

Name of Medicine

COMVAX[®]

haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine
0.5 mL Vial

Presentation

After thorough agitation, COMVAX is a slightly opaque, white suspension, each 0.5 mL dose containing 7.5 mcg haemophilus influenzae type b purified capsular polysaccharide (PRP), 125 mcg neisseria meningitidis (OMPC) and 5 mcg of hepatitis B surface antigen (HBsAg).

Therapeutic Class

COMVAX is a sterile bivalent vaccine made of the antigenic components used in producing PedvaxHIB[®] ¹ [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] and HBvaxPRO[®] [Hepatitis B (Recombinant) Vaccine].

Indications

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 receive Hepatitis B Immune Globulin and Hepatitis B Vaccine (Recombinant) at birth and should complete the hepatitis B vaccination series given according to a particular schedule (see package insert or data sheet for Hepatitis B Vaccine [Recombinant]).

Infants born of mothers of unknown HBsAg status should receive Hepatitis B Vaccine (Recombinant) at birth and should complete the hepatitis B vaccination series given according to a particular schedule (see package insert or data sheet for Hepatitis B Vaccine [Recombinant]).

Vaccination with COMVAX 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 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.

Dosage and Administration

FOR INTRAMUSCULAR ADMINISTRATION

Do not inject intravenously, intradermally, or subcutaneously.

Recommended Schedule

Infants born of HBsAg negative mothers 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

¹ PedvaxHIB is not available in New Zealand

be followed exactly, the interval between the first two doses should be approximately 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 receive Hepatitis B Immune Globulin and Hepatitis B Vaccine (Recombinant) at birth and should complete the hepatitis B vaccination series given according to a particular schedule (see package insert or data sheet for Hepatitis B Vaccine [Recombinant]).

Infants born of mothers of unknown HBsAg status should receive Hepatitis B Vaccine (Recombinant) at birth and should complete the hepatitis B vaccination series given according to a particular schedule (see data sheet for Hepatitis B Vaccine [Recombinant]).

The subsequent administration of COMVAX for completion of the hepatitis B vaccination series in infants who were born of HBsAg positive mothers and received HBIG or infants born of mothers of unknown status has not been studied.

COMVAX should not be administered to any infant before the age of 6 weeks.

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 hepatitis B vaccine (recombinant) and monovalent PRP-OMPC vaccine.

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 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. For intramuscular injections, the needle should be of sufficient length to reach the muscle mass itself. In a clinical trial with COMVAX vaccination was accomplished with a needle length of 5/8 inches.

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 medicines should be inspected visually for extraneous particulate matter and discolouration 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.

Contraindications

Hypersensitivity to any component of the vaccine.

Individuals who develop symptoms suggestive of hypersensitivity after an injection should not receive further injections of the vaccine.

Warnings and Precautions

COMVAX should not be used in infants younger than 6 weeks of age because this will lead to a reduced anti-PRP response and may lead to immune tolerance (impaired ability to respond to subsequent exposure to the PRP antigen).

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.

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 a long incubation period for Hepatitis B, it is possible for unrecognised infection to be present at the time the vaccine is given. The vaccine may not prevent hepatitis B in such patients.

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 vaccine.

Use caution when vaccinating latex-sensitive individuals since the vial stopper contains dry natural latex rubber that may cause allergic reactions.

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

The decision to administer or delay vaccination because of current or recent febrile illness depends on the severity of symptoms and on the aetiology of the disease. It has been recommended that immunisation should be delayed during the course of an acute febrile illness. All vaccines can be administered to persons with minor illnesses such as diarrhoea, 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.

Pregnancy

Animal reproduction studies have not been conducted with COMVAX. It is not known whether COMVAX can cause foetal harm when administered to pregnant women or can affect reproductive capacity.

COMVAX is not recommended for use in women of child bearing age.

Paediatric 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 monovalent PRP-OMPC vaccine is safe and immunogenic when administered to infants and children up to the age of 71 months and hepatitis B vaccine (recombinant) is safe and immunogenic in persons of all ages.

Animal Toxicology

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

Ability to Drive and Use Machines

Not applicable for a paediatric product.

