PEDIARIXÔ

[Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined]

DESCRIPTION

PEDIARIX™ [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined] is a noninfectious, sterile, multivalent vaccine for intramuscular administration manufactured by SmithKline Beecham Biologicals. It contains diphtheria and tetanus toxoids, 3 pertussis antigens (inactivated pertussis toxin [PT], filamentous hemagglutinin [FHA], and pertactin [69 kiloDalton outer membrane protein]), hepatitis B surface antigen, plus poliovirus Type 1 (Mahoney), Type 2 (MEF-1), and Type 3 (Saukett). The diphtheria toxoid, tetanus toxoid, and pertussis antigens are the same as those in INFANRIX® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed). The hepatitis B surface antigen is the same as that in ENGERIX-B® [Hepatitis B Vaccine (Recombinant)].

The diphtheria toxin is produced by growing *Corynebacterium diphtheriae* in Fenton medium containing a bovine extract. Tetanus toxin is produced by growing *Clostridium tetani* in a modified Latham medium derived from bovine casein. The bovine materials used in these extracts are sourced from countries which the United States Department of Agriculture (USDA) has determined neither have nor are at risk of bovine spongiform encephalopathy (BSE). Both toxins are detoxified with formaldehyde, concentrated by ultrafiltration, and purified by precipitation, dialysis, and sterile filtration.

The 3 acellular pertussis antigens (PT, FHA, and pertactin) are isolated from *Bordetella pertussis* culture grown in modified Stainer-Scholte liquid medium. PT and FHA are isolated from the fermentation broth; pertactin is extracted from the cells by heat treatment and flocculation. The antigens are purified in successive chromatographic and precipitation steps. PT is detoxified using glutaraldehyde and formaldehyde. FHA and pertactin are treated with formaldehyde.

The hepatitis B surface antigen (HBsAg) is obtained by culturing genetically engineered *Saccharomyces cerevisiae* cells, which carry the surface antigen gene of the hepatitis B virus, in synthetic medium. The surface antigen expressed in the *S. cerevisiae* cells is purified by several physiochemical steps, which include precipitation, ion exchange chromatography, and ultrafiltration. The purified HBsAg undergoes dialysis with cysteine to remove residual thimerosal.

The inactivated poliovirus component of PEDIARIX is an enhanced potency component. Each of the 3 strains of poliovirus is individually grown in VERO cells, a continuous line of monkey kidney cells, cultivated on microcarriers. Calf serum and lactalbumin hydrolysate are used during VERO cell culture and/or virus culture. Calf serum is sourced from countries the USDA has determined neither have nor are at risk of BSE. After clarification, each viral suspension is purified by ultrafiltration, diafiltration, and successive chromatographic steps, and inactivated with formaldehyde. The 3 purified viral strains are then pooled to form a trivalent concentrate.

The diphtheria, tetanus, and pertussis antigens are individually adsorbed onto aluminum hydroxide; hepatitis B component is adsorbed onto aluminum phosphate. All antigens are then diluted and combined to produce the final formulated vaccine. Each 0.5-mL dose is formulated to contain 25 Lf of diphtheria toxoid, 10 Lf of tetanus toxoid, 25 mcg of inactivated PT, 25 mcg of FHA, 8 mcg of pertactin, 10 mcg of HBsAg, 40 D-antigen Units (DU) of Type 1 poliovirus, 8 DU of Type 2 poliovirus, and 32 DU of Type 3 poliovirus.

Diphtheria and tetanus toxoid potency is determined by measuring the amount of neutralizing antitoxin in previously immunized guinea pigs. The potency of the acellular pertussis components (PT, FHA, and pertactin) is determined by enzyme-linked immunosorbent assay (ELISA) on sera from previously immunized mice. Potency of the hepatitis B component is established by HBsAg ELISA. The potency of the inactivated poliovirus component is determined by using the D-antigen ELISA and by a poliovirus neutralizing cell culture assay on sera from previously immunized rats.

Each 0.5-mL dose also contains 2.5 mg of 2-phenoxyethanol as a preservative, 4.5 mg of NaCl, and aluminum adjuvant (not more than 0.85 mg aluminum by assay). Each dose also contains ≤100 mcg of residual formaldehyde and ≤100 mcg of polysorbate 80 (Tween 80). Thimerosal is used at the early stages of manufacture and is removed by subsequent purification steps to below the analytical limit of detection (<25 ng of mercury/20 mcg HBsAg) which upon calculation is <12.5 ng mercury per dose. Neomycin sulfate and polymyxin B are used in the polio vaccine manufacturing process and may be present in the final vaccine at ≤0.05 ng neomycin and ≤0.01 ng polymyxin B per dose. The procedures used to manufacture the HBsAg antigen result in a product that contains ≤5% yeast protein.

The vaccine must be well shaken before administration and is a turbid white suspension after shaking.

Diphtheria and Tetanus Toxoids Adsorbed Bulk Concentrate (For Further Manufacturing) is manufactured by Chiron Behring GmbH & Co, Marburg, Germany. The acellular pertussis antigens, the hepatitis B surface antigen, and the inactivated poliovirus antigens are manufactured by SmithKline Beecham Biologicals, Rixensart, Belgium. Formulation, filling, testing, packaging, and release of the vaccine are performed by SmithKline Beecham Biologicals Manufacturing (wholly-owned subsidiary of SmithKline Beecham Biologicals).

CLINICAL PHARMACOLOGY

The efficacy of PEDIARIX is based on the immunogenicity of the individual antigens compared to licensed vaccines. The efficacy of the pertussis component, which does not have a well established correlate of protection, was determined in clinical trials of INFANRIX. The efficacy of the HBsAg was determined in clinical studies of ENGERIX-B. Serological correlates of protection exist for the diphtheria, tetanus, hepatitis B, and poliovirus components.

Diphtheria: Diphtheria is an acute toxin-mediated infectious disease caused by toxigenic strains of *C. diphtheriae*. Although the incidence of diphtheria in the United States has decreased from more than 200,000 cases reported in 1921,[1] before the general use of diphtheria toxoid, to only 51 cases of respiratory diphtheria reported from 1980 through 2000,[2] the case-fatality rate has remained constant at about 10%. Of 41 cases reported between 1980 and 1994, 15 (37%) patients had never been immunized, 21 (51%) had been inadequately immunized, and immunization history was unknown for 5

(12%). All 4 (10%) fatalities in this time period occurred in unvaccinated children 9 years and younger.[3] Although diphtheria is rare in the United States, toxigenic *C. diphtheriae* strains continue to circulate in previously endemic areas.[4] Protection against disease is due to the development of neutralizing antibodies to the diphtheria toxin. Following adequate immunization with diphtheria toxoid, it is thought that protection persists for at least 10 years. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection.[5] Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective.[5] Immunization with diphtheria toxoid does not, however, eliminate carriage of *C. diphtheriae* in the pharynx or nares or on the skin.[1]

Efficacy of diphtheria toxoid used in INFANRIX was determined on the basis of immunogenicity studies. A VERO cell toxin neutralizing test confirmed the ability of infant sera (N = 45), obtained 1 month after a 3-dose primary series, to neutralize diphtheria toxin. Levels of diphtheria antitoxin ≥0.01 IU/mL were achieved in 100% of the sera tested.

Tetanus: Tetanus is a condition manifested primarily by neuromuscular dysfunction caused by a potent exotoxin released by *C. tetani*. Following the introduction of vaccination with tetanus toxoid in the 1940s, the overall incidence of tetanus declined from 0.4 per 100,000 population in 1947 to 0.02 during the latter half of the 1990s.[6] Adults 60 years of age and older are at greatest risk for tetanus and tetanus-related mortality.[6] Of 124 cases of tetanus reported from 1995 through 1997, 12 (9.7%) occurred among persons younger than 25 years, one of which was a case of neonatal tetanus.[7] Overall, the case-fatality rate was 11%. The disease continues to occur almost exclusively among persons who are unvaccinated, inadequately vaccinated, or whose vaccination histories are unknown or uncertain.[7]

Spores of *C. tetani* are ubiquitous. Naturally acquired immunity to tetanus toxin does not occur. Thus, universal primary immunization and timed booster doses to maintain adequate tetanus antitoxin levels are necessary to protect all age groups.[1] Protection against disease is due to the development of neutralizing antibodies to the tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assays, is considered the minimum protective level.[8,9] More recently a level ≥0.1 to 0.2 IU/mL has been considered as protective.[10] It is thought that protection persists for at least 10 years.[1]

Efficacy of tetanus toxoid used in INFANRIX was determined on the basis of immunogenicity studies. An in vivo mouse neutralization assay confirmed the ability of infant sera (N = 45), obtained 1 month after a 3-dose primary series, to neutralize tetanus toxin. Levels of tetanus antitoxin ≥0.01 IU/mL were achieved in 100% of the sera tested.

