MERCK & CO., INC.
West Point, PA 19486, USA

COMVAX™
[HAEMOPHILUS b CONJUGATE (MENINGOCOCCAL PROTEIN CONJUGATE) and HEPATITIS B (RECOMBINANT) VACCINE]

DESCRIPTION

COMVAX* [Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine] is a sterile bivalent vaccine made of the antigenic components used in producing PedvaxHIB† [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] and RECOMBIVAX HB† [Hepatitis B Vaccine (Recombinant)]. These components are the *Haemophilus influenzae* type b capsular polysaccharide (PRP) that is covalently bound to an outer membrane protein complex (OMPC) of *Neisseria meningitidis* and hepatitis B surface antigen (HBsAg) from recombinant yeast cultures.

Haemophilus influenzae type b and *Neisseria meningitidis* serogroup B are grown in complex fermentation media. The PRP is purified from the culture broth by purification procedures which include ethanol fractionation, enzyme digestion, phenol extraction and diafiltration. The OMPC from *Neisseria meningitidis* is purified by detergent extraction, ultracentrifugation, diafiltration and sterile filtration.

The PRP-OMPC conjugate is prepared by the chemical coupling of the highly purified PRP (polyribosylribitol phosphate) of *Haemophilus influenzae* type b (Haemophilus b, Ross strain) to an OMPC of the B11 strain of *Neisseria meningitidis* serogroup B. The coupling of the PRP to the OMPC, which is necessary for enhanced immunogenicity of the PRP, is confirmed by analysis of the conjugate's components following chemical treatment which yields a unique amino acid. After conjugation, the aqueous bulk is then adsorbed onto an aluminum hydroxide adjuvant.

HBsAg is produced in recombinant yeast cells. A portion of the 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 according to methods developed in the Merck Research Laboratories. The antigen is harvested and purified from fermentation cultures of a recombinant strain of the yeast *Saccharomyces cerevisiae* containing the gene for the *adw* subtype of HBsAg. The HBsAg protein is released from the yeast cells by cell disruption and purified by a series of physical and chemical methods. The vaccine contains no detectable yeast DNA but may contain not more than 1% yeast protein. The aqueous bulk is treated with formaldehyde and then adsorbed onto an aluminum hydroxide adjuvant.

After each PRP-OMPC and HBsAg aqueous bulk is adsorbed onto the aluminum hydroxide adjuvant, they are then combined to produce COMVAX. Each 0.5 mL dose of COMVAX is formulated to contain 7.5 mcg of Haemophilus b PRP, 125 mcg of *Neisseria meningitidis* OMPC, 5 mcg of HBsAg, approximately 225 mcg of aluminum as aluminum hydroxide, and 35 mcg sodium borate (decahydrate) as a pH stabilizer, in 0.9% sodium chloride.

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The product contains no preservative.

COMVAX is a sterile suspension for intramuscular injection.

CLINICAL PHARMACOLOGY

Haemophilus influenzae type b Disease

Prior to the introduction of *Haemophilus b* conjugate vaccines, *Haemophilus influenzae* type b (Hib) was the most frequent cause of bacterial meningitis and a leading cause of serious, systemic bacterial disease in young children worldwide.[1-4]

Hib disease occurred primarily in children under 5 years of age, and in the United States prior to the initiation of a vaccine program was estimated to account for nearly 20,000 cases of invasive infections annually, approximately 12,000 of which were meningitis. The mortality rate from Hib meningitis is about 5%. In addition, up to 35% of survivors develop neurologic sequelae including seizures, deafness, and mental retardation.[5,6] Other invasive diseases caused by this bacterium include cellulitis, epiglottitis, sepsis, pneumonia, septic arthritis, osteomyelitis, and pericarditis.

Prior to the introduction of the vaccine, it was estimated that 17% of all cases of Hib disease occurred in infants less than 6 months of age. The peak incidence of Hib meningitis occurred between 6 to 11 months of age. Forty-seven percent of all cases occurred by one year of age with the remaining 53% of cases occurring over the next four years.[2,20]

Among children under 5 years of age, the risk of invasive Hib disease is increased in certain populations including the following:

- Daycare attendees[7,8,9]
- Lower socio-economic groups[10]
- Blacks[11] (especially those who lack the Km(1) immunoglobulin allotype)[12]
- Caucasians who lack the G2m (23) immunoglobulin allotype[13]
- Native Americans[14-16]
- Household contacts of cases[17]
- Individuals with asplenia, sickle cell disease, or antibody deficiency syndromes.[18,19]

