SUMMARY FOR BASIS OF APPROVAL

Reference No. 87-0556

Drug Licensed Name: Hepatitis B Vaccine (Recombinant)

Mfr: SmithKline Biologicals

Drug Trade Name: ENGERIX-B

Hepatitis B Vaccine (Recombinant), Engerix-B, is a noninfectious recombinant DNA vaccine which contains the purified surface antigen (HBsAg) of the hepatitis B virus (HBV). It is produced by fermenting genetically engineered yeast cells which contain a plasmid that carries the HBsAg gene.

I. INDICATIONS FOR USE:

Engerix-B [Hepatitis B Vaccine (Recombinant)] is indicated for immunization against infection caused by all known subtypes of HBV. Hepatitis D (caused by the delta virus) should also be prevented by Engerix-B since delta virus replicates only in presence of HBV infection.

Vaccination against HBV has been shown to reduce the overall incidence of HBV infection. It may also reduce the incidence of the complications of HBV infection such as chronic active hepatitis, cirrhosis and primary hepatocellular carcinoma.

Engerix-B will not prevent hepatitis caused by other agents, such as hepatitis A virus, non-A/non-B hepatitis viruses, or other pathogens known to infect the liver.

Vaccination is recommended for persons of all ages who are, or may be, at risk of exposure to HBV, for example: health care personnel; selected patients and patient contacts, including adult hemodialysis patients and patients requiring frequent and/or large volume transfusions of blood or clotting concentrates; residents and staff of institutions for the mentally handicapped; infants born to mothers who are carriers of HBsAg; subpopulations with a known high incidence of HBV infections such as immigrants from Southeast Asia; persons who have travel to areas where HBV infection is endemic and receive blood from or have close contact with the native populations; military personnel identified as being at increased risk; morticians and embalmers; persons at increased risk of HBV infection due to their sexual practices; prisoners; and users of illicit injectable drugs.

For those persons who require a booster dose of Hepatitis B Vaccine, Engerix-B may be used whether the primary course of vaccination has been with a recombinant or plasma derived vaccine. However, the indication for booster doses is unclear for persons other than hemodialysis patients at this time.

II. DOSAGE AND ADMINISTRATION:

Engerix-B is supplied as a sterile suspension for intramuscular administration. For adults, the injection should be given in the deltoid muscle but it may be preferable to inject in the anterolateral thigh in neonates and infants, who have smaller deltoid muscles.' Engerix-B should not be administered in the gluteal region, since such injections may result in suboptimal immunogenic responses.

Each 1 mL adult dose of vaccine consists of 20 micrograms of antigen protein adsorbed on 0.5 mg aluminum as aluminum hydroxide. Each 0.5 mL pediatric dose of vaccine consists of 10 micrograms of antigen protein adsorbed on 0.25 mg aluminum as aluminum hydroxide. Both formulations contain 1:20,000 thimerosol (mercury derivative) as a preservative, sodium chloride (9 mg/ml) and phosphate buffers (disodium phosphate dihydrate, 0.98 mg/ml and sodium dihydrogen phosphate dihydrate, 0.71 mg/ml).

The usual dosage for adults and children over 10 years of age is 20 mcg, and the usual dosage for neonates and children up to 10 years of age is 10 mcg, injected on a 0, 1, 6 month schedule. There is an alternate schedule with injections at 0, 1 and 2 months for certain populations (e.g., neonates born of infected mothers, others who have or might have been recently exposed to HBV, certain persons traveling to high-risk areas). On this alternate schedule, an additional dose at 12 months is recommended for neonates and for those for whom prolonged maintenance of protective titers is desired. The recommended schedule for hemodialysis patients is 40 mcg administered at 0, 1, 2 and 6 months.

III. MANUFACTURING AND CONTROLS:

A. MANUFACTURING AND CONTROLS

The S gene of an adw_2 subtype of the HBV is cloned in a functional expression plasmid for introduction into Saccharomyces cerevisiae, strain DC5. After fermentation, the yeast cells are disrupted. Residual solids are precipitated, soluble contaminants are removed by diafiltration; diafiltered medium is then concentrated. Purification of the HBsAg protein is accomplished by gel permeation chromatography, ion exchange chromatography and CsCl gradient ultracentrifugation. CsCl is removed by gel filtration.

Fermentations are monitored for temperature, pH and dissolved oxygen. The fermentation product is assayed for plasmid retention, microbial purity and consistency of yield (as assessed by dry cell weight and antigen content). Bulk, non-adsorbed vaccine is tested for HBsAg identification and proteinic contaminants by sodium dodecyl sulfate-poly acrylamide gel electrophoresis (SDS-PAGE). Assays for cesium, polysaccharides, DNA, pyrogens and sterility are performed.

