

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

Single-dose vials and 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-, 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 tip caps of the prefilled syringes contain natural rubber latex which may cause allergic reactions. (5.2)

- Syncope (fainting) can occur in association with administration of injectable vaccines, including INFANRIX. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope. (5.3)
- If temperature $\geq 105^{\circ}\text{F}$, 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. (5.4)
- For children at higher risk for seizures, an antipyretic may be administered at the time of vaccination with INFANRIX. (5.5)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including INFANRIX, 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. (5.6)

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: /xxxx

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

1 FULL PRESCRIBING INFORMATION

2 1 INDICATIONS AND USAGE

3 INFANRIX[®] is indicated for active immunization against diphtheria, tetanus, and pertussis as a
4 5-dose series in infants and children 6 weeks to 7 years of age (prior to seventh birthday).

5 2 DOSAGE AND ADMINISTRATION

6 2.1 Preparation for Administration

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

11 For the prefilled syringes, attach a sterile needle and administer intramuscularly.

12 For the vials, use a sterile needle and sterile syringe to withdraw the 0.5-mL dose and administer
13 intramuscularly. Changing needles between drawing vaccine from a vial and injecting it into a
14 recipient is not necessary unless the needle has been damaged or contaminated. Use a separate
15 sterile needle and syringe for each individual.

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

17 2.2 Dose and Schedule

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

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

26 2.3 Use of INFANRIX with Other DTaP Vaccines

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

33 **2.4 Additional Dosing Information**

34 If any recommended dose of pertussis vaccine cannot be given [*see Contraindications (4.2, 4.3),*
35 *Warnings and Precautions (5.5)*], Diphtheria and Tetanus Toxoids Adsorbed (DT) For Pediatric
36 Use should be given according to its prescribing information.

37 **3 DOSAGE FORMS AND STRENGTHS**

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

40 **4 CONTRAINDICATIONS**

41 **4.1 Hypersensitivity**

42 Severe allergic reaction (e.g., anaphylaxis) after a previous dose of any diphtheria toxoid-,
43 tetanus toxoid-, or pertussis-containing vaccine, or to any component of INFANRIX is a
44 contraindication [*see Description (11)*]. Because of the uncertainty as to which component of the
45 vaccine might be responsible, no further vaccination with any of these components should be
46 given. Alternatively, such individuals may be referred to an allergist for evaluation if
47 immunization with any of these components is being considered.

48 **4.2 Encephalopathy**

49 Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within 7 days
50 of administration of a previous dose of a pertussis-containing vaccine that is not attributable to
51 another identifiable cause is a contraindication to administration of any pertussis-containing
52 vaccine, including INFANRIX.

53 **4.3 Progressive Neurologic Disorder**

54 Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or
55 progressive encephalopathy is a contraindication to administration of any pertussis-containing
56 vaccine, including INFANRIX. Pertussis vaccine should not be administered to individuals with
57 these conditions until a treatment regimen has been established and the condition has stabilized.

58 **5 WARNINGS AND PRECAUTIONS**

59 **5.1 Guillain-Barré Syndrome**

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

64 **5.2 Latex**

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

66 reactions.

67 **5.3 Syncope**

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

72 **5.4 Adverse Events following Prior Pertussis Vaccination**

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

- 76 • Temperature of $\geq 40.5^{\circ}\text{C}$ (105°F) within 48 hours not due to another identifiable cause;
- 77 • Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours;
- 78 • Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours;
- 79 • Seizures with or without fever occurring within 3 days.

80 **5.5 Children at Risk for Seizures**

81 For children at higher risk for seizures than the general population, an appropriate antipyretic
82 may be administered at the time of vaccination with a pertussis-containing vaccine, including
83 INFANRIX, and for the ensuing 24 hours to reduce the possibility of post-vaccination fever.

84 **5.6 Apnea in Premature Infants**

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

89 **5.7 Preventing and Managing Allergic Vaccine Reactions**

90 Prior to administration, the healthcare provider should review the patient's immunization history
91 for possible vaccine hypersensitivity. Epinephrine and other appropriate agents used for the
92 control of immediate allergic reactions must be immediately available should an acute
93 anaphylactic reaction occur.

