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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Pentacel (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine Suspension for Intramuscular Injection
Initial U.S. Approval: 2008

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

- Pentacel is a vaccine indicated for active immunization against diphtheria, tetanus, pertussis, poliomyelitis and invasive disease due to *Haemophilus influenzae* type b. Pentacel is approved for use as a four dose series in children 6 weeks through 4 years of age (prior to 5th birthday). (1)

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

- The four dose immunization series consists of a 0.5 mL intramuscular injection, after reconstitution, administered at 2, 4, 6 and 15-18 months of age. (2.1)
- Pentacel consists of a liquid vaccine component (DTaP-IPV component) and a lyophilized vaccine component (ActHIB vaccine). Reconstitute the ActHIB vaccine component with the DTaP-IPV component immediately before administration. (2.2)

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

- Suspension for injection (0.5 mL dose) supplied as a liquid vaccine component that is combined through reconstitution with a lyophilized vaccine component, both in single-dose vials. (3)

-----CONTRAINDICATIONS-----

- Severe allergic reaction (eg, anaphylaxis) after a previous dose of Pentacel, any ingredient of Pentacel, or any other diphtheria toxoid, tetanus toxoid, pertussis-containing vaccine, inactivated poliovirus vaccine or *H. influenzae* type b vaccine. (4.1)
- Encephalopathy within 7 days of a previous pertussis-containing vaccine with no other identifiable cause. (4.2)
- Progressive neurologic disorder until a treatment regimen has been established and the condition has stabilized. (4.3)

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

- Carefully consider benefits and risks before administering Pentacel to persons with a history of:
 - fever $\geq 40.5^{\circ}\text{C}$ ($\geq 105^{\circ}\text{F}$), hypotonic-hyporesponsive episode (HHE) or persistent, inconsolable crying lasting ≥ 3 hours within 48 hours after a previous pertussis-containing vaccine. (5.2)
 - seizures within 3 days after a previous pertussis-containing vaccine. (5.2)

- If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk for Guillain-Barré syndrome may be increased following Pentacel. (5.3)
- For infants and children with a history of previous seizures, an antipyretic may be administered (in the dosage recommended in its prescribing information) at the time of vaccination with Pentacel and for the next 24 hours. (5.4)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. The decision about when to administer an intramuscular vaccine, including Pentacel, to an infant born prematurely should be based on consideration of the individual infant's medical status and the potential benefits and possible risks of vaccination. (5.7)

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

- Rates of adverse reactions varied by dose number. Systemic reactions that occurred in $>50\%$ of participants following any dose included fussiness/irritability and inconsolable crying. Fever $\geq 38.0^{\circ}\text{C}$ occurred in 6-16% of participants, depending on dose number. Injection site reactions that occurred in $>30\%$ of participants following any dose included tenderness and increase in arm circumference. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pharmacovigilance Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 and <http://vaers.hhs.gov>.

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

- Do not mix Pentacel or any of its components with any other vaccine or diluent. (7.1)
- Immunosuppressive therapies may reduce the immune response to Pentacel. (7.2)
- Urine antigen detection may not have definitive diagnostic value in suspected *H. influenzae* type b disease within one week following Pentacel. (7.3)

See 17 for PATIENT COUNSELING INFORMATION.

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1 FULL PRESCRIBING INFORMATION

2 1 INDICATIONS AND USAGE

3 Pentacel® is a vaccine indicated for active immunization against diphtheria, tetanus, pertussis,
4 poliomyelitis and invasive disease due to *Haemophilus influenzae* type b. Pentacel is approved
5 for use as a four dose series in children 6 weeks through 4 years of age (prior to fifth birthday).

6 2 DOSAGE AND ADMINISTRATION

7 2.1 Immunization Series

8 Pentacel is to be administered as a 4 dose series at 2, 4, 6 and 15-18 months of age. The first dose
9 may be given as early as 6 weeks of age. Four doses of Pentacel constitute a primary
10 immunization course against pertussis. Three doses of Pentacel constitute a primary immunization
11 course against diphtheria, tetanus, *H. influenzae* type b invasive disease, and poliomyelitis; the
12 fourth dose is a booster for diphtheria, tetanus, *H. influenzae* type b invasive disease, and
13 poliomyelitis immunizations [see *Clinical Studies (14.1, 14.2, 14.3, 14.4, 14.5)*].

