Unit: Technical Assessment Unit

Public assessment report for biological products

Euvax- B

Administrative information:

Trade name of the medicinal product:	Euvax- B.
INN (or common name) of the active substance(s):	Purified Hepatitis B surface antigen.
Manufacturer of the finished product	LG Chem, Ltd.
Marketing Authorization holder	LG Chem, Ltd.
Applied Indication(s):	Immunization against infection caused by all known subtypes of Hepatitis B Virus.
Pharmaceutical form(s) and strength(s):	Solution for injection.
Route of administration	Solution for IM injection.
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

DNA	Deoxyribonucleic acid
GCP	Good clinical practice
GMT	geometric mean antibody titre
HBsAg	Hepatitis B surface antigen
IM	Intramuscular
TRS	Technical Report Series
WHO	World Health Organization

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1. **General introduction about the product including brief description of the AI, its mode of action and indications.**
Euvax B is the trade name of Hepatitis B vaccine manufactured in LG Chem, Ltd. and administrated for prevention of Hepatitis B disease. Hepatitis B vaccine (recombinant) refers to aqueous formulations of recombinant hepatitis B virus (HBV) surface antigen (rHBsAg), lipoprotein complex. This surface protein of hepatitis B virus is the primary viral envelope protein responsible for antigenicity and immunity from hepatitis B virus infection.

Quality aspects:

1.2.1 Introduction

As mentioned in the aforementioned section.

1.2.2 Drug Substance (Active ingredient)

- **General information**

The proposed INN is hepatitis B vaccine (recombinant).
Hepatitis B vaccine (recombinant) refers to aqueous formulations of recombinant hepatitis B virus (HBV) surface antigen (rHBsAg), lipoprotein complex. This surface protein of hepatitis B virus is the primary viral envelope protein responsible for antigenicity and immunity from hepatitis B virus infection. The recombinant HBsAg polypeptide is composed of 226 amino acids. Recombinant HBsAg, like native human HBsAg, readily self-assembles in solution to form liposome-like 22 nm particles presenting antigenic HBsAg epitopes on their surface.

- **Manufacture, process controls and characterization:**
LG Chem, Ltd. is responsible for all manufacturing operations and QC testing of Euvax B drug substance.
The detailed manufacturing process is mentioned in the MA file along with flow diagram highlighting the process steps with their IPCs.
- **Control of Materials:**
List of raw materials of Pharmacopeial and In-House Standard with relevant COAs are provided. Most of raw materials are supplied and tested under either USP or Eur. Ph. specifications. All raw materials, are tested upon receipt, and released against individual specifications before use.
- **Controls of Critical Steps and Intermediates.**
Critical process steps and critical process parameters are mentioned in the manufacturing process and process control flow chart.
A series of characterization tests have been performed on the MCB, ICB and WCB to verify the purity, HBsAg expression, and other relevant characteristics of this strain, and found compliant with the requirements of USP, Eu.Ph & NF.

- **Process Validation**
  The Critical Process Parameters and Critical Control Parameters of the manufacturing process were identified and validated.
  All critical manufacturing processes were validated by taking three consistency runs at commercial scale.
  Validation protocols and reports are attached to the MA file illustrating the details of the batches used.
- **Manufacturing Process Development**
  The process parameters have been established on the basis of long-term production experiences at commercial scale. The quality and processes of those batches was controlled in accordance with CGMP.
- **Characterization.**
  For the description and evaluation of the product characteristics a comprehensive analysis was performed for the in-house reference standards and other drug substances, and the results demonstrate that the physicochemical, structural, biological and immunological properties of the recombinant HBsAg particle are indistinguishable from the bibliographical information for the plasma-derived HBsAg particle.
- **Specification**
  The test methods and acceptance criteria of the materials which are tested according to corresponding compendial requirements. The test methods and acceptance criteria for the materials which are supplied in non-compendial grade or tested by in-house specifications. Euvax B drug substance complies with the requirement of the monographs of Ph. Eur. on hepatitis B vaccine (rDNA). The specifications and test methods for routine release of the drug substance is presented in detailed in MA file.
- **Batch analysis.**
  The results of release testing for the batches of non-clinical trial, clinical trials demonstrate the consistency of the production process and QC testing.
  In order to demonstrate the consistency of the production process and its ability to provide reproducible quality the results of the routine release tests performed on all the batches of the drug substance were found compliant and showed conformity.
- **Reference Standards or Materials.**
  The information provided regarding reference standards was sufficient, with the applicant submitting testing, specifications, and qualification protocols for both primary and working standards. These were accompanied by their certificates of analysis (COAs) and traceability to the primary standard, along with characterizations.

