EUVAX B
HEPATITIS B VACCINE, RECOMBINANT

Euvax B consists of highly purified, non infectious particles of Hepatitis surface antigen (HBsAg) adsorbed onto aluminium salt as an adjuvant and preserved with thimerosal. It is a recombinant DNA hepatitis B vaccine derived from HBsAg produced by DNA recombinant technology in yeasts (Saccharomyces cerevisiae). The vaccine meets the WHO requirements for recombinant hepatitis B vaccines. No substances of human origin are used in its manufacture.

DESCRIPTION
Euvax B is a white, slightly opalescent suspension.

COMPOSITION
0.5 mL of the above vaccine contains:
- Active ingredient: Purified HBsAg: ........................................... 10 μg
- Adjuvant: Aluminium Hydroxide Gel (as aluminium) ...........................................0.25 mg
- Preservative: Thimerosal: ........................................... 0.01 μg/mL
- Excipients: Potassium phosphate, monobasic, Sodium phosphate, dibasic, Sodium Chloride.

INDICATION AND USAGE
Immunization against infection caused by known subtypes of hepatitis B virus.

PHARMACOLOGICAL PROPERTIES
Relevant information for Euvax B

In order to evaluate the immunogenicity and safety of recombinant DNA yeast-derived hepatitis B vaccine (Euvax B) by administration at intervals of 0-, 1-, and 2-months and 0-, 1-, and 6-months and at different concentrations of 0.1, 0.2, and 0.4 mg/kg. There was no significant increase of protective antibody titers after vaccination by a plasma-derived HBV vaccine with that of the recombinant HBV vaccine. Clinical trials were conducted among healthy Koreans. In addition, a small-scale clinical trial was done in Vietnam to evaluate the immunogenicity and safety of Euvax B. Several different parameters were compared in these studies: difference in age and sex distribution, seroconversion rate, geometric mean titers between the experimental vaccine group (Euvax B) and control group vaccine (plasma-derived vaccine), as well as safety in the Euvax B group. When small differences in age and sex distribution were observed, they had no consequence on the comparison of antibody titers after vaccination by a plasma-derived HBV vaccine with that of the recombinant HBV vaccine. In conclusion, acute toxicological effect of Euvax B on rats and mice was negligible.

Preclinical safety data
The toxicity of Euvax B has been studied in single-dose studies (oral and intraperitoneal) in the rat and mouse, and in repeat-dose studies of up to 4 weeks duration in the rat (subcutaneous). The protective potential of Euvax B was tested in the Ames bacterial mutation test, chromosomal aberration test and micronucleus test. A series of antigenicity studies have been conducted, as well as the positive cutaneous anaphylaxis (PCA) test in the mouse-rat systems and the guinea-pig HBsAg pig system, plus active systemic anaphylaxis in the guinea pig. In conclusion, the test of local irritation of Euvax B was conducted in the rabbit.

In acute studies, mice and rats received a single oral or intraperitoneal dose of 0, 0.125, 0.25, 0.5, 1, or 2 mg/kg body weight. The LD50 values in male and female mice were >2 mg/kg (50 mL/kg), and were the same in rats. There were no changes in death rate or weight caused by the test material. Any abnormalities in clinical findings and at necropsy also were observed in the control group, so it is considered that they were not specific reactions caused by the test material itself. In conclusion, acute toxicological effect of Euvax B on rats and mice was negligible.

In subacute studies, rats received 4 weeks treatment (5 times per week) by subcutaneous route at doses of 0, 50, 100, or 200 μg/kg. There were no toxicologically significant, treatment-related changes in clinical findings, body weight, food consumption, water consumption, hematological, blood biochemistry, gross findings on necropsy, and organ weights. In conclusion, no important treatment related abnormalities were observed.

The potential for Euvax B to induce genetic damage was investigated in in vitro studies. The results demonstrated the lack of mutagenic potential of Euvax B.

In a small-scale clinical trial in the guinea-pig, the induction rate of reverse mutations in Salmonella typhimurium according to the method of Ames was conducted, both with and without metabolic activation, at Euvax B concentrations ranging between 10 and 20 ng/ml. Euvax B from any concentration did not induce an increase in the number of mutants with reverse mutation.

The induction of chromosomal aberration was evaluated in cultures of Chinese hamster cell line fibroblast at an Euvax B concentration range of 5, 10, and 20 μM. Chromosomal aberration was not observed.

