HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PEDIARIX safely and effectively. See full prescribing information for PEDIARIX.

PEDIARIX [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine]
Suspension for Intramuscular Injection
Initial U.S. Approval: 2002

----------INDICATIONS AND USAGE----------

PEDIARIX is a vaccine indicated for active immunization against diphtheria, tetanus, pertussis, infection caused by all known subtypes of hepatitis B virus, and poliomyelitis. PEDIARIX is approved for use as a three-dose series in infants born of hepatitis B surface antigen (HBsAg)-negative mothers. PEDIARIX may be given as early as 6 weeks of age through 6 years of age (prior to the 7th birthday). (1)

---------- DOSAGE AND ADMINISTRATION ----------

Three doses (0.5-mL each) by intramuscular injection at 2, 4, and 6 months of age. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------

Single-dose prefilled syringes containing a 0.5-mL suspension for injection. (3)

----------CONTRAINDICATIONS----------

- Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any diphtheria toxoid-, tetanus toxoid-, pertussis-, hepatitis B-, or poliovirus-containing vaccine, or to any component of PEDIARIX. (4.1)
- Encephalopathy within 7 days of administration of a previous pertussis-containing vaccine. (4.2)
- Progressive neurologic disorders. (4.3)

---------- WARNINGS AND PRECAUTIONS----------

- In clinical trials, PEDIARIX was associated with higher rates of fever, relative to separately administered vaccines. (5.1)
- If Guillain-Barré syndrome occurs within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give PEDIARIX should be based on potential benefits and risks. (5.2)
- The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions. (5.3)
- Syncope (fainting) can occur in association with administration of injectable vaccines, including PEDIARIX. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.4)
- If specified adverse events (i.e., temperature ≥105°F, collapse or shock-like state, or inconsolable crying lasting ≥3 hours, within 48 hours after vaccination; seizures within 3 days after vaccination) have occurred following a pertussis-containing vaccine, the decision to give PEDIARIX should be based on potential benefits and risks. (5.5)
- For children at higher risk for seizures, an antipyretic may be administered at the time of vaccination with PEDIARIX. (5.6)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including PEDIARIX, to infants born prematurely should be based on consideration of the individual infant's medical status, and the potential benefits and possible risks of vaccination. (5.7)

---------- ADVERSE REACTIONS ----------

Common solicited adverse events following any dose (≥25%) included local injection site reactions (pain, redness, and swelling), fever (≥100.4°F), drowsiness, irritability/fussiness, and loss of appetite. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

----------DRUG INTERACTIONS----------

Do not mix PEDIARIX with any other vaccine in the same syringe or vial. (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: xx/xxxx

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PEDIARIX® is indicated for active immunization against diphtheria, tetanus, pertussis, infection caused by all known subtypes of hepatitis B virus, and poliomyelitis. PEDIARIX is approved for use as a three-dose series in infants born of hepatitis B surface antigen (HBsAg)-negative mothers. PEDIARIX may be given as early as 6 weeks of age through 6 years of age (prior to the 7th birthday).

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Shake vigorously to obtain a homogeneous, turbid, white suspension. Do not use if resuspension does not occur with vigorous shaking. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

Attach a sterile needle and administer intramuscularly.

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 intravenously, intradermally, or subcutaneously.

2.2 Recommended Dose and Schedule

Immunization with PEDIARIX consists of 3 doses of 0.5 mL each, by intramuscular injection, at 2, 4, and 6 months of age (at intervals of 6 to 8 weeks, preferably 8 weeks). The first dose may be given as early as 6 weeks of age. Three doses of PEDIARIX constitute a primary immunization course for diphtheria, tetanus, pertussis, and poliomyelitis and the complete vaccination course for hepatitis B.

2.3 Modified Schedules in Previously Vaccinated Children

Children Previously Vaccinated with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP)

PEDIARIX may be used to complete the first 3 doses of the DTaP series in children who have received 1 or 2 doses of INFANRIX® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed), manufactured by GlaxoSmithKline, identical to the DTaP component of PEDIARIX *[see Description (11)]* and are also scheduled to receive the other vaccine

components of PEDIARIX. Data are not available on the safety and effectiveness of using PEDIARIX following one or more doses of a DTaP vaccine from a different manufacturer.