An important virulence factor of the Hib bacterium is its polysaccharide capsule (PRP). Antibody to PRP (anti-PRP) has been shown to correlate with protection against Hib disease.[3,21] While the anti-PRP level associated with protection using conjugated vaccines has not yet been determined, the level of anti-PRP associated with protection in studies using bacterial polysaccharide immune globulin or nonconjugated PRP vaccines ranged from ≥0.15 to ≥1.0 mcg/mL.[22-28]

Nonconjugated PRP vaccines are capable of stimulating B-lymphocytes to produce antibody without the help of T-lymphocytes (T-independent). The responses to many other antigens are augmented by helper T-lymphocytes (T-dependent). PedvaxHIB is a PRP-conjugate vaccine in which the PRP is covalently bound to the OMPC carrier[29] producing an antigen which is postulated to convert the T-independent antigen (PRP alone) into a T-dependent antigen resulting in both an enhanced antibody response and immunologic memory.

The protective efficacy of the PRP-OMPC component of COMVAX was demonstrated in a randomized, double-blind, placebo-controlled study involving 3,486 Native American (Navajo) infants (The Protective Efficacy Study) who completed the primary two-dose regimen for lyophilized PedvaxHIB. This population has a much higher incidence of Hib disease than the United States population as a whole and also has a lower antibody response to Haemophilus b conjugate vaccines, including PedvaxHIB.[14-16,30,31]

Each infant in this study received two doses of either placebo or lyophilized PedvaxHIB (15 mcg Haemophilus b PRP) with the first dose administered at a mean of 8 weeks of age and the second administered approximately two months later; DTP and OPV were administered concomitantly. In a subset of 416 subjects, lyophilized PedvaxHIB (15 mcg Haemophilus b PRP) induced anti-PRP levels >0.15 mcg/mL in 88% and >1.0 mcg/mL in 52% with a geometric mean titer (GMT) of 0.95 mcg/mL one to three months after the first dose; the corresponding anti-PRP levels one to three months following the second dose were 91% and 60%, respectively, with a GMT of 1.43 mcg/mL. These antibody responses were associated with a high level of protection.

Most subjects were initially followed until 15 to 18 months of age. During this time, 22 cases of invasive Haemophilus b disease occurred in the placebo group (8 cases after the first dose and 14 cases after the second dose) and only 1 case in the vaccine group (none after the first dose and 1 after the second dose). Following the primary two-dose regimen, the protective efficacy of lyophilized PedvaxHIB was calculated to be 93% with a 95% confidence interval of 57-98%. In the two months between the first and second doses, the difference in number of cases of disease between placebo and vaccine recipients (8 vs 0 cases, respectively) was statistically significant (p=0.008). [31]

Thus, in this study, a protective efficacy of 93% was achieved with an anti-PRP level of >1.0 mcg/mL in 60% of vaccinees and a GMT of 1.43 mcg/mL one to three months after the second dose. In a randomized, multicenter study comparing COMVAX (7.5 mcg Haemophilus b PRP; 5 mcg HBsAg) to concurrent administration of monovalent Liquid PedvaxHIB and monovalent RECOMBIVAX HB, anti-PRP levels were measured in 576 of 645 infants who received two doses of COMVAX. In these infants, COMVAX induced anti-PRP levels >0.15 mcg/mL in 95% and >1.0 mcg/mL in 72% with a GMT of 2.5 mcg/mL, approximately two months after the second dose (see Table 1). Because the PRP-OMPC component of COMVAX induces a comparable anti-PRP response (see Table 1), the efficacy of COMVAX is expected to be similar to that obtained with monovalent Lyophilized PedvaxHIB in the Protective Efficacy Trial in the prevention of invasive Hib disease.

Hepatitis B Disease

Hepatitis B virus is an important cause of viral hepatitis. There is no specific treatment for this disease. The incubation period for hepatitis B is relatively long; six weeks to six months may elapse between exposure and the onset of clinical symptoms. The prognosis following infection with hepatitis B virus is variable and dependent on at least three factors : (1) Age - Infants and younger children usually experience milder initial disease than older persons but are much more likely to remain persistently infected and become at risk of developing serious chronic liver disease; (2) Dose of virus - The higher the dose, the more likely acute icteric hepatitis B will result; and, (3) Severity of associated underlying disease - underlying malignancy or pre-existing hepatic disease predisposes to increased mortality and morbidity.[32]

Hepatitis B infection fails to resolve and progresses to a chronic carrier state in 5 to 10% of older children and adults and in up to 90% of infants; chronic infection also occurs more frequently after initial anicteric hepatitis B than after initial icteric disease.[32] Consequently, carriers of HBsAg frequently give no history of having had recognized acute hepatitis. It has been estimated that more than 285 million people in the world today are persistently infected with hepatitis B virus.[33] The Centers for Disease Control (CDC) estimates that there are approximately 0.75 to 1 million chronic carriers of hepatitis B virus in the USA.[34] Chronic carriers represent the largest human reservoir of hepatitis B virus.

