SUMMARY FOR BASIS OF APPROVAL

Reference No. 88-0192

Drug Licensed Name: Hepatitis B Vaccine (Recombinant)

Mfr: Merck Sharp & Dohme (MSD)

Drug Trade Name: RECOMBIVAX HB

Hepatitis B Vaccine (Recombinant), RECOMBIVAX HB, is a noninfectious subunit viral vaccine derived from synthetic hepatitis B surface antigen (HBsAg) produced in yeast cells. A plasmid containing a portion of hepatitis B virus gene coding for HBsAg is cloned into yeast, and the vaccine for hepatitis B is produced from cultures of this recombinant yeast strain.

I. INDICATION FOR USE IN DIALYSIS/PREDIALYSIS PATIENTS

RECOMBIVAX HB is indicated for immunization against infection caused by all known subtypes of hepatitis B virus (HBV). **The vaccine has been shown to be** effective in inducing an immune response (anti-HBs) in a substantial proportion of initially seronegative dialysis/predialysis patients.

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

II. DOSAGE AND ADMINISTRATION

RECOMBIVAX HB consists of hepatitis B surface antigen (HBsAg) which is produced in yeast cells. The isolated and purified antigen is adsorbed onto aluminum hydroxide as an adjuvant, and thimerosal is added as a preservative. A 1.0 mL dose of the formulation of the vaccine for use in dialysis/predialysis patients contains 40 mcg of HBsAg.

III. MANUFACTURING AND CONTROLS

A. MANUFACTURING AND CONTROLS

The organism, Saccharomyces cerevisiae, strain 2150-2-3 (pHBS56-GAP347/33), which is utilized for the production of HBsAg, contains a plasmid containing a gene for the adw subtype of HBsAg. **The culture is grown in a** Yeast Extract/Soy Peptone/Dextrose (YEHD) medium at [redacted] for at least [redacted] hours. The fermentations are monitored for [redacted] and [redacted] at frequent intervals. The final fermentation culture is assayed for [redacted] strain identity and [redacted] and HBsAg by Enzyme Immunoassay (EIA).

The cells are harvested, washed and concentrated by [redacted] followed by cell disruption. The HBsAg is [redacted] Purification is achieved by adsorption/desorption (fumed silica), hydrophobic interaction and size exclusion chromatography and diafiltration through selective membranes. During purification, each significant intermediate is assayed for HBsAg by EIA and protein by the Lowry procedure. The purified product is tested for yeast protein impurities by size exclusion HPLC (less than or equal to 1.0% or less of p60), and by Western blot reacted with anti-veast antiserum. The [redacted] is tested for HBsAg content by Lowry protein assay [redacted] and by polyacrylamide gel electrophoresis (SDS-PAGE) on reduced samples. The gels are stained with silver stain, and Western blots are done and examined for the major band between 20,000 and 25,000 daltons. The silver stained gel is scanned by densitometry to determine the proportions of the sample at the 24,000 molecular weight band.

The purified HBsAg is treated with formaldehyde. The formaldehyde is then removed, the HBsAg is adsorbed onto alum, filled into final containers and labeled. Testing for formaldehyde [redacted] and after formaldehyde removal [redacted] mcg/mL) is carried out. The [redacted] is also tested for sterility (no growth after 14 days), [redacted] mcg/mL), and thiocyanate ([redacted] mcg/mL).

The final container is tested for sterility, general safety, endotoxin by LAL, ([redacted] EU/mL), thimerosal, [redacted] mcg/mL), aluminum [redacted] mg/mL) and potency in mice (ED_{50} [redacted] mcg/mL).

The manufacturer submitted for evaluation samples and protocols of four final container lots of vaccine derived from four different bulk lots produced initially at production scale. These lots met the release specifications listed at the time of their manufacture.

B. STABILITY STUDIES

The recommended storage temperature of the vaccine, adsorbed onto alum is 2-8°C. Stability of the vaccine was monitored by the demonstration of potency in an in vivo mouse model and by in vitro enzyme immunoassay.

Two lots of 40 mcg/mL vaccine are currently being studied.

A review of the accelerated and long-term stability data available to date indicates stability comparable with that of other RECOMBIVAX HB dosage forms.