Pertussis: Pertussis (whooping cough) is a disease of the respiratory tract caused by *B. pertussis*. Pertussis is highly communicable (attack rates in unimmunized household contacts of up to 100% have been reported[1,11]) and can cause severe disease, particularly in young infants.[1] Since immunization against pertussis became widespread, the number of reported cases and associated mortality in the United States has declined from an average annual incidence and mortality of 150 cases and 6 deaths per 100,000 population, respectively, in the early 1940s to an annual reported incidence of 2.7 cases per 100,000 population in 2000.[12] Of 28,187 cases of pertussis reported among all ages from 1997 to 2000, 62 (0.2%) resulted in death.[12] The highest number of pertussis cases (7,867) since 1967 was reported in 2000. From 1997 to 2000, infants younger than 1 year had the highest average annual

incidence rate (55.5 cases per 100,000 population). During this period, of the 8,276 pertussis cases reported nationally in infants younger than 1 year, 59% were hospitalized, 11% had pneumonia, 1.3% had seizures, 0.2% had encephalopathy, and 0.7% died. Older children, adolescents, and adults, in whom classic signs are often absent, may go undiagnosed and may serve as reservoirs of disease.[1,13] The incidence of reported pertussis among adolescents and adults increased during the 1980s and 1990s.[12,14]

The role of the different components produced by *B. pertussis* in either the pathogenesis of, or the immunity to, pertussis is not well understood.

Efficacy of a 3-dose primary series of INFANRIX has been assessed in 2 clinical studies.[15,16]

A double-blind, randomized, active Diphtheria and Tetanus Toxoids (DT)-controlled trial conducted in Italy, sponsored by the National Institutes of Health (NIH), assessed the absolute protective efficacy of INFANRIX when administered at 2, 4, and 6 months of age.[15] A total of 15,601 infants were immunized with 1 of 2 acellular DTP (DTaP) vaccines, a US-licensed whole-cell DTP vaccine, or with DT vaccine alone. The mean length of follow-up was 17 months (mean age 24 months), beginning 30 days after the third dose of vaccine. The population used in the primary analysis of the efficacy of INFANRIX included 4,481 infants vaccinated with INFANRIX and 1,470 DT vaccinees. After 3 doses, the absolute protective efficacy of INFANRIX against WHO-defined typical pertussis (21 days or more of paroxysmal cough with infection confirmed by culture and/or serologic testing) was 84% (95% CI: 76% to 89%). When the definition of pertussis was expanded to include clinically milder disease with respect to type and duration of cough, with infection confirmed by culture and/or serologic testing, the efficacy of INFANRIX was calculated to be 71% (95% CI: 60% to 78%) against >7 days of any cough and 73% (95% CI: 63% to 80%) against ≥14 days of any cough. A second follow-up period to a mean age of 33 months was conducted in a partially unblinded cohort (children who received DT were offered pertussis vaccine and those who declined were retained in the study cohort). A longer unblinded follow-up period showed that after 3 doses and with no booster dose in the second year of life, the efficacy of INFANRIX against WHO-defined pertussis was 86% (95% CI: 79% to 91%) among children followed to 6 years of age.[17]

A prospective efficacy trial was also conducted in Germany employing a household contact study design.[16] In preparation for this study, 3 doses of INFANRIX were administered at 3, 4, and 5 months of age to more than 22,000 children living in 6 areas of Germany in a safety and immunogenicity study. Infants who did not participate in the safety and immunogenicity study could have received a whole-cell DTP vaccine or DT vaccine. Index cases were identified by spontaneous presentation to a physician. Households with at least one other member (i.e., besides index case) aged 6 through 47 months were enrolled. Household contacts of index cases were monitored for incidence of pertussis by a physician who was blinded to the vaccination status of the household. Calculation of vaccine efficacy was based on attack rates of pertussis in household contacts classified by vaccination status. Of the 173 household contacts who had not received a pertussis vaccine, 96 developed WHO-defined pertussis, as compared to 7 of 112 contacts vaccinated with INFANRIX. The protective efficacy of INFANRIX was calculated to be 89% (95% CI: 77% to 95%), with no indication of waning of protection up until the time of the booster vaccination. The average age of infants vaccinated with INFANRIX at the end

of follow-up in this trial was 13 months (range 6 to 25 months). When the definition of pertussis was expanded to include clinically milder disease, with infection confirmed by culture and/or serologic testing, the efficacy of INFANRIX against ≥7 days of any cough was 67% (95% CI: 52% to 78%) and against ≥7 days of paroxysmal cough was 81% (95% CI: 68% to 89%). The corresponding efficacy rates of INFANRIX against ≥14 days of any cough or paroxysmal cough were 73% (95% CI: 59% to 82%) and 84% (95% CI: 71% to 91%), respectively.

Hepatitis B: Several hepatitis viruses are known to cause a systemic infection resulting in major pathologic changes in the liver (e.g., A, B, C, D, and E). The estimated lifetime risk of hepatitis B infection in the United States varies from almost 100% for the highest-risk groups to approximately 5% for the population as a whole.[18] The modes of transmission of hepatitis B include sexual contact (contaminated body secretions including semen, vaginal secretions, blood, and saliva); parenteral exposure (e.g., blood transfusions, accidental needlesticks or sharing needles from infected individuals); or maternal-neonatal transmission.[19] Hepatitis B infection can have serious consequences including acute massive hepatic necrosis, chronic active hepatitis, and cirrhosis of the liver. Up to 90% of neonates, 30% to 50% of children aged 1 to 5 years, and 6% to 10% of older children and adults who are infected in the United States will become hepatitis B virus carriers.[19] It has been estimated that 200 to 300 million people in the world are chronically infected with hepatitis B virus,[19] and that there are approximately 1.25 million chronic carriers of hepatitis B virus in the United States.[20] Those patients who become chronic carriers can infect others and are at increased risk of developing primary hepatocellular carcinoma. Among other factors, infection with hepatitis B may be the single most important factor for development of this carcinoma.[20,21]

Mothers infected with hepatitis B virus can infect their infants at, or shortly after, birth if they are carriers of the HBsAg or develop an active infection during the third trimester of pregnancy. Infected infants usually become chronic carriers. Therefore, screening of pregnant women for hepatitis B is recommended.[10] There is no specific treatment for acute hepatitis B infection. Persons who develop anti-HBs antibodies after active infection are usually protected against subsequent infection. Antibody concentrations ≥10 mIU/mL against HBsAg are recognized as conferring protection against hepatitis B.[22]

Protective efficacy with ENGERIX-B has been demonstrated in a clinical trial in neonates at high risk of hepatitis B infection.[23,24] Fifty-eight neonates born of mothers who were both HBsAg- and HBeAg-positive were given ENGERIX-B (10 mcg at 0, 1, and 2 months) without concomitant hepatitis B immune globulin. Two infants became chronic carriers in the 12-month follow-up period after initial inoculation. Assuming an expected carrier rate of 70%, the protective efficacy rate against the chronic carrier state during the first 12 months of life was 95%.

