IPM203700-4

Euvax B

Hepatitis B vaccine, recombinant

Euvax B® consists of highly purified, non infectious particles of Hepatitis B 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 yeast cells (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

Adult

1 ml of the above vaccine contains:
– Active ingredient: Purified HBsAg..... 20 µg
– Adjuvant: Aluminium Hydroxide Gel (as Al)..... 0.5 mg
– Excipients: Potassium phosphate, monobasic, Sodium phosphate, dibasic, Sodium chloride.

Pediatric uses

0.5 ml of the above vaccine contains:
- Active ingredient: Purified HBsAg..... 10 µg
- Adjuvant: Aluminium Hydroxyde Gel (as aluminium)..... 0.25 mg
- 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

Relevent 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 to compare the antibody titers after vaccination by a plasma-derived HBV vaccine with that by the recombinant HBV vaccine, 5 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 vaccine group (plasma-derived vaccine), as well as safety in the Euvax B® group.

When small differences in sex and age distribution were observed, they had no consequence on the ability to compare between-group immunogenicity. There was no difference in the immunogenicity between the two groups when the same vaccination schedule was compared, but the 0-, 1-, and 6- month schedule was considered to be better than the 0-, 1-, and 2-month schedule for long -term immunogenicity. The immunogenicity of the recombinant HBV vaccine was as good as the plasma derived HBV vaccine, when considering the seroconversion rates and the antibody titer levels.

There was no case observed of HBsAg seropositivity or episode of clinical hepatitis among study subjects during these studies. Adverse reactions observed in study groups after vaccination were mild and symptoms were temporary. Overall, available data indicate that immunization against hepatitis B using the yeast-derived recombinant hepatitis B vaccine produced by LG Life Sciences Ltd. (Euvax B®) is efficacious for both the 2- and the 6- month schedules, making it possible to choose between the 2- and the 6- month schedule according to the vaccinee's convenience. The safety and immunogenicity of Euvax B® was documented in all age groups.

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 mutagenic 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 passive cutaneous anaphylaxis (PCA) test in the mouse-rat systems and the guinea pig-guinea pig system, plus active systemic anaphylaxis in the guinea pig. In addition, 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 LD_{50} 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 it self. 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, hematology, 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®.

The induction 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 2000 ng/plate. Euvax B® at any concentration did not induce an increase in the number of colonies with reverse mutation.

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

The induction of micronucleus formation in bone marrow cells was evaluated in the rat at Euvax B® concentration 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 defacation. In a guinea pig passive cutaneous anaphylaxis (PCA) test, serum from guinea pigs sensitized with Euvax B® produced no response 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.
– One pediatric, 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:
- 1st dose: at elected date
- 2nd dose: 1 month after the first dose
- 3rd 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 titters (>10 IU/l) 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. (see Adverse Reactions)
– It is considered that protection cannot be obtained by vaccination in patients in latent or progressive state of Hepatitis B.
– As with all injectable vaccines, appropriate medical treatment should always be readily available in case of rare anaphylactic reactions following the administration of the vaccine.
– Thimerosal (an organomercuric compound) has been used in the manufacturing process of this medicinal product and residues of it are present in the final product. Therefore, sensitization reactions may occur.
– In preterm babies (<2,000 grams), it is advisable to check antibody titers one month after the third dose to assess the need for a booster dose.

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 HBsAg 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 contraindication has been established.

Adverse reactions

Gastrointestinal disorders	Rare : nausea Common: abdominal pain, diarrhea, vomiting
General disorders and administration site conditions	Rare : malaise, fatigue Common : fever, induration, oedema, tenderness, inflammation Very common : injection site pain
Infections and infestations	Uncommon : moniliasis, rhinitis
Investigations	Rare : transient increase of transaminase
Metabolism and nutrition disorders	Common : anorexia
Musculoskeletal and connective tissue disorders	Rare : myalgia, arthritis
Nervous system disorders	Very rare: optic neuritis, facial paralysis, Guillain-Barre syndrome, aggraviation of disseminated sclerosis. Rare : headache, dizziness Common : crying abnormal, somnolence.
Pregnancy, puerperium and perinatal conditions	Uncommon : jaundice neonatal
Psychiatric disorders	Common : insomnia, nervousness, irritability
Skin and subcutaneous tissue disorders	Common : rash erythematous, erythema Uncommon : pityriasis rosea, rash, rash maculo-papular
Vascular disorders	Common : hematoma

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.
shelf-life is 36months

Presentations

Dus, 1 Vial @ 1 dose (0.5 ml) [Pediatric]
Dus, 20 Vials @ 1 dose (0.5 ml) [Pediatric]
Dus, 1 Vial @ 1 dose (1 ml) [Adult]
Dus, 20 Vials @ 1 dose (1 ml) [Adult]
Dus, 1 Vial @ 10 doses (10 ml) [Adult]
Dus, 10 Vials @ 10 doses (10 ml) [Adult]

Reg. n°: DKI0301300143A1 - Pediatric presentation
DKI0301300143B1 - Adult presentation

Harus dengan resep dokter

Manufactured by
LG Chem
129, Seokam-ro, Iksan-si,
Jeollabuk-do, Korea

Imported:
PT Aventis Pharma
Jl. Jend. A. Yani No.2,
Pulo Mas, Jakarta,
Indonesia

SANOFI PASTEUR