Adverse Effects

In clinical trials involving the administration of 7350 doses of COMVAX to 2993 healthy infants 6 weeks to 15 months of age, COMVAX was generally well tolerated. Of these infants, 1177 were involved in clinical trials in which most received COMVAX concomitantly with other licensed paediatric vaccines. Of these 1177 infants in clinical trials, 1110 were monitored for both serious and non-serious adverse experiences. The remaining 1816 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.

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 monovalent PRP-OMPC vaccine and hepatitis B vaccine (recombinant) at separate sites. As judged by the investigators, no serious vaccine-related adverse experiences were observed during clinical trials.

Table 1 summarises the local reactions and systemic complaints within five days of vaccination that were reported to occur among $\geq 1.0\%$ 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 PRP-OMPC vaccine and hepatitis B vaccine (recombinant). In this randomised, multicentre study, 882 infants were assigned in a 3:1 ratio to receive either COMVAX or monovalent PRP-OMPC vaccine plus hepatitis B vaccine (recombinant) 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 1: Local reactions and systemic complaints within 5 days after injection reported to occur in $\geq 1.0\%$ [†] of children given a 3-dose course of COMVAX compared to these events in children given concomitant injections of monovalent PRP-OMPC vaccine & hepatitis B vaccine (recombinant)

Event	Injection 1 [‡]		Injection 2 [‡]		Injection 3	
	COMVAX (N=660) %	Monovalent PRP-OMPC vaccine and hepatitis B vaccine (recombinant) ^{***} (N=221) %	COMVAX (N=645) %	Monovalent PRP-OMPC vaccine and hepatitis B vaccine (recombinant) ^{***} (N=213) %	COMVAX (N=593) %	Monovalent PRP-OMPC vaccine and hepatitis B vaccine (recombinant) ^{***} (N=193) %
<i>Injection Site Reactions</i>						
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)
<i>Systemic Complaints</i>						
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* not otherwise specified prolonged (>4 hrs)*	10.6 2.3 2.4	8.6 2.3 2.3	6.7 1.4 0.8	2.3 2.3 1.4	2.9 0.7 0.2	3.6 1.6 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 ≥103.0	14.2 0.8	11.9 0	13.8 1.6	12.2 1.4	10.5 2.7	6.4 4.3
Diarrhoea	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
Rhinorrhoea	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 $\geq 1\%$ 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 monovalent PRP-OMPC vaccine and hepatitis B vaccine (recombinant).

* 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 monovalent PRP-OMPC vaccine and hepatitis B vaccine (recombinant).

*** Injection site reactions for monovalent PRP-OMPC vaccine and hepatitis B vaccine (recombinant) based on occurrence with either of the monovalent components.

Studies involving 1216 infants (856 given COMVAX) showed that COMVAX was well tolerated; rates of local injection site reactions and systemic adverse experiences in vaccinees given COMVAX were similar to those vaccinees given separate but concurrent injections of monovalent PRP-OMPC vaccine and hepatitis B vaccine (recombinant). The most frequently cited events were mild, transient signs and symptoms of inflammation at the injection site (i.e. pain/soreness, erythema, and swelling/induration), somnolence, and irritability, all of which were prompted for on report cards filled out by parents of vaccinated children (see Table 1). No child withdrew from these studies because of adverse experience.

Across the entire clinical program, the frequency of serious adverse experiences within 14 days of vaccination was low, with 33 of 2993 (1.1%) children given COMVAX and 6 of 290 (2.1%) children given concomitant injections of monovalent PRP-OMPC vaccine and hepatitis B vaccine (recombinant) having such an event. None of these serious adverse experiences was judged by the study investigator to be related to these vaccines.

Marketed Experience

As with any vaccine, there is the possibility that broad use of COMVAX could reveal adverse experiences not observed in clinical trials. The following additional adverse reactions have been reported with the use of the marketed vaccine:

Hypersensitivity: rarely, anaphylaxis, angioedema, urticaria, erythema multiforme

Interactions

Use With Other Vaccines

Results from clinical studies indicate that COMVAX can be administered concomitantly with the primary series of DTP and OPV. At 12 to 15 months of age, COMVAX may be given concomitantly with VARIVAX, M-M-R II, or OPV or with a booster dose of DTaP at 15 months of age in children who received the primary series of DTP, using separate sites and syringes for injectable vaccines.

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 lyophilised monovalent PRP-OMPC vaccine; in clinical studies with lyophilised monovalent PRP-OMPC vaccine, such children demonstrated a normal immune response to the vaccine. It is not known whether antigenuria will occur after vaccination with COMVAX.

