PEDIARIX®

[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 GlaxoSmithKline Biologicals. It contains diphtheria and tetanus toxoids, 3 pertussis antigens (inactivated pertussis toxin [PT] and formaldehyde-treated 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 (inactivated PT and formaldehyde-treated 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 to obtain a homogeneous, turbid, white suspension.

Diphtheria and Tetanus Toxoids Adsorbed Combined Bulk (For Further Manufacturing Use) is manufactured by Chiron Behring GmbH & Co KG, Marburg, Germany. The acellular pertussis antigens, the hepatitis B surface antigen, and the inactivated poliovirus antigens are manufactured by GlaxoSmithKline Biologicals, Rixensart, Belgium. Formulation, filling, testing, packaging, and release of the vaccine are performed by GlaxoSmithKline 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*. Diphtheria in the United States has been controlled through the use of diphtheria toxoid-containing vaccines. Protection against disease is due to the development of neutralizing antibodies to the diphtheria toxin. Following adequate immunization with diphtheria toxoid, 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; a level of 0.1 IU/mL is regarded as protective.[1] Levels of 1.0 IU/mL are associated with long-term protection.[1] Immunization with diphtheria toxoid does not, however, eliminate carriage of *C. diphtheriae* in the pharynx or nares or on the skin.[2]

Tetanus: Tetanus is a condition manifested primarily by neuromuscular dysfunction caused by a potent exotoxin released by *C. tetani*. 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.[2] 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.[3,4] A level ≥0.1 to 0.2 IU/mL has been considered as protective.[5] Following immunization, protection persists for at least 10 years.[2]

Pertussis: Pertussis (whooping cough) is a disease of the respiratory tract caused by *B. pertussis*. 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.[6,7]

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.[6] 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 infection confirmed by culture and/or serologic testing, the efficacy of INFANRIX was 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 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.[8] For details see INFANRIX prescribing information.

A prospective efficacy trial was also conducted in Germany employing a household contact study design.[7] In this study, the protective efficacy of INFANRIX administered to infants at 3, 4, and 5 months of age, against WHO-defined pertussis was 89% (95% CI: 77% to 95%). 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%). For details see INFANRIX prescribing information.

Hepatitis B: Infection with hepatitis B virus can have serious consequences including acute massive hepatic necrosis and chronic active hepatitis. Chronically infected persons are at increased risk for cirrhosis and hepatocellular carcinoma. According to the Centers for Disease Control and Prevention (CDC), hepatitis B vaccine is recognized as an anti-cancer vaccine because it can prevent primary liver cancer.[9] 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.[10] 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.[11]

Modes of transmission of hepatitis B virus include sexual contact with an infected person, percutaneous or mucosal exposure to infectious blood, and perinatal exposure to an infected mother. Antibody concentrations ≥10 mIU/mL against HBsAg are recognized as conferring protection against hepatitis B.[12]

Protective efficacy with ENGERIX-B has been demonstrated in a clinical trial in neonates at high risk of hepatitis B infection.[13,14] 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 against the chronic carrier state during the first 12 months of life was 95%.

Poliomyelitis: Poliovirus is an enterovirus that belongs to the picornavirus family. Three serotypes of poliovirus have been identified (Types 1, 2, and 3). Whereas poliovirus infections are usually asymptomatic or cause nonspecific symptoms, up to 2% of infected persons have central nervous system involvement and develop paralytic disease.[15]

Poliomyelitis in the United States has been controlled through the use of poliovirus vaccines.

IPV induces the production of neutralizing antibodies against each poliovirus serotype; these neutralizing antibodies are recognized as conferring protection against poliomyelitis disease.[16]

Immune Response to PEDIARIX: In a US multicenter study, infants were randomized to 1 of 3 groups: (1) a combination vaccine group that received PEDIARIX coadministered with US-licensed 7-valent pneumococcal and Hib conjugate vaccines [Wyeth Pharmaceuticals Inc.]; (2) a separate vaccine group that received US-licensed INFANRIX, ENGERIX-B, and IPV [sanofi pasteur] coadministered with the same pneumococcal and Hib conjugate vaccines; and (3) a staggered vaccine group that received PEDIARIX coadministered with the same Hib conjugate vaccine but with the same pneumococcal conjugate vaccine administered 2 weeks later. The schedule of administration was 2, 4, and 6 months of age. Infants either did not receive a dose of hepatitis B vaccine prior to enrollment or were permitted to receive one dose of hepatitis B vaccine administered at least 30 days prior to enrollment. For the separate vaccine group, ENGERIX-B was not administered at 4 months of age to subjects who received a dose of hepatitis B vaccine prior to enrollment. Among subjects in all 3 vaccine groups combined, 84%

were white, 7% were Hispanic, 6% were black, 0.7% Oriental, and 2.4% were of other racial/ethnic groups.