94 **6 ADVERSE REACTIONS**

95 **6.1 Clinical Trials Experience**

96 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
97 observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical
98 trials of another vaccine and may not reflect the rates observed in practice. There is the
99 possibility that broad use of INFANRIX could reveal adverse reactions not observed in clinical

100 trials.

101 Approximately 95,000 doses of INFANRIX have been administered in clinical studies. In these
102 studies, 29,243 infants have received INFANRIX in primary series studies, 6,081 children have
103 received a fourth consecutive dose of INFANRIX, 1,764 children have received a fifth
104 consecutive dose of INFANRIX, and 559 children have received a dose of INFANRIX following
105 3 doses of PEDIARIX.

106 Solicited Adverse Events

107 In a US study, 335 infants received INFANRIX, ENGERIX-B[®] [Hepatitis B Vaccine
108 (Recombinant)], inactivated poliovirus vaccine (IPV, Sanofi Pasteur SA), Haemophilus b (Hib)
109 conjugate vaccine (Wyeth Pharmaceuticals Inc.), and pneumococcal 7-valent conjugate (PCV7)
110 vaccine (Wyeth Pharmaceuticals Inc.) concomitantly at separate sites. All vaccines were
111 administered at 2, 4, and 6 months of age. Data on solicited local reactions and general adverse
112 events were collected by parents using standardized diary cards for 4 consecutive days following
113 each vaccine dose (i.e., day of vaccination and the next 3 days) (Table 1). Among subjects, 69%
114 were white, 16% were Hispanic, 8% were black, 4% were Asian, and 2% were of other
115 racial/ethnic groups.

116 **Table 1. Solicited Local Reactions and General Adverse Events (%) Occurring within**
 117 **4 Days of Vaccination^a with Separate Concomitant Administration of INFANRIX,**
 118 **ENGERIX-B, IPV, Haemophilus b (Hib) Conjugate Vaccine, and Pneumococcal Conjugate**
 119 **Vaccine (PCV7) (Modified Intent-to-Treat 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

120 Hib conjugate vaccine and PCV7 manufactured by Wyeth Pharmaceuticals Inc. IPV

121 manufactured by Sanofi Pasteur SA.

122 Modified intent-to-treat cohort = All vaccinated subjects for whom safety data were available.

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

125 Grade 2: Pain defined as cried/protected on touch; drowsiness defined as interfered with normal
 126 daily activities; irritability/fussiness defined as crying more than usual/interfered with normal
 127 daily activities; loss of appetite defined as eating less than usual/interfered with normal daily
 128 activities.

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

132 ^a Within 4 days of vaccination defined as day of vaccination and the next 3 days.

133 ^b Local reactions at the injection site for INFANRIX.

134 ^c Axillary temperatures increased by 1°C and oral temperatures increased by 0.5°C to derive
135 equivalent rectal temperature.

136 In a US study, the safety of a booster dose of INFANRIX was evaluated in children 15 to 18
137 months of age whose previous 3 DTaP doses were with INFANRIX (N = 251) or PEDIARIX
138 (N = 559). Vaccines administered concurrently with the fourth dose of INFANRIX included
139 measles, mumps, and rubella (MMR) vaccine (Merck & Co., Inc.), varicella vaccine (Merck &
140 Co., Inc.), pneumococcal 7-valent conjugate (PCV7) vaccine (Wyeth Pharmaceuticals Inc.), and
141 any US-licensed Hib conjugate vaccine; these were given concomitantly in 13.2%, 6.3%, 37.4%,
142 and 41.2% of subjects, respectively. Data on solicited adverse events were collected by parents
143 using standardized diary cards for 4 consecutive days following each vaccine dose (i.e., day of
144 vaccination and the next 3 days) (Table 2). Among subjects, 85% were white, 6% were Hispanic,
145 6% were black, 1% were Asian, and 2% were of other racial/ethnic groups.

146 **Table 2. Solicited Local Reactions and General Adverse Events (%) Occurring within**
 147 **4 Days of Vaccination^a with INFANRIX Administered as the Fourth Dose following 3**
 148 **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

149 Total Vaccinated Cohort = All subjects who received a dose of study vaccine.

150 N = Number of subjects for whom at least one symptom sheet was completed.

151 Grade 2: Pain defined as cried/protected on touch; drowsiness defined as interfered with normal
 152 daily activities; irritability defined as crying more than usual/interfered with normal daily
 153 activities; loss of appetite defined as eating less than usual/no effect on normal daily activities.