A serious complication of acute hepatitis B virus infection is massive hepatic necrosis while sequelae of chronic hepatitis B include cirrhosis of the liver, chronic active hepatitis, and hepatocellular carcinoma. Chronic carriers of HBsAg appear to be at increased risk of developing hepatocellular carcinoma. Although a number of etiologic factors are associated with development of hepatocellular carcinoma, the single most important etiologic factor appears to be chronic infection with hepatitis B virus.[34]

The vehicles for transmission of the virus are most often blood and blood products but the viral antigen has also been found in tears, saliva, breast milk, urine, semen, and vaginal secretions. Hepatitis B virus is capable of surviving for days on environmental surfaces exposed to body fluids containing hepatitis B virus. Infection may occur when hepatitis B virus, transmitted by infected body fluids, is implanted via mucous surfaces or percutaneously introduced through accidental or deliberate breaks in the skin. Transmission of hepatitis B virus infection is often associated with close interpersonal contact with an infected individual and with crowded living conditions.[35]

Hepatitis B is endemic throughout the world and is a serious medical problem in population groups at increased risk. Because vaccination limited to high-risk individuals has failed to substantially lower the overall incidence of hepatitis B infection, both the Advisory Committee on Immunization Practices (ACIP) and the Committee on Infectious Diseases of the American Academy of Pediatrics (AAP) have also endorsed universal infant immunization as part of a comprehensive strategy for the control of hepatitis B infection.[36,37]

Multiple clinical studies have defined a protective antibody (anti-HBs) level as 1) 10 or more sample ratio units (SRU or S/N) as determined by radioimmunoassay or 2) a positive result as determined by enzyme immunoassay.[38-44] Note: 10 SRU is comparable to 10 mIU/mL of antibody.[34] The ACIP and an international group of hepatitis B experts consider an anti-HBs titer ≥10 mIU/mL an adequate response to a complete course of hepatitis B vaccine and protective against clinically significant infection (antigenemia with or without clinical disease).[34,44]

In clinical studies, 99% of 125 infants under 1 year of age born of non-carrier mothers developed a protective level of antibody (anti-HBs≥ 10 mIU/mL) after receiving three 2.5-mcg doses of RECOMBIVAX HB at intervals of 0, 1, and 6 months.[31]

In another clinical study, protective levels of antibody were achieved in 98% of 52 healthy infants after receiving 2.5 mcg of RECOMBIVAX HB at 2, 4, and 12 months of age. Protective anti-HBs levels were achieved in 100% of an additional 50 infants who also received three 2.5-mcg doses of RECOMBIVAX HB but at 2, 4, and 15 months of age.[45]

The protective efficacy of three 5 mcg doses of RECOMBIVAX HB has been demonstrated in neonates born of mothers positive for both HBsAg and HBeAg (a core-associated antigenic complex which correlates with high infectivity). In a clinical study of infants who received one dose of Hepatitis B Immune Globulin at birth followed by the recommended three-dose regimen of RECOMBIVAX HB, chronic infection had not occurred in 96% of 130 infants after nine months of follow-up.[62] The estimated efficacy in prevention of chronic hepatitis B infection was 95% as compared to the infection rate in untreated historical controls.[63]

In a randomized, multicenter study comparing COMVAX to Liquid PedvaxHIB and RECOMBIVAX HB, anti-HBs levels were measured in 571 of 598 infants who received 3 doses of COMVAX. In these infants, COMVAX induced protective anti-HBs levels (≥ 10 mIU/mL) in 98%. Because the HBs component of COMVAX induces a comparable anti-HBs response to that obtained with RECOMBIVAX HB, the efficacy of COMVAX is expected to be similar (Table 1).

