

## 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

#### RECENT MAJOR CHANGES

Warnings and Precautions, Latex (5.2) X/XXXX  
Warnings and Precautions, Apnea in Premature Infants (5.5) 02/2010

#### 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)
- INFANRIX is available in vials and 2 types of prefilled syringes. One

type of prefilled syringe has a tip cap which may contain natural rubber latex. The other type has a tip cap and a rubber plunger which contain dry natural latex rubber. Use of these syringes may cause allergic reactions in latex sensitive individuals. (5.2, 16)

- If temperature  $\geq 105^{\circ}\text{F}$ , collapse or shock-like state, or persistent, inconsolable crying lasting  $\geq 3$  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)
- 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. (5.5)

#### 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](http://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

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## 1 FULL PRESCRIBING INFORMATION

### 2 1 INDICATIONS AND USAGE

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

### 6 2 DOSAGE AND ADMINISTRATION

#### 7 2.1 Preparation for Administration

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

#### 12 2.2 Dose and Schedule

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

18 The preferred administration site is the anterolateral aspect of the thigh for most infants  
19 younger than 12 months of age and the deltoid muscle of the upper arm for most children  
20 12 months of age to 7 years of age.

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

#### 22 2.3 Use of INFANRIX With Other DTaP Vaccines

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

#### 30 2.4 Additional Dosing Information

31 If any recommended dose of pertussis vaccine cannot be given [*see Contraindications*  
32 (4.2, 4.3) and *Warnings and Precautions (5.4)*], Diphtheria and Tetanus Toxoids Adsorbed (DT)  
33 For Pediatric Use should be given according to its prescribing information.

### 34 3 DOSAGE FORMS AND STRENGTHS

35 INFANRIX is a suspension for injection available in 0.5-mL single-dose vials and  
36 prefilled TIP-LOK<sup>®</sup> syringes.

## 37 **4 CONTRAINDICATIONS**

### 38 **4.1 Hypersensitivity**

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

### 45 **4.2 Encephalopathy**

46 Encephalopathy (e.g., coma, decreased level of consciousness, prolonged seizures) within  
47 7 days of administration of a previous dose of a pertussis-containing vaccine that is not  
48 attributable to another identifiable cause is a contraindication to administration of any pertussis-  
49 containing vaccine, including INFANRIX.

### 50 **4.3 Progressive Neurologic Disorder**

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

## 55 **5 WARNINGS AND PRECAUTIONS**

### 56 **5.1 Guillain-Barré Syndrome**

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

### 62 **5.2 Latex**

63 INFANRIX is available in vials and 2 types of prefilled syringes. One type of prefilled  
64 syringe has a tip cap which may contain natural rubber latex and a plunger which does not  
65 contain latex. The other type has a tip cap and a rubber plunger which contain dry natural latex  
66 rubber. Use of these syringes may cause allergic reactions in latex sensitive individuals. The vial  
67 stopper does not contain latex. [See How Supplied/Storage and Handling (16).]

### 68 **5.3 Adverse Events Following Prior Pertussis Vaccination**

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

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

76 **5.4 Children at Risk for Seizures**

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

81 **5.5 Apnea in Premature Infants**

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

86 **5.6 Preventing and Managing Allergic Vaccine Reactions**

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

91 **6 ADVERSE REACTIONS**

92 **6.1 Clinical Trials Experience**

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

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

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

112  
113 **Table 1. Solicited Local Reactions and General Adverse Events (%) Occurring Within**  
114 **4 Days of Vaccination<sup>a</sup> With Separate Concomitant Administration of INFANRIX,**  
115 **ENGERIX-B, IPV, Haemophilus b (Hib) Conjugate Vaccine, and Pneumococcal Conjugate**

116 **Vaccine (PCV7) (Modified Intent To Treat Cohort)**

	<b>INFANRIX, ENGERIX-B, IPV, Hib Vaccine, &amp; PCV7</b>		
	<b>Dose 1</b>	<b>Dose 2</b>	<b>Dose 3</b>
<b>Local<sup>b</sup></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
<b>General</b>			
N	333	321	311
Fever <sup>c</sup> (≥100.4°F)	19.8	30.2	23.8
Fever <sup>c</sup> (>101.3°F)	4.5	9.7	5.8
Fever <sup>c</sup> (>102.2°F)	0.3	3.1	2.3
Fever <sup>c</sup> (>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

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

118 manufactured by Sanofi Pasteur SA.

119 Modified intent to treat cohort = all vaccinated subjects for whom safety data were available.

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

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

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

129 <sup>a</sup> Within 4 days of vaccination defined as day of vaccination and the next 3 days.

130 <sup>b</sup> Local reactions at the injection site for INFANRIX.

131 <sup>c</sup> Axillary temperatures increased by 1°C and oral temperatures increased by 0.5°C to derive  
132 equivalent rectal temperature.