154 Grade 3: Pain defined as cried when limb was moved/spontaneously painful; drowsiness defined
 155 as prevented normal daily activities; irritability defined as crying that could not be
 156 comforted/prevented normal daily activities; loss of appetite defined as eating less than
 157 usual/interfered with normal daily activities.

158 ^a Within 4 days of vaccination defined as day of vaccination and the next 3 days.

159 ^b Received INFANRIX, ENGERIX-B, IPV (Sanofi Pasteur SA), PCV7 vaccine (Wyeth

160 Pharmaceuticals Inc.), and Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.) at 2, 4, and 6
161 months of age.

162 ^c Received PEDIARIX, PCV7 vaccine (Wyeth Pharmaceuticals Inc.), and Hib conjugate
163 vaccine (Wyeth Pharmaceuticals Inc.) at 2, 4, and 6 months of age or PCV7 vaccine 2 weeks
164 later.

165 ^d Local reactions at the injection site for INFANRIX.

166 ^e Axillary temperatures.

167 In a US study, the safety of a fifth consecutive dose of INFANRIX coadministered at separate
168 sites with a fourth dose of IPV (Sanofi Pasteur SA) and a second dose of MMR vaccine (Merck
169 & Co., Inc.) was evaluated in 1,053 children 4 to 6 years of age. Data on solicited adverse events
170 were collected by parents using standardized diary cards for 4 consecutive days following each
171 vaccine dose (i.e., day of vaccination and the next 3 days) (Table 3). Among subjects, 43% were
172 white, 18% Hispanic, 15% Asian, 7% black, and 17% were of other racial/ethnic groups.

173 **Table 3. Solicited Local Reactions and General Adverse Events (%) Occurring within**
 174 **4 Days of Vaccination^a with a Fifth Consecutive Dose of INFANRIX When Coadministered**
 175 **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	37.8
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

176 IPV manufactured by Sanofi Pasteur SA. MMR vaccine manufactured by Merck & Co., Inc.

177 Total Vaccinated Cohort = All vaccinated subjects for whom safety data were available.

178 N = Number of children with evaluable data for the events listed.

179 ^a Within 4 days of vaccination defined as day of vaccination and the next 3 days.

180 ^b Local reactions at the injection site for INFANRIX.

181 ^c Grade 2 defined as painful when the limb was moved; Grade 3 defined as preventing normal
 182 daily activities.

183 ^d Grade 3 defined as preventing normal daily activities.

184 ^e Grade 3 defined as not eating at all.

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

188 In the fourth-dose study, a large swelling reaction was defined as injection site swelling with a
 189 diameter of >50 mm, a >50 mm increase in the mid-thigh circumference compared with the pre-

190 vaccination measurement, and/or any diffuse swelling that interfered with or prevented daily
 191 activities. The overall incidence of large swelling reactions occurring within 4 days (Day 0-
 192 Day 3) following INFANRIX was 2.3%.

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

197 **Less Common and Serious General Adverse Events**

198 Selected adverse events reported from a double-blind, randomized Italian clinical efficacy trial
 199 involving 4,696 children administered INFANRIX or 4,678 children administered whole-cell
 200 DTP vaccine (DTwP) (manufactured by Connaught Laboratories, Inc.) as a 3-dose primary series
 201 are shown in Table 4. The incidence of rectal temperature $\geq 104^\circ\text{F}$, hypotonic-hyporesponsive
 202 episodes, and persistent crying ≥ 3 hours following administration of INFANRIX was
 203 significantly less than that following administration of whole-cell DTP vaccine.

204 **Table 4. Selected Adverse Events Occurring within 48 Hours following Vaccination with**
 205 **INFANRIX or Whole-Cell DTP in Italian Infants at 2, 4, or 6 Months of Age**

Event	INFANRIX (N = 13,761 Doses)		Whole-Cell DTP Vaccine (N = 13,520 Doses)	
	Number	Rate/1,000 Doses	Number	Rate/1,000 Doses
Fever ($\geq 104^\circ\text{F}$) ^{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

206 ^a $P < 0.001$.

207 ^b Rectal temperatures.