The product will have an expiration dating of twenty-four months at 2-8°C. The package insert recommends storage at 2-8°C which is supported by the stability studies. Merck has committed to conduct ongoing stability studies.

IV. CLINICAL STUDIES

RECOMBIVAX HB has been administered to 365 previously unvaccinated seronegative patients with chronic renal insufficiency (275 dialysis patients and 90 predialysis patients) in 6 studies.

Several vaccination regimens were evaluated. These included both 3 and 6 injection regimens with 10-100 mcg HBsAg per dose as shown below:

1. 10 mcg HBsAg at 0, 1, 6 months
2. 20 mcg HBsAg at 0, 1, 6 months
3. 40 mcg HBsAg at 0, 1, 6 months
4. 100 mcg HBsAg at 0, 1, 6 months
5. 20 mcg HBsAg at 0, 1, 2, 3, 4, 5 months
6. 40 mcg HBsAg at 0, 1, 2, 3, 4, 5 months

The effect of injection site was also investigated. In four studies, patients received vaccine in the deltoid muscle, while in two other studies, vaccine was administered in the buttock.

Vaccine recipients were asked to report their temperature and any injection site or systemic complaints that occurred within a five-day period following each injection of vaccine.

Post-vaccination blood samples were obtained for the determination of antibody to hepatitis B surface antigen (anti-HBs), other hepatitis B virus serologic markers (HBsAg, anti-HBc), and serum alanine aminotransferase (ALT) activity.

A. SAFETY/TOLERABILITY

RECOMBIVAX HB has been well tolerated by dialysis/predialysis patients. There were no reports of serious reactions attributable to vaccination among patients in any of the clinical studies.

Clinical complaints that were reported were mild and transient. There appeared to be no relationship between dose of vaccine administered and the frequencies of injection site discomfort, systemic complaints, or elevated temperatures. **Complaints did not become more frequent with increasing** injection number.

Tables 1 and 2 show the frequencies of specific complaints within body system (summed over all injections and dosages) for patients given vaccine in the buttock or deltoid muscle, respectively. Local injection site discomfort was reported following 0.4% of injections in the buttock and after 6% of injections given in the deltoid muscle. The most common systemic complaints were fatigue/weakness, headache, nausea, and vomiting, each occurring at a frequency of 1-2%.

B. IMMUNOGENICITY

Antibody (anti-HBs) responses of the dialysis/predialysis patients to the various vaccination regimens are summarized in Tables 3-5. In general, the vaccine was found to be less immunogenic in these patients than in healthy adults. However, 86% of 28 patients given three 40 mcg doses of vaccine in the deltoid muscle developed a protective level of anti-HBs (greater than or equal to 10 mIU/mL), and these responders had a geometric mean titer (GMT) of 375 mIU/mL. Increasing the number of injections to six or increasing the dosage to 100 mcg did not improve the antibody response. Consequently, a regimen of three 40 mcg doses of RECOMBIVAX HB administered in the deltoid muscle is recommended for dialysis/predialysis patients.

C. EFFICACY

Direct studies of the efficacy of RECOMBIVAX HB in dialysis/predialysis patients have not been done. Efficacy is imputed from the presence of antibody, with an anti-HBs titer greater than or equal to 10 mIU/mL considered to be protective.

TABLE 1

Frequencies of Local and Systemic Complaints Among
Dialysis and Predialysis Patients
During a Five-Day Period Following 500 Buttock Injections of
Hepatitis B Vaccine (Recombinant)
(3 and 6 Dose Regimens)

STUDIES: 811, 838

Number of Vaccine Recipients = 142

Body System/Complaint	% Frequency (Number)
Local/Injection Site	0.4 (2)
Soreness	0.2 (1)
Pruritis	0.2 (1)
Whole Body/General	3 (16)
Fatigue/Weakness	2 (9)
Headache	1 (5)
Chills	0.4 (2)
Lightheaded	0.4 (2)
Fever (Temperature not reported)	0.2 (1)
Illness NOS *	0.2 (1)
Digestive	2 (9)
Nausea	1 (5)
Diarrhea	0.4 (2)
Diminished Appetite	0.2 (1)
Abdominal Pains/Cramps	0.2 (1)
Cardiovascular	0.8 (4)
Hypotension	0.2 (1)
Inconstant Blood Pressure	0.2 (1)
Circulatory Disturbances NOS *	0.2 (1)
Hypertension	0.2 (1)
Musculoskeletal	0.6 (3)
Arthralgia (other)	0.6 (3)
Respiratory	0.2 (1)
Cough	0.2 (1)
Nervous System	0.2 (1)
Vertigo	0.2 (1)
Psychiatric/Behavioral	0.2 (1)
Depression	0.2 (1)

