HIGHLIGHTS OF PRESCRIBING INFORMATION

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

INFANRIX (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed)
Suspension for Intramuscular Injection
Initial U.S. Approval: 1997

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

INFANRIX is a vaccine indicated for active immunization against diphtheria, tetanus, and pertussis as a 5-dose series in infants and children 6 weeks to 7 years of age. (1)

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

A 0.5 mL intramuscular injection given as a 5-dose series: (2.2)

- One dose each at 2, 4, and 6 months of age.
- One booster dose at 15 to 20 months of age and another booster dose at 4 to 6 years of age.

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

Suspension for intramuscular injection supplied in single-dose (0.5 mL) vials and prefilled syringes. (3)

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

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

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

- If Guillain-Barré syndrome occurs within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give INFANRIX should be based on potential benefits and risks. (5.1)
- The needleless prefilled syringes contain dry natural latex rubber and may cause allergic reactions. (5.2)
- If temperature ≥105°F, collapse or shock-like state, or persistent, inconsolable crying lasting ≥3 hours have occurred within 48 hours after receipt of a pertussis-containing vaccine, or if seizures have occurred within 3 days after receipt of a pertussis-containing vaccine, the decision to give INFANRIX should be based on potential benefits and risks. (5.3)
- For children at higher risk for seizures, an antipyretic may be administered at the time of vaccination with INFANRIX. (5.4)

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

Rates of injection site reactions (pain, redness, swelling) ranged from 10% to 53%, depending on reaction and dose number, and were highest following doses 4 and 5. Fever was common (20% to 30%) following doses 1-3. Other common solicited adverse events were drowsiness, irritability/fussiness, and loss of appetite, reported in approximately 15% to 60% of subjects, depending on event and dose number. (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 INFANRIX with any other vaccine in the same syringe or vial. (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: Month Year
INF:XPI

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

INFANRIX® is indicated for active immunization against diphtheria, tetanus, and pertussis as a 5-dose series in infants and children 6 weeks to 7 years of age (prior to seventh 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. INFANRIX also should be inspected visually for cracks in the vial or syringe prior to administration. If any of these conditions exist, the vaccine should not be administered.

2.2 Dose and Schedule

A 0.5 mL dose of INFANRIX is approved for intramuscular administration in infants and children 6 weeks to 7 years of age (prior to the seventh birthday) as a 5-dose series. The series consists of a primary immunization course of 3 doses administered at 2, 4, and 6 months of age (at intervals of 4 to 8 weeks), followed by 2 booster doses, administered at 15 to 20 months of age and at 4 to 6 years of age. The first dose may be given as early as 6 weeks of age.

The preferred administration site is the anterolateral aspect of the thigh for most infants younger than 12 months of age and the deltoid muscle of the upper arm for most children 12 months of age to 7 years of age.

Do not administer this product intravenously, intradermally, or subcutaneously.

2.3 Use of INFANRIX With Other DTaP Vaccines

Sufficient data are not available on the safety and effectiveness of interchanging INFANRIX and Diphtheria and Tetanus Toxoids and Acellular Pertussis (DTaP) vaccines from different manufacturers for successive doses of the DTaP vaccination series. Because the pertussis antigen components of INFANRIX and PEDIARIX® [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined] are the same, INFANRIX may be used to complete a DTaP vaccination series initiated with PEDIARIX.

2.4 Additional Dosing Information

If any recommended dose of pertussis vaccine cannot be given *[see Contraindications (4.2, 4.3) and Warnings and Precautions (5.3)]*, Diphtheria and Tetanus Toxoids Adsorbed (DT) For Pediatric Use should be given according to its prescribing information.

3 DOSAGE FORMS AND STRENGTHS

INFANRIX is a suspension for intramuscular injection available in 0.5-mL single-dose vials and prefilled TIP-LOK® syringes.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any diphtheria toxoid, tetanus toxoid, or pertussis-containing vaccine, or to any component of INFANRIX is a contraindication *[see Description (11)]*. 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 being considered.

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 INFANRIX.

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 INFANRIX. Pertussis vaccine should not be administered to individuals with these conditions until a treatment regimen has been established and the condition has stabilized.

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

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

5.2 Latex

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 does not contain latex.

5.3 Adverse Events Following Prior Pertussis Vaccination

If any of the following events occur in temporal relation to receipt of a pertussis-containing vaccine, the decision to give any pertussis-containing vaccine, including INFANRIX, 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.