The adsorbed vaccine, as finished product, is tested for HBsAg identification by SDS - PAGE (silver stained), pH, volume, aluminum content, thimerosal, sterility, general safety, endotoxin and potency in mice.

The manufacturer submitted samples and protocols from five final container lots for evaluation from five different production scale bulk lots. They met the release specifications established by the manufacturer. Additional lots have been submitted in support of the license application and have also met current release specifications.

B. STABILITY STUDIES

The stability of the adsorbed vaccine is assayed by its ability to induce antibodies against HBsAg in mice. Potency is determined by probit analysis and antibody titers are measured by radioimmunoassay. The recommended storage temperature of the adsorbed vaccine is 2-8°C Eight lots stored at 2-8°C for 12 months demonstrated stability and three lots were stored at 20-25°C for 12 months without significantly affecting potency.

The recommended expiration date is eighteen months with storage at 2-8°C. The manufacturer has agreed to continue long term stability studies.

C. VALIDATION

All major equipment and analytical methodology has been appropriately validated by SmithKline Biologicals, at the Rixensart, Belgium facility, and found to be adequate for control and regulatory purposes.

D. LABELING

Labels and labeling have been reviewed for compliance with 21 CFR 610.60, 610.61, 610.62, 201.56 and 201.57 and have been found satisfactory. Container labels include a warning which indicates the following, "Shake well. For I.M. use only. Store at 2°-8°C. Do not freeze." Carton labels indicate that the product should be discarded if frozen. A cautionary statement notes "Federal law prohibits dispensing without prescription." A statement to refer to the complete prescribing information for the vaccination schedule is included.

The package insert (attached) contains appropriate statements regarding product description, clinical pharmacology, indications and usage, contraindications, warnings, precautions, adverse reactions dosage and administration, storage and handling conditions, and how supplied.

E. ESTABLISHMENT INSPECTION

A pre-license inspection of the SmithKline Biologicals, biological production facility in Rixensart, Belgium, was conducted January 16-18, 1989. Deviations from current Good Manufacturing Practices (GMP) were noted and they were corrected by the manufacturer. The facility is now considered to be in compliance with current GMP regulations.

F. ENVIRONMENTAL IMPACT ANALYSIS REPORT

In accordance with 21 CFR 25.31a, an environmental assessment was prepared. No potential adverse environmental impact is expected from the manufacture and use of Engerix-B. The information supports a finding of no significant impact on the environment (attached).

IV. PHARMACOLOGY, BIOCHEMISTRY AND SEROLOGY

Engerix-B contains purified surface antigen (HBsAg) of HBV. The S gene of an adw_2 subtype of HBV was cloned in a functional expression plasmid into Saccharomyces cerevisiae. It is expressed as a 24 kD polypeptide and is obtained in large quantities in the form of 22 nm particles. Although it is not glycosylated, the polypeptide is immunogenically and physically similar to the antigen isolated from the plasma of chronic carriers. The similarity is suggested by in vitro recognition with antibodies specific for HBsAg, in vivo stimulation of antibodies specific for HBsAg, amino acid composition and sequencing, buoyant density of the HBsAg product, molecular weight, and electron microscopic appearance of the particles into which the polypeptide spontaneously aggregates.

Vaccinated chimpanzees were protected from HBV challenge infection. Inhibition studies carried out with a panel of 5 mouse monoclonal antibodies against HBsAg (designated RF1, RF6, RF7, RF13 and RF18) indicated that the chimpanzees' sera contained antibodies of the corresponding specificities.

The formation of antibodies to yeast-derived impurities was studied quantitatively by radioimmunoassay of anti-yeast IgG antibodies (179 human vaccinees) and qualitatively by Western blot analysis (32 human vaccinees). All vaccinees had anti-yeast IgG before inoculation with Engerix-B. Post-vaccination values of anti-yeast IgG increased in 4% of vaccinees and were not more than 2.9 times their pre-vaccination values. Anti-yeast IgG values decreased in 2.2% of vaccinees by a similar ratio. The observation suggests that variations in anti-yeast IgG titers are not related to the administration of the vaccine but reflect a variation of the anti-yeast IgG levels in a population naturally exposed to yeasts. Therefore, it is concluded that Engerix-B does not induce a significant modification of the anti-yeast IgG titers in vaccinees.

The susceptibility to anaphylactic reactions induced by yeast-derived impurities was evaluated via analysis of anti-yeast IgE antibodies post-vaccination in 258 human vaccinees. There were no significant changes between pre- and post-vaccination sera.