133

134 In a US study, the safety of a booster dose of INFANRIX was evaluated in children 15 to  
135 18 months of age whose previous 3 DTaP doses were with INFANRIX (N = 251) or PEDIARIX  
136 (N = 559). Vaccines administered concurrently with the fourth dose of INFANRIX included  
137 measles, mumps, and rubella (MMR) vaccine (Merck & Co., Inc.), varicella vaccine (Merck &  
138 Co., Inc.), pneumococcal 7-valent conjugate (PCV7) vaccine (Wyeth Pharmaceuticals Inc.), and  
139 any US-licensed Hib conjugate vaccine; these were given concomitantly in 13.2%, 6.3%, 37.4%,  
140 and 41.2% of subjects, respectively. Data on solicited adverse events were collected by parents  
141 using standardized diary cards for 4 consecutive days following each vaccine dose (i.e., day of  
142 vaccination and the next 3 days) (Table 2). Among subjects, 85% were White, 6% were  
143 Hispanic, 6% were Black, 1% were Asian, and 2% were of other racial/ethnic groups.

144

145 **Table 2. Solicited Local Reactions and General Adverse Events (%) Occurring Within**  
 146 **4 Days of Vaccination<sup>a</sup> With INFANRIX Administered as the Fourth Dose Following 3**  
 147 **Previous Doses of INFANRIX or PEDIARIX (Total Vaccinated Cohort)**

	<b>Group Primed With INFANRIX<sup>b</sup> N = 247</b>	<b>Group Primed With PEDIARIX<sup>c</sup> N = 553</b>
<b>Local<sup>d</sup></b>		
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
<b>General</b>		
Fever <sup>e</sup> (>99.5°F)	8.9	15.4
Fever <sup>e</sup> (>100.4°F)	4.5	6.7
Fever <sup>e</sup> (>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

148 Total Vaccinated Cohort = all subjects who received a dose of study vaccine.

149 N = number of subjects for whom at least one symptom sheet was completed.

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

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

157 <sup>a</sup> Within 4 days of vaccination defined as day of vaccination and the next 3 days.

- 158 <sup>b</sup> Received INFANRIX, ENGERIX-B, IPV (Sanofi Pasteur SA), PCV7 vaccine (Wyeth  
159 Pharmaceuticals Inc.), and Hib conjugate vaccine (Wyeth Pharmaceuticals Inc.) at 2, 4, and 6  
160 months of age.
- 161 <sup>c</sup> Received PEDIARIX, PCV7 vaccine (Wyeth Pharmaceuticals Inc.), and Hib conjugate  
162 vaccine (Wyeth Pharmaceuticals Inc.) at 2, 4, and 6 months of age or PCV7 vaccine 2 weeks  
163 later.
- 164 <sup>d</sup> Local reactions at the injection site for INFANRIX.
- 165 <sup>e</sup> Axillary temperatures.

166

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

174

175 **Table 3. Solicited Local Reactions and General Adverse Events (%) Occurring Within**  
 176 **4 Days of Vaccination<sup>a</sup> With a Fifth Consecutive Dose of INFANRIX When**  
 177 **Coadministered With IPV and MMR Vaccine (Total Vaccinated Cohort)**

<b>Local<sup>b</sup></b>	<b>N = 1,039-1,043</b>
Pain, any	53.3
Pain, grade 2 or 3 <sup>c</sup>	12.0
Pain, grade 3 <sup>c</sup>	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
<b>General</b>	<b>N = 993-1,036</b>
Drowsiness, any	17.5
Drowsiness, grade 3 <sup>d</sup>	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 <sup>e</sup>	0.6

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

179 Total Vaccinated Cohort = all vaccinated subjects for whom safety data were available.

180 N = number of children with evaluable data for the events listed.

181 <sup>a</sup> Within 4 days of vaccination defined as day of vaccination and the next 3 days.

182 <sup>b</sup> Local reactions at the injection site for INFANRIX.

183 <sup>c</sup> Grade 2 defined as painful when the limb was moved; Grade 3 defined as preventing normal  
 184 daily activities.

185 <sup>d</sup> Grade 3 defined as preventing normal daily activities.

186 <sup>e</sup> Grade 3 defined as not eating at all.

187

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

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

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

196 In the fifth dose study, a large swelling reaction was defined as swelling that involved  
197 >50% of the injected upper arm length and that was associated with a >30 mm increase in mid-  
198 upper arm circumference within 4 days following vaccination. The incidence of large swelling  
199 reactions following the fifth consecutive dose of INFANRIX was 1.0%.