- **Container closure system**
  Bottles and caps are purchased from the same company. The glass bottle complies with the relevant requirement of the current US and European pharmacopoeia.

All batches of articles are subject to a statistical quality inspection in accordance with standard ISO 2859 and those articles that have passed this inspection are released or shipped. The cap is polypropylene and is autoclavable up to 140°C.
There was no evidence of deterioration of the drug substance caused by the material of the container. And no decrease in the Hepatitis B surface antigen content was observed during the period of the stability studies, which implies that no significant adsorption of the product to the surface of the bottle occurred during the storage period.

- **Stability of drug substance**
  The Euvax B drug substance is stored at 5˚C±3˚C until manufacturing., and is stable for 18 month under this condition.

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**
  Euvax B is slightly opaque white suspension for injection which is intended for prevention of Hepatitis B virus. Euvax B Injection is a medicinal product containing recombinant hepatitis B surface antigen which is adsorbed to an adjuvant.
  Euvax B Injection is prepared in 3 different sized glass vials with a nominal capacity of 3 mL for single pediatric or adult dose, 10mL for multi pediatric dose or 20mL for multi adult dose. Each vial is closed with a rubber stopper, covered with an aluminum cap seal and a polypropylene flip-off cap.
  Pharmaceutical Development including brief description on Components of drug product.
  The drug product Euvax B contains recombinant hepatitis B surface antigen as the drug substance. The drug substance is produced as a recombinant protein particle by fermentation of a genetically engineered yeast strain and subsequent purification by a conventional process. The recombinant hepatitis B surface antigen is adsorbed to an adjuvant.
  Formulation Development
  The composition of Euvax B has not changed during the course of clinical development and the formulation intended for marketing is exactly the same as that tested in non-clinical studies and clinical trials. The section is clearly presented in the MA file.

Physicochemical and Biological Properties
The physicochemical, biological and immunological properties, and characteristics of the drug substance hepatitis B surface antigen are clearly illustrated in MA file. The Euvax B injection is a suspension, which may show a sediment which is readily dispersed on shaking to give a suspension which remains sufficiently stable to enable the correct dose to be withdrawn. This suspension character of Euvax B injection is due to the used constituents. Euvax B injection is

an isotonic solution of proteins at near neutral pH. Therefore, the Euvax B injection is suitable for injection, as long as it fulfills the specifications that is described in the MA file.

Manufacturing Process Development.

- The manufacturing process has not changed during the course of clinical development. The Material tested in non-clinical studies and clinical trials.
- The manufacturing facility was modified to be more acceptable for cGMP requirements in pharmaceutical plant. This modification doesn't imply the change of major equipment or process but the movement of production area and the change of layout. The new facility is presented in MA file.
- Equipment qualification, sterilization process validation, and personnel training were performed and environmental monitoring has demonstrated that the new facility is under the desired state of control. Three consecutive successful process simulation tests were performed to evaluate a new facility. More detail information is described MA file. Euvax B drug product was demonstrated not to be affected by the modification of facility when evaluating the qualification or validation results on the new facility and QC release testing results.

Container closure system and their compatibility.

- Euvax B drug product is presented as a liquid formulation in glass vials with a nominal capacity of 3, 10 or 20mL. The vial is closed with a rubber stopper, which, in turn, is covered with an aluminum cap seal and a polypropylene flip-off cap. Euvax B drug product is intended for use as single or multi dose preparation and each vial contains a sufficient volume of product to ensure the removal of individual dose.
- The container closure system described above is used for storage, transportation and presentation of the drug product. The materials employed are standard; compendial materials -USP Ph.& Eu Ph.- for liquid pharmaceutical preparations.
- In conclusion, the container closure system of Euvax B drug product is suitable for Protection, Compatibility, Safety and Performance when considered the material of the vial and the rubber stopper, long term and accelerated stability studies including test for even inverted vials, and in-use stability study.

Microbiological Attributes.