* NOS = Not otherwise specified

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TABLE 2

Frequencies of Local and Systemic Complaints Among
Dialysis and Predialysis Patients
During a Five-Day Period Following 570 Deltoid Injections of
Hepatitis B Vaccine (Recombinant)

STUDIES: 789, 816, 825, 837

Number of Vaccine Recipients = 210

Body System/Complaint	% Frequency (Number)
Local/Injection Site	**6 (32)**
Soreness	5 (29)
Stiffness/Tightness	1 (6)
Ecchymosis	0.5 (3)
Swelling	0.4 (2)
Pain	0.2 (1)
Inflammation	0.2 (1)
Erythema	0.2 (1)
Pruritis	0.2 (1)
Whole Body/General	**5 (27)**
Fatigue/Weakness	1 (8)
Headache	1 (8)
Chills	0.8 (5)
Sensation of Warmth General	0.5 (3)
Lightheaded	0.4 (2)
Illness, NOS *	0.4 (2)
Malaise	0.2 (1)
Sunburn	0.2 (1)
Flush	0.2 (1)
Hot and Cold Flashes	0.2 (1)
Digestive	**3 (14)**
Nausea	2 (11)
Vomiting	1 (6)
Diarrhea	0.2 (1)
Appetite Increased	0.2 (1)
Abdominal Tenderness	0.2 (1)
Respiratory	**2 (12)**
Pharyngitis	0.5 (3)
Upper Respiratory Infection, NOS *	0.5 (3)
Cough	0.4 (2)
Wheezes	0.2 (1)
Cold Symptoms	0.2 (1)
Bronchitis	0.2 (1)
Dyspnea	0.2 (1)
Nose Bleed	0.2 (1)
Musculoskeletal	**1 (7)**
Arthralgia	0.4 (2)
Myalgia	0.2 (1)
Muscle Cramps	0.2 (1)
Shoulder Pain	0.2 (1)
Arm Pain	0.2 (1)
Knee Pain	0.2 (1)
Hand Cramps	0.2 (1)
Nervous System	**0.5 (3)**
Vertigo	0.2 (1)
Somnolence	0.2 (1)
Tremor	0.2 (1)
Psychiatric/Behavioral	**0.5 (3)**
Depression	0.4 (2)
Insomnia/Disturbed Sleep	0.2 (1)
Infectious Syndromes	**0.2 (1)**
Influenza, NOS *	0.2 (1)

* NOS = Not otherwise specified

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TABLE 3

Antibody Responses Among Initially
Seronegative Dialysis/Predialysis Patients
Receiving Buttock Injections of
Hepatitis B Vaccine (Recombinant)
at 0, 1, 6 Months

STUDIES: 811, 838

Dose (mcg)	Time of Serum Sampling (Months)	% (Proportion) with Anti-HBs		All Vaccinees	GMT (mIU/ml) Responders	
		S/N ≥2.1	mIU/ml ≥10		S/N ≥2.1	mIU/ml ≥10
10	1	0 (0/14)	0 (0/14)	0.3	--	--
	3	0 (0/14)	0 (0/14)	0.3	--	--
	6	0 (0/13)	0 (0/13)	0.3	--	--
	7/8	15 (2/13)	15 (2/13)	0.7	67.7	67.7
	12	8 (1/12)	0 (0/12)	0.4	6.0	--
20	1	0 (0/14)	0 (0/14)	0.3	--	--
	3	7 (1/14)	7 (1/14)	0.5	90.0	90.0
	6	28 (4/14)	28 (4/14)	1.0	23.6	23.6
	7/8	58 (7/12)	58 (7/12)	13.8	213.7	213.7
	12	60 (6/10)	60 (6/10)	8.5	78.5	78.5
40	1	1 (1/69)	0 (0/69)	0.3	4.6	--
	3	27 (16/59)	17 (10/59)	1.0	16.5	31.0
	6	37 (20/54)	28 (15/54)	1.5	18.5	27.6
	7/8	62 (29/47)	55 (26/47)	13.2	125.4	173.6
	12	59 (17/29)	52 (15/29)	8.4	69.4	105.0