COMVAX

The safety and immunogenicity of COMVAX (7.5 mcg Haemophilus b PRP, 5 mcg HBsAg) were compared with those of the component monovalent vaccines, liquid PedvaxHIB (7.5 mcg Haemophilus b PRP) and RECOMBIVAX HB (5 mcg HBsAg) given concurrently at separate sites, in combined clinical trials involving 1216 healthy infants. Each infant received a three-dose regimen of either COMVAX (n=856) or liquid PedvaxHIB and RECOMBIVAX HB administered either concomitantly (n=290) or one month apart (n=70) beginning at approximately 2 months of age; other standard pediatric vaccines (M-M-R[†]II [Measles, Mumps, and Rubella Virus Vaccine, Live], DTP [diphtheria, tetanus, pertussis] or DTaP [diphtheria, tetanus, acellular pertussis]or OPV [oral poliovirus vaccine]) were administered concomitantly to most subjects. Antibody responses following the recommended three-dose regimen of COMVAX were similar to those following concurrent administration of the monovalent vaccines according to the same schedule. Table 1 summarizes antibody responses in a subset of infants from one multicenter, randomized, open-label study. These infants received a three-dose regimen of either COMVAX or liquid PedvaxHIB plus RECOMBIVAX HB at approximately 2, 4, and 12-15 months of age.

The anti-HBs GMT associated with the use of COMVAX was 4467.5 mIU/mL and the anti-HBs GMT associated with the concomitant use of monovalent PedvaxHIB plus monovalent RECOMBIVAX HB was 6943.9 mIU/mL. Although the difference is statistically significant (p=0.011), both values are much greater than the level of 10 mIU/mL previously established as marking a protective response to hepatitis B. [40,42-44,48,49] These GMTs are also higher than those reported in a number of studies wherein healthy neonates or young infants received the currently licensed regimen of RECOMBIVAX HB consisting of 2.5 mcg doses administered on the standard 0, 1 and 6-month schedule. In those studies, the infants developed GMTs of 216-1269 mIU/mL. Another study has shown that infants given 2.5 mcg doses of RECOMBIVAX HB according to the schedule used for COMVAX (2, 4, and 12 or 15 months of age) developed GMTs of 1356-3424 mIU/mL.[45,50-55] While a difference in the GMT between two vaccination regimens may result in differential retention of ≥ 10 mIU/mL of anti-HBs after a number of years, this is of no apparent clinical significance because of immunologic memory. [59,60]

Table 1
Antibody Responses to COMVAX, liquid PedvaxHIB, and RECOMBIVAX HB

Vaccine	Age (months)	Time	N	Anti-PRP % Subjects with >0.15 mcg/mL	Anti-PRP % Subjects with >1.0mcg/mL	Anti-PRP GMT (mcg/mL)	N	% Subjects ≥10 mIU/mL Anti-HBs	Anti-HBs GMT
COMVAX (7.5 mcg PRP, 5 mcg HBsAg)		Prevaccination	633	34.4	4.7	0.1	603	10.6	0.6
	2	Dose 1*	620	88.9	51.5	1.0	595	34.3	4.2
	4	Dose 2*	576	94.8	72.4	2.5	571	92.1	113.9
	12/15	Dose 3**	570	99.3	92.6	9.5	571	98.4	4467.5
Liquid PedvaxHIB (7.5 mcg PRP) + RECOMBIVAX HB (5 mcg HBsAg)		Prevaccination	208	33.7	5.8	0.1	196	7.1	0.5
	2	Dose 1*	202	90.1	53.5	1.1	198	41.9	5.3
	4	Dose 2*	186	95.2	76.3	2.8	185	98.4	255.7
	12/15	Dose 3**	181	98.9	92.3	10.2	179	100	6943.9

* Postvaccination responses were determined approximately two months after doses 1 and 2.
** Postvaccination responses were determined approximately one month after administration of dose 3.

An additional 1756 infants were involved in clinical trials where COMVAX was administered concomitantly with either an investigational pneumococcal polysaccharide protein conjugate vaccine or an investigational preparation of diphtheria, tetanus, pertussis, and enhanced inactivated poliovirus vaccine. The serious adverse experience information for these subjects is provided in this circular (see ADVERSE REACTIONS).