208 ^c $P = 0.002$.

209 ^d Not statistically significant at $P < 0.05$.

210 ^e Maximum rectal temperature within 72 hours of vaccination = 103.1°F .

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

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

219 supplemented by spontaneous reporting by parents and a medical history after the first and
220 second doses of vaccine. In the subset of 2,457, adverse events following the third dose of
221 vaccine were reported via standardized diaries and spontaneous reporting at a follow-up visit.
222 Adverse events in the remainder of the cohort were reported via report cards which were
223 returned by mail approximately 28 days after the third dose of vaccine. Adverse events (rates per
224 1,000 doses) occurring within 7 days following any of the first 3 doses included: unusual crying
225 (0.09), febrile seizure (0.0), afebrile seizure (0.13), and hypotonic-hyporesponsive episodes
226 (0.01).

227 **6.2 Postmarketing Experience**

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

233 Infections and Infestations

234 Bronchitis, cellulitis, respiratory tract infection.

235 Blood and Lymphatic System Disorders

236 Lymphadenopathy, thrombocytopenia.

237 Immune System Disorders

238 Anaphylactic reaction, hypersensitivity.

239 Nervous System Disorders

240 Encephalopathy, headache, hypotonia, syncope.

241 Ear and Labyrinth Disorders

242 Ear pain.

243 Cardiac Disorders

244 Cyanosis.

245 Respiratory, Thoracic, and Mediastinal Disorders

246 Apnea, cough.

247 Skin and Subcutaneous Tissue Disorders

248 Angioedema, erythema, pruritus, rash, urticaria.

249 General Disorders and Administration Site Conditions

250 Fatigue, injection site induration, injection site reaction, Sudden Infant Death Syndrome.

251 **7 DRUG INTERACTIONS**

252 **7.1 Concomitant Vaccine Administration**

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

256 When INFANRIX is administered concomitantly with other injectable vaccines, they should be
257 given with separate syringes. INFANRIX should not be mixed with any other vaccine in the
258 same syringe or vial.

259 **7.2 Immunosuppressive Therapies**

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

263 **8 USE IN SPECIFIC POPULATIONS**

264 **8.1 Pregnancy**

265 Pregnancy Category C

266 Animal reproduction studies have not been conducted with INFANRIX. It is also not known
267 whether INFANRIX can cause fetal harm when administered to a pregnant woman or can affect
268 reproduction capacity.

269 **8.4 Pediatric Use**

270 Safety and effectiveness of INFANRIX in infants younger than 6 weeks of age and children 7 to
271 16 years of age have not been established. INFANRIX is not approved for use in these age
272 groups.

273 **11 DESCRIPTION**

274 INFANRIX (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) is a
275 noninfectious, sterile vaccine for intramuscular administration. Each 0.5-mL dose is formulated
276 to contain 25 Lf of diphtheria toxoid, 10 Lf of tetanus toxoid, 25 mcg of inactivated pertussis
277 toxin (PT), 25 mcg of filamentous hemagglutinin (FHA), and 8 mcg of pertactin (69 kiloDalton
278 outer membrane protein).

279 The diphtheria toxin is produced by growing *Corynebacterium diphtheriae* in Fenton medium
280 containing a bovine extract. Tetanus toxin is produced by growing *Clostridium tetani* in a
281 modified Latham medium derived from bovine casein. The bovine materials used in these
282 extracts are sourced from countries which the United States Department of Agriculture (USDA)
283 has determined neither have nor present an undue risk for bovine spongiform encephalopathy
284 (BSE). Both toxins are detoxified with formaldehyde, concentrated by ultrafiltration, and

285 purified by precipitation, dialysis, and sterile filtration.

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

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

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

297 Each 0.5-mL dose contains aluminum hydroxide as adjuvant (not more than 0.625 mg aluminum
298 by assay) and 4.5 mg of sodium chloride. Each dose also contains ≤ 100 mcg of residual
299 formaldehyde and ≤ 100 mcg of polysorbate 80 (Tween 80).

300 INFANRIX is available in vials and prefilled syringes. The tip caps of the prefilled syringes
301 contain natural rubber latex; the plungers are not made with natural rubber latex. The vial
302 stoppers are not made with natural rubber latex.