Reduced Risk of Hepatocellular Carcinoma: According to the Centers for Disease Control and Prevention (CDC), hepatitis B vaccine is recognized as the first anti-cancer vaccine because it can prevent primary liver cancer.[25] A clear link has been demonstrated between chronic hepatitis B infection and the occurrence of hepatocellular carcinoma. In a Taiwanese study, the institution of universal childhood immunization against hepatitis B virus has been shown to decrease the incidence of hepatocellular carcinoma among children.[26] In a Korean study in adult males, vaccination against the

hepatitis B virus has been shown to decrease the incidence and risk of developing hepatocellular carcinoma in adults.[27]

Poliomyelitis: Poliovirus is an enterovirus that belongs to the picornavirus family.[28] Three serotypes of poliovirus have been identified (Types 1, 2, and 3). Poliovirus is highly contagious with the predominant mode of transmission being person-to-person via the fecal-oral route. The virus may also be spread indirectly through contact with infectious saliva or feces or by contaminated water or sewage.[29]

Replication of poliovirus in the pharynx and intestine is followed by a viremic phase in which involvement of the central nervous system (CNS) can occur. Whereas poliovirus infections are asymptomatic or cause nonspecific symptoms (low-grade fever, malaise, anorexia, and sore throat) in 90% to 95% of individuals, up to 2% of infected persons develop paralytic disease.[28]

As a result of the introduction of poliovirus vaccines in the 1950s and 1960s, and their subsequent widespread use, poliomyelitis control has been achieved in the United States.[30,31] After introduction of conventional (non-enhanced) inactivated poliovirus vaccine (IPV) in 1955, the annual incidence of paralytic disease of 11.4 cases per 100,000 population declined to 0.5 cases per 100,000 population in 1961, when oral poliovirus vaccine (OPV) was introduced. Incidence continued to decline thereafter, with rates of 0.00-0.01 cases per 100,000 population during the years 1990-2000.[32] Evidence suggests that endemic circulation of wild polioviruses ceased in the United States in the 1960s. The last indigenously acquired cases of poliomyelitis caused by wild poliovirus were detected in 1979 and were due to imported viruses. Since then, vaccine-associated paralytic poliomyelitis (VAPP) attributable to live OPV has been the only indigenous form of the disease in the United States.[33] To eliminate the risk for VAPP, since 2000, an all IPV schedule has been recommended for routine childhood polio vaccination in the United States. Although the likelihood of poliovirus importation has decreased substantially since 1997 as a result of decreases in the number of polio cases worldwide, the potential for importation will remain until global eradication is achieved.

IPV induces the production of neutralizing antibodies against each poliovirus serotype; these neutralizing antibodies are recognized as conferring protection against poliomyelitis disease.[34]

Immune Response to PEDIARIX Administered as a 3-Dose Primary Series: In a study conducted in the United States, the immune responses to each of the antigens contained in PEDIARIX were evaluated in sera obtained 1 month after the third dose of vaccine and were compared to those following administration of US-licensed vaccines (INFANRIX and ENGERIX-B concomitantly at separate sites, and OPV [Poliovirus Vaccine Live Oral Trivalent, Lederle Laboratories]).[35] Both groups received a US-licensed *Haemophilus influenzae* type b (Hib) vaccine (Aventis Pasteur) concomitantly at separate sites. The schedule of administration was 2, 4, and 6 months of age. One month after the third dose of PEDIARIX, vaccine response rates for each of the pertussis antigens (with the exception of FHA), geometric mean antibody concentrations for each of the pertussis antigens, and seroprotection rates for diphtheria, tetanus, hepatitis B, and the polioviruses, were shown to be non-inferior to those achieved following separately administered vaccines (see Table 1). The vaccine response to FHA marginally exceeded the 10% limit for non-inferiority.[35]

Table 1. Antibody Responses to Each Antigen Following PEDIARIX as Compared to INFANRIX, ENGERIX-B, and OPV (One Month After Administration of Dose 3) in US Infants Vaccinated at 2, 4, and 6 Months of Age

	PEDIARIX (N = 86-91)	INFANRIX, ENGERIX-B, OPV (N = 73-78)
Anti-Diphtheria		
% ≥0.1 IU/mL*	98.9	100
Anti-Tetanus		
% ≥0.1 IU/mL*	100	100
Anti-PT		
% VR*	98.9	98.7
GMC†	97.1	47.5
Anti-FHA		
% VR	95.6	100
GMC†	119.1	153.2
Anti-Pertactin		
% VR*	95.6	91.0
GMC†	150.4	108.6
Anti-HBsAg		
% ≥10 mIU/mL*	100	100
GMC†	1661.2	804.9
Anti-Polio 1		
% ≥1:8*‡	100	98.6
Anti-Polio 2		
% ≥1:8*‡	98.8	100
Anti-Polio 3		
% ≥1:8*‡	100	100

Both groups received Hib vaccine (Aventis Pasteur) concomitantly at a separate site.
OPV manufactured by Lederle Laboratories.
VR = Vaccine response: In initially seronegative infants, appearance of antibodies (concentration ≥5 EL.U./mL); in initially seropositive infants, at least maintenance of pre-vaccination concentration.
GMC = Geometric mean antibody concentration.
* Seroprotection rate or vaccine response rate to PEDIARIX not inferior to separately administered vaccines (upper limit of 90% CI on the difference for separate administration minus PEDIARIX <10%).
† GMC in the group that received PEDIARIX not inferior to separately administered vaccines (upper limit of 90% CI on the ratio of GMC for separate administration/PEDIARIX <1.5 for anti-PT, anti-FHA, and anti-pertactin, and <2.0 for anti-HBsAg).
‡ Poliovirus neutralizing antibody titer.

Immune Response to Concomitantly Administered Vaccines: In a clinical trial in the United States, PEDIARIX was given concomitantly, at separate sites, with Hib vaccine (Aventis Pasteur) to infants at 2, 4, and 6 months of age.[35] Immunogenicity data are available in 90 infants one month after the third dose of the vaccines; 98.9% (95% CI: 94% to 100%) of infants demonstrated anti-PRP antibodies ≥0.15 mcg/mL and 94.4% (95% CI: 87.5% to 98.2%) demonstrated anti-PRP antibodies ≥1.0 mcg/mL.

Immunogenicity data are not available on the concurrent administration of PEDIARIX with pneumococcal conjugate vaccine.

INDICATIONS AND USAGE

PEDIARIX is indicated for active immunization against diphtheria, tetanus, pertussis (whooping cough), all known subtypes of hepatitis B virus, and poliomyelitis caused by poliovirus Types 1, 2, and 3 as a three-dose primary series in infants born of HBsAg-negative mothers, beginning as early as 6 weeks of age. PEDIARIX should not be administered to any infant before the age of 6 weeks, or to individuals 7 years of age or older.

Infants born of HBsAg-positive mothers should receive Hepatitis B Immune Globulin (Human) (HBIG) and monovalent Hepatitis B Vaccine (Recombinant) within 12 hours of birth and should complete the hepatitis B vaccination series according to a particular schedule.[36] (See manufacturer's prescribing information for Hepatitis B Vaccine [Recombinant]) (see DOSAGE AND ADMINISTRATION).

Infants born of mothers of unknown HBsAg status should receive monovalent Hepatitis B Vaccine (Recombinant) within 12 hours of birth and should complete the hepatitis B vaccination series according to a particular schedule.[36] (See manufacturer's prescribing information for Hepatitis B Vaccine [Recombinant]) (see DOSAGE AND ADMINISTRATION).

PEDIARIX will not prevent hepatitis caused by other agents, such as hepatitis A, C, and E viruses, or other pathogens known to infect the liver. As hepatitis D (caused by the delta virus) does not occur in the absence of hepatitis B infection, hepatitis D will also be prevented by vaccination with PEDIARIX.

Hepatitis B has a long incubation period. Vaccination with PEDIARIX may not prevent hepatitis B infection in individuals who had an unrecognized hepatitis B infection at the time of vaccine administration.

When passive protection against tetanus or diphtheria is required, Tetanus Immune Globulin or Diphtheria Antitoxin, respectively, should be administered at separate sites.[1]

As with any vaccine, PEDIARIX may not protect 100% of individuals receiving the vaccine, and is not recommended for treatment of actual infections.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including yeast, neomycin, and polymyxin B, is a contraindication (see DESCRIPTION).

It is a contraindication to use this vaccine after a serious allergic reaction (e.g., anaphylaxis) temporally associated with a previous dose of this vaccine or with any components of this vaccine. Because of the uncertainty as to which component of the vaccine might be responsible, no further vaccination with any of these components should be given. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are to be considered.[1]

In addition, the following events are contraindications to administration of any pertussis-containing vaccine, including PEDIARIX:[10]

- Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within 7 days of administration of a previous dose of a pertussis-containing vaccine that is not attributable to another identifiable cause;
- Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy. Pertussis vaccine should not be administered to individuals with such conditions until a treatment regimen has been established and the condition has stabilized.

PEDIARIX is not contraindicated for use in individuals with HIV infection.[10,37]

WARNINGS

Administration of PEDIARIX is associated with higher rates of fever relative to separately administered vaccines. In one study that evaluated medically attended fever after the first dose of PEDIARIX or separately administered vaccines, infants who received PEDIARIX had a higher rate of medical encounters for fever within the first 4 days following vaccination. In some infants, these encounters included the performance of diagnostic studies to evaluate other causes of fever (see ADVERSE REACTIONS).

The vial stopper is latex-free. The tip cap and the rubber plunger of the needleless prefilled syringes contain dry natural latex rubber that may cause allergic reactions in latex sensitive individuals.