The immune responses to the pertussis (PT, FHA, and pertactin), diphtheria, tetanus, poliovirus, and hepatitis B antigens were evaluated in sera obtained one month (range 20 to 60 days) after the third dose of PEDIARIX or INFANRIX. Geometric mean antibody concentrations (GMCs) adjusted for prevaccination values for PT, FHA, and pertactin and the seroprotection rates for diphtheria, tetanus, and the polioviruses among subjects who received PEDIARIX in the combination vaccine group were shown to be non-inferior to those achieved following separately administered vaccines (see Table 1). There was no evidence for interference with the immune responses to PEDIARIX when 7-valent pneumococcal conjugate vaccine was concomitantly administered.

Because of differences in the hepatitis B vaccination schedule among subjects in the study, no clinical limit for non-inferiority was pre-defined for the hepatitis B immune response. However, in a previous US study, non-inferiority of PEDIARIX relative to separately administered INFANRIX, ENGERIX-B, and an oral poliovirus vaccine, with respect to the hepatitis B immune response was demonstrated.[17]

Table 1. Antibody Responses Following PEDIARIX as Compared to Separate Concomitant Administration of INFANRIX, ENGERIX-B, and IPV (One Month* After Administration of Dose 3) in Infants Vaccinated at 2, 4, and 6 Months of Age When Coadministered With Hib Conjugate Vaccine and Pneumococcal Conjugate Vaccine (PCV7)

	PEDIARIX, Hib Vaccine, & PCV7	INFANRIX, ENGERIX-B, IPV, Hib Vaccine, & PCV7
	(N = 154-168)	**(N = 141-155)**
Anti-Diphtheria % ≥0.1 IU/mL†	99.4	98.7
Anti-Tetanus % ≥0.1 IU/mL†	100	98.1
Anti-PT % VR‡ GMC†	98.7 48.1	95.1 28.6
Anti-FHA % VR‡ GMC†	98.7 111.9	96.5 97.6
Anti-Pertactin % VR‡ GMC†	91.7 95.3	95.1 80.6
Anti-Polio 1 % ≥1:8†§	100	100
Anti-Polio 2 % ≥1:8†§	100	100
Anti-Polio 3 % ≥1:8†§	100	100
	(N = 114-128)	**(N = 111-121)**
Anti-HBsAg‖ % ≥10 mIU/mL¶ GMC (mIU/mL)¶	97.7 1032.1	99.2 614.5

Hib Conjugate Vaccine and PCV7 manufactured by Wyeth Pharmaceuticals Inc. IPV manufactured by sanofi pasteur.

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. GMCs are adjusted for pre-vaccination levels.

*One month blood sampling, range 20 to 60 days.

†Seroprotection rate or GMC for PEDIARIX not inferior to separately administered vaccines [upper limit of 90% CI on GMC ratio (separate vaccine group/combination vaccine group) <1.5 for anti-PT, anti-FHA, and anti-pertactin, and upper limit of 95% CI for the difference in seroprotection rates (separate vaccine group minus combination vaccine group) <10% for diphtheria and tetanus and <5% for the 3 polioviruses]. GMCs are adjusted for pre-vaccination levels.

[‡]The upper limit of 95% CI for differences in vaccine response rates (separate vaccine group minus combination group) was 0.31, 1.52, and 9.46 for PT, FHA, and PRN, respectively. No clinical limit defined for non-inferiority.
[§]Poliovirus neutralizing antibody titer.
[‖]Subjects who received a previous dose of hepatitis B vaccine were excluded from the analysis of hepatitis B seroprotection rates and GMCs presented in the table.
[¶]No clinical limit defined for non-inferiority.

Immune Responses to Concomitantly Administered Vaccines: Anti-PRP seroprotection rates and GMCs of pneumococcal antibodies one month (range 20 to 60 days) after the third dose of vaccines for the combination vaccine group and the separate vaccine group from the US multicenter study described previously are presented in Table 2.