Interchangeability of COMVAX and Licensed Haemophilus b Conjugate Vaccines or Recombinant Hepatitis B Vaccines

One multicenter study has shown similar safety profiles and similar anti-PRP and anti-HBs responses among children vaccinated with a three-dose course of COMVAX or a three-dose course of monovalent PedvaxHIB and monovalent RECOMBIVAX HB. Therefore, it is expected that responses would be comparable if COMVAX were used as a component of a mixed Haemophilus b conjugate vaccine series involving PedvaxHIB or a mixed hepatitis B vaccine series involving RECOMBIVAX HB. Published studies presenting limited clinical data have examined the interchangeability of other licensed Haemophilus b conjugate vaccines and PedvaxHIB. [58-61] In addition, a clinical study has shown that in healthy neonates a regimen of hepatitis B vaccine can be initiated with another currently licensed hepatitis B vaccine and completed with RECOMBIVAX HB.[31]

INDICATIONS AND USAGE

COMVAX is indicated for vaccination against invasive disease caused by *Haemophilus influenzae* type b and against infection caused by all known subtypes of hepatitis B virus in infants 6 weeks to 15 months of age born of HBsAg negative mothers. Infants born of HBsAg positive mothers should be vaccinated with a passive-active regimen that includes the administration of Hepatitis B Immune Globulin and Hepatitis B Vaccine (Recombinant) at birth given according to a particular schedule; (see manufacturer's circular for Hepatitis B Vaccine [Recombinant]).

Vaccination should ideally begin at approximately 2 ~~months~~ of age or as soon thereafter as possible. In order to complete the three-dose regimen of COMVAX, vaccination should be initiated no later than 10 months of age. Infants in whom vaccination with a PRP-OMPC-containing product (i.e., PedvaxHIB, COMVAX) is not initiated until 11 months of age do not require three doses of PRP-OMPC; however, three doses of an HBsAg-containing product are required for complete vaccination against hepatitis B, regardless of age. For infants and children not vaccinated according to the recommended schedule see DOSAGE AND ADMINISTRATION.

Use With Other Vaccines

Results from clinical studies indicate that COMVAX can be administered concomitantly with DTP, OPV, and M-M-R II, and with a booster dose of DTaP at approximately 15 months of age, using separate sites and syringes for injectable vaccines (see CLINICAL PHARMACOLOGY, *COMVAX*). No impairment of immune response to these individually tested vaccine antigens was demonstrated.

Data are currently not available regarding concomitant administration with IPV, VARIVAX† [Varicella virus vaccine, live (Oka/Merck)] or with the primary series of DTaP.

COMVAX SHOULD NOT BE USED IN INFANTS YOUNGER THAN 6 WEEKS OF AGE.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine.

WARNINGS

If COMVAX is used in persons with malignancies or those receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

Patients who develop symptoms suggestive of hypersensitivity after an injection should not receive further injections of the vaccine (see CONTRAINDICATIONS).

PRECAUTIONS

General

COMVAX will not protect against invasive disease caused by *Haemophilus influenzae* other than type b or against invasive disease (such as meningitis or sepsis) caused by other microorganisms. COMVAX will not prevent hepatitis caused by other viruses known to infect the liver. Because of the long incubation period for hepatitis B, it is possible for unrecognized infection to be present at the time the vaccine is given. The vaccine may not prevent hepatitis B in such patients.

As for any vaccine, adequate treatment provisions, including epinephrine, should be available for immediate use should an anaphylactic or anaphylactoid reaction occur.

As with other vaccines, COMVAX may not induce protective antibody levels immediately following vaccination and may not result in a protective antibody response in all individuals given the vaccine.

As reported with Haemophilus b Polysaccharide Vaccine and another Haemophilus b Conjugate Vaccine, cases of Haemophilus b disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccines.

The decision to administer or delay vaccination because of current or recent febrile illness depends on the severity of symptoms and on the etiology of the disease. The ACIP has recommended that immunization should be delayed during the course of an acute febrile illness. All vaccines can be administered to persons with minor illnesses such as diarrhea, mild upper-respiratory infection with or without low-grade fever, or other low-grade febrile illness. Persons with moderate or severe febrile illness should be vaccinated as soon as they have recovered from the acute phase of the illness.

Instructions to Health-care Provider

The health-care provider should determine the current health status and previous vaccination history of the vaccinee.

The health-care provider should question the patient, parent, or guardian about reactions to a previous dose of COMVAX, PedvaxHIB or other Haemophilus b conjugate vaccines or RECOMBIVAX HB or other hepatitis B vaccines.

Information for Patients

The health-care provider should provide the vaccine information required to be given with each vaccination to the patient, parent or guardian.

The health-care provider should inform the patient, parent or guardian of the benefits and risks associated with vaccination. For risks associated with vaccination, see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.

