformed yeast cells and purified from the disrupted cell mass. At least 95% of the total protein amount contained in the vaccine is HBsAg. The vaccine also contains a pH buffer, an adsorbent or adjuvant and sodium chloride for isotonicity.

Description and Composition Pediatric

The active ingredient of HBV vaccine is hepatitis B surface antigen (HBsAg) produced by recombinant technology. HBsAg is produced in transformed yeast cells and purified from the disrupted cell mass. At least 95% of the total protein amount contained in the vaccine is HBsAg. The vaccine also contains a pH buffer, an adsorbent or adjuvant and sodium chloride for isotonicity.

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

HBV vaccine is indicated for active immunization against Hepatitis B virus infection. The dosage of the active ingredient was based on experience gained in clinical trials. The 20 µg dose vaccine (in 1.0 ml suspension) is intended for use in subjects 16 years of age and above. The 10 µg dose vaccine (in 0.5 ml suspension) is intended for use in subjects up to and including 15 years of age, including neonates. However, the 20 µg vaccine can also be used in subjects from 11 years up to and including 15 years of age as a 2-dose schedule in situations when there is a low risk of hepatitis B infection during the vaccination course and when compliance with the complete vaccination course can be assured.

- Container closure system and their compatibility.

Vials

Neutral glass vials (Type I) and vial's closures used are identical to the containers used for other liquid non-infectious vaccines and have been shown to be highly acceptable.

Syringes

The prefilled syringes used as container-closure system for the HBV vaccine, are identical to those used for multiple vaccines registered by the Company. This container-closure system includes plunger stoppers and tip caps manufactured from grey butyl rubber formulations FM457 (plunger stoppers) and FM27 (tip caps).

- 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.

  Manufacture:

The drug product is manufactured at GlaxoSmithKline Biologicals S.A., 89, rue de l'Institut, B-1330 Rixensart -Belgium.
GlaxoSmithKline Biologicals S.A., Pare de la Noire Epine, 20, rue Fleming, B-1300 Wavre - Belgium

- Control of critical steps and intermediates
There is no intermediate produced between the HBsAg purified bulks and end of filling. Quality Controls tests are performed at the final bulk stage and on the vaccine in final container prior to labelling. These QC tests are performed for release of the vaccine. The specifications and analytical methods are detailed in the MA file
- Process validation and / or evaluation.

- **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.**
The reference material used at the final container stage for the HBsAg identity and the HBsAg potency tests by ELISA is the EngerixTM-B vaccine
This reference material lot was prepared according to the routine commercial manufacturing process by GSK Biologicals and complied with the commercial specifications set at the time of release.
The reference material is stored at +2 - +8°C.
The equivalence between consecutive reference standard lots has been evaluated by statistical analyses.
- **Container closure system.**
GLASS SYRINGE 1.25 ML CCT
Syringes for vaccines and diluents meet Ph. Eur. requirements for "Glass containers for pharmaceutical use".
Sterile, siliconized, ready to fill 1.25 ml glass syringes are obtained from the manufacturer. Siliconisation is carried out by the manufacturer by spraying Dow Corning DC 360, medical grade silicone. The fluid silicone conforms to Ph. Eur. 0138.
- **Stability of the drug product.**
All available results are within specifications applicable at the time of testing. Therefore, a 36-month shelf life is proposed for the HBV vaccine in final container.

3. **Non –clinical aspect:**
The Engerix-B vaccine is a sterile suspension containing a purified r-DNA yeast-derived Hepatitis B virus surface antigen (HBsAg) produced by recombinant technology as active ingredient, a pH buffer, an adsorbent (aluminium hydroxide) and sodium chloride for isotonicity. It is indicated for active immunization against hepatitis B virus (HBV) infection caused by all known subtypes in subjects of all ages considered at risk of exposure to HBV. It can be expected that hepatitis D will also be prevented by immunization with Engerix-B, as hepatitis D does not occur in the absence of hepatitis B infection. Engerix-B has been prequalified by the WHO since 01/01/1987.

- **Pharmacology:** The efficacy of the vaccine was tested in chimpanzees. Animals were injected with 20 µg of HBsAg, then repeated after one and two months. The vaccinated animals both showed an anti-HBsAg response within one week after the second vaccination. The antibody level rose already to high levels before the third vaccination and maintained during the whole observation period. One month after the last injection, vaccinated animals and controls were challenged with HBV. The vaccinated animals were protected, while the two unvaccinated controls showed all normal signs of hepatitis infection. During the three months before challenge and six months after challenge, safety pharmacology endpoints were evaluated. No abnormalities were observed in the parameters measured in the study regarding health status, clinical chemistry and hematology results.