Table 2. Anti-PRP Seroprotection Rates and GMCs (mcg/mL) of Pneumococcal Antibodies One Month* Following the Third Dose of Hib Conjugate Vaccine and Pneumococcal Conjugate Vaccine (PCV7) Administered Concomitantly with PEDIARIX or With INFANRIX, ENGERIX-B, and IPV

	PEDIARIX, Hib Vaccine, & PCV7	**INFANRIX, ENGERIX-B, IPV, Hib Vaccine, & PCV7**
	(N = 161-168)	**(N = 146-156)**
	% (95% CI)	**% (95% CI)**
Anti-PRP ≥0.15 mcg/mL	100 (97.8-100)	99.4 (96.5-100)
Anti-PRP ≥1.0 mcg/mL	95.8 (91.6-98.3)	91.0 (85.3-95.0)
	GMC (95% CI)	**GMC (95% CI)**
Pneumococcal Serotype		
4	1.7 (1.5-2.0)	2.1 (1.8-2.4)
6B	0.8 (0.7-1.0)	0.7 (0.5-0.9)
9V	1.6 (1.4-1.8)	1.6 (1.4-1.9)
14	4.7 (4.0-5.4)	6.3 (5.4-7.4)
18C	2.6 (2.3-3.0)	3.0 (2.5-3.5)
19F	1.1 (1.0-1.3)	1.1 (0.9-1.2)
23F	1.5 (1.2-1.8)	1.8 (1.5-2.3)

Hib Conjugate Vaccine and PCV7 manufactured by Wyeth Pharmaceuticals Inc. IPV manufactured by sanofi pasteur.
GMC = Geometric mean antibody concentration.
*One month blood sampling, range 20 to 60 days.

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.[18] (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.[18] (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.

As with any vaccine, PEDIARIX may not protect 100% of individuals receiving the vaccine. PEDIARIX 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 immunization with any of these components is considered.[2]

In addition, the following events are contraindications to administration of any pertussis-containing vaccine, including PEDIARIX:[5]

- 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 these conditions until a treatment regimen has been established and the condition has stabilized.

WARNINGS

Administration of PEDIARIX is associated with higher rates of fever relative to separately administered vaccines. In a safety study that evaluated medically attended fever after PEDIARIX or separately administered vaccines when coadministered with 7-valent pneumococcal and Hib conjugate vaccines, infants who received PEDIARIX had a higher rate of medical encounters for fever within the first 4 days following the first vaccination. In some infants, these encounters included the performance of diagnostic studies to evaluate other causes of fever (see ADVERSE REACTIONS).

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. The vial stopper is latex-free.

If any of the following events occur in temporal relation to receipt of DTwP or a vaccine containing an acellular pertussis component, the decision to give any pertussis vaccine, including PEDIARIX, should be based on careful consideration of the potential benefits and possible risks:[19,20]

- 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 vaccination, DT vaccine, hepatitis B vaccine, and IPV should be given, as indicated.

If Guillain-Barré syndrome occurs within 6 weeks of receipt of prior vaccine containing tetanus toxoid, the decision to give any tetanus toxoid-containing vaccine, including PEDIARIX, should be based on careful consideration of the potential benefits and possible risks.[5] If tetanus toxoid is withheld, other available vaccines should be given, as indicated.

The decision to administer a pertussis-containing vaccine to individuals 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) has issued guidelines for such individuals.[19] The parent or guardian should be advised of the potential increased risk involved (see PRECAUTIONS, Information for Vaccine Recipients and Parents or Guardians).

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.[5,19]

The ACIP has published guidelines for vaccination of persons with recent or acute illness (www.cdc.gov/nip).[5]

PRECAUTIONS

PEDIARIX should be given with caution in children with bleeding disorders such as hemophilia or thrombocytopenia and in children on anticoagulant therapy, with steps taken to avoid the risk of hematoma following the injection.[5]

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 (1:1,000) 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.

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. The healthcare provider 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 United States 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.[5] The VAERS toll-free number is 1-800-822-7967. Reporting forms may also be obtained at the VAERS website at www.vaers.hhs.gov.

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. The ACIP has published guidelines for vaccination of persons on such therapies (www.cdc.gov/nip).[21]

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.

PEDIARIX is not recommended for persons 7 years of age or older.