If any of the following events occur in temporal relation to receipt of whole-cell DTP or a vaccine containing an acellular pertussis component, the decision to give subsequent doses of PEDIARIX or any vaccine containing a pertussis component should be based on careful consideration of the potential benefits and possible risks:[38,39]

- Temperature of ≥40.5°C (105°F) within 48 hours not due to another identifiable cause;
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours;
- Persistent, inconsolable crying lasting ≥3 hours, occurring within 48 hours;
- Seizures with or without fever occurring within 3 days.

When a decision is made to withhold pertussis vaccine, immunization with DT vaccine, hepatitis B vaccine, and IPV should be continued.

If Guillain-Barré syndrome occurs within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give subsequent doses of PEDIARIX or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks.[10]

A committee of the Institute of Medicine (IOM) has concluded that evidence is consistent with a causal relationship between whole-cell DTP vaccine and acute neurologic illness, and under special circumstances, between whole-cell DTP vaccine and chronic neurologic disease in the context of the

National Childhood Encephalopathy Study (NCES) report.[40,41] However, the IOM committee concluded that the evidence was insufficient to indicate whether or not whole-cell DTP vaccine increased the overall risk of chronic neurologic disease.[41] Acute encephalopathy and permanent neurologic damage have not been reported causally linked or in temporal association with administration of PEDIARIX, but the experience with PEDIARIX is insufficient to rule this out. Encephalopathy has been reported following INFANRIX (see ADVERSE REACTIONS, Postmarketing Reports), but data are not sufficient to evaluate a causal relationship.

The decision to administer a pertussis-containing vaccine to children with stable CNS disorders must be made by the physician on an individual basis, with consideration of all relevant factors, and assessment of potential risks and benefits for that individual. The Advisory Committee on Immunization Practices (ACIP) and the Committee on Infectious Diseases of the American Academy of Pediatrics (AAP) have issued guidelines for such children.[38,42] The parent or guardian should be advised of the potential increased risk involved (see PRECAUTIONS, Information for Vaccine Recipients and Parents or Guardians).

A family history of seizures or other CNS disorders is not a contraindication to pertussis vaccine.[38]

For children at higher risk for seizures than the general population, an appropriate antipyretic may be administered at the time of vaccination with a vaccine containing an acellular pertussis component (including PEDIARIX) and for the ensuing 24 hours according to the respective prescribing information recommended dosage to reduce the possibility of post-vaccination fever.[10,38]

Vaccination should be deferred during the course of a moderate or severe illness with or without fever. Such children should be vaccinated as soon as they have recovered from the acute phase of the illness.[10]

As with other intramuscular injections, PEDIARIX should not be given to children on anticoagulant therapy unless the potential benefit clearly outweighs the risk of administration (see PRECAUTIONS).

PRECAUTIONS

PEDIARIX should be given with caution in children with bleeding disorders such as hemophilia or thrombocytopenia, with steps taken to avoid the risk of hematoma following the injection.

Before the injection of any biological, the physician should take all reasonable precautions to prevent allergic or other adverse reactions, including understanding the use of the biological concerned, and the nature of the side effects and adverse reactions that may follow its use.

Prior to immunization, the patient's current health status and medical history should be reviewed. The physician should review the patient's immunization history for possible vaccine sensitivity, previous vaccination-related adverse reactions and occurrence of any adverse–event-related symptoms and/or signs, in order to determine the existence of any contraindication to immunization with PEDIARIX and to allow an assessment of benefits and risks. Epinephrine injection (1:1000) and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

A separate sterile syringe and sterile disposable needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another. Needles should be disposed of properly and should not be recapped.

Special care should be taken to prevent injection into a blood vessel.

As with any vaccine, if administered to immunosuppressed persons, including individuals receiving immunosuppressive therapy, the expected immune response may not be obtained.[37]

Information for Vaccine Recipients and Parents or Guardians: Parents or guardians should be informed by the healthcare provider of the potential benefits and risks of the vaccine, and of the importance of completing the immunization series. When a child returns for the next dose in a series, it is important that the parent or guardian be questioned concerning occurrence of any symptoms and/or signs of an adverse reaction after a previous dose of the same vaccine. The physician should inform the parents or guardians about the potential for adverse events that have been temporally associated with administration of PEDIARIX or other vaccines containing similar components. The parent or guardian accompanying the recipient should be told to report severe or unusual adverse events to the physician or clinic where the vaccine was administered.

The parent or guardian should be given the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the CDC website (www.cdc.gov/nip).

The US Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986.[10] The VAERS toll-free number is 1-800-822-7967.

Drug Interactions: For information regarding concomitant administration with other vaccines, refer to DOSAGE AND ADMINISTRATION.

PEDIARIX should not be mixed with any other vaccine in the same syringe or vial.

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Although no specific data from studies with PEDIARIX under these conditions are available, if immunosuppressive therapy will be discontinued shortly, it would be reasonable to defer immunization until the patient has been off therapy for 3 months; otherwise, the patient should be vaccinated while still on therapy.[37] If PEDIARIX is administered to a person receiving immunosuppressive therapy, or who received a recent injection of immune globulin, or who has an immunodeficiency disorder, an adequate immunologic response may not be obtained.

Tetanus Immune Globulin or Diphtheria Antitoxin, if needed, should be given at a separate site, with a separate needle and syringe.

Carcinogenesis, Mutagenesis, Impairment of Fertility: PEDIARIX has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

Pregnancy: Pregnancy Category C: PEDIARIX is not indicated for women of child-bearing age. Animal reproduction studies have not been conducted with PEDIARIX. It is not known whether

PEDIARIX can cause fetal harm when administered to a pregnant woman or if PEDIARIX can affect reproductive capacity.

Geriatric Use: PEDIARIX is not indicated for use in adult populations.

Pediatric Use: Safety and effectiveness of PEDIARIX in infants younger than 6 weeks of age have not been evaluated (see DOSAGE AND ADMINISTRATION). PEDIARIX is not recommended for persons 7 years of age or older. Tetanus and Diphtheria Toxoids Adsorbed (Td) For Adult Use, IPV, and Hepatitis B Vaccine (Recombinant) should be used in individuals 7 years of age or older.

ADVERSE REACTIONS

A total of 20,739 doses of PEDIARIX have been administered to 7,028 infants as a 3-dose primary series. The most common adverse reactions observed in clinical trials were local injection site reactions (pain, redness, or swelling), fever, and fussiness. In comparative studies, administration of PEDIARIX was associated with higher rates of fever relative to separately administered vaccines (see WARNINGS; see ADVERSE REACTIONS Tables 2 and 4). The prevalence of fever was highest on the day of vaccination and the day following vaccination. More than 98% of episodes of fever resolved within the 4-day period following vaccination (i.e., the period including the day of vaccination and the next 3 days). Rates of most other solicited adverse events following PEDIARIX were comparable to rates observed following separately administered US-licensed vaccines (see ADVERSE REACTIONS Table 2).

The adverse event information from clinical trials provides a basis for identifying adverse events that appear to be related to vaccine use and for approximating rates. However, because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine, and may not reflect the rates observed in practice.

A total of 5,472 infants were enrolled in a German safety study that was originally designed to compare the safety and reactogenicity of PEDIARIX administered concomitantly at separate sites with 1 of 4 Hib vaccines (SmithKline Beecham Biologicals [not US-licensed]; Lederle Laboratories, Aventis Pasteur, or Merck & Co [all US-licensed]) at 3, 4, and 5 months of age.[43] After enrollment of 1,569 infants, the study was amended to include a control group that received separate US-licensed vaccines (INFANRIX, Hib vaccine [Aventis Pasteur], and OPV [Lederle Laboratories]). Infants in the separate administration group received one less antigen (hepatitis B) than the infants who received PEDIARIX. Safety data were available for 4,666 infants who received PEDIARIX administered concomitantly at separate sites with 1 of 4 Hib vaccines and for 768 infants in the control group that received separate vaccines. Data on adverse events were collected by parents using standardized diary cards for 4 consecutive days following each vaccine dose (i.e., day of vaccination and the next 3 days).