303 INFANRIX is formulated without preservatives.

304 **12 CLINICAL PHARMACOLOGY**

305 **12.1 Mechanism of Action**

306 Diphtheria

307 Diphtheria is an acute toxin-mediated infectious disease caused by toxigenic strains of
308 *C. diphtheriae*. Protection against disease is due to the development of neutralizing antibodies to
309 the diphtheria toxin. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving
310 some degree of protection; a level of 0.1 IU/mL is regarded as protective.¹

311 Tetanus

312 Tetanus is an acute toxin-mediated infectious disease caused by a potent exotoxin released by *C.*
313 *tetani*. Protection against disease is due to the development of neutralizing antibodies to the
314 tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization
315 assays, is considered the minimum protective level.^{2,3} A level of 0.1 IU/mL is considered
316 protective.⁴

317 Pertussis

318 Pertussis (whooping cough) is a disease of the respiratory tract caused by *B. pertussis*. The role

319 of the different components produced by *B. pertussis* in either the pathogenesis of, or the
320 immunity to, pertussis is not well understood. There is no well established serological correlate
321 of protection for pertussis.

322 **13 NONCLINICAL TOXICOLOGY**

323 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

326 **14 CLINICAL STUDIES**

327 **14.1 Diphtheria and Tetanus**

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

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

336 **14.2 Pertussis**

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

338 A double-blind, randomized, active Diphtheria and Tetanus Toxoids (DT)-controlled trial
339 conducted in Italy assessed the absolute protective efficacy of INFANRIX when administered at
340 2, 4, and 6 months of age. The population used in the primary analysis of the efficacy of
341 INFANRIX included 4,481 infants vaccinated with INFANRIX and 1,470 DT vaccinees. The
342 mean length of follow-up was 17 months, beginning 30 days after the third dose of vaccine.
343 After 3 doses, the absolute protective efficacy of INFANRIX against WHO-defined typical
344 pertussis (21 days or more of paroxysmal cough with infection confirmed by culture and/or
345 serologic testing) was 84% (95% CI: 76, 89). When the definition of pertussis was expanded to
346 include clinically milder disease with respect to type and duration of cough, with infection
347 confirmed by culture and/or serologic testing, the efficacy of INFANRIX was calculated to be
348 71% (95% CI: 60, 78) against >7 days of any cough and 73% (95% CI: 63, 80) against ≥ 14 days
349 of any cough. Vaccine efficacy after 3 doses and with no booster dose in the second year of life
350 was assessed in 2 subsequent follow-up periods. A follow-up period from 24 months to a mean
351 age of 33 months was conducted in a partially unblinded cohort (children who received DT were
352 offered pertussis vaccine and those who declined were retained in the study cohort). During this
353 period, the efficacy of INFANRIX against WHO-defined pertussis was 78% (95% CI: 62, 87).
354 During the third follow-up period which was conducted in an unblinded manner among children

355 from 3 to 6 years of age, the efficacy of INFANRIX against WHO-defined pertussis was 86%
356 (95% CI: 79, 91). Thus, protection against pertussis in children administered 3 doses of
357 INFANRIX in infancy was sustained to 6 years of age.

358 A prospective efficacy trial was also conducted in Germany employing a household contact
359 study design. In preparation for this study, 3 doses of INFANRIX were administered at 3, 4, and
360 5 months of age to more than 22,000 children living in 6 areas of Germany in a safety and
361 immunogenicity study. Infants who did not participate in the safety and immunogenicity study
362 could have received a DTwP vaccine or DT vaccine. Index cases were identified by spontaneous
363 presentation to a physician. Households with at least one other member (i.e., besides index case)
364 aged 6 through 47 months were enrolled. Household contacts of index cases were monitored for
365 incidence of pertussis by a physician who was blinded to the vaccination status of the household.
366 Calculation of vaccine efficacy was based on attack rates of pertussis in household contacts
367 classified by vaccination status. Of the 173 household contacts who had not received a pertussis
368 vaccine, 96 developed WHO-defined pertussis, as compared with 7 of 112 contacts vaccinated
369 with INFANRIX. The protective efficacy of INFANRIX was calculated to be 89% (95% CI: 77,
370 95), with no indication of waning of protection up until the time of the booster vaccination. The
371 average age of infants vaccinated with INFANRIX at the end of follow-up in this trial was
372 13 months (range: 6 to 25 months). When the definition of pertussis was expanded to include
373 clinically milder disease, with infection confirmed by culture and/or serologic testing, the
374 efficacy of INFANRIX against ≥ 7 days of any cough was 67% (95% CI: 52, 78) and against
375 ≥ 7 days of paroxysmal cough was 81% (95% CI: 68, 89). The corresponding efficacy of
376 INFANRIX against ≥ 14 days of any cough or paroxysmal cough were 73% (95% CI: 59, 82) and
377 84% (95% CI: 71, 91), respectively.