ADVERSE REACTIONS

A total of 23,849 doses of PEDIARIX have been administered to 8,088 infants who received one or more doses as part of a 3-dose primary series during 14 clinical studies. 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 Table 3). The prevalence of fever was highest on the day of vaccination and the day following vaccination. More than 96% 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).

In the largest of the 14 studies, conducted in Germany, safety data were available for 4,666 infants who received PEDIARIX administered concomitantly at separate sites with 1 of 4 Hib vaccines (GlaxoSmithKline Biologicals [not US-licensed]; Wyeth Pharmaceuticals Inc., sanofi pasteur, or Merck & Co [all US-licensed]) at 3, 4, and 5 months of age and for 768 infants in the control group that received separate US-licensed vaccines (INFANRIX, Hib vaccine [sanofi pasteur], and OPV [Wyeth Pharmaceuticals Inc.]). 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). 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. More than 95% of study participants were white.

In a US study, the safety of PEDIARIX administered to 673 infants was compared to the safety of separately administered INFANRIX, ENGERIX-B, IPV (sanofi pasteur) in 335 infants. In both groups, infants received Hib and 7-valent pneumococcal conjugate vaccines (Wyeth Pharmaceuticals Inc.) concomitantly at separate sites. All vaccines were administered at 2, 4, and

6 months of age. The study was powered to evaluate fever >101.3°F following dose 1. Data on solicited 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) and are presented in Table 3. Telephone follow-up was conducted 1 month and 6 months after the third vaccination to inquire about serious adverse events. At the 6-month follow-up, information also was collected on new onset of chronic illnesses. 638 subjects who received PEDIARIX and 313 subjects who received INFANRIX, ENGERIX-B, and IPV completed the 6-month follow-up. Among subjects in both study groups combined, 69% were white, 18% were Hispanic, 7% were black, 3% were Oriental, and 3% were of other racial/ethnic groups.

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

Deaths: In 14 clinical trials, 5 deaths were reported among 8,088 (0.06%) recipients of PEDIARIX and 1 death was reported among 2,287 (0.04%) 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 14 trials was 0.25/1,000. 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).[22] The reported rate of SIDS in the United States from 1990 to 1994 was 1.2/1,000 live births.[23] By chance alone, some cases of SIDS can be expected to follow receipt of pertussis-containing vaccines.[20]

Serious Adverse Events: Within 30 days following any dose of vaccine in the US safety study in which all subjects received concomitant pneumococcal and Hib conjugate vaccines, 7 serious adverse events were reported in 7 subjects (1% [7/673]) who received PEDIARIX (1 case each of pyrexia, gastroenteritis, and culture negative clinical sepsis and 4 cases of bronchiolitis) and 5 serious adverse events were reported in 4 subjects (1% [4/335]) who received INFANRIX, ENGERIX-B, and IPV (uteropelvic junction obstruction and testicular atrophy in one subject and 3 cases of bronchiolitis).

Onset of Chronic Illnesses: In the US safety study in which all subjects received concomitant pneumococcal and Hib conjugate vaccines, 21 subjects (3%) who received PEDIARIX and 14 subjects (4%) who received INFANRIX, ENGERIX-B, and IPV reported new onset of a chronic illness during the period from 1 to 6 months following the last dose of study vaccines. Among the chronic illnesses reported in the subjects who received PEDIARIX,

there were 4 cases of asthma and 1 case each of diabetes mellitus and chronic neutropenia. There were 4 cases of asthma in subjects who received INFANRIX, ENGERIX-B, and IPV.

Seizures: In the German safety study 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).

Over the entire study period in the US safety study in which all subjects received concomitant pneumococcal and Hib conjugate vaccines, 4 subjects in the group that received PEDIARIX reported seizures. Three of these subjects had a febrile seizure and 1 had an afebrile seizure. Over the entire study period, 2 subjects in the group that received INFANRIX, ENGERIX-B, and IPV reported febrile seizures. There were no afebrile seizures in this group. No subject in either study group had seizures within 7 days following vaccination.

Other Neurological Events of Interest: No cases of hypotonic-hyporesponsiveness or encephalopathy were reported in either the German safety study or the US safety study.