Patients, parents and guardians should be instructed to report any serious adverse reactions to their health-care provider who in turn should report such events to the U. S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7967.

Laboratory Test Interactions

Sensitive tests (e.g., Latex Agglutination Kits) may detect PRP derived from the vaccine in the urine of some vaccinees for at least 30 days following vaccination with lyophilized PedvaxHIB[46]; in clinical studies with lyophilized PedvaxHIB, such children demonstrated a normal immune response to the vaccine. It is not known whether antigenuria will occur after vaccination with COMVAX.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

COMVAX has not been evaluated for its carcinogenic or mutagenic potential, or its potential to impair fertility.

Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with COMVAX. It is also not known whether COMVAX can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. COMVAX is not recommended for use in women of childbearing age.

Pediatric Use

COMVAX has been shown to be generally well tolerated and highly immunogenic in infants 6 weeks to 15 months of age. See DOSAGE AND ADMINISTRATION for recommended dosage schedules.

Safety and effectiveness of COMVAX in infants below the age of 6 weeks and above the age of 15 months have not been established. However, studies have demonstrated that PedvaxHIB is safe and immunogenic when administered to infants and children up to the age of 71 months and RECOMBIVAX HB is safe and immunogenic in persons of all ages.

Comvax should not be used in infants younger than 6 weeks of age.

Infants born of HBsAg-positive mothers should not receive COMVAX but instead should be vaccinated with a passive-active regimen that includes the administration of Hepatitis B Immune Globulin and Hepatitis B Vaccine (Recombinant) at birth given according to a particular schedule; (see manufacturer's circular for Hepatitis B Vaccine [Recombinant]).

ADVERSE REACTIONS

In clinical trials involving the administration of 6705 doses of COMVAX to 2612 healthy infants 6 weeks to 15 months of age, COMVAX was generally well tolerated. Of these infants, 856 were involved in clinical trials (730 infants in controlled, randomized trials) in which most received COMVAX concomitantly with other licensed pediatric vaccines. These 856 infants were monitored for both serious and non-serious adverse experiences. The remaining 1756 infants were involved in trials where COMVAX was administered concomitantly with either an investigational pneumococcal polysaccharide protein conjugate vaccine or an investigational preparation of diphtheria, tetanus, pertussis, and inactivated poliovirus vaccine and were under surveillance for serious adverse experiences. The serious adverse experiences for these subjects are described following Table 2.

Adverse experiences observed within a five-day period following each dose of COMVAX were generally similar in type and frequency to those observed in infants who received concurrent injections of liquid PedvaxHIB and RECOMBIVAX HB at separate sites.

As judged by the investigators, no serious vaccine-related adverse experiences were observed during clinical trials.

Table 2 summarizes the local reactions and systemic complaints within five days of vaccination that were reported to occur among ≥ 1.0% of children given a three-dose course of COMVAX as well as the frequencies of these events among children in the study given concomitant injections of monovalent PedvaxHIB and RECOMBIVAX HB. In this randomized, multicenter study, 882 infants were assigned in a 3:1 ratio to receive either COMVAX or PedvaxHIB plus RECOMBIVAX HB at 2, 4, and 12-15 months of age, with the children monitored daily for five days after each injection for local reactions and systemic complaints.

Table 2

Local Reactions and Systemic Complaints Within 5 Days After Injection Reported to Occur in ≥ 1.0%† of Children Given a 3-Dose Course of COMVAX™ Compared to These Events in Children Given Concomitant Injections of PedvaxHIB® and RECOMBIVAX HB®