Children Previously Vaccinated with Hepatitis B Vaccine

PEDIARIX may be used to complete the hepatitis B vaccination series following 1 or 2 doses of another hepatitis B vaccine (monovalent or as part of a combination vaccine), including vaccines from other manufacturers, in children born of HBsAg-negative mothers who are also scheduled to receive the other vaccine components of PEDIARIX.

A 3-dose series of PEDIARIX may be administered to infants born of HBsAg-negative mothers and who received a dose of hepatitis B vaccine at or shortly after birth. However, data are limited regarding the safety of PEDIARIX in such infants *[see Adverse Reactions (6.1)]*. 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.

Children Previously Vaccinated with Inactivated Poliovirus Vaccine (IPV)

PEDIARIX may be used to complete the first 3 doses of the IPV series in children who have received 1 or 2 doses of IPV from a different manufacturer and are also scheduled to receive the other vaccine components of PEDIARIX.

2.4 Booster Immunization following PEDIARIX

Children who have received a 3-dose series with PEDIARIX should complete the DTaP and IPV series according to the recommended schedule.[1] Because the pertussis antigens contained in INFANRIX and KINRIX® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine), manufactured by GlaxoSmithKline, are the same as those in PEDIARIX, these children should receive INFANRIX as their fourth dose of DTaP and either INFANRIX or KINRIX as their fifth dose of DTaP, according to the respective prescribing information for these vaccines. KINRIX or another manufacturer's IPV may be used to complete the 4-dose IPV series according to the respective prescribing information.

3 DOSAGE FORMS AND STRENGTHS

PEDIARIX is a suspension for injection available in 0.5-mL single-dose prefilled TIP-LOK® syringes.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

A severe allergic reaction (e.g., anaphylaxis) after a previous dose of any diphtheria toxoid-, tetanus toxoid-, pertussis antigen-, hepatitis B-, or poliovirus-containing vaccine or any component of this vaccine, including yeast, neomycin, and polymyxin B, is a contraindication to administration of PEDIARIX *[see Description (11)]*.

4.2 Encephalopathy

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 is a contraindication to administration of any pertussis-containing vaccine, including PEDIARIX.

4.3 Progressive Neurologic Disorder

Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy is a contraindication to administration of any pertussis-containing vaccine, including PEDIARIX. PEDIARIX should not be administered to individuals with such conditions until the neurologic status is clarified and stabilized.

5 WARNINGS AND PRECAUTIONS

5.1 Fever

In clinical trials, administration of PEDIARIX in infants was associated with higher rates of fever, relative to separately administered vaccines *[see Adverse Reactions (6.1)]*.

5.2 Guillain-Barré Syndrome

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

5.3 Latex

The tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions.

5.4 Syncope

Syncope (fainting) can occur in association with administration of injectable vaccines, including PEDIARIX. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

5.5 Adverse Events following Prior Pertussis Vaccination

If any of the following events occur in temporal relation to receipt of a vaccine containing a pertussis component, the decision to give any pertussis-containing vaccine, including PEDIARIX, should be based on careful consideration of the potential benefits and possible risks:

- 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.

5.6 Children at Risk for Seizures

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 a pertussis component, including PEDIARIX, and for the ensuing 24 hours to reduce the possibility of post-vaccination fever.

5.7 Apnea in Premature Infants

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including PEDIARIX, to infants born prematurely should be based on consideration of the individual infant's medical status, and the potential benefits and possible risks of vaccination.

5.8 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions to allow an assessment of benefits and risks. Epinephrine and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine, and may not reflect the rates observed in practice.

A total of 23,849 doses of PEDIARIX have been administered to 8,088 infants who received one or more doses as part of the 3-dose series during 14 clinical studies. Common adverse events that occurred in ≥25% of subjects following any dose of PEDIARIX included local injection site reactions (pain, redness, and swelling), fever, drowsiness, irritability/fussiness, and loss of appetite. In comparative studies (including the German and US studies described below), administration of PEDIARIX was associated with higher rates of fever relative to separately administered vaccines *[see Warnings and Precautions (5.1)]*. 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 *Haemophilus influenzae* type b (Hib) conjugate vaccines (GlaxoSmithKline [licensed in the US only for booster immunization], Wyeth Pharmaceuticals Inc. [no longer licensed in the US], Sanofi Pasteur SA [US-licensed], or Merck & Co, Inc. [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 conjugate vaccine [Sanofi Pasteur SA], and oral poliovirus vaccine [OPV] [Wyeth Pharmaceuticals, Inc.; no longer licensed in the US]). In this study, information on adverse events that occurred within 30 days following vaccination was collected. More than 95% of study participants were white.