Characterization of the antibodies induced by Engerix-B was performed by 1) determination of the percentage of antibodies raised against the common a determinant of all subtypes of HBV, 2) competition studies with monoclonal antibodies and 3) HBsAg avidity constants. More than 90% of the anti-HBs induced by Engerix-B after 3 injected doses were directed against the common a determinant. The kinetics of appearance of anti-HBs and the percentage of

anti-a antibodies were similar to those seen post-immunization with plasma-derived vaccine. Results of competition assays using monoclonal antibodies raised against plasma-derived HBsAg and using sera of convalescent (hepatitis B) patients indicated that the same species of antibodies were produced in response to vaccination with either Engerix-B or with plasma-derived vaccine. Avidity constants against HBsAg ranged from $0.6\text{-}6 \times 10^9$ l/mol in pools of human sera (35 "initial" vaccinees, 27 convalescent vaccinees) obtained after a three-dose vaccination course. Avidity constants for the plasma-derived vaccines Heptavax-B and Hevac B ranged from $0.1 - 3.9 \times 10^9$ L/mol (Heptavax-B, 20 vaccinees; Hevac B, 16 vaccinees). The studies demonstrate that there is no significant difference between antibodies induced by Engerix-B or plasma-derived vaccines, or HBV infection.

V. MEDICAL

A. GENERAL INFORMATION

Hepatitis B virus causes a systemic infection characterized by liver inflammation. An estimated 300,000 cases occur in the United States annually, associated with morbidity and mortality due to fulminant hepatitis, hepatitis-related cirrhosis and hepatitis-related primary liver cancer.

It is known that antibodies directed against the virus' surface antigen (HBsAg) will protect against infection. Passive immunoprophylaxis with hepatitis B immune globulin has been demonstrated and immunity can be induced by Hepatitis B Vaccine.

B. CLINICAL STUDIES

Clinical studies with Engerix-B were initiated in February 1984. Through July 1, 1988, over 10,000 persons had participated in 87 studies (see Table 1). In addition to safety and immunogenicity studies, protective efficacy was assessed in certain high-risk populations such as neonates born to mothers who were carriers of HBV with HBsAg in the blood.

Vaccine was administered at dose levels according to predetermined schedules in order to assess the optimal inoculation regimen.

Adverse reactions were solicited using a symptom checklist by recording clinical signs and symptoms reported by all vaccinees both immediately post-vaccination and for four days thereafter. Neonatal symptom checklists did not include headache, fatigue or dizziness.

Blood samples were taken before and one month after each vaccine dose. Serological assays included HBsAg, HBeAg, antibodies to hepatitis B surface and core antigens, anti-yeast IgG antibodies or anti-yeast IgE antibodies.

1. SAFETY

In clinical trials Engerix-B was found to be well tolerated. No serious adverse reactions attributable to the vaccine were reported. Table 2 summarizes the experiences reported. The most common reactions were at the injection site and included soreness, induration, erythema and swelling. The most commonly reported systemic complaints were fatigue, headache, dizziness and fever. The local and systemic reactions occurred at frequencies similar to those observed after vaccination with plasma-derived vaccines, and tended to decrease after successive doses.

The number of symptoms reported by the parents or guardians of vaccinated children and neonates was much lower than that reported by vaccinated adults. Overall, 90% of children and 96% of newborns were without symptoms. Approximately 80% of the children who are symptomatic developed soreness at the injection site. The most common effect of vaccination in neonates was mild to moderate fever.

2. IMMUNOGENICITY

In clinical trials, 96-99% of healthy adult vaccinees achieved protective levels of antibody ($\geq$ 10mIU/mL). Two dosing schedules were studied extensively in independent investigations -- administration at 0, 1 and 6 months and at 0, 1 and 2 months with an additional dose at month 12. The 0,1,2 month dosing schedule provided protective antibody titers in 99% of individuals by one month after the third vaccine dose (month 3 after initiation). Five months after the second vaccine dose (month 6 after initiation) 79% of individuals on the 0, 1, 6 month schedule had developed protective antibody titers. At one month after the third dose (month 7), 96% of individuals had antibodies in the protective range.

Since Engerix-B trials in healthy adults showed that a fourth dose at month 12 following the 0, 1, 2-month schedule substantially increased the geometric mean titer (GMT) of antibody, four-dose Engerix-B regimens were studied in hemodialysis patients.

A dosage of 40 mcg administered at 0,1,2 and 6 months has been determined to be immunogenic for adult hemodialysis patients.