- Euvax B drug product is manufactured under aseptic conditions. The aseptic filling process of the vials is validated periodically. All equipment used for the manufacture of Euvax drug product is pre-cleaned. The sterility, and pyrogen of the drug product are routinely controlled during release and stability testing. The release and stability data presented in MA file confirm the integrity and appropriateness of the container closure system to prevent microbiological contamination.

Compatibility.

In conclusion, the findings of the in-use stability study confirmed that the container closure system, the filling volume and the efficacy of the preservative agents are compatible with the product and suitable for its intended use as a multi dose presentation.

- **Manufacture of the drug product:**
  LG Chem, Ltd. is responsible for all manufacturing operations involved in the formulation, filling and testing of Euvax B injection that is manufacturing at Iksan plant of LG Chem, Ltd.
  Control of critical steps and intermediates
  Critical steps in the manufacturing process have been identified and validated either as part of the plant related process validation program or within the framework of a product-specific process validation program.
  No intermediates are defined or isolated during the manufacture of Euvax B drug product.
  Process validation and / or evaluation.
  Euvax B injection is manufactured by a conventional, straightforward process, which is controlled by a number of in-process tests. An overview of the plant-related process validation and the product-specific process validation performed with respect to Euvax B injection is described in MA file.
- **Product specification:**
  - Euvax B drug product complies with the requirement of the monographs of Ph. Eur. on hepatitis B vaccine(rDNA). The specifications and test methods for routine release of the drug product are presented MA.
  - All excipients used in Euvax B drug product are described in Ph. Eur. and USP and are tested accordingly they also comply with the requirements of Ph. Eur, if tested. The specifications of each excipient are presented MA file.
  - Representative certificates of analysis were provided.
  - The compendial excipients are described in the Ph. Eur. and US pharmacopoeia. The quality of each of these excipients fulfils the requirements defined in the relevant monograph. These specifications are considered to be adequate for the control of the compendial excipients.
  - All the excipients used in Euvax B drug product are not derived from human or animal but are prepared in the process of chemical synthesis, novel excipients are not used as well.

Justification of Specification
The specifications proposed for release of the drug product are provided MA file. References that have been considered in the selection of appropriate specifications are Hepatitis B vaccine (rDNA) monograph in Ph. Eur. and Hepatitis B vaccine (rDNA) monograph in Korean pharmacopoeia (Biologics).
Characterization of Impurities
Information and data on potential impurities, dealing with the characterization and determination of potential impurities in the drug substance is described in MA file.
Reference Standards or Materials.

The explanation for Reference standard is described in Hepatitis B vaccine (rDNA) monograph in Ph. Eur. List of reference materials used in the tests of the finished product is described in MA file.

Stability of the drug product.
The storage temperature: 5±3°C.
Shelf-life: 36 months.

2. **Non –clinical aspect:**

Euvax B injection contains recombinant DNA hepatitis B surface antigen as the drug substance, Each mL of Euvax B Injection contains 20 µg of purified hepatitis B surface antigen, 0.5 mg of aluminium gel and 0.01% of thimerosal. It is turbid white suspension in appearance, miscible with saline and filled into the glass vial. The proposed adult dose for Euvax B injection is 1 mL. The recommended vaccination schedule is 0,1,6 month (or 3 injections monthly) intramuscular route.

Pharmacology

No preclinical test on the pharmacology activity of Euvax B Injection was submitted. The efficacy of the vaccination was assessed as a part of the repeated dose toxicity in rats by determining the total antibody production against the antigens of the vaccine formulation in serum at day 28.
Although 4 individuals turned out non-responders, the overall response rate was 87% (26 out of 30) when the antibody was analyzed at 4 weeks post-immunization. This response rate is quite comparable to those in the published literature, considering that the anti-HBsAg responses also depend on the strain used, and doses and schedules applied. Regarding of the non-responder of the hepatitis B vaccine, this result showed that the test vaccine induced the normal immune response in the test animals.

Pharmacokinetic studies are not applicable for vaccines in accordance with the WHO TRS 927.