The induction of micronucleus formation in bone marrow cells was evaluated in the rat at Euvax B concentrations of 0.1, 0.2, and 0.4 mg/kg. There was no significant increase of micronuclei in the Euvax B treated groups.

In a rat/mouse passive cutaneous anaphylaxis (PCA) test, serum from mice sensitized with Euvax B produced no responses in challenged rats.

In a guinea pig active anaphylaxis test, Euvax B showed some potential to induce mild anaphylactic responses like urination or defection. In a guinea pig/guinea pig passive cutaneous anaphylaxis (PCA) test, serum from guinea pigs sensitized with Euvax B produced no responses in challenged guinea pigs. In conclusion, Euvax B showed no antigenicity in studies using the PCA test, and it showed a low potential for antigenicity in the guinea pig active anaphylaxis test.

In a local irritation test in the rabbit, the Primary Irritation Index (P.I.I.) of Euvax B following the Draize method was 0 under the experimental conditions, and it is concluded that Euvax B is without skin irritation properties.

DOSAGE AND ADMINISTRATION
Euvax B is for intramuscular use only.

- 0.5 mL/dose (neonates, infants, and children aged up to including 15 years of age) is 0.5 mL containing 10 μg of HBsAg.
- One adult dose (from 16 years) is 1.0 mL containing 20 μg of HBsAg.

The immunization regimen consists of three doses of vaccine given according to the following schedule:
1. First dose: at elected date
2. Second dose: 1 month after the first dose
3. Third dose: 6 months after the first dose

Booster vaccination: every 5 years after the first vaccination, a single dose may be considered.

An alternative 0-, 1- and 2-months schedule and a 12-months booster can be used in certain populations (e.g. neonates born from Hepatitis B-infected mothers, someone who has or might have been recently exposed to the virus, certain travelers to high-risk areas). Additional dose(s) of vaccine may be required in hemodialysis or immunodeficient patients since protective antibody titers (>10 mIU) may not be obtained after the primary immunization course.

CONTRAINDICATIONS
Hepatitis B vaccine is contraindicated for use in persons with hypersensitivity to any component of Euvax B.

WARNINGS AND PRECAUTIONS
General precautions:
- The administration of Euvax B should be postponed in patients suffering from acute severe febrile illness.
- In patients suffering from multiple sclerosis, any stimulation of the immune system can induce exacerbation of their symptoms. Therefore, for these patients the benefits of vaccination against Hepatitis B should be weighed against the risks of exacerbation of multiple sclerosis.

Precautions for usage:
- Shake before administration, since a fine white deposit with a clear colorless supernatant may form during storage.
- Euvax B should not be administered in the gluteal region and it must not be administered intravenously.

Pregnancy and lactation:
- The effect of the HBV vaccine on foetal development has not been assessed. However, as with all inactivated viral vaccines, the risks to the foetus are considered to be negligible. Euvax B should be used during pregnancy only when clearly needed.
- The effect on breast-fed infants of the administration of Euvax B to their mothers has not been evaluated in clinical studies. No contraception indication has been established.

ADVERSE REACTIONS
Common:
- Local reactions such as erythema, pain, swelling or minor fever may rarely occur; these symptoms disappear in 2 days.
- Rare:
  - Hyperthermia (above 38.8°C).
  - Systemic reactions such as malaise, asthenia, headache, nausea, vomiting, diarrhea, myalgia, arthrosis.
  - Skin rash and transient increase of transaminases.

Very rare:
- A causal sequence of cause and effect could not be established for reports of multiple neuritis, optic neuritis facial paralysis, exacerbation of multiple sclerosis, and Guillain-Barre syndrome.

STORAGE CONDITIONS
Do not exceed the expiry date stated on the external packaging. Store between +2°C and +8°C (in a refrigerator). Do not freeze.

PRESENTATIONS
0.5 mL/vial × 20 vials - 0.5 mL/vial × 1 vial
1 mL/vial × 20 vials - 1 mL/vial × 1 vial
5 mL/vial × 1 vial - 10 mL/vial × 1 vial
5 mL/vial × 10 vials - 10 mL/vial × 10 vials
Reg. No. DK35301300143(A) (Adult)
Reg. No. DK35301300143(A) (Pediatric)

Manuf.:
LG Life Sciences
401, Yongji-dong, Iksan-si
Jeonbuk-do, 570-350, Korea

Imported:
PT Aventis Pharma
J. Jend. A. Yani No. 2.
Pulu Mas, Jakarta
Indonesia