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

207  
208 **Table 4. Selected Adverse Events Occurring Within 48 Hours Following Vaccination With**  
209 **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 ( $\geq 104^\circ\text{F}$ ) <sup>ab</sup>	5	0.36	32	2.4
Hypotonic-hyporesponsive episode <sup>c</sup>	0	0	9	0.67
Persistent crying $\geq 3$ hours <sup>a</sup>	6	0.44	54	4.0
Seizures <sup>d</sup>	1 <sup>e</sup>	0.07	3 <sup>f</sup>	0.22

210 <sup>a</sup>  $P < 0.001$ .

211 <sup>b</sup> Rectal temperatures.

212 <sup>c</sup>  $P = 0.002$ .

213 <sup>d</sup> Not statistically significant at  $P < 0.05$ .

214 <sup>e</sup> Maximum rectal temperature within 72 hours of vaccination =  $103.1^\circ\text{F}$ .

215 <sup>f</sup> Maximum rectal temperature within 72 hours of vaccination =  $99.5^\circ\text{F}$ ,  $101.3^\circ\text{F}$ , and  $102.2^\circ\text{F}$ .

216  
217 In a German safety study that enrolled 22,505 infants (66,867 doses of INFANRIX  
218 administered as a 3-dose primary series at 3, 4, and 5 months of age), all subjects were monitored  
219 for unsolicited adverse events that occurred within 28 days following vaccination using report  
220 cards. In a subset of subjects (N = 2,457), these cards were standardized diaries which solicited  
221 specific adverse events that occurred within 8 days of each vaccination in addition to unsolicited  
222 adverse events which occurred from enrollment until approximately 30 days following the third  
223 vaccination. Cards from the whole cohort were returned at subsequent visits and were  
224 supplemented by spontaneous reporting by parents and a medical history after the first and  
225 second doses of vaccine. In the subset of 2,457, adverse events following the third dose of

226 vaccine were reported via standardized diaries and spontaneous reporting at a follow-up visit.  
227 Adverse events in the remainder of the cohort were reported via report cards which were  
228 returned by mail approximately 28 days after the third dose of vaccine. Adverse events (rates per  
229 1,000 doses) occurring within 7 days following any of the first 3 doses included: unusual crying  
230 (0.09), febrile seizure (0.0), afebrile seizure (0.13), and hypotonic-hyporesponsive episodes  
231 (0.01).

## 232 **6.2 Postmarketing Experience**

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

238 Infections and Infestations: Bronchitis, cellulitis, respiratory tract infection.

239 Blood and Lymphatic System Disorders: Lymphadenopathy, thrombocytopenia.

240 Immune System Disorders: Anaphylactic reaction, hypersensitivity.

241 Nervous System Disorders: Encephalopathy, headache, hypotonia.

242 Ear and Labyrinth Disorders: Ear pain.

243 Cardiac Disorders: Cyanosis.

244 Respiratory, Thoracic, and Mediastinal Disorders: Apnea, cough.

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

247 General Disorders and Administration Site Conditions: Fatigue, injection site  
248 induration, injection site reaction, Sudden Infant Death Syndrome.

## 249 **7 DRUG INTERACTIONS**

### 250 **7.1 Concomitant Vaccine Administration**

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

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

### 257 **7.2 Immunosuppressive Therapies**

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

## 261 **8 USE IN SPECIFIC POPULATIONS**

### 262 **8.1 Pregnancy**

263 Pregnancy Category C

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

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

#### 267 **8.4 Pediatric Use**

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

### 271 **11 DESCRIPTION**

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

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

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

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

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

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

299 INFANRIX is available in vials and 2 types of prefilled syringes. One type of prefilled  
300 syringe has a tip cap which may contain natural rubber latex and a plunger which does not  
301 contain latex. The other type has a tip cap and a rubber plunger which contain dry natural latex  
302 rubber. The vial stopper does not contain latex. [See *How Supplied/Storage and Handling (16).*]

303 INFANRIX is formulated without preservatives.

304 **12 CLINICAL PHARMACOLOGY**

305 **12.1 Mechanism of Action**

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

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

315 Pertussis: Pertussis (whooping cough) is a disease of the respiratory tract caused by  
316 *B. pertussis*. The role of the different components produced by *B. pertussis* in either the  
317 pathogenesis of, or the immunity to, pertussis is not well understood. There is no well established  
318 serological correlate of protection for pertussis.