The primary end-point of the study was the percentage of infants with any grade 3 solicited symptom (redness or swelling >20 mm, fever >103.1°F, or crying, pain, vomiting, diarrhea, loss of appetite, or restlessness that prevented normal daily activities) over the 3-dose primary series in infants who received PEDIARIX (4 groups that received PEDIARIX and Hib vaccines pooled) compared to the group that received INFANRIX and Hib vaccine separately with OPV. Analysis for the primary

end-point was performed on the according-to-protocol (ATP) cohort that included only those infants who were enrolled after the protocol amendment to include a control group. Of 3,773 infants in the ATP cohort for whom safety data were available, 16.2% (95% CI: 14.9% to 17.5%) of 3,029 infants who received PEDIARIX and Hib vaccine compared to 20.3% (95% CI: 17.5% to 23.4%) of 744 infants who received separate vaccines were reported to have had at least one grade 3 solicited symptom within 4 days of vaccination (i.e., day of vaccination and the next 3 days). The difference between groups in the rate of grade 3 symptoms was 4.1% (90% CI: 1.4% to 7.1%).

Data for selected solicited symptoms following each dose in a 3-dose primary series are presented in Table 2 for the intent-to-treat (ITT) cohort (includes all infants enrolled before and after the amendment who received the indicated vaccine and for whom at least one symptom sheet was completed).

Table 2. Percentage of Infants in a German Safety Study With Solicited Local Reactions or Selected Systemic Adverse Events Within 4 Days of Vaccination* at 3, 4, and 5 Months of Age With PEDIARIX Administered Concomitantly With Hib Vaccine or With Separate Concomitant Administration of INFANRIX, Hib Vaccine, and OPV (ITT Cohort)

	PEDIARIX & Hib			INFANRIX, Hib, & OPV		
	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3
N	**4,666**	**4,619**	**4,574**	**768**	**757**	**750**
Local†						
Pain, any	14.0	10.2	9.9	14.2	9.8	8.1
Pain, grade 2 or 3	2.9	1.2	1.5	3.6	1.7	1.1
Pain, grade 3	0.7	0.3	0.3	1.3	0.4	0.1
Redness, any	18.6	26.6	25.6	16.1	21.4	20.8
Redness, >5 mm	6.7	9.9	9.0	5.9	8.2	7.7
Redness, >20 mm	1.2	1.0	1.1	1.8	0.7	1.1
Swelling, any	12.7	18.5	18.4	9.6	12.9	13.6
Swelling, >5 mm	5.6	7.7	7.8	3.6	5.2	4.8
Swelling, >20 mm	1.2	1.6	1.5	1.3	1.1	1.2
Systemic						
Restlessness, any	41.4	32.0	26.7	46.4	35.0	27.6
Restlessness, grade 2 or 3	14.4	10.0	8.9	20.2	11.5	8.4
Restlessness, grade 3	3.0	1.5	1.6	5.7	3.0	1.7
Fever‡, ≥100.4°F	25.1	19.3	19.7	13.2	13.1	11.2
Fever‡, >101.3°F	5.8	4.1	4.6	2.2	2.8	2.1
Fever‡, >103.1°F	0.3	0.5	0.7	0.3	0.3	0.5
Unusual cry§, any	24.9	16.5	13.1	36.5	19.7	14.3
Unusual cry§, grade 2 or 3	12.7	7.1	5.7	20.8	10.0	5.7
Unusual cry§, grade 3	3.9	1.7	1.4	6.8	2.1	1.1
Loss of appetite, any	17.9	13.3	12.5	19.1	16.2	11.3
Loss of appetite, grade 2 or 3	4.0	2.9	2.7	4.4	2.9	2.3
Loss of appetite, grade 3	0.6	0.5	0.4	0.5	0.7	0.0

N = number of infants in the intent-to-treat (ITT) cohort (infants who received the indicated vaccine and for whom at least one symptom sheet was completed).

Grade 2 defined as sufficiently discomforting to interfere with daily activities.

Grade 3 defined as preventing normal daily activities.

* Within 4 days of vaccination defined as day of vaccination and the next 3 days.

† Local reactions at the injection site for PEDIARIX or INFANRIX.

‡ Rectal temperatures.

§ Unusual cry lasting >1 hour.

In this study, infants were also monitored for unsolicited adverse events that occurred within 30 days following vaccination using diaries which were returned at subsequent visits and were supplemented by spontaneous reports and a medical history as reported by parents. Over the entire study period, 6 subjects in the group that received PEDIARIX reported seizures. Two of these subjects had a febrile seizure, 1 of whom also developed afebrile seizures. The remaining 4 subjects had afebrile seizures, including 2 with infantile spasms. Two subjects reported seizures within 7 days following vaccination (1 subject had both febrile and afebrile seizures, and 1 subject had afebrile seizures), corresponding to a rate of 0.22 seizures per 1,000 doses (febrile seizures 0.07 per 1,000 doses, afebrile seizures 0.14 per 1,000 doses). No subject who received concomitant INFANRIX, Hib vaccine, and OPV reported seizures. In a separate German study that evaluated the safety of INFANRIX in 22,505 infants who received 66,867 doses of INFANRIX administered as a 3-dose primary series, the rate of seizures within 7 days of vaccination with INFANRIX was 0.13 per 1,000 doses (febrile seizures 0.0 per 1,000 doses, afebrile seizures 0.13 per 1,000 doses).

No cases of hypotonic-hyporesponsiveness, encephalopathy, or anaphylaxis were reported in the German study that evaluated the safety of PEDIARIX.

Rates of serious adverse events that are less common than those reported in this safety study are not known at this time.

Additional safety data for PEDIARIX are available for 482 infants enrolled in a US study designed to evaluate lot-to-lot consistency and a bridge for a new manufacturing step. Table 3 presents the local reactions and selected adverse events within 4 days of vaccination with PEDIARIX administered concomitantly with a US-licensed Hib vaccine (Aventis Pasteur) at 2, 4, and 6 months of age. Data on adverse events were collected by parents using standardized diaries for 4 consecutive days after each vaccine dose (i.e., day of vaccination and the next 3 days) with follow-up telephone calls made by study personnel between days 1 and 3.

Table 3. Percentage of Infants in a US Lot Consistency Study With Solicited Local Reactions or Selected Systemic Adverse Events Within 4 Days of Vaccination* at 2, 4, and 6 Months of Age With PEDIARIX Administered Concomitantly With Hib Vaccine (ITT Cohort)

	PEDIARIX & Hib		
	Dose 1	**Dose 2**	**Dose 3**
Local†	**N = 482**	**N = 469**	**N = 466**
Pain, any	30.5	25.4	23.0
Pain, grade 2 or 3	6.2	5.5	3.6
Pain, grade 3	1.2	0.6	0.6
Redness, any	25.3	32.6	35.6
Redness, >5 mm	9.3	10.4	8.6
Redness, >20 mm	0.6	1.5	1.3
Swelling, any	15.1	16.6	22.3
Swelling, >5 mm	6.8	6.2	6.4
Swelling, >20 mm	1.0	1.3	1.3
Systemic	**N = 482**	**N = 469**	**N = 467**
Restlessness, any	28.8	30.3	28.5
Restlessness, grade 2 or 3	7.1	9.0	9.4
Restlessness, grade 3	1.0	1.1	0.6
Fever‡, ≥100.4°F	26.6	31.3	25.9
Fever‡, >101.3°F	2.9	6.2	4.7
Fever‡, >103.1°F	0.0	0.2	0.6
Fussiness, any	61.8	63.8	57.0
Fussiness, grade 2 or 3	14.9	21.5	17.1
Fussiness, grade 3	2.7	3.4	1.7
Loss of appetite, any	21.6	19.8	18.8
Loss of appetite, grade 2 or 3	3.1	3.2	2.4
Loss of appetite, grade 3	0.2	0.4	0.0
Sleeping more than usual, any	46.7	31.8	28.1
Sleeping more than usual, grade 2 or 3	10.2	6.0	4.7
Sleeping more than usual, grade 3	1.7	0.4	0.6

N = number of infants in the intent-to-treat (ITT) cohort (infants who received the indicated vaccine and for whom at least one symptom sheet was completed).

Grade 2 defined as sufficiently discomforting to interfere with daily activities.

Grade 3 defined as preventing normal daily activities.

* Within 4 days of vaccination defined as day of vaccination and the next 3 days.

† Local reactions at the injection site for PEDIARIX.

‡ Rectal temperatures.

Post-dose 1 safety data are available from a US study initiated in December 2001, which was designed to assess the safety of PEDIARIX administered concomitantly at separate sites with Hib and pneumococcal conjugate vaccines (Lederle Laboratories), relative to separately administered INFANRIX, ENGERIX-B, IPV (Aventis Pasteur), Hib vaccine (Lederle Laboratories), and pneumococcal conjugate vaccine (Lederle Laboratories) at 2, 4, and 6 months of age. The study was powered to evaluate fever >101.3°F. Enrollment for this study is complete, with 673 infants in the group that received PEDIARIX and 335 infants in the separate vaccines group. Safety data following the second and third doses are expected in 2003. Data for fever within 4 days following dose 1 (i.e., day of vaccination and the next 3 days) are presented in Table 4.