Event	Injection 1‡		Injection 2‡		Injection 3	
	COMVAX™ (N=660) %	PedvaxHIB and RECOMBIVAX HB*** (N=221) %	COMVAX™ (N=645) %	PedvaxHIB and RECOMBIVAX HB*** (N=213) %	COMVAX™ (N=593) %	PedvaxHIB and RECOMBIVAX HB*** (N=193) %
Injection Site Reactions						
Pain/Soreness*	34.5	37.6	24.3	25.8	23.9	21.2
Erythema (>1 in.)*	22.4 (2.7)	25.8 (2.7)	25.7 (1.4)	23.5 (3.3)	27.2 (3.0)	24.4 (1.6)
Swelling/Induration (>1 in.)*	27.6 (3.0)	33.5 (4.1)	30.4 (2.9)	31.0 (3.8)	27.2 (3.2)	29.5 (4.1)
Systemic Complaints						
Irritability*	57.0	46.6	50.7	44.1	32.2	29.0
Somnolence*	49.5	47.1	37.4	31.9	21.1	22.3
Crying--						
unusual, high pitched*	10.6	8.6	6.7	2.3	2.9	3.6
not otherwise specified	2.3	2.3	1.4	2.3	0.7	1.6
prolonged (>4 hrs.)*	2.4	2.3	0.8	1.4	0.2	0
Anorexia	3.9	2.3	2.0	0.9	0.8	0.5
Vomiting	2.1	1.8	2.5	0.9	1.0	1.6
Otitis media	0.5	0	2.0	1.4	2.7	1.6
Fever (°F, rectal equiv.)**						
101.0-102.9	14.2	11.9	13.8	12.2	10.5	6.4
≥103.0	0.8	0	1.6	1.4	2.7	4.3
Diarrhea	1.7	1.8	0.8	0.9	2.2	0.5
Upper respiratory infection	0.5	0.5	1.1	0.9	1.3	0.5
Rash	0.8	0	0.9	0	0.8	0.5
Rhinorrhea	0.2	0	1.1	0.9	1.3	2.1
Respiratory congestion	0.6	0.5	1.2	0.9	0.3	0.5
Cough	0.2	0	0.9	0.5	0.2	1.0
Candidiasis, oral	0.3	0.5	0.8	0	0.2	0
Rash, diaper	0.5	0.5	0.5	0.9	0.2	0

† Overall frequency of each event listed above is ≥ 1% even though the frequency after a given dose may be <1%.

‡ Most children received DTP and OPV concomitantly with the first two doses of COMVAX™ or PedvaxHIB and RECOMBIVAX HB

* Events prompted for on Vaccination Report Card given to parents/guardians of vaccinees

** N for injections 1, 2, and 3 equals 655, 639, and 588, respectively, for COMVAX™; N for injections 1, 2, and 3 equals 218, 213, and 187, respectively, for PedvaxHIB and RECOMBIVAX HB

*** Injection site reactions for PedvaxHIB and RECOMBIVAX HB based on occurrence with either of the monovalent components.

Among 856 infants from combined clinical trials who were monitored for both serious and non-serious adverse experiences, the following serious events were reported to occur in 13 infants during a 14-day period following vaccination with COMVAX (usually coadministered with other pediatric vaccines). These adverse experiences are grouped by case: viral infection; febrile seizure; asthma; diarrhea, vomiting, acidosis, dehydration, hypoglycemia, and seizure disorder; bacterial infection; bronchiolitis and reflux esophagitis; dehydration and fever; asthma, respiratory congestion, and tachypnea; asthma and upper respiratory infection; urinary tract infection and vomiting; pneumonia and asthma; apnea and reflux esophagitis; and vitreous hemorrhage. A causal relationship to the vaccine is unknown; however, these serious adverse events were judged not to be related to vaccination with COMVAX by the investigator.

Among 1756 infants who received COMVAX concomitantly with either an investigational pneumococcal polysaccharide protein conjugate vaccine or an investigational preparation of diphtheria, tetanus, pertussis, and inactivated poliovirus vaccine, the following serious events were reported to occur in 9 infants during a 14-day period following vaccination with COMVAX. These adverse experiences are grouped by case: respiratory syncytial virus; respiratory distress and otitis media; bronchiolitis in two vaccinees; viral gastroenteritis; skull fracture; bronchiolitis, respiratory syncytial virus, and pneumonia; respiratory syncytial virus and bronchiolitis; and upper respiratory infection, viral (see CLINICAL PHARMACOLOGY). A causal relationship to the vaccine is unknown; however, these serious events were judged not to be related to vaccination with COMVAX by the investigator.

In a group of infants (n=126) given a three-dose course of COMVAX after previously receiving a dose of Hepatitis B Vaccine (Recombinant) at or shortly after birth, the type, frequency, and severity of adverse experiences did not appear to be greater or different from those observed in infants given only COMVAX.

As with any vaccine, there is the possibility that broad use of COMVAX could reveal adverse experiences not observed in clinical trials.

Potential Adverse Effects

In addition, a variety of adverse effects have been reported with marketed use of either PedvaxHIB or RECOMBIVAX HB in infants and children through 71 months of age. These adverse effects are listed below.