Solicited Adverse Events: Table 3 presents data from the US safety study on solicited local and systemic adverse events within 4 days of vaccination with PEDIARIX or INFANRIX, ENGERIX-B, and IPV, administered concomitantly with Hib and 7-valent pneumococcal conjugate vaccines (Wyeth Pharmaceuticals Inc.). In this study, medical attention (a visit to or from medical personnel) for fever within 4 days following vaccination was sought in the group who received PEDIARIX for 8 infants after the first dose (1.2%), 1 infant following the second dose (0.2%), and 5 infants following the third dose (0.8%) (Table 3). Following dose 2, medical attention for fever was sought for 2 infants (0.6%) who received separately administered vaccines (Table 3). Among infants who had a medical visit for fever within 4 days following vaccination, 9 of 14 who received PEDIARIX and 1 of 2 who received separately administered vaccines, had one or more diagnostic studies performed to evaluate the cause of fever.

Safety of PEDIARIX after a previous dose of hepatitis B vaccine: Limited data are available on the safety of administering PEDIARIX after a previous dose of hepatitis B vaccine. In 2 separate studies, 160 Moldovan infants and 96 US infants, respectively, received 3 doses of PEDIARIX following 1 previous dose of hepatitis B vaccine. Neither study was designed to detect significant differences in rates of adverse events associated with PEDIARIX administered after a previous dose of hepatitis B vaccine compared to PEDIARIX administered without a previous dose of hepatitis B vaccine.

Table 3. Percentage of US Infants With Solicited Local Reactions or Systemic Adverse Events Within 4 Days of Vaccination* at 2, 4, and 6 Months of Age With PEDIARIX Administered Concomitantly With Hib Conjugate Vaccine and 7-valent Pneumococcal Conjugate Vaccine (PCV7) or With Separate Concomitant Administration of INFANRIX, ENGERIX-B, IPV, Hib Conjugate Vaccine, and PCV7 (Modified ITT cohort)

	PEDIARIX, Hib Vaccine, & PCV7			INFANRIX, ENGERIX-B, IPV, Hib Vaccine, & PCV7		
	Dose 1	**Dose 2**	**Dose 3**	**Dose 1**	**Dose 2**	**Dose 3**
Local[†]						
N	**671**	**653**	**648**	**335**	**323**	**315**
Pain, any	36.1	36.1	31.2	31.9	30.0	29.8
Pain, grade 2 or 3	11.5	10.9	10.6	9.0	8.7	8.9
Pain, grade 3	2.4	2.5	1.7	2.7	1.5	1.3
Redness, any	24.9[§]	37.2	40.1	18.2	32.8	39.0
Redness, >5 mm	6.0[§]	9.6[§]	12.7[§]	1.8	5.9	7.3
Redness, >20 mm	0.9	1.2[§]	2.8	0.3	0.0	1.9
Swelling, any	17.3[§]	26.5[§]	28.7	9.6	20.4	24.8
Swelling, >5 mm	5.8[§]	9.6[§]	9.3[§]	1.8	5.0	4.1
Swelling, >20 mm	1.9	2.5[§]	3.1	0.6	0.0	1.3
Systemic						
N	**667**	**644**	**645**	**333**	**321**	**311**
Fever[‡], ≥100.4˚F	27.9[§]	38.8[§]	33.5[§]	19.8	30.2	23.8
Fever[‡], >101.3˚F	7.0	14.1[§]	8.8	4.5	9.7	5.8
Fever[‡], >102.2˚F	2.2[§]	3.6	3.4	0.3	3.1	2.3
Fever[‡], >103.1˚F	0.4	1.4	1.1	0.0	0.3	0.3
Fever[‡], M.A.	1.2[§]	0.2	0.8	0.0	0.6	0.0
N	**671**	**653**	**648**	**335**	**323**	**315**
Drowsiness, any	57.2	51.6	40.9	54.0	48.3	38.4
Drowsiness, grade 2 or 3	15.8	13.8	11.4	17.6	12.4	11.1
Drowsiness, grade 3	2.5	1.2	0.9	3.6	0.6	1.9
Irritability/Fussiness, any	60.5	64.9	61.1	61.5	61.6	56.5
Irritability/Fussiness, grade 2 or 3	19.8	27.9[§]	25.2[§]	19.4	21.1	19.4
Irritability/Fussiness, grade 3	3.4	4.4	3.5	3.9	3.4	3.2
Loss of appetite, any	30.4	30.6	26.2	27.8	26.6	23.8
Loss of appetite, grade 2 or 3	6.6	7.8[§]	5.9	5.1	3.4	5.4
Loss of appetite, grade 3	0.7	0.3	0.2	0.6	0.3	0.0

Modified ITT cohort = all vaccinated subjects for whom safety data were available.