In a US study, the safety of PEDIARIX administered to 673 infants was compared with the safety of separately administered INFANRIX, ENGERIX-B® [Hepatitis B Vaccine (Recombinant)], and IPV (Sanofi Pasteur SA) in 335 infants. In both groups, infants received Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the US) and 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) concomitantly at separate sites. All vaccines were administered at 2, 4, and 6 months of age. Data on solicited local reactions and general 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). 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. A total of 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.

Solicited Adverse Events

Data on solicited local reactions and general adverse events from the US safety study are presented in Table 1. This study was powered to evaluate fever >101.3°F following Dose 1. The rate of fever ≥100.4°F following each dose was significantly higher in the group that received PEDIARIX compared with separately administered vaccines. Other statistically significant differences between groups in rates of fever, as well as other solicited adverse events, are noted in Table 1. 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 1). Following Dose 2, medical attention for fever was sought for 2 infants (0.6%) who received separately administered vaccines (Table 1). 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.

Table 1. Percentage of Infants with Solicited Local Reactions or General Adverse Events within 4 Days of Vaccination[a] 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 Intent-to-Treat 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[b]						
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[c]	37.2	40.1	18.2	32.8	39.0
Redness, >5 mm	6.0[c]	9.6[c]	12.7[c]	1.8	5.9	7.3
Redness, >20 mm	0.9	1.2[c]	2.8	0.3	0.0	1.9
Swelling, any	17.3[c]	26.5[c]	28.7	9.6	20.4	24.8
Swelling, >5 mm	5.8[c]	9.6[c]	9.3[c]	1.8	5.0	4.1
Swelling, >20 mm	1.9	2.5[c]	3.1	0.6	0.0	1.3
General						
N	**667**	**644**	**645**	**333**	**321**	**311**
Fever[d], ≥100.4°F	27.9[c]	38.8[c]	33.5[c]	19.8	30.2	23.8
Fever[d], >101.3°F	7.0	14.1[c]	8.8	4.5	9.7	5.8
Fever[d], >102.2°F	2.2[c]	3.6	3.4	0.3	3.1	2.3
Fever[d], >103.1°F	0.4	1.4	1.1	0.0	0.3	0.3
Fever[d], M.A.	1.2[c]	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[c]	25.2[c]	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[c]	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

Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the US); PCV7 (Wyeth Pharmaceuticals Inc.); IPV (Sanofi Pasteur SA).

Modified intent-to-treat 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.
[a] Within 4 days of vaccination defined as day of vaccination and the next 3 days.
[b] Local reactions at the injection site for PEDIARIX or INFANRIX.
[c] Rate significantly higher in the group that received PEDIARIX compared with 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).
[d] Axillary temperatures increased by 1°C and oral temperatures increased by 0.5°C to derive equivalent rectal temperature.

Serious Adverse Events

Within 30 days following any dose of vaccine in the US safety study in which all subjects received concomitant Hib and pneumococcal 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).

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). The reported rate of SIDS in the United States from 1990 to 1994 was 1.2/1,000 live births. By chance alone, some cases of SIDS can be expected to follow receipt of pertussis-containing vaccines.

Onset of Chronic Illnesses

In the US safety study in which all subjects received concomitant Hib and pneumococcal 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 (N = 4,666) 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 (N = 768) 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 Hib and pneumococcal conjugate vaccines, 4 subjects in the group that received PEDIARIX (N = 673) 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 (N = 335) 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 or US safety studies.

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 with PEDIARIX administered without a previous dose of hepatitis B vaccine.

6.2 Postmarketing Safety Surveillance Study

In a safety surveillance study conducted at a health maintenance organization in the US, infants who received one or more doses of PEDIARIX from approximately mid-2003 through mid-2005 were compared with age-, gender-, and area-matched historical controls who received one or more doses of separately administered US-licensed DTaP vaccine from 2002 through approximately mid-2003. Only infants who received 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) concomitantly with PEDIARIX or DTaP vaccine were included in the cohorts. Other US-licensed vaccines were administered according to routine practices at the study sites, but concomitant administration with PEDIARIX or DTaP was not a criterion for

inclusion in the cohorts. A birth dose of hepatitis B vaccine had been administered routinely to infants in the historical DTaP control cohort, but not to infants who received PEDIARIX. For each of Doses 1-3, a random sample of 40,000 infants who received PEDIARIX was compared with the historical DTaP control cohort for the incidence of seizures (with or without fever) during the 8-day period following vaccination. For each dose, random samples of 7,500 infants in each cohort were also compared for the incidence of medically-attended fever (fever ≥100.4°F that resulted in hospitalization, an emergency department visit, or an outpatient visit) during the 4-day period following vaccination. Possible seizures and medical visits plausibly related to fever were identified by searching automated inpatient and outpatient data files. Medical record reviews of identified events were conducted to verify the occurrence of seizures or medically-attended fever. The incidence of verified seizures and medically-attended fever from this study are presented in Table 2.