Table 4. Percentage of Infants in a US Coadministration Safety Study With Fever Within 4 Days of Dose 1* at 2 Months of Age With PEDIARIX Administered Concomitantly With Hib Vaccine and Pneumococcal Conjugate Vaccine or With Separate Concomitant Administration of INFANRIX, ENGERIX-B, IPV, Hib Vaccine, and Pneumococcal Conjugate Vaccine

	PEDIARIX, Hib, & Pneumococcal Conjugate (N = 667)	INFANRIX, ENGERIX-B, IPV, Hib, & Pneumococcal Conjugate (N = 333)	Separate Vaccine Group Minus Combination Vaccine Group
Fever†	**%**	**%**	**Difference (95% CI)**
≥100.4ºF‡	27.9	19.8	-8.07 (-13.54, -2.60)
>101.3ºF	7.0	4.5	-2.54 (-5.50, 0.41)
>102.2ºF‡	2.2	0.3	-1.95 (-3.22, -0.68)
>103.1ºF	0.4	0.0	-0.45 (-0.96, 0.06)
M.A.‡	1.2	0.0	-1.20 (-2.03, -0.37)

N = number of infants for whom at least one symptom sheet was completed, excluding 3 infants for whom temperature was not measured and 3 infants whose temperature was measured by the tympanic method.

* Within 4 days of dose 1 defined as day of vaccination and the next 3 days.

† Rectal temperatures.

‡ The group that received PEDIARIX compared to separate vaccine group p value <0.05 (2-sided Fisher Exact test) or the 95% confidence interval on the difference between groups does not include 0.

M.A. = Medically attended (a visit to or from medical personnel).

In this study, medical attention (a visit to or from medical personnel) for fever within 4 days following vaccination was sought for 8 infants who received PEDIARIX (1.2%) and no infants who received separately administered vaccines. Four infants were seen by medical personnel in an office setting; no diagnostic tests were performed in 2 of the infants and a complete blood count (CBC) was done in the other 2 infants. Of 3 infants who were seen in an emergency room, all had a CBC and a blood and urine culture performed; chest X-rays were done in 2 of the infants and a nasopharyngeal specimen was tested for Respiratory Syncytial Virus in one of the infants. One infant was hospitalized for a work-up

that included a CBC, blood and urine cultures, a lumbar puncture, and a chest X-ray. All episodes of medically attended fever resolved within 4 days post-vaccination.

In 12 clinical trials, 5 deaths were reported in 7,028 (0.07%) recipients of PEDIARIX and 1 death was reported in 1,764 (0.06%) recipients of comparator vaccines. Causes of death in the group that received PEDIARIX included 2 cases of Sudden Infant Death Syndrome (SIDS) and one case of each of the following: Convulsive disorder, congenital immunodeficiency with sepsis, and neuroblastoma. One case of SIDS was reported in the comparator group. The rate of SIDS among all recipients of PEDIARIX across the 12 trials was 0.3/1,000. The rate of SIDS observed for recipients of PEDIARIX in the German safety study was 0.2/1,000 infants (reported rate of SIDS in Germany in the latter part of the 1990s was 0.7/1,000 newborns).[44] The reported rate of SIDS in the United States from 1990 to 1994 was 1.2/1,000 live births.[45] By chance alone, some cases of SIDS can be expected to follow receipt of pertussis-containing vaccines.[39]

Limited data are available on the safety of administering PEDIARIX after a birth dose of hepatitis B vaccine (see Table 5). In a study conducted in Moldova, 160 infants received a dose of hepatitis B vaccine within 48 hours of birth followed by 3 doses of PEDIARIX at 6, 10, and 14 weeks of age. No information was collected on the HBsAg status of mothers of enrolled infants.

Table 5. Percentage of Infants in a Moldovan Study With Solicited Local Reactions or Selected Systemic Adverse Events Within 4 Days of Vaccination* at 6, 10, and 14 Weeks of Age With PEDIARIX Administered Concomitantly With Hib Vaccine Following a Birth Dose of Hepatitis B Vaccine (ITT Cohort)

	PEDIARIX & Hib		
	Dose 1	**Dose 2**	**Dose 3**
N	**160**	**158**	**157**
Local†			
Pain, any	25.6	18.4	14.0
Pain, grade 3	3.1	0.6	1.9
Redness, any	41.9	41.8	47.1
Redness, >20 mm	1.9	2.5	4.5
Swelling, any	20.6	18.4	28.0
Swelling, >20 mm	4.4	2.5	7.0
Systemic			
Restlessness, any	13.1	10.8	8.9
Restlessness, grade 3	1.3	0.6	0.6
Fever‡, ≥100.4°F	14.4	11.4	5.1
Fever‡, >103.1°F	0.0	0.6	0.0
Fussiness, any	25.0	21.5	17.8
Fussiness, grade 3	2.5	0.6	0.6

N = number of infants in the intent-to-treat (ITT) cohort (infants who received the indicated vaccine and for whom at least one symptom sheet was completed).
Grade 3 defined as preventing normal daily activities.
* Within 4 days of vaccination defined as day of vaccination and the next 3 days.
† Local reactions at the injection site for PEDIARIX.
‡ Rectal temperatures.

Although there was no comparator group who received PEDIARIX without a birth dose of hepatitis B vaccine, available data suggest that some local adverse events may occur at a higher rate when PEDIARIX is administered after a birth dose of hepatitis B vaccine.

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

Additional Adverse Events: Rarely, an anaphylactic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) has been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.[39] Arthus-type hypersensitivity reactions, characterized by severe local reactions, may follow receipt of tetanus toxoid. A review by the IOM found evidence for a causal relationship between receipt of tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome.[46] A few cases of demyelinating diseases of the CNS have been reported following some tetanus toxoid-containing vaccines or tetanus and diphtheria toxoid-containing vaccines, although the

IOM concluded that the evidence was inadequate to accept or reject a causal relationship.[46] A few cases of peripheral mononeuropathy and of cranial mononeuropathy have been reported following tetanus toxoid administration, although the IOM concluded that the evidence was inadequate to accept or reject a causal relationship.

Postmarketing Reports: Worldwide voluntary reports of adverse events received for INFANRIX and ENGERIX-B in children younger than 7 years of age since market introduction of these US-licensed vaccines are listed below. This list includes adverse events for which 20 or more reports were received with the exception of intussusception, idiopathic thrombocytopenic purpura, thrombocytopenia, anaphylactic reaction, angioedema, encephalopathy, hypotonic-hyporesponsive episode, and alopecia for which fewer than 20 reports were received. These latter events are included either because of the seriousness of the event or the strength of causal connection to components of this or other vaccines or drugs.

Body as a whole: Asthenia[b], fever[a+b], lethargy[b], malaise[b], Sudden Infant Death Syndrome[a+b].

Cardiovascular system: Cyanosis[a+b], edema[b], pallor[b].

Gastrointestinal system: Abdominal pain[b], anorexia[b], diarrhea[a+b], intussusception[a+b], nausea[b], vomiting[a+b].

Hematologic/lymphatic: Idiopathic thrombocytopenic purpura[a+b], lymphadenopathy[a], thrombocytopenia[a+b].

Hepatic: Jaundice[b], liver function tests abnormal[b].

Hypersensitivity: Anaphylactic reaction[a+b], angioedema[b], hypersensitivity[a].

Infections: Cellulitis[a].

Injection site reactions: Injection site reactions[a+b].

Musculoskeletal: Arthralgia[b], limb swelling[a+b].

Nervous system: Convulsions[a+b], encephalopathy[a], headache[b], hypotonia[a+b], hypotonic-hyporesponsive episode[a], somnolence[a+b].

Psychiatric: Crying[a+b], irritability[a+b].

Respiratory system: Respiratory tract infection[a].

Skin and appendages: Alopecia[b], erythema[a+b], erythema multiforme[b], petechiae[b], pruritis[a+b], rash[a+b], urticaria[a+b].

Special senses: Ear pain[a].

[a] Following INFANRIX.

[b] Following ENGERIX-B.

[a+b] Following either INFANRIX or ENGERIX-B.

These reactions were reported voluntarily from a population of uncertain size; therefore, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccination.