Similar to other previous reports, antibody response is age dependent and inversely proportional to increasing years. Comparable serologic data have been obtained using plasma-derived hepatitis B vaccines. Table 3 provides a summary of immunogenicity data.

Based on the comparable antibodies produced by Engerix-B and plasma-derived vaccine (see Section IV, Pharmacology, Biochemistry and Serology), it may be possible to interchange these vaccines. A

controlled study (N=48) demonstrated that completion of immunization with one dose of Engerix-B (20 mcg, month 6) after two doses of Recombivax HB (10 mcg, months 0 and 1) produced a GMT similar to immunization with three doses of Recombivax HB (10 mcg, months 0, 1, and 6). Thus, Engerix-B can be used to complete a vaccination course initiated with Recombivax HB.

3. EFFICACY

The protective efficacy of Engerix-B was demonstrated in persons at high risk of hepatitis B infection including neonates born to mothers who were carriers of HBsAg and HBeAg.

In a study of 58 neonates born to mothers who were carriers of HBsAg and HBeAg, all babies were vaccinated with 10 mcg of Engerix-B at 0, 1 and 2 months, and received an additional dose at month 12. Only two infants were chronic carriers at 12 months. No hepatitis B immune globulin was given. In this study only two (3%) of vaccinated neonates became chronic carriers, as compared to the historical category in which 60-90% of neonates born to carrier mothers have become carriers themselves in reported series.

4. OTHER CLINICAL STUDIES

In a clinical study of 244 homosexually active males, four individuals became infected prior to completion of the three-dose vaccination regimen (20 mcg at 0, 1, 6 months). No additional patients became infected during the 18 months follow-up period after completion of the immunization course.

VI. ADVISORY PANEL CONSIDERATION

Data regarding the manufacture, safety and efficacy of Engerix-B were discussed at the July 28, 1988 Vaccines and Related Biological Products Advisory Committee meeting.

VII. APPROVED PACKAGE INSERT

A copy of the approved package insert is attached.

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Table 1

Completed and On-going Clinical Trials with Engerix-B

Population	Number of Studies	Subjects Vaccinated (≥ 1 Dose)
Healthy adults	45	6022
Healthy children	9	1131
Newborns of HBsAg/HBeAg or HBsAg positive mothers	15	828
Newborns of HBsAg negative mothers	11	998
Thalassemics	2	89
Hemodialysis patients	6	573
Hemophiliacs	1	79
Cirrhotic patients	2	62
Homosexual males	3	424
Institutionalized mentally handicapped subjects	1	262
Parental drug users	1	79
TOTAL	87*	10547

*Some studies included subjects from two populations.

Table 2

Adverse Experiences Associated with the Administration of 'Engerix-B' in Clinical Trials

INCIDENCE > 10% OF INJECTIONS

Local reactions at injection site: Soreness (22%).

Body as a Whole: Fatigue (14%).*

INCIDENCE 1 to 10% OF INJECTIONS

Local reactions at injection site: Induration; erythema, swelling.

Body as a Whole: Fever (> 37.5°C).

Nervous System: Headache;* dizziness.*

INCIDENCE < 1% OF INJECTIONS

Local reactions at injection site: Pain; pruritus; ecchymosis.

Body as a Whole: Sweating; malaise; chills; weakness; flushing; tingling.

Cardiovascular system: Hypotension.

Respiratory system: Influenza-like symptoms; upper respiratory tract illnesses.

Gastrointestinal System: Nausea; anorexia; abdominal pain/cramps; vomiting; constipation; diarrhea.

Lymphatic system: Lymphadenopathy.

Musculoskeletal System: Pain/stiffness in arm, shoulder or neck; arthralgia; myalgia; back pain.

Skin and appendages: Rash; urticaria; petechiae; pruritus; erythema.

Nervous system: Somnolence; insomnia; irritability; agitation.

*Not solicited in neonatal clinical studies.

Table 3

Overall Seroconversion Rates and Geometric Mean Antibody Titers (GMT)
One Month After Last Scheduled Vaccine Dose

Population	No.	Dose (mcg)	Schedule (Months)	Sero-Protection@ (%)	GMT (mIU/mL)
Healthy adults	510	20	0, 1, 2	99	167
	111	20	0, 1, 6	96	2204
	50*	20	0, 1, 6	88	610
Hemodialysis Patients	43	40	0, 1, 2, 6	67+	93+
Children (1-10 years)	242	10	0, 1, 6	98	4023
Neonates	311	10	0, 1, 2	93	210
	52	10	0, 1, 6**	97	713

@ $\geq$ 10 mIU/ml

+two months after last vaccine dose.

*over age 40.

**actual administration = 0, 1 1/2, 5 months