Table 2. Percentage of Infants with Seizures (with or without Fever) within 8 Days of Vaccination and Medically-attended Fever within 4 Days of Vaccination with PEDIARIX Compared with Historical Controls

	PEDIARIX			Historical DTaP Controls			Difference (PEDIARIX–DTaP Controls)
	N	n	% (95% CI)	N	n	% (95% CI)	% (95% CI)
All Seizures (with or without fever)							
Dose 1, Days 0-7	40,000	7	0.02 (0.01, 0.04)	39,232	6	0.02 (0.01, 0.03)	0.00 (-0.02, 0.02)
Dose 2, Days 0-7	40,000	3	0.01 (0.00, 0.02)	37,405	4	0.01 (0.00, 0.03)	0.00 (-0.02, 0.01)
Dose 3, Days 0-7	40,000	6	0.02 (0.01, 0.03)	40,000	5	0.01 (0.00, 0.03)	0.00 (-0.01, 0.02)
Total doses	120,000	16	0.01 (0.01, 0.02)	116,637	15	0.01 (0.01, 0.02)	0.00 (-0.01, 0.01)
Medically-attended Fever[a]							
Dose 1, Days 0-3	7,500	14	0.19 (0.11, 0.30)	7,500	14	0.19 (0.11, 0.30)	0.00 (-0.14, 0.14)
Dose 2, Days 0-3	7,500	25	0.33 (0.22, 0.48)	7,500	15	0.20 (0.11, 0.33)	0.13 (-0.03, 0.30)
Dose 3, Days 0-3	7,500	21	0.28 (0.17, 0.43)	7,500	19	0.25 (0.15, 0.39)	0.03 (-0.14, 0.19)
Total doses	22,500	60	0.27 (0.20, 0.34)	22,500	48	0.21 (0.16, 0.28)	0.05 (-0.01, 0.14)

DTaP – any US-licensed DTaP vaccine. Infants received 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) concomitantly with each dose of PEDIARIX or DTaP. Other US-licensed vaccines were administered according to routine practices at the study sites.
N = Number of subjects in the given cohort.
n = Number of subjects with events reported in the given cohort.
[a] Medically-attended fever defined as fever ≥100.4°F that resulted in hospitalization, an

emergency department visit, or an outpatient visit.

6.3 Postmarketing Spontaneous Reports for PEDIARIX

In addition to reports in clinical trials, 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 that have a suspected causal connection to components of PEDIARIX. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Cardiac Disorders

Cyanosis.

Gastrointestinal Disorders

Diarrhea, vomiting.

General Disorders and Administration Site Conditions

Fatigue, injection site cellulitis, injection site induration, injection site itching, injection site nodule/lump, injection site reaction, injection site vesicles, injection site warmth, limb pain, limb swelling.

Immune System Disorders

Anaphylactic reaction, anaphylactoid reaction, hypersensitivity.

Infections and Infestations

Upper respiratory tract infection.

Investigations

Abnormal liver function tests.

Nervous System Disorders

Bulging fontanelle, depressed level of consciousness, encephalitis, hypotonia, hypotonic-hyporesponsive episode, lethargy, somnolence, syncope.

Psychiatric Disorders

Crying, insomnia, nervousness, restlessness, screaming, unusual crying.

Respiratory, Thoracic, and Mediastinal Disorders

Apnea, cough, dyspnea.

Skin and Subcutaneous Tissue Disorders

Angioedema, erythema, rash, urticaria.

Vascular Disorders

Pallor, petechiae.