N = number of infants for whom at least one symptom sheet was completed; for fever, numbers exclude missing temperature recordings or tympanic measurements.

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

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 or axillary temperatures increased by 1°C to derive equivalent rectal temperature.
§Rate significantly higher in the group that received PEDIARIX compared to separately administered vaccines [p value < 0.05 (2-sided Fisher Exact test) or the 95% CI on the difference between groups (Separate minus PEDIARIX) does not include 0].

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.[20] 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.[24] 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.[24] 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 With PEDIARIX: Worldwide voluntary reports of adverse events received for PEDIARIX since market introduction of this vaccine are listed below. This list includes serious adverse events or events which have a suspected causal connection to components of PEDIARIX or other vaccines or drugs. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Cardiac Disorders: Cyanosis.

Gastrointestinal Disorders: Diarrhea, vomiting.

General Disorders and Administrative Site Conditions: Fatigue, injection site cellulitis, injection site induration, injection site itching, injection site nodule/lump, injection site pain, injection site reactions, injection site redness, injection site swelling, injection site warmth, irritability, limb pain, limb swelling, pyrexia, Sudden Infant Death Syndrome.

Immune System Disorders: Anaphylactic reaction, anaphylactoid reaction, hypersensitivity.

Infections and Infestations: Upper respiratory tract infection.

Investigations: Abnormal liver function tests.

Metabolism and Nutrition Disorders: Anorexia.

Nervous System Disorders: Bulging fontanelle, convulsions, depressed level of consciousness, febrile convulsion, hypotonia, hypotonic-hyporesponsive episode, lethargy, somnolence.

Psychiatric Disorders: Crying, insomnia, irritability, nervousness, restlessness, screaming, unusual crying.

Respiratory, Thoracic and Mediastinal Disorders: Apnea, dyspnea.

Skin and Subcutaneous Tissue Disorders: Angioedema, erythema, rash, urticaria.

Vascular Disorders: Pallor, petechiae.

Postmarketing Reports With INFANRIX and/or ENGERIX-B: Worldwide voluntary reports of adverse events received for INFANRIX and/or ENGERIX-B in children younger than 7 years of age but not already reported for PEDIARIX are listed below. This list includes serious adverse events or events which have a suspected causal connection to components of INFANRIX and/or ENGERIX-B or other vaccines or drugs. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Blood and Lymphatic System Disorders: Idiopathic thrombocytopenic purpura[a,b], lymphadenopathy[a], thrombocytopenia[a,b].

Gastrointestinal Disorders: Abdominal pain[b], intussusception[a,b], nausea[b].

General Disorders and Administrative Site Conditions: Asthenia[b], malaise[b].

Hepatobiliary Disorders: Jaundice[b].

Immune System Disorders: Anaphylactic shock[a], serum sickness–like disease[b].

Musculoskeletal and Connective Tissue Disorders: Arthralgia[b], myalgia[b].

Nervous System Disorders: Encephalopathy[a], headache[b].

Skin and Subcutaneous Tissue Disorders: Alopecia[b], erythema multiforme[b], pruritus[a,b], Stevens-Johnson syndrome[a].

[a] Following INFANRIX.

[b] Following ENGERIX-B.

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.[25] The Act further requires the healthcare provider to report to the US Department of Health and Human Services 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.[25,26] These events should be reported to VAERS. The VAERS toll-free number is 1-800-822-7967. Reporting forms may also be obtained at the VAERS website at www.vaers.hhs.gov.

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.

Before injection, the skin at the injection site should be cleaned and prepared with a suitable germicide.

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. The preferred administration site is the anterolateral aspect of the thigh for children younger than 1 year. In older children, the deltoid muscle is usually large enough for an intramuscular injection. 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.

Do not administer this product subcutaneously or intravenously.

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.[18] (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.[18] (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 DTaP 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.[5]

Preterm infants should be vaccinated according to their chronological age from birth.[5]

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 and fifth 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 conjugate vaccine (see CLINICAL PHARMACOLOGY). Data are also available from 2 clinical studies in which PEDIARIX was administered concomitantly, at separate sites, with Hib and 7-valent pneumococcal conjugate vaccines (see CLINICAL PHARMACOLOGY and 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)

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