5.4 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 pertussis-containing vaccine, including INFANRIX, and for the ensuing 24 hours to reduce the possibility of post-vaccination fever.

5.5 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the patient's immunization history for possible vaccine hypersensitivity. 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 reaction 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. There is the possibility that broad use of INFANRIX could reveal adverse reactions not observed in clinical trials.

Approximately 95,000 doses of INFANRIX have been administered in clinical studies. In these studies, 29,243 infants have received INFANRIX in primary series studies, 6,081 children have received a fourth consecutive dose of INFANRIX, 1,764 children have received a fifth consecutive dose of INFANRIX, and 559 children have received a dose of INFANRIX following 3 doses of PEDIARIX.

Solicited Adverse Events: In a US study, 335 infants received INFANRIX, ENGERIX-B® [Hepatitis B Vaccine (Recombinant)], inactivated poliovirus vaccine (IPV, Sanofi Pasteur SA), Haemophilus b (Hib) conjugate vaccine (Wyeth Pharmaceuticals Inc.) and pneumococcal 7-valent conjugate (PVC7) 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) (Table 1). Among subjects, 69% were White, 16% were Hispanic, 8% were Black, 4% were Asian, and 2% were of other racial/ethnic groups.

Table 1. Solicited Local Reactions and General Adverse Events (%) Occurring Within 4 Days of Vaccination[a] With Separate Concomitant Administration of INFANRIX, ENGERIX-B, IPV, Haemophilus b (Hib) Conjugate Vaccine and Pneumococcal Conjugate Vaccine (PCV7) (Modified ITT cohort)

	INFANRIX, ENGERIX-B, IPV, Hib Vaccine, & PCV7		
	Dose 1	**Dose 2**	**Dose 3**
Local[b]			
N	335	323	315
Pain, any	31.9	30.0	29.8
Pain, grade 2 or 3	9.0	8.7	8.9
Pain, grade 3	2.7	1.5	1.3
Redness, any	18.2	32.8	39.0
Redness, >20 mm	0.3	0.0	1.9
Swelling, any	9.6	20.4	24.8
Swelling, >20 mm	0.6	0.0	1.3
General			
N	333	321	311
Fever[c] (≥100.4°F)	19.8	30.2	23.8
Fever[c] (>101.3°F)	4.5	9.7	5.8
Fever[c] (>102.2°F)	0.3	3.1	2.3
Fever[c] (>103.1°F)	0.0	0.3	0.3
N	335	323	315
Drowsiness, any	54.0	48.3	38.4
Drowsiness, grade 2 or 3	17.6	12.4	11.1
Drowsiness, grade 3	3.6	0.6	1.9
Irritability/Fussiness, any	61.5	61.6	56.5
Irritability/Fussiness, grade 2 or 3	19.4	21.1	19.4
Irritability/Fussiness, grade 3	3.9	3.4	3.2
Loss of appetite, any	27.8	26.6	23.8
Loss of appetite, grade 2 or 3	5.1	3.4	5.4
Loss of appetite, grade 3	0.6	0.3	0.0

Hib conjugate vaccine and PCV7 manufactured by Wyeth Pharmaceuticals Inc. IPV manufactured by Sanofi Pasteur SA.

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.

Grade 2: pain defined as cried/protested on touch; drowsiness defined as interfered with normal daily activities; irritability/fussiness defined as crying more than usual/interfered with normal daily activities; loss of appetite defined as eating less than usual/interfered with normal daily activities.

Grade 3: pain defined as cried when limb was moved/spontaneously painful; drowsiness defined as prevented normal daily activities; irritability/fussiness defined as crying that could not be comforted/prevented normal daily activities; loss of appetite defined as no eating at all.

[a] Within 4 days of vaccination defined as day of vaccination and the next 3 days.

[b] Local reactions at the injection site for INFANRIX.

[c] Rectal temperatures or axillary temperatures increased by 1°C to derive equivalent rectal temperature.