6.4 Postmarketing Spontaneous Reports for 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 that have a suspected causal connection to components of INFANRIX and/or ENGERIX-B. Because these events are reported voluntarily from a population of uncertain size, it is not 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 Administration 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] arthritis,[b] muscular weakness,[b] myalgia.[b]

Nervous System Disorders

Encephalopathy,[a] headache,[a] meningitis,[b] neuritis,[b] neuropathy,[b] paralysis.[b]

Skin and Subcutaneous Tissue Disorders

Alopecia,[b] erythema multiforme,[b] lichen planus,[b] pruritus,[a,b] Stevens Johnson syndrome.[a]

Vascular Disorders

Vasculitis.[b]

[a] Following INFANRIX (licensed in the United States in 1997).

[b] Following ENGERIX-B (licensed in the United States in 1989).

7 DRUG INTERACTIONS

7.1 Concomitant Vaccine Administration

Immune responses following concomitant administration of PEDIARIX, Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the US), and 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) were evaluated in a clinical trial *[see Clinical Studies (14.3)]*.

When PEDIARIX is administered concomitantly with other injectable vaccines, they should be given with separate syringes and at different injection sites. PEDIARIX should not be mixed with any other vaccine in the same syringe or vial.

7.2 Immunosuppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to PEDIARIX.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

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 reproduction capacity.

8.4 Pediatric Use

Safety and effectiveness of PEDIARIX were established in the age group 6 weeks through 6 months on the basis of clinical studies *[see Adverse Reactions (6.1), Clinical Studies (14.1, 14.2)]*. Safety and effectiveness of PEDIARIX in the age group 7 months through 6 years are supported by evidence in infants 6 weeks through 6 months of age. Safety and effectiveness of PEDIARIX in infants younger than 6 weeks of age and children 7 to 16 years of age have not been evaluated.

11 DESCRIPTION

PEDIARIX [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine] is a noninfectious, sterile vaccine for intramuscular administration. Each 0.5-mL dose is formulated to contain 25 Lf of diphtheria toxoid, 10 Lf of tetanus toxoid, 25 mcg of inactivated pertussis toxin (PT), 25 mcg of filamentous hemagglutinin (FHA), 8 mcg of pertactin (69 kiloDalton outer membrane protein), 10 mcg of HBsAg, 40 D-antigen Units (DU) of Type 1 poliovirus (Mahoney), 8 DU of Type 2 poliovirus (MEF-1), and 32 DU of Type 3 poliovirus (Saukett). The diphtheria, tetanus, and

pertussis components are the same as those in INFANRIX and KINRIX. The hepatitis B surface antigen is the same as that in ENGERIX-B.

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 present an undue risk for bovine spongiform encephalopathy (BSE). Both toxins are detoxified with formaldehyde, concentrated by ultrafiltration, and purified by precipitation, dialysis, and sterile filtration.

The 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 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 inactivated poliovirus component 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 present an undue risk for 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.

Diphtheria and tetanus toxoids and pertussis antigens (inactivated PT, FHA, and pertactin) are individually adsorbed onto aluminum hydroxide. The hepatitis B component is adsorbed onto aluminum phosphate.

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 component (inactivated 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 contains aluminum salts as adjuvant (not more than 0.85 mg aluminum by

assay) and 4.5 mg of sodium chloride. Each dose also contains ≤100 mcg of residual formaldehyde and ≤100 mcg of polysorbate 80 (Tween 80). Neomycin sulfate and polymyxin B are used in the poliovirus 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 tip caps of the prefilled syringes contain natural rubber latex; the plungers are not made with natural rubber latex.

PEDIARIX is formulated without preservatives.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Diphtheria

Diphtheria is an acute toxin-mediated infectious disease caused by toxigenic strains of *C. diphtheriae*. Protection against disease is due to the development of neutralizing antibodies to the diphtheria toxin. 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.[2]

Tetanus

Tetanus is an acute toxin-mediated disease caused by a potent exotoxin released by *C. tetani*. 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 IU/mL is considered protective.[5]

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. There is no established serological correlate of protection for pertussis.

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.

Antibody concentrations ≥10 mIU/mL against HBsAg are recognized as conferring protection against hepatitis B virus infection.[6]

Poliomyelitis

Poliovirus is an enterovirus that belongs to the picornavirus family. Three serotypes of poliovirus have been identified (Types 1, 2, and 3). Poliovirus neutralizing antibodies confer protection

against poliomyelitis disease.[7]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

PEDIARIX has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

14 CLINICAL STUDIES

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

14.1 Efficacy of INFANRIX

Efficacy of a 3-dose primary series of INFANRIX has been assessed in 2 clinical studies.