PedvaxHIB

Hypersensitivity
Rarely, angioedema
Hematologic/Lymphatic
Lymphadenopathy
Nervous System
Febrile seizures
Skin
Sterile injection-site abscess; pain at the injection site

RECOMBIVAX HB

Hypersensitivity
Anaphylaxis and symptoms of hypersensitivity including reports of rash, pruritus, urticaria, edema, angioedema, arthralgia, dyspnea, hypotension, erythema multiforme, and ecchymoses
Cardiovascular System
Tachycardia; syncope
Digestive System
Elevation of liver enzymes
Hematologic
Increased erythrocyte sedimentation rate; thrombocytopenia

Musculoskeletal System
Arthritis

Nervous System
Bell's Palsy; Guillain-Barre Syndrome
Psychiatric/Behavioral
Agitation; somnolence; irritability
Skin
Stevens-Johnson Syndrome
Special Senses
Conjunctivitis; visual disturbances

DOSAGE AND ADMINISTRATION

FOR INTRAMUSCULAR ADMINISTRATION

Do not inject intravenously, intradermally, or subcutaneously.

Recommended Schedule

Infants should be vaccinated with three 0.5 mL doses of COMVAX, ideally at 2, 4, and 12-15 months of age. If the recommended schedule cannot be followed exactly, the interval between the first two doses should be at least two months and the interval between the second and third dose should be as close as possible to eight to eleven months.

Infants born of HBsAg-positive mothers should NOT receive COMVAX at birth but instead should be vaccinated with a passive-active regimen that includes the administration of Hepatitis B Immune Globulin and Hepatitis B Vaccine (Recombinant) at birth given according to a particular schedule (see manufacturer's circular for Hepatitis B Vaccine [Recombinant]).

Modified Schedules

Children previously vaccinated with one or more doses of either hepatitis B vaccine or Haemophilus b conjugate vaccine.

Children who receive one dose of hepatitis B vaccine at or shortly after birth may be administered COMVAX on the schedule of 2,4, and 12-15 months of age. There are no data to support the use of a three-dose series of COMVAX in infants who have previously received more than one dose of hepatitis B vaccine. However, COMVAX may be administered to children otherwise scheduled to receive concurrent RECOMBIVAX HB and PedvaxHIB.

Children not vaccinated according to recommended schedule

Vaccination schedules for children not vaccinated according to the recommended schedule should be considered on an individual basis. The number of doses of a PRP-OMPC-containing product (i.e.,COMVAX, PedvaxHIB) depends on the age that vaccination is begun. An infant 2 to 10 months of age should receive three doses of a product containing PRP-OMPC. An infant 11 to 14 months of age should receive two doses of a product containing PRP-OMPC. A child 15 to 71 months of age should receive one dose of a product containing PRP-OMPC. Infants and children, regardless of age, should receive three doses of an HBsAg-containing product.

COMVAX is for intramuscular injection The *anterolateral thigh* is the recommended site for intramuscular injection in infants. Data suggests that injections given in the buttocks frequently are given into fatty tissue instead of into muscle. Such injections have resulted in a lower seroconversion rate (for hepatitis B vaccine) than was expected.

Injection must be accomplished with a needle long enough to ensure intramuscular deposition of the vaccine. The ACIP has recommended that for intramuscular injections, the needle should be of sufficient length to reach the muscle mass itself. In a clinical trial with COMVAX (see CLINICAL PHARMACOLOGY, COMVAX, Table 1) vaccination was accomplished with a needle length of 5/8 inches in accordance with ACIP recommendations in effect at that time.[64] ACIP currently recommends that needles of longer length (7/8 to 1 inch) be used.[47]

The vaccine should be used as supplied; no reconstitution is necessary.

Shake well before withdrawal and use. Thorough agitation is necessary to maintain suspension of the vaccine.

Parenteral drug products should be inspected visually for extraneous particulate matter and discoloration prior to administration whenever solution and container permit. After thorough agitation, COMVAX is a slightly opaque, white suspension.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of infectious agents from one person to another.

HOW SUPPLIED

No. 4843 - COMVAX is supplied as 7.5 mcg Haemophilus b PRP and 5 mcg HBsAg/0.5mL in a 0.5mL single dose vial.
NDC 0006-4843-00.

No. 4898 -- COMVAX is supplied as 7.5 mcg Haemophilus b PRP and 5 mcg HBsAg/0.5 mL in a 0.5 mL single dose vial, in a box of 10 single dose vials.
NDC 0006-4898-00.

Storage

Store vaccine at 2-8°C (36-46ºF). Storage above or ~~below~~ the recommended temperature may reduce potency.

DO NOT FREEZE since freezing destroys potency.

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