378 Pertussis Immune Response to INFANRIX Administered as a 3-Dose Primary Series

379 The immune responses to each of the 3 pertussis antigens contained in INFANRIX were
380 evaluated in sera obtained 1 month after the third dose of vaccine in each of 3 studies (schedule
381 of administration: 2, 4, and 6 months of age in the Italian efficacy study and one US study; 3, 4,
382 and 5 months of age in the German efficacy study). One month after the third dose of
383 INFANRIX, the response rates to each pertussis antigen were similar in all 3 studies. Thus,
384 although a serologic correlate of protection for pertussis has not been established, the antibody
385 responses to these 3 pertussis antigens (PT, FHA, and pertactin) in a US population were similar
386 to those achieved in 2 populations in which efficacy of INFANRIX was demonstrated.

387 **14.3 Immune Response to Concomitantly Administered Vaccines**

388 In a US study, INFANRIX was given concomitantly, at separate sites, with Hib conjugate
389 vaccine (Sanofi Pasteur SA) at 2, 4, and 6 months of age. Subjects also received ENGERIX-B
390 and oral poliovirus vaccine (OPV). One month after the third dose of Hib conjugate vaccine,
391 90% of 72 infants had anti-PRP (polyribosyl-ribitol-phosphate) ≥ 1.0 mcg/mL.

392 In a US study, INFANRIX was given concomitantly, at separate sites, with ENGERIX-B, IPV

393 (Sanofi Pasteur SA), pneumococcal 7-valent conjugate (PCV7), and Hib conjugate vaccines
394 (Wyeth Pharmaceuticals Inc.) at 2, 4, and 6 months of age. Immune responses were measured in
395 sera obtained approximately one month after the third dose of vaccines. Among 121 subjects
396 who had not received a birth dose of hepatitis B vaccine, 99.2% had anti-HBsAg (hepatitis B
397 surface antigen) ≥ 10 mIU/mL following the third dose of ENGERIX-B. Among 153 subjects,
398 100% had anti-poliovirus 1, 2, and 3, $\geq 1:8$ following the third dose of IPV. Although serological
399 correlates for protection have not been established for the pneumococcal serotypes, a threshold
400 level of ≥ 0.3 mcg/mL was evaluated. Following the third dose of PCV7 vaccine, 91.8% to 99.4%
401 of subjects (N = 146-156) had anti-pneumococcal polysaccharide ≥ 0.3 mcg/mL for serotypes 4,
402 9V, 14, 18C, 19F, and 23F, and 73.0% had a level ≥ 0.3 mcg/mL for serotype 6B.

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414 **16 HOW SUPPLIED/STORAGE AND HANDLING**

415 INFANRIX is available in 0.5-mL single-dose vials and disposable prefilled TIP-LOK syringes
416 (packaged without needles):

417 NDC 58160-810-01 Vial in Package of 10: NDC 58160-810-11

418 NDC 58160-810-43 Syringe in Package of 10: NDC 58160-810-52

419 Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has
420 been frozen.

421 **17 PATIENT COUNSELING INFORMATION**

422 The parent or guardian should be:

- 423 • informed of the potential benefits and risks of immunization with INFANRIX, and of the
424 importance of completing the immunization series.
- 425 • informed about the potential for adverse reactions that have been temporally associated with
426 administration of INFANRIX or other vaccines containing similar components.

- 427 • instructed to report any adverse events to their healthcare provider.
428 • given the Vaccine Information Statements, which are required by the National Childhood
429 Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available
430 free of charge at the Centers for Disease Control and Prevention (CDC) website
431 (www.cdc.gov/vaccines).

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433 group of companies.



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