Reporting Adverse Events: The National Childhood Vaccine Injury Act requires that the manufacturer and lot number of the vaccine administered be recorded by the healthcare provider in the vaccine recipient's permanent medical record, along with the date of administration of the vaccine and the name, address, and title of the person administering the vaccine.[47] The Act further requires the healthcare provider to report to the US Department of Health and Human Services via VAERS the

occurrence following immunization of any event set forth in the Vaccine Injury Table including: Anaphylaxis or anaphylactic shock within 7 days, encephalopathy or encephalitis within 7 days, brachial neuritis within 28 days, or an acute complication or sequelae (including death) of an illness, disability, injury, or condition referred to above, or any events that would contraindicate further doses of vaccine, according to this prescribing information.[47,48] The VAERS toll-free number is 1-800-822-7967.

DOSAGE AND ADMINISTRATION

Preparation for Administration: PEDIARIX contains an adjuvant; therefore shake vigorously to obtain a homogeneous, turbid, white suspension. DO NOT USE IF RESUSPENSION DOES NOT OCCUR WITH VIGOROUS SHAKING. Inspect visually for particulate matter or discoloration prior to administration. After removal of the dose, any vaccine remaining in the vial should be discarded.

PEDIARIX should be administered by intramuscular injection. The preferred sites are the anterolateral aspects of the thigh or the deltoid muscle of the upper arm. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk. Gluteal injections may result in suboptimal hepatitis B immune response. Before injection, the skin at the injection site should be cleaned and prepared with a suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

Do not administer this product subcutaneously or intravenously.

Recommended Schedule: The primary immunization series for PEDIARIX is 3 doses of 0.5 mL, given intramuscularly, at 6- to 8-week intervals (preferably 8 weeks). The customary age for the first dose is 2 months of age, but it may be given starting at 6 weeks of age.

PEDIARIX should not be administered to any infant before the age of 6 weeks. Only monovalent hepatitis B vaccine can be used for the birth dose.

Infants born of HBsAg-positive mothers should receive HBIG and Hepatitis B Vaccine (Recombinant) within 12 hours of birth at separate sites and should complete the hepatitis B vaccination series according to a particular schedule.[36] (See manufacturer's prescribing information for Hepatitis B Vaccine [Recombinant]).

Infants born of mothers of unknown HBsAg status should receive Hepatitis B Vaccine (Recombinant) within 12 hours of birth and should complete the hepatitis B vaccination series according to a particular schedule.[36] (See manufacturer's prescribing information for Hepatitis B Vaccine [Recombinant]).

The administration of PEDIARIX for completion of the hepatitis B vaccination series in infants who were born of HBsAg-positive mothers and who received monovalent Hepatitis B Vaccine (Recombinant) and HBIG has not been studied.

Modified Schedules: *Children Previously Vaccinated With One or More Doses of Hepatitis B Vaccine:* Infants born of HBsAg-negative mothers and who received a dose of hepatitis B vaccine at or shortly after birth may be administered 3 doses of PEDIARIX according to the recommended schedule. However, data are limited regarding the safety of PEDIARIX in such infants (see ADVERSE REACTIONS). There are no data to support the use of a 3-dose series of PEDIARIX in infants who have previously received more than one dose of hepatitis B vaccine.

PEDIARIX may be used to complete a hepatitis B vaccination series in infants who have received 1 or more doses of Hepatitis B Vaccine (Recombinant) and who are also scheduled to receive the other vaccine components of PEDIARIX. However, the safety and efficacy of PEDIARIX in such infants have not been studied.

Children Previously Vaccinated With One or More Doses of INFANRIX: PEDIARIX may be used to complete the first 3 doses of the DTaP series in infants who have received 1 or 2 doses of INFANRIX and are also scheduled to receive the other vaccine components of PEDIARIX. However, the safety and efficacy of PEDIARIX in such infants have not been evaluated.

Children Previously Vaccinated With One or More Doses of IPV: PEDIARIX may be used to complete the first 3 doses of the IPV series in infants who have received 1 or 2 doses of IPV and are also scheduled to receive the other vaccine components of PEDIARIX. However, the safety and efficacy of PEDIARIX in such infants have not been studied.

Interchangeability of PEDIARIX and Licensed DTaP, IPV, or Recombinant Hepatitis B Vaccines: It is recommended that PEDIARIX be given for all 3 doses because data are limited regarding the safety and efficacy of using acellular pertussis vaccines from different manufacturers for successive doses of the pertussis vaccination series. PEDIARIX is not recommended for completion of the first 3 doses of the DTaP vaccination series initiated with a DTaP vaccine from a different manufacturer because no data are available regarding the safety or efficacy of using such a regimen.

PEDIARIX may be used to complete a hepatitis B vaccination series initiated with a licensed Hepatitis B Vaccine (Recombinant) vaccine from a different manufacturer.

PEDIARIX may be used to complete the first 3 doses of the IPV vaccination series initiated with IPV from a different manufacturer.

Additional Dosing Information: If any recommended dose of pertussis vaccine cannot be given, DT (For Pediatric Use), Hepatitis B (Recombinant), and inactivated poliovirus vaccines should be given as needed to complete the series.

Interruption of the recommended schedule with a delay between doses should not interfere with the final immunity achieved with PEDIARIX. There is no need to start the series over again, regardless of the time elapsed between doses.

The use of reduced volume (fractional doses) is not recommended. The effect of such practices on the frequency of serious adverse events and on protection against disease has not been determined.[10]

Preterm infants should be vaccinated according to their chronological age from birth.[10]

PEDIARIX is not indicated for use as a booster dose following a 3-dose primary series of PEDIARIX. Children who have received a 3-dose primary series of PEDIARIX should receive a fourth dose of IPV at 4 to 6 years of age and a fourth dose of DTaP vaccine at 15 to 18 months of age. Because the pertussis antigen components of INFANRIX are the same as those components in PEDIARIX, these children should receive INFANRIX as their fourth dose of DTaP. However, data are insufficient to evaluate the safety of INFANRIX following 3 doses of PEDIARIX.

Concomitant Vaccine Administration: In clinical trials, PEDIARIX was routinely administered, at separate sites, concomitantly with Hib vaccine (see CLINICAL PHARMACOLOGY). Safety data

are available following the first dose of PEDIARIX administered concomitantly, at separate sites, with Hib and pneumococcal conjugate vaccines (see ADVERSE REACTIONS).

When concomitant administration of other vaccines is required, they should be given with separate syringes and at different injection sites.

STORAGE

Store PEDIARIX refrigerated between 2º and 8ºC (36º and 46ºF). **Do not freeze.** Discard if the vaccine has been frozen. Do not use after expiration date shown on the label.

HOW SUPPLIED

PEDIARIX is supplied as a turbid white suspension in single-dose (0.5 mL) vials and disposable prefilled Tip-Lok® syringes.

Single-Dose Vials
NDC 58160-841-11 (package of 10)

Single-Dose Prefilled Disposable Tip-Lok® Syringes (packaged without needles)
NDC 58160-841-46 (package of 5)
NDC 58160-841-50 (package of 25)

Single-Dose Prefilled Disposable Tip-Lok® Syringes with 1-inch 25-gauge BD SafetyGlide™ Needles
NDC 58160-841-56 (package of 25)

Single-Dose Prefilled Disposable Tip-Lok® Syringes with 5/8-inch 25-gauge BD SafetyGlide™ Needles
NDC 58160-841-57 (package of 25)

REFERENCES

1. Centers for Disease Control. Diphtheria, tetanus, and pertussis: Recommendations for vaccine use and other preventive measures — Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR* 1991;40(RR-10):1-28. **2.** Centers for Disease Control and Prevention. Diphtheria. In: Atkinson W and Wolfe C, eds. *Epidemiology and prevention of vaccine-preventable diseases*. 7th ed. Atlanta, GA: Public Health Foundation; 2002:39-48. **3.** Bisgard KM, Hardy I, Popovic T, et al. Respiratory diphtheria in the United States, 1980 through 1995. *Am J Public Health* 1998;88(5):787-791. **4.** Centers for Disease Control and Prevention. Toxigenic *Corynebacterium diphtheriae* — Northern Plains Indian community, August-October 1996. *MMWR* 1997;46(22):506-510. **5.** Mortimer EA and Wharton M. Diphtheria Toxoid. In: Plotkin SA and Orenstein WA, eds. *Vaccines.* 3rd ed. Philadelphia, PA: W.B. Saunders Company; 1999:140-157. **6.** Centers for Disease Control and Prevention. Tetanus — Puerto Rico, 2002. *MMWR* 2002;51(28):613-615. **7.** Centers for Disease Control and Prevention. Tetanus surveillance — United States, 1995-1997. *MMWR* 1998;47(SS-2):1-13. **8.** Wassilak SGF, Orenstein WA, and Sutter RW.