Overdosage

There are no data with regard to overdose.

Actions

Prevention of Hib Disease with Vaccine

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. 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 non-conjugated PRP vaccines ranged from ≥ 0.15 to ≥ 1.0 mcg/mL.

Non-conjugated 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). Monovalent PRP-OMPC vaccine is a PRP-conjugate vaccine in which the PRP is covalently bound to the OMPC carrier 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.

Prevention of Hepatitis B Disease with Vaccine

Hepatitis B infection and disease can be prevented through immunisation with vaccines comprised of viral surface antigen (HBsAg) that induce formation of protective antibody (anti-HBs).

Pharmacokinetics

Nil

Pharmaceutical Precautions

The vaccine should be used as supplied, no reconstitution is necessary
Store vaccine at 2-8°C (36-46°F).

Storage above or below the recommended temperature may reduce potency.

DO NOT FREEZE since freezing destroys the potency.

Medicine Classification

Prescription Medicine

Package Quantities

COMVAX is supplied as a 0.5 mL vial either in a single carton, or cartons of 10 vials.

Further Information

Chemistry

COMVAX is a sterile bivalent vaccine made of the antigenic components used in producing monovalent PRP-OMPC vaccine and 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 digesting, phenol extraction, ultracentrifugation, dial-filtration 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, is necessary for enhanced immunogenicity of the PRP. This coupling is confirmed by analysis of the components of the conjugate following chemical treatment which yields a unique amino acid. After conjugation, the aqueous bulk is then adsorbed onto an amorphous aluminium hydroxyphosphate sulfate adjuvant (previously referred to as aluminium hydroxide).

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 purified protein is treated in phosphate buffer with formaldehyde and then coprecipitated with alum (potassium aluminium sulfate) to form bulk vaccine adjuvanted with amorphous aluminium hydroxyphosphate sulfate. The vaccine contains no detectable DNA, and 1% or less of the protein is of yeast origin. The individual PRP-OMPC and HBsAg adjuvanted bulks are combined to produce COMVAX.

Composition

Inactive Ingredients

Each 0.5 mL dose contains approximately 225 mcg of aluminium as amorphous aluminium hydroxyphosphate sulfate, and 35 mcg sodium borate (decahydrate) as a pH stabiliser, in 0.9% sodium chloride.

The product contains no preservative.

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

The ACIP* has stated that the primary series of Hib vaccine should preferably be completed with the same Hib conjugate vaccine. However, if different vaccines are used, three doses are adequate for the primary series, and after the primary series is completed, any of the licensed Hib conjugate vaccines may be used as a booster at age 12-15 months. The ACIP has also stated that comparable immune responses are obtained when one of two doses of hepatitis B vaccine produced by one manufacturer are followed by subsequent doses from a different manufacturer. Consequently COMVAX may be given whenever a child is scheduled to receive both Hib and hepatitis B vaccines. However, if COMVAX is used as part of a mixed primary series with any Hib vaccine other than monovalent PRP-OMPC vaccine, a total of three doses of Hib-containing vaccine are required to complete the Hib vaccine series, followed by a fourth dose in the second year of life.

Table 2 shows how children previously given a primary three-dose course of a licensed combination DTP-Hib conjugate vaccine and 2 doses of monovalent hepatitis B vaccine responded to a dose of COMVAX at 12-15 months of age. COMVAX induced a substantial secondary increase in the levels of both anti-PRP and anti-HBs.

Group *	Time	N	Anti-PRP % Subjects with		Anti-PRP GMT (mcg/mL)	N	Anti-HBs % Subjects ≥10 mIU/mL	Anti-HBs GMT (mIU/mL)
			>0.15 mcg/mL	>1.0 mcg/mL				
1	Prevaccination	30	93.3	63.3	1.5	13	92.3	193
	Postvaccination	30	100	100	20.3	13	100	5978
2	Prevaccination	31	96.8	54.8	0.9	7	71.4	30
	Postvaccination	30	100	100	15.4	7	100	1199

*Children in Group 1 received VARIVAX [Varicella Virus Vaccine Live (Oka/Merck)] and Measles-Mumps-Rubella vaccine (M-M-R II) concomitantly with COMVAX while those in Group 2 received these vaccines 6 weeks after COMVAX.

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* Advisory Committee on Immunisation Practices