TABLE 4

Antibody Responses Among Initially Seronegative Dialysis Patients Receiving Buttock Injections of Hepatitis B Vaccine (Recombinant) at 0, 1, 2, 3, 4, 5 Months

STUDIES: 838

Dose (mcg)	Time of Serum Sampling (Months)	% (Proportion) with Anti-HBs		All Vaccinees	GMT (mIU/ml) Responders	
		S/N ≥2.1	mIU/ml ≥10		S/N ≥2.1	mIU/ml ≥10
20	1	0 (0/20)	0 (0/20)	0.3	--	--
	3	30 (6/20)	25 (5/20)	1.1	23.6	31.4
	6	53 (8/15)	40 (6/15)	7.7	73.2	171.2
	12	40 (6/15)	33 (5/15)	3.0	43.0	58.7
40	1	0 (0/20)	0 (0/20)	0.3	--	--
	3	32 (6/19)	21 (0/19)	1.1	19.5	33.5
	6	73 (11/15)	73 (11/15)	42.6	189.8	189.8
	12	73 (11/15)	67 (10/15)	12.1	38.4	46.1

TABLE 5

Antibody Responses Among Initially Seronegative Dialysis/Predialysis Patients Receiving Deltoid Injections of Hepatitis B Vaccine (Recombinant) at 0, 1, 6 Months

STUDIES: 789, 816, 825, 837

Dose (mcg)	Time of Serum Sampling (Months)	% (Proportion) with Anti-HBs		All Vaccinees	GMT (mIU/ml) Responders	
		S/N ≥2.1	mIU/ml ≥10		S/N ≥2.1	mIU/ml ≥10
20 *	1	4 (2/45)	2 (1/45)	0.4	5.4	18.5
	3	23 (10/43)	2 (1/43)	0.6	6.5	76.1
	6	35 (15/43)	14 (6/43)	1.1	6.7	21.7
	7/8.	57 (27/46)	43 (20/46)	7.0	73.1	132.4
	12	51 (21/41)	34 (14/41)	4.4	52.9	91.5
40 *	1	13 (6/46)	4 (2/46)	0.6	6.7	17.9
	3	48 (21/44)	25 (11/44)	2.3	17.0	37.1
	6	73 (22/30)	50 (15/30)	10.8	21.5	35.2
	7/8	89 (25/28)	86 (24/28)	180.8	277.0	375.0
	12	80 (24/30)	67 (20/30)	36.2	96.4	150.1
100	1	16 (13/83)	1 (1/83)	0.5	4.5	263.3
	3	60 (48/80)	34 (27/80)	3.6	16.9	46.2
	6	72 (46/64)	47 (30/64)	6.4	21.4	44.0
	7/8	79 (30/38)	76 (29/38)	44.2	167.3	191.7
	12	77 (31/40)	67 (27/40)	23.3	82.3	114.4

* Responses to 20 and 40 mcg doses include data from Study 789 in which anti-HBs levels were determined only in units of S/N. For purposes of calculating overall proportions of vaccinees with antibody, an S/N ratio of 10 was considered to be comparable to 10 mIU/ml. However, GMTs in units of S/N cannot be merged with GMTs in units of mIU/ml. Consequently, the GMTs shown in the table above for recipients of 20 and 40 mcg doses of vaccine are based only on those patients for whom titers were calculated in units of mIU/ml (N = 26-29 for 20 mcg dose; N = 16-31 for 40 mcg dose) and do not include values for subjects vaccinated in Study 789 (N = 12-17 for 20 mcg dose; N = 10-16 for 40 mcg dose). Responses of 11 subjects who received vaccine at mixed sites (deltoid and buttock; 5 in the 20 mcg group and 6 in the 40 mcg group) are excluded from the table.