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. 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%, 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%, 78%) against >7 days of any cough and 73% (95% CI: 63%, 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%, 91%) among children followed to 6 years of age. For details see INFANRIX prescribing information.

A prospective efficacy trial was also conducted in Germany employing a household contact study design. 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%, 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%, 78%) and against ≥7 days of paroxysmal cough was 81% (95% CI: 68%, 89%). For details see INFANRIX prescribing information.

14.2 Immunological Evaluation of PEDIARIX

In a US multicenter study, infants were randomized to 1 of 3 groups: (1) a combination vaccine

group that received PEDIARIX concomitantly with Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the US) and US-licensed 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.); (2) a separate vaccine group that received US-licensed INFANRIX, ENGERIX-B, and IPV (Sanofi Pasteur SA) concomitantly with the same Hib and pneumococcal conjugate vaccines; and (3) a staggered vaccine group that received PEDIARIX concomitantly 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% were 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 pre-vaccination 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 (Table 3).

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.

Table 3. Antibody Responses following PEDIARIX as Compared with Separate Concomitant Administration of INFANRIX, ENGERIX-B, and IPV (One Month[a] after Administration of Dose 3) in Infants Vaccinated at 2, 4, and 6 Months of Age When Administered Concomitantly 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 Toxoid % ≥0.1 IU/mL[b]	99.4	98.7
Anti-tetanus Toxoid % ≥0.1 IU/mL[b]	100	98.1
Anti-PT % VR[c] GMC[b]	98.7 48.1	95.1 28.6
Anti-FHA % VR[c] GMC[b]	98.7 111.9	96.5 97.6
Anti-pertactin % VR[c] GMC[b]	91.7 95.3	95.1 80.6
Anti-polio 1 % ≥1:8[b,d]	100	100
Anti-polio 2 % ≥1:8[b,d]	100	100
Anti-polio 3 % ≥1:8[b,d]	100	100
	(N = 114-128)	**(N = 111-121)**
Anti-HBsAg[e] % ≥10 mIU/mL[f] GMC (mIU/mL)[f]	97.7 1032.1	99.2 614.5

Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.; no longer licensed in the US); PCV7 (Wyeth Pharmaceuticals Inc.); IPV (Sanofi Pasteur SA).

Assay methods used: ELISA for anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, anti-pertactin, and anti-HBsAg; micro-neutralization for anti-polio (1, 2, and 3).

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.

[a] One month blood sampling, range: 20 to 60 days.

[b] 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.

[c] 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 pertactin, respectively. No clinical limit defined for non-inferiority.

[d] Poliovirus neutralizing antibody titer.

[e] 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.

[f] No clinical limit defined for non-inferiority.

14.3 Concomitant Vaccine Administration

In a US multicenter study *[see Clinical Studies (14.2)]*, there was no evidence for interference with the immune responses to PEDIARIX when administered concomitantly with 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.) relative to 2 weeks prior.

Anti-PRP (Hib polyribosyl-ribitol-phosphate) 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 *[see Clinical Studies (14.2)]*, are presented in Table 4.

Table 4. Anti-PRP Seroprotection Rates and GMCs (mcg/mL) of Pneumococcal Antibodies One Month[a] 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 (Wyeth Pharmaceuticals Inc.; no longer licensed in the US); PCV7 (Wyeth Pharmaceuticals Inc.); IPV (Sanofi Pasteur SA).

Assay method used: ELISA for anti-PRP and 7 pneumococcal serotypes.

GMC = Geometric mean antibody concentration.

[a] One month blood sampling, range: 20 to 60 days.

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16 HOW SUPPLIED/STORAGE AND HANDLING

PEDIARIX is available in 0.5-mL single-dose disposable prefilled TIP-LOK syringes (packaged without needles):

NDC 58160-811-43 Syringe in Package of 10: NDC 58160-811-52

Store refrigerated between 2º and 8ºC (36º and 46ºF). Do not freeze. Discard if the vaccine has been frozen.

17 PATIENT COUNSELING INFORMATION

The parent or guardian should be:

- informed of the potential benefits and risks of immunization with PEDIARIX, and of the importance of completing the immunization series.
- informed about the potential for adverse reactions that have been temporally associated with administration of PEDIARIX or other vaccines containing similar components.
- instructed to report any adverse events to their healthcare provider.
- 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 Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/nip).

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Rixensart, Belgium, US License 1617, and

Novartis Vaccines and Diagnostics GmbH

Marburg, Germany, US License 1754

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