Toxicology

Single dose toxicity with Euvax B injection in male and female rats did not show any other abnormal findings except the inflammation at the inoculation site. The overall severity of the inflammation at the inoculation site was not or only slightly more severe in the test groups than in the vehicle-treated animals and it is concluded that local tissue reactions depend predominantly on the alum-based vehicle.
Repeated dose toxicity study with Euvax B injection in male and female rats did not show any other abnormal findings except the inflammation and necrosis at the injection site, including the low dose group. These changes were non-specific reactions induced by physical stimulus at the time of the injection or by the irritability of the injected materials. Some microscopic changes were considered to

be incidental and of no toxicological importance. The remaining histopathological findings detected were those commonly observed in rats of the strain and age employed. None of these findings had a toxicological significance.
In a study to examine the local adverse tissue reactions after a single intramuscular injection in albino rabbits, it is concluded that Euvax B injection induced local inflammation at the inoculation sites after intramuscular injection, of a type and severity that were to be expected with this type of vaccine formulation.

3. Clinical aspect:

Clinical overview:

The clinical development program for Euvax B was designed to evaluate its immunogenicity and safety and to demonstrate comparability with licensed hepatitis B vaccines. The submitted clinical package comprised nine clinical studies, including two pivotal comparative studies (AVP-EUV01 and AVP-EUV04) and seven supportive studies conducted in neonates, infants, children, adolescents, and adults.

The pivotal studies were conducted in accordance with applicable ethical principles and Good Clinical Practice (GCP) standards and evaluated the immunogenicity and safety of Euvax B in comparison with licensed hepatitis B vaccines, including Engerix B, a recombinant hepatitis B vaccine with a well-established efficacy and safety profile. Additional supportive studies assessed the performance of Euvax B under different vaccination schedules and when administered concomitantly with routine pediatric vaccines.

Overall, the clinical development program provided comprehensive evidence supporting the ability of Euvax B to induce protective immune responses against hepatitis B virus infection while demonstrating a safety profile consistent with licensed hepatitis B vaccines.

Clinical Efficacy:

The clinical efficacy of Euvax B (recombinant hepatitis B vaccine) was evaluated in a comprehensive clinical development program comprising randomized controlled studies, comparative immunogenicity studies, and supportive open-label investigations conducted in neonates, infants, children, adolescents, and adults across multiple countries.

The primary efficacy endpoint across studies was the achievement of seroprotection against hepatitis B virus infection, generally defined as an anti-HBs antibody concentration ≥10 mIU/mL following completion of the vaccination schedule.

The pivotal comparative studies demonstrated that Euvax B induced seroprotection rates comparable to those achieved with licensed hepatitis B vaccines, including Engerix B and plasma-derived hepatitis B vaccines. High seroprotection rates were consistently observed across different age groups, including healthy neonates, infants, adolescents, and adults.

Key efficacy findings included:

- In randomized comparative studies conducted in neonates and adolescents, Euvax B demonstrated immunogenicity comparable to Engerix B, with high rates of protective anti-HBs antibody responses following the standard three-dose vaccination schedule (0, 1, and 6 months).
- Studies conducted in healthy infants confirmed effective induction of protective antibody responses when Euvax B was administered concomitantly with routine childhood vaccines, including diphtheria, tetanus, pertussis, poliomyelitis, and *Haemophilus influenzae* type b vaccines.
- Studies evaluating different vaccination schedules (0, 1, 2 months and 0, 1, 6 months) demonstrated satisfactory seroprotection rates with both schedules, although the longer schedule generally resulted in higher antibody concentrations.
- Supportive studies in adolescents and adults confirmed robust immune responses following intramuscular administration of the recommended vaccination regimen.
- Across studies, seroprotection rates were maintained at levels considered protective according to established international criteria for hepatitis B vaccination.

Overall, the available clinical efficacy data demonstrate that Euvax B is highly immunogenic and capable of inducing protective antibody responses against hepatitis B virus infection in neonates, infants, children, adolescents, and adults. The efficacy profile was comparable to that of established licensed hepatitis B vaccines and supports the approved immunization schedules.

Clinical Efficacy

The clinical efficacy of Euvax B (recombinant hepatitis B vaccine) was evaluated in two pivotal randomized controlled studies and supported by several additional clinical studies conducted in neonates, infants, adolescents, and adults.

The pivotal studies compared Euvax B with a licensed recombinant hepatitis B vaccine (Engerix B) using the standard three-dose vaccination schedule (0, 1, and 6 months). In healthy newborns and adolescents, Euvax B demonstrated seroprotection rates comparable to those achieved with the comparator vaccine. Following completion of the primary vaccination series, seroprotection rates reached approximately 98–100%, demonstrating effective induction of protective immunity against hepatitis B infection.