In a US study, the safety of a booster dose of INFANRIX was evaluated in children 15 to 18 months of age whose previous 3 DTaP doses were with INFANRIX (N = 251) or PEDIARIX (N = 559). Vaccines administered concurrently with the fourth dose of INFANRIX included measles, mumps, and rubella (MMR) vaccine (Merck & Co., Inc.), varicella vaccine (Merck & Co., Inc.), pneumococcal 7-valent conjugate (PVC7) vaccine (Wyeth Pharmaceuticals Inc.), and any US-licensed Hib conjugate vaccine; these were given concomitantly in 13.2%, 6.3%, 37.4%, and 41.2% of subjects, respectively. 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) (Table 2). Among subjects, 85% were White, 6% were Hispanic, 6% were Black, 1% were Asian, and 2% were of other racial/ethnic groups.

Table 2. Solicited Local Reactions and General Adverse Events (%) Occurring Within 4 Days of Vaccination[a] With INFANRIX Administered as the Fourth Dose Following 3 Previous Doses of INFANRIX or PEDIARIX (Total Vaccinated Cohort)

	Group Primed With INFANRIX[b] N = 247	Group Primed With PEDIARIX[c] N = 553
Local[d]		
Pain, any	44.5	48.3
Pain, grade 2 or 3	19.0	18.6
Pain, grade 3	3.6	3.4
Redness, any	48.2	49.9
Redness, >20 mm	6.1	6.0
Swelling, any	32.8	32.7
Swelling, >20 mm	3.6	5.2
Increase in mid-thigh circumference, any	33.2	26.2
Increase in mid-thigh circumference, >40 mm	0.0	1.3
General		
Fever[e] (>99.5°F)	8.9	15.4
Fever[e] (>100.4°F)	4.5	6.7
Fever[e] (>101.3°F)	2.0	2.0
Drowsiness, any	35.6	31.3
Drowsiness, grade 2 or 3	9.3	6.7
Drowsiness, grade 3	2.4	1.3
Irritability, any	52.2	53.9
Irritability, grade 2 or 3	18.2	19.7
Irritability, grade 3	3.2	1.4
Loss of appetite, any	24.7	23.3
Loss of appetite, grade 2 or 3	5.3	4.9
Loss of appetite, grade 3	2.4	0.5

Total Vaccinated Cohort = all subjects who received a dose of study vaccine.
N = number of subjects for whom at least one symptom sheet was completed.
Grade 2: pain defined as cried/protested on touch; drowsiness defined as interfered with normal daily activities; irritability defined as crying more than usual/interfered with normal daily activities; loss of appetite defined as eating less than usual/no effect on normal daily activities.
Grade 3: pain defined as cried when limb was moved/spontaneously painful; drowsiness defined as prevented normal daily activities; irritability defined as crying that could not be comforted/prevented normal daily activities; loss of appetite defined as eating less than usual/interfered with normal daily activities.
[a] Within 4 days of vaccination defined as day of vaccination and the next 3 days.

[b] Received INFANRIX, ENGERIX-B, IPV (Sanofi Pasteur SA), PVC7 vaccine (Wyeth Pharmaceuticals Inc.) and Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.) at 2, 4, and 6 months of age.

[c] Received PEDIARIX, PVC7 vaccine (Wyeth Pharmaceuticals Inc.) and Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.) at 2, 4, and 6 months of age or PVC7 vaccine 2 weeks later.

[d] Local reactions at the injection site for INFANRIX.

[e] Axillary temperatures.

In a US study, the safety of a fifth consecutive dose of INFANRIX co-administered at separate sites with a fourth dose of IPV (Sanofi Pasteur SA) and a second dose of MMR vaccine (Merck & Co., Inc.) was evaluated in 1,053 children 4 to 6 years of age. 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) (Table 3). Among subjects, 43% were White, 18% Hispanic, 15% Asian, 7% Black, and 17% were of other racial/ethnic groups.

Table 3. Solicited Local Reactions and General Adverse Events (%) Occurring Within 4 Days of Vaccination[a] With a Fifth Consecutive Dose of INFANRIX When Coadministered With IPV and MMR Vaccine (Total Vaccinated Cohort)

Local[b]	**N = 1,039-1,043**
Pain, any	53.3
Pain, grade 2 or 3[c]	12.0
Pain, grade 3[c]	0.6
Redness, any	36.6
Redness, ≥50 mm	20.0
Redness, ≥110 mm	4.1
Arm circumference increase, any	38.1
Arm circumference increase, >20 mm	7.4
Arm circumference increase, >30 mm	3.2
Swelling, any	27.0
Swelling, ≥50 mm	11.5
Swelling, ≥110 mm	1.8
General	**N = 993-1,036**
Drowsiness, any	17.5
Drowsiness, grade 3[d]	0.8
Fever, ≥99.5°F	14.8
Fever, >100.4°F	4.4
Fever, >102.2°F	1.1
Fever, >104°F	0.0
Loss of appetite, any	16.0
Loss of appetite, grade 3[e]	0.6