Tetanus Toxoid. In: Plotkin SA and Orenstein WA, eds. *Vaccines.* 3rd ed. Philadelphia, PA: W.B. Saunders Company; 1999:441-474. **9.** Department of Health and Human Services, Food and Drug Administration. Biological products; Bacterial vaccines and toxoids; Implementation of efficacy review; Proposed rule. *Federal Register* December 13, 1985;50(240):51002-51117. **10.** Centers for Disease Control and Prevention. General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). *MMWR* 2002;51(RR-2):1-35. **11.** Long SS. Pertussis (*Bordetella pertussis* and *B. parapertussis*). In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*. 16th ed. Philadelphia, PA: W.B. Saunders; 2000:838-842. **12.** Centers for Disease Control and Prevention. Pertussis — United States, 1997-2000. *MMWR* 2002;51(4):73-76. **13.** Nennig ME, Shinefield HR, Edwards KM, et al. Prevalence and incidence of adult pertussis in an urban population. *JAMA* 1996;275(21):1672-1674. **14.** Güris D, Strebel PM, Bardenheier B, et al. Changing epidemiology of pertussis in the United States: Increasing reported incidence among adolescents and adults, 1990-1996. *Clin Infect Dis* 1999;28:1230-1237. **15.** Greco D, Salmaso S, Mastrantonio P, et al. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. *N Engl J Med* 1996;334(6):341-348. **16.** Schmitt H-J, von König CHW, Neiss A, et al. Efficacy of acellular pertussis vaccine in early childhood after household exposure. *JAMA* 1996;275(1):37-41. **17.** Salmaso S, Mastrantonio P, Tozzi AE, et al. Sustained efficacy during the first 6 years of life of 3-component acellular pertussis vaccines administered in infancy: The Italian experience. *Pediatrics* 2001;108(5):E81. **18.** Centers for Disease Control. Recommendations for protection against viral hepatitis: Recommendation of the Immunization Practices Advisory Committee (ACIP). *MMWR* 1985;34(22):313-324. **19.** Centers for Disease Control and Prevention. Hepatitis B. In: Atkinson W and Wolfe C, eds. *Epidemiology and prevention of vaccine-preventable diseases*. 7th ed. Atlanta, GA: Public Health Foundation; 2002:169-189. **20.** Lee WM. Hepatitis B virus infection. *N Engl J Med* 1997;337(24):1733-1745. **21.** Centers for Disease Control. Protection against viral hepatitis: Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR* 1990;39(RR-2):1-26. **22.** Ambrosch F, Frisch-Niggemeyer W, Kremsner P, et al. Persistence of vaccine-induced antibodies to hepatitis B surface antigen and the need for booster vaccination in adult subjects. *Postgrad Med J* 1987;63(Suppl. 2):129-135. **23.** Andre FE and Safary A. Clinical experience with a yeast-derived hepatitis B vaccine. In: Zuckerman AJ, ed. *Viral hepatitis and liver disease.* New York, NY: Alan R Liss, Inc.; 1988:1025-1030. **24.** Poovorawan Y, Sanpavat S, Pongpunlert W, et al. Protective efficacy of a recombinant DNA hepatitis B vaccine in neonates of HBe antigen-positive mothers. *JAMA* 1989;261(22):3278-3281. **25.** Centers for Disease Control and Prevention. Proposed vaccine information materials for hepatitis B, Haemophilus influenza type B (Hib), varicella (chickenpox), and measles, mumps, rubella (MMR) vaccines. *Federal Register* September 3, 1998;63(171):47026-47031. **26.** Chang MH, Chen CJ, Lai MS. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. *N Engl J Med* 1997;336:1855-1859. **27.** Lee MS, Kim DH, Kim H, et al. Hepatitis B vaccination and reduced risk of primary liver cancer among male adults: A cohort study in Korea. *Int J Epidemiol* 1998;27(2):316-319. **28.** Centers for Disease Control and Prevention. Poliomyelitis. In: Atkinson W and Wolfe C, eds. *Epidemiology and*

prevention of vaccine-preventable diseases. 7th ed. Atlanta, GA: Public Health Foundation; 2002:71-82. **29.** Centers for Disease Control and Prevention. Poliomyelitis prevention in the United States: Introduction of a sequential vaccination schedule of inactivated poliovirus vaccine followed by oral poliovirus vaccine — Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1997;46(RR-3):1-25. **30.** Kim-Farley RJ, Bart KJ, Schonberger LP, et al. Poliomyelitis in the USA: Virtual elimination of disease caused by wild virus. *Lancet* 1984;2:1315-1317. **31.** Nathanson N, Martin JR. The epidemiology of poliomyelitis: Enigmas surrounding its appearance, epidemiology, and disappearance. *Am J Epidemiol* 1979;110(6):672-692. **32.** Centers for Disease Control and Prevention. Summary of notifiable diseases, United States, 2000. *MMWR* 2000;49(53):83. **33.** Centers for Disease Control and Prevention. Poliomyelitis prevention in the United States: Updated recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2000;49(RR-5):1-22. **34.** Sutter RW, Pallansch MA, Sawyer LA, et al. Defining surrogate serologic tests with respect to predicting protective vaccine efficacy: Poliovirus vaccination. In: Williams JC, Goldenthal KL, Burns DL, Lewis Jr BP, eds. Combined vaccines and simultaneous administration. Current issues and perspectives. New York, NY: The New York Academy of Sciences; 1995:289-299. **35.** Yeh SH, Ward JI, Partridge S, et al. Safety and immunogenicity of a pentavalent diphtheria, tetanus, pertussis, hepatitis B and polio combination vaccine in infants. *Pediatr Infect Dis J* 2001;20:973-980. **36.** Centers for Disease Control and Prevention. Recommended childhood immunization schedule — United States, 2002. *MMWR* 2002;51(2):31-33. **37.** Centers for Disease Control and Prevention. Use of vaccines and immune globulins in persons with altered immunocompetence: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1993;42(RR-4):1-18. **38.** Centers for Disease Control and Prevention. Pertussis vaccination: Use of acellular pertussis vaccines among infants and young children — Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1997;46(RR-7):1-25. **39.** Centers for Disease Control and Prevention. Update: Vaccine side effects, adverse reactions, contraindications, and precautions — Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1996;45(RR-12):1-35. **40.** Institute of Medicine (IOM). Howson CP, Howe CJ, Fineberg HV, eds. *Adverse effects of pertussis and rubella vaccines*. Washington, DC: National Academy Press; 1991. **41.** Institute of Medicine (IOM). Stratton KR, Howe CJ, Johnston RB, eds. *DPT vaccine and chronic nervous dysfunction: A new analysis*. Washington, DC: National Academy Press; 1994. **42.** American Academy of Pediatrics. Pertussis. In: Pickering LK, ed. *2000 Red Book: Report of the Committee on Infectious Diseases*. 25th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2000:442-448. **43.** Zepp F, Schuind A, Meyer C, et al. Safety and reactogenicity of a novel DTPa-HBV-IPV combined vaccine given along with commercial Hib vaccines in comparison with separate concomitant administration of DTPa, Hib, and OPV vaccines in infants. *Pediatrics* 2002;109(4):E58. **44.** Poets CF. Plötzlicher Säuglingstod. Neue Erkenntnisse. *Pädiat prax* 2001;60:285-292. **45.** Centers for Disease Control and Prevention. Sudden Infant Death Syndrome — United States, 1983-94. *MMWR* 1996;45(40):859-863. **46.** Institute of Medicine (IOM). Stratton KR, Howe CJ, Johnston RB, eds. *Adverse events associated with childhood vaccines. Evidence bearing on causality*. Washington, DC: National Academy Press; 1994. **47.** Centers for Disease

Control. National Childhood Vaccine Injury Act: Requirements for permanent vaccination records and for reporting of selected events after vaccination. *MMWR* 1988;37(13):197-200. **48.** National Vaccine Injury Compensation Program: Vaccine injury table. www.hrsa.gov/osp/vicp/table.htm. Accessed April 29, 2002.

Manufactured by **SmithKline Beecham Biologicals**
Rixensart, Belgium, US License 1090, and
Chiron Behring GmbH & Co
Marburg, Germany, US License 0097
Distributed by **SmithKline Beecham Pharmaceuticals,** Philadelphia, PA 19101

DATE OF ISSUANCE DEC. 2002

PE:L1