- **Pharmacokinetics:** Pharmacokinetic 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 non-clinical testing of vaccines.

- **Toxicology:** The nonclinical toxicity of Engerix B has been evaluated in single and repeated GLP toxicity studies on rats and rabbits (in which Engerix B was co-administered with Tetract-Hib). All of these GLP toxicity studies demonstrated that single or repeated IM injection of Engerix B produced no signs of systemic toxicity and was well tolerated. Treatment-related effects were limited to transient hematology/clinical chemistry alterations and injection site inflammation reactions typical for alum-adjuvanted vaccines. Consequently, the risk/benefit ratio for Engerix B remains positive.
- **Overall conclusion:** the non-clinical toxicology and immunogenicity data are consistent with the clinical safety profile for Engerix B, which shows that HBsAg

vaccine is well tolerated and induces the appropriate immunological protection in human subjects.

4. **Clinical aspect:**

ENGERIX-B is a recombinant hepatitis B vaccine containing hepatitis B surface antigen (HBsAg) produced in yeast using rDNA technology. It is formulated as a sterile suspension adsorbed on aluminium hydroxide and administered intramuscularly. The vaccine is indicated for infants, children, adolescents, adults, and special populations, including immunocompromised individuals and patients undergoing hemodialysis. Vaccination schedules include standard (0, 1, 6 months) and accelerated regimens (e.g., 0, 1, 2 months with a booster at 12 months) to allow rapid protection when needed.

- **Clinical Efficacy and Immunogenicity**

ENGERIX-B consistently demonstrates high immunogenicity across all age groups and clinical populations:

- Healthy adults: 96 - 99% achieve protective antibody levels (≥10 IU/mL) following primary vaccination.
- Children and neonates: 95 - 98% seroprotection achieved.
- Special populations: Hemodialysis patients, individuals with chronic liver disease, and patients with type 2 diabetes achieve clinically meaningful protection, though responses may be slightly lower with advanced age or comorbidities.
- Vaccination schedules: Accelerated schedules provide earlier seroprotection, with standard schedules ensuring robust long-term immunity. Boosters further enhance antibody levels, particularly in immunocompromised individuals.
- Combination and adjuvanted vaccines: Engerix-B in combination formulations (e.g., DTPa-HBV-IPV, Twinrix) and adjuvanted forms (Fendrix, HB-AS04C) maintain strong seroprotection, faster onset of immunity, and long-lasting antibody persistence.

- **Clinical Safety**

ENGERIX-B is well tolerated across all populations:

- Local reactions: Mild to moderate pain, redness, or swelling at the injection site; typically, transient.
- Systemic reactions: Fatigue, headache, mild fever; generally short-lived.
- Severe reactions: Grade 3 reactions are rare (<2-3%) and resolve without complications.
- Serious adverse events: No vaccine-related serious adverse events reported in any study.
- Special formulations and combinations: Preservative-free, heat-treated vaccines, and co-administration with other vaccines did not increase safety concerns.

- **Benefit-Risk Analysis**

The benefit-risk profile of ENGERIX-B is highly favorable:

Benefits:

- Strong and consistent protection against hepatitis B
- Flexibility in standard and accelerated dosing schedules
- Long-term antibody persistence and immune memory
- Suitable for vulnerable populations and co-administration with other vaccines

Risks:

- Primarily mild, transient local or systemic reactions
- Slightly increased reactogenicity with adjuvanted formulations, without safety concerns

Overall: The demonstrated high immunogenicity, rapid and durable protection, and excellent safety profile strongly outweigh any minor risks, supporting the vaccine's use in routine and accelerated hepatitis B immunization programs globally.

- **Overall Conclusion**

ENGERIX-B consistently induces strong protective immunity across all age groups and populations. It provides:

- High seroprotection rates (>95% in most populations)
- Rapid and sustained immune responses, particularly with accelerated or adjuvanted schedules
- Robust immune memory lasting several years
- Excellent safety and tolerability, including in high-risk and immunocompromised populations

5. General Conclusion and Recommendations if any:

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