IPV manufactured by Sanofi Pasteur SA. MMR vaccine manufactured by Merck & Co., Inc.
Total Vaccinated Cohort = all vaccinated subjects for whom safety data were available.
N = number of children with evaluable data for the events listed.

[a] Within 4 days of vaccination defined as day of vaccination and the next 3 days.
[b] Local reactions at the injection site for INFANRIX.
[c] Grade 2 defined as painful when the limb was moved; Grade 3 defined as preventing normal daily activities.
[d] Grade 3 defined as preventing normal daily activities.
[e] Grade 3 defined as not eating at all.

In the US booster immunization studies in which INFANRIX was administered as the fourth or fifth dose in the DTaP series following previous doses with INFANRIX or PEDIARIX, large swelling reactions of the limb injected with INFANRIX were assessed.

In the fourth dose study, a large swelling reaction was defined as injection site swelling with a diameter of >50 mm, a >50 mm increase in the mid-thigh circumference compared to the pre-vaccination measurement, and/or any diffuse swelling that interfered with or prevented daily

activities. The overall incidence of large swelling reactions occurring within 4 days (Day 0-Day 3) following INFANRIX was 2.3%.

In the fifth dose study, a large swelling reaction was defined as swelling that involved >50% of the injected upper arm length and that was associated with a >30 mm increase in mid-upper arm circumference within 4 days following vaccination. The incidence of large swelling reactions following the fifth consecutive dose of INFANRIX was 1.0%.

Less Common and Serious General Adverse Events: Selected adverse events reported from a double-blind, randomized Italian clinical efficacy trial involving 4,696 children administered INFANRIX or 4,678 children administered whole-cell DTP vaccine (DTwP) (manufactured by Connaught Laboratories, Inc.) as a 3-dose primary series are shown in Table 4. The incidence of rectal temperature ≥104°F, hypotonic-hyporesponsive episodes and persistent crying ≥3 hours following administration of INFANRIX was significantly less than that following administration of whole-cell DTP vaccine.

Table 4. Selected Adverse Events Occurring Within 48 Hours Following Vaccination With INFANRIX or Whole-Cell DTP in Italian Infants at 2, 4, or 6 Months of Age

	INFANRIX (N = 13,761 Doses)		Whole-Cell DTP Vaccine (N = 13,520 Doses)	
Event	**Number**	**Rate/1,000 Doses**	**Number**	**Rate/1,000 Doses**
Fever (≥104°F)[ab]	5	0.36	32	2.4
Hypotonic-hyporesponsive episode[c]	0	0	9	0.67
Persistent crying ≥3 hours[a]	6	0.44	54	4.0
Seizures[d]	1[e]	0.07	3[f]	0.22

[a] P <0.001.

[b] Rectal temperatures.

[c] P = 0.002.

[d] Not statistically significant at P <0.05.

[e] Maximum rectal temperature within 72 hours of vaccination = 103.1°F.

[f] Maximum rectal temperature within 72 hours of vaccination = 99.5°F, 101.3°F, and 102.2°F.

In a German safety study that enrolled 22,505 infants (66,867 doses of INFANRIX administered as a 3-dose primary series at 3, 4, and 5 months of age), all subjects were monitored for unsolicited adverse events that occurred within 28 days following vaccination using report cards. In a subset of subjects (N = 2,457), these cards were standardized diaries which solicited specific adverse events that occurred within 8 days of each vaccination in addition to unsolicited adverse events which occurred from enrollment until approximately 30 days following the third vaccination. Cards from the whole cohort were returned at subsequent visits and were supplemented by spontaneous reporting by parents and a medical history after the first and second doses of vaccine. In the subset of 2,457, adverse events following the third dose of

vaccine were reported via standardized diaries and spontaneous reporting at a follow-up visit. Adverse events in the remainder of the cohort were reported via report cards which were returned by mail approximately 28 days after the third dose of vaccine. Adverse events (rates per 1,000 doses) occurring within 7 days following any of the first 3 doses included: unusual crying (0.09), febrile seizure (0.0), afebrile seizure (0.13), and hypotonic-hyporesponsive episodes (0.01).