319 **13 NONCLINICAL TOXICOLOGY**

320 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

323 **14 CLINICAL STUDIES**

324 **14.1 Diphtheria and Tetanus**

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

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

333 **14.2 Pertussis**

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

335 A double-blind, randomized, active Diphtheria and Tetanus Toxoids (DT)-controlled trial  
336 conducted in Italy assessed the absolute protective efficacy of INFANRIX when administered at  
337 2, 4, and 6 months of age. The population used in the primary analysis of the efficacy of  
338 INFANRIX included 4,481 infants vaccinated with INFANRIX and 1,470 DT vaccinees. The  
339 mean length of follow-up was 17 months, beginning 30 days after the third dose of vaccine.  
340 After 3 doses, the absolute protective efficacy of INFANRIX against WHO-defined typical  
341 pertussis (21 days or more of paroxysmal cough with infection confirmed by culture and/or  
342 serologic testing) was 84% (95% CI: 76, 89). When the definition of pertussis was expanded to

343 include clinically milder disease with respect to type and duration of cough, with infection  
344 confirmed by culture and/or serologic testing, the efficacy of INFANRIX was calculated to be  
345 71% (95% CI: 60, 78) against >7 days of any cough and 73% (95% CI: 63, 80) against  $\geq 14$  days  
346 of any cough. Vaccine efficacy after 3 doses and with no booster dose in the second year of life  
347 was assessed in 2 subsequent follow-up periods. A follow-up period from 24 months to a mean  
348 age of 33 months was conducted in a partially unblinded cohort (children who received DT were  
349 offered pertussis vaccine and those who declined were retained in the study cohort). During this  
350 period, the efficacy of INFANRIX against WHO-defined pertussis was 78% (95% CI: 62, 87).  
351 During the third follow-up period which was conducted in an unblinded manner among children  
352 from 3 to 6 years of age, the efficacy of INFANRIX against WHO-defined pertussis was 86%  
353 (95% CI: 79, 91). Thus, protection against pertussis in children administered 3 doses of  
354 INFANRIX in infancy was sustained to 6 years of age.

355 A prospective efficacy trial was also conducted in Germany employing a household  
356 contact study design. In preparation for this study, 3 doses of INFANRIX were administered at 3,  
357 4, and 5 months of age to more than 22,000 children living in 6 areas of Germany in a safety and  
358 immunogenicity study. Infants who did not participate in the safety and immunogenicity study  
359 could have received a DTwP vaccine or DT vaccine. Index cases were identified by spontaneous  
360 presentation to a physician. Households with at least one other member (i.e., besides index case)  
361 aged 6 through 47 months were enrolled. Household contacts of index cases were monitored for  
362 incidence of pertussis by a physician who was blinded to the vaccination status of the household.  
363 Calculation of vaccine efficacy was based on attack rates of pertussis in household contacts  
364 classified by vaccination status. Of the 173 household contacts who had not received a pertussis  
365 vaccine, 96 developed WHO-defined pertussis, as compared with 7 of 112 contacts vaccinated  
366 with INFANRIX. The protective efficacy of INFANRIX was calculated to be 89% (95% CI: 77,  
367 95), with no indication of waning of protection up until the time of the booster vaccination. The  
368 average age of infants vaccinated with INFANRIX at the end of follow-up in this trial was  
369 13 months (range 6 to 25 months). When the definition of pertussis was expanded to include  
370 clinically milder disease, with infection confirmed by culture and/or serologic testing, the  
371 efficacy of INFANRIX against  $\geq 7$  days of any cough was 67% (95% CI: 52, 78) and against  
372  $\geq 7$  days of paroxysmal cough was 81% (95% CI: 68, 89). The corresponding efficacy of  
373 INFANRIX against  $\geq 14$  days of any cough or paroxysmal cough were 73% (95% CI: 59, 82) and  
374 84% (95% CI: 71, 91), respectively.

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

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

### 384 **14.3 Immune Response to Concomitantly Administered Vaccines**

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

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

## 400 **15 REFERENCES**

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## 411 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

414 NDC 58160-810-01 Vial (contains no latex) in Package of 10: NDC 58160-810-11

415 NDC 58160-810-43 Syringe (tip cap may contain latex; plunger contains no latex) in Package of  
416 10: NDC 58160-810-52

417 NDC 58160-810-41 Syringe (tip cap and plunger contain latex) in Package of 5: NDC 58160-  
418 810-46

419 NDC 58160-810-41 Syringe (tip cap and plunger contain latex) in Package of 10: NDC 58160-  
420 810-51

421 Store refrigerated between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the

422 vaccine has been frozen.

## 423 **17 PATIENT COUNSELING INFORMATION**

424 The parent or guardian should be:

- 425 • informed of the potential benefits and risks of immunization with INFANRIX, and of the  
426 importance of completing the immunization series.
- 427 • informed about the potential for adverse reactions that have been temporally associated with  
428 administration of INFANRIX or other vaccines containing similar components.
- 429 • instructed to report any adverse events to their healthcare provider.
- 430 • given the Vaccine Information Statements, which are required by the National Childhood  
431 Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available  
432 free of charge at the Centers for Disease Control and Prevention (CDC) website  
433 ([www.cdc.gov/vaccines](http://www.cdc.gov/vaccines)).

434

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436 GlaxoSmithKline.

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