Supportive studies conducted in neonates, infants, adolescents, and adults consistently demonstrated high rates of seroprotection and seroconversion across different age groups and vaccination schedules. Additional studies evaluating co-administration with routine childhood vaccines showed that concomitant administration did not adversely affect the immune response to hepatitis B vaccination.

Overall, the available clinical evidence demonstrates that Euvax B provides effective protection against hepatitis B virus infection and performs comparably to established licensed hepatitis B vaccines.

Clinical Immunogenicity

The immunogenicity of Euvax B was assessed primarily through measurement of anti-hepatitis B surface antigen (anti-HBs) antibody concentrations following vaccination.

Across the pivotal studies, seroprotection rates (anti-HBs ≥10 mIU/mL) exceeded 97% and reached 100% in several study populations following completion of the three-dose vaccination schedule. High geometric mean antibody titres (GMTs) were also observed, indicating a robust immune response.

Supportive studies confirmed the immunogenicity of Euvax B in both pediatric and adult populations. In comparative studies against plasma-derived hepatitis B vaccines, Euvax B demonstrated comparable or superior immunogenicity. Studies evaluating different vaccination schedules showed that both accelerated (0, 1, 2 months) and standard (0, 1, 6 months) regimens induced high seroprotection rates, although the standard schedule generally produced higher antibody titres.

Studies in infants receiving Euvax B concomitantly with routine childhood vaccines demonstrated maintained seroprotection rates exceeding 95%, supporting compatibility with national immunization programs.

Collectively, the immunogenicity data support the ability of Euvax B to induce strong and sustained protective antibody responses across all studied populations.

Clinical Safety

The safety profile of Euvax B was evaluated in clinical studies involving neonates, infants, adolescents, and adults receiving the vaccine according to various vaccination schedules.

The most frequently reported adverse reactions were mild-to-moderate local injection-site reactions, including pain, erythema, induration, and swelling. These reactions were generally transient and resolved without intervention.

The most commonly reported systemic adverse events included fever, irritability, drowsiness, decreased appetite, fatigue, headache, myalgia, and gastrointestinal symptoms. These events were generally mild in severity and consistent with the known safety profile of hepatitis B vaccines.

Across the pivotal studies, the incidence and pattern of adverse events were comparable between Euvax B and the licensed comparator vaccine. No vaccine-related serious adverse events were identified. Serious adverse events reported during the clinical development program were considered unrelated to vaccination by study investigators and resolved without sequelae.

The overall safety findings demonstrate that Euvax B is well tolerated in neonates, infants, adolescents, and adults.

Benefit-Risk Analysis

The clinical development program provides substantial evidence supporting the efficacy, immunogenicity, and safety of Euvax B across a broad range of age groups.

The vaccine consistently achieved high seroprotection rates comparable to those observed with licensed recombinant hepatitis B vaccines. Supportive studies further confirmed the ability of Euvax B to induce protective immune responses in neonates, infants, adolescents, and adults, including when administered concomitantly with routine childhood vaccines.

The safety profile was favorable and consistent with the established safety profile of hepatitis B vaccines. Adverse reactions were predominantly mild and transient, and no vaccine-related serious safety concerns were identified during clinical development.

Considering the demonstrated protective immune response, comparable efficacy to established hepatitis B vaccines, and acceptable safety profile, the overall benefits of vaccination with Euvax B outweigh the identified risks.

Overall Conclusion

The submitted clinical data demonstrate that Euvax B induces robust protective immune responses and achieves high seroprotection rates across the indicated age groups. Comparative studies established immunogenicity comparable to licensed hepatitis B vaccines, while supportive studies confirmed consistent performance across different populations, vaccination schedules, and co-administration settings.

The vaccine was generally well tolerated, with a safety profile characterized primarily by mild and transient local and systemic adverse reactions and no identified vaccine-related serious adverse events.

Based on the totality of the available clinical evidence, Euvax B demonstrates an acceptable efficacy, immunogenicity, and safety profile, and the overall benefit-risk balance is considered favorable for active immunization against hepatitis B virus infection.

4. General Conclusion and Recommendations if any:

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