6.2 Postmarketing Experience

In addition to reports in clinical trials, worldwide voluntary reports of adverse events received for INFANRIX since market introduction are listed below. This list includes serious events and events which have a probable causal connection to components of INFANRIX. These adverse events were reported voluntarily from a population of uncertain size; therefore, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccination.

Body as a Whole: Sudden Infant Death Syndrome.

Cardiovascular System: Cyanosis.

Hematologic/Lymphatic: Lymphadenopathy, thrombocytopenia.

Hypersensitivity: Anaphylactic reaction, hypersensitivity.

Infections: Cellulitis.

Injection Site Reactions: Injection site reaction.

Nervous System: Encephalopathy, hypotonia

Respiratory System: Respiratory tract infection.

Skin and Appendages: Erythema, pruritus, rash, urticaria.

Special Senses: Ear pain.

7 DRUG INTERACTIONS

7.1 Concomitant Vaccine Administration

In clinical trials, INFANRIX was given concomitantly with Hib conjugate vaccine, pneumococcal 7-valent conjugate vaccine, hepatitis B vaccine, IPV, and the second dose of MMR vaccine *[see Adverse Reactions (6.1) and Clinical Studies (14.3)]*.

When INFANRIX is administered concomitantly with other injectable vaccines, they should be given with separate syringes. INFANRIX 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 INFANRIX.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with INFANRIX. It is also not

known whether INFANRIX can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

8.4 Pediatric Use

Safety and effectiveness of INFANRIX in infants younger than 6 weeks of age and children 7 to 16 years of age have not been established. INFANRIX is not approved for use in these age groups.

11 DESCRIPTION

INFANRIX (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) 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), and 8 mcg of pertactin (69 kiloDalton outer membrane protein).

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.

Diphtheria and tetanus toxoids and pertussis antigens (PT, FHA, and pertactin) are individually adsorbed onto aluminum hydroxide.

Diphtheria and tetanus toxoid potency is determined by measuring the amount of neutralizing antitoxin in previously immunized guinea pigs. The potency of the acellular pertussis components (PT, FHA, and pertactin) is determined by enzyme-linked immunosorbent assay (ELISA) on sera from previously immunized mice.

Each 0.5-mL dose contains 4.5 mg of NaCl and aluminum adjuvant (not more than 0.625 mg aluminum by assay). Each dose also contains ≤100 mcg of residual formaldehyde and ≤100 mcg of polysorbate 80 (Tween 80).

The tip cap and the rubber plunger of the needleless prefilled syringes contain dry natural latex rubber. The vial stopper does not contain latex.

INFANRIX 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 infectious 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 well established serological correlate of protection for pertussis.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

14.1 Diphtheria and Tetanus

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

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

14.2 Pertussis

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 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. The mean length of follow-up was 17 months, beginning 30 days after the third dose of vaccine. 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 respect to type and duration of cough, with infection confirmed by culture and/or serologic testing, the efficacy of INFANRIX was calculated to be 71% (95% CI: 60, 78) against >7 days of any cough and 73% (95% CI: 63, 80) against ≥14 days of any cough. Vaccine efficacy after 3 doses and with no booster dose in the second year of life was assessed in 2 subsequent follow-up periods. A follow-up period from 24 months to a mean age of 33 months was conducted in a partially unblinded cohort (children who received DT were offered pertussis vaccine and those who declined were retained in the study cohort). During this period, the efficacy of INFANRIX against WHO-defined pertussis was 78% (95% CI: 62, 87). During the third follow-up period which was conducted in an unblinded manner among children from 3 to 6 years of age, the efficacy of INFANRIX against WHO-defined pertussis was 86% (95% CI: 79, 91). Thus, protection against pertussis in children administered 3 doses of INFANRIX in infancy was sustained to 6 years of age.

A prospective efficacy trial was also conducted in Germany employing a household contact study design. In preparation for this study, 3 doses of INFANRIX were administered at 3, 4, and 5 months of age to more than 22,000 children living in 6 areas of Germany in a safety and immunogenicity study. Infants who did not participate in the safety and immunogenicity study could have received a DTwP vaccine or DT vaccine. Index cases were identified by spontaneous presentation to a physician. Households with at least one other member (i.e., besides index case) aged 6 through 47 months were enrolled. Household contacts of index cases were monitored for incidence of pertussis by a physician who was blinded to the vaccination status of the household. Calculation of vaccine efficacy was based on attack rates of pertussis in household contacts classified by vaccination status. Of the 173 household contacts who had not received a pertussis vaccine, 96 developed WHO-defined pertussis, as compared with 7 of 112 contacts vaccinated with INFANRIX. The protective efficacy of INFANRIX was calculated to be 89% (95% CI: 77, 95), with no indication of waning of protection up until the time of the booster vaccination. The average age of infants vaccinated with INFANRIX at the end of follow-up in this trial was 13 months (range 6 to 25 months). When the definition of pertussis was expanded to include clinically milder disease, with infection confirmed by culture and/or serologic testing, the efficacy of INFANRIX against ≥7 days of any cough was 67% (95% CI: 52, 78) and against ≥7 days of paroxysmal cough was 81% (95% CI: 68, 89). The corresponding efficacy of INFANRIX against ≥14 days of any cough or paroxysmal cough were 73% (95% CI: 59, 82) and 84% (95% CI: 71, 91), respectively.

Pertussis Immune Response to INFANRIX Administered as a 3-Dose Primary Series: The immune responses to each of the 3 pertussis antigens contained in INFANRIX were evaluated in sera obtained 1 month after the third dose of vaccine in each of 3 studies (schedule of administration: 2, 4, and 6 months of age in the Italian efficacy study and one US study; 3, 4, and 5 months of age in the German efficacy study). One month after the third dose of INFANRIX, the response rates to each pertussis antigen were similar in all 3 studies. Thus, although a serologic correlate of protection for pertussis has not been established, the antibody responses to these 3 pertussis antigens (PT, FHA, and pertactin) in a US population were similar

to those achieved in 2 populations in which efficacy of INFANRIX was demonstrated.

14.3 Immune Response to Concomitantly Administered Vaccines

In a US study, INFANRIX was given concomitantly, at separate sites, with Hib conjugate vaccine (Sanofi Pasteur SA) at 2, 4, and 6 months of age. Subjects also received ENGERIX-B and oral poliovirus vaccine (OPV). One month after the third dose of Hib conjugate vaccine, 90% of 72 infants had anti-PRP (polyribosyl-ribitol-phosphate) ≥1.0 mcg/mL.

In a US study, INFANRIX was given concomitantly, at separate sites, with ENGERIX-B, IPV (Sanofi Pasteur SA), pneumococcal 7-valent conjugate (PVC7) and Hib conjugate vaccines (Wyeth Pharmaceuticals Inc) at 2, 4, and 6 months of age. Immune responses were measured in sera obtained approximately one month after the third dose of vaccines. Among 121 subjects who had not received a birth dose of hepatitis B vaccine, 99.2% had anti-HBsAg (hepatitis B surface antigen) ≥10 mIU/mL following the third dose of ENGERIX-B. Among 153 subjects, 100% had anti-poliovirus 1, 2, and 3, ≥1:8 following the third dose of IPV. Although serological correlates for protection have not been established for the pneumococcal serotypes, a threshold level of ≥0.3 mcg/mL was evaluated. Following the third dose of PVC7 vaccine, 91.8% to 99.4% of subjects (N = 146-156) had anti-pneumococcal polysaccharide ≥0.3 mcg/mL for serotypes 4, 9V, 14, 18C, 19F, and 23F, and 73.0% had a level ≥0.3 mcg/mL for serotype 6B.

15 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

INFANRIX is available in 0.5-mL single-dose vials and disposable prefilled TIP-LOK syringes.

Single-Dose Vials and Prefilled Syringes

NDC 58160-810-11 Package of 10 Single-Dose Vials

NDC 58160-810-46 Package of 5 Single-Dose Prefilled Disposable TIP-LOK Syringes (packaged without needles)

Store refrigerated between 2° and 8°C (36° and 46°F). 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 INFANRIX, and of the importance of completing the immunization series.
- informed about the potential for adverse reactions that have been temporally associated with administration of INFANRIX or other vaccines containing similar components.
- instructed to report any adverse events to their healthcare provider where the vaccine was administered.
- 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/vaccines).

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