14 Mixed Sequences of Pentacel and DTaP Vaccine

15 While Pentacel and DAPTACEL (Diphtheria and Tetanus Toxoids and Acellular Pertussis
16 Vaccine Adsorbed [DTaP], Sanofi Pasteur Limited) vaccines contain the same pertussis antigens,
17 manufactured by the same process, Pentacel contains twice the amount of detoxified pertussis
18 toxin (PT) and four times the amount of filamentous hemagglutinin (FHA) as DAPTACEL.
19 Pentacel may be used to complete the first 4 doses of the 5-dose DTaP series in infants and
20 children who have received 1 or more doses of DAPTACEL and are also scheduled to receive the
21 other antigens of Pentacel. However, data are not available on the safety and immunogenicity of
22 such mixed sequences of Pentacel and DAPTACEL for successive doses of the primary DTaP
23 series. Children who have completed a 4-dose series with Pentacel should receive a fifth dose of
24 DTaP vaccine using DAPTACEL at 4-6 years of age. (1)

25 Data are not available on the safety and effectiveness of using mixed sequences of Pentacel and
26 DTaP vaccine from different manufacturers.

27 Mixed Sequences of Pentacel and IPV Vaccine

28 Pentacel may be used in infants and children who have received 1 or more doses of another
29 licensed IPV vaccine and are scheduled to receive the antigens of Pentacel. However, data are not
30 available on the safety and immunogenicity of Pentacel in such infants and children.

31 The Advisory Committee on Immunization Practices (ACIP) recommends that the final dose in
32 the 4-dose IPV series be administered at age ≥ 4 years. (2) When Pentacel is administered at ages
33 2, 4, 6, and 15-18 months, an additional booster dose of IPV vaccine should be administered at
34 age 4-6 years, resulting in a 5-dose IPV series. (2)

35 Mixed Sequences of Pentacel and Haemophilus b Conjugate Vaccine

36 Pentacel may be used to complete the vaccination series in infants and children previously
37 vaccinated with one or more doses of Haemophilus b Conjugate Vaccine (either separately
38 administered or as part of another combination vaccine), who are also scheduled to receive the
39 other antigens of Pentacel. However, data are not available on the safety and immunogenicity of
40 Pentacel in such infants and children. If different brands of Haemophilus b Conjugate Vaccines

41 are administered to complete the series, three primary immunizing doses are needed, followed by
42 a booster dose.

43 **2.2 Administration**

44 The package contains a vial of the DTaP-IPV component and a vial of lyophilized ActHIB
45 vaccine component.

46 Before use, thoroughly but gently shake the vial of DTaP-IPV component, withdraw the entire
47 liquid content and inject into the vial of the lyophilized ActHIB vaccine component. Gently swirl
48 the vial now containing Pentacel until a cloudy, uniform, white to off-white (yellow tinge)
49 suspension results.

50 Parenteral drug products should be inspected visually for particulate matter and discoloration
51 prior to administration, whenever solution and container permit. If these conditions exist, Pentacel
52 should not be administered.

53 Withdraw and administer a single 0.5 mL dose of Pentacel intramuscularly. Pentacel should be
54 used immediately after reconstitution. Discard unused portion. Refer to Figures 1, 2, 3, 4 and 5.

55

56 **Pentacel: Instructions for Reconstitution of ActHIB Vaccine Component with DTaP-IPV**
57 **Component**

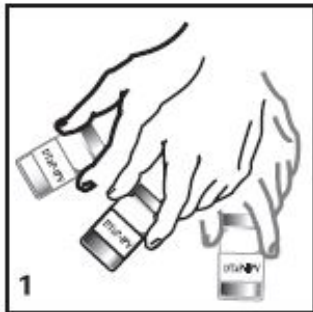


Figure 1
Gently shake the vial of DTaP-IPV component.



Figure 2
Withdraw the entire liquid content.



Figure 3
Insert the syringe needle through the stopper of the vial of lyophilized ActHIB vaccine component and inject the liquid into the vial.

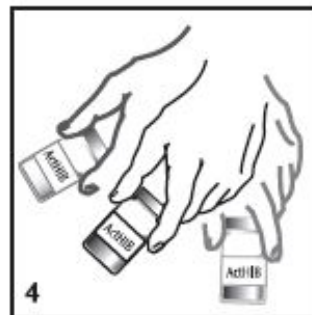


Figure 4
Swirl vial gently.



Figure 5
After reconstitution, immediately withdraw 0.5 mL of Pentacel vaccine and administer intramuscularly. Pentacel vaccine should be used immediately after reconstitution.

58

59 In infants younger than 1 year, the anterolateral aspect of the thigh provides the largest muscle
60 and is the preferred site of injection. In older children, the deltoid muscle is usually large enough
61 for injection. The vaccine should not be injected into the gluteal area or areas where there may be
62 a major nerve trunk.

63 Do not administer this product intravenously or subcutaneously.

64 Pentacel should not be mixed in the same syringe with other parenteral products.

65 **3 DOSAGE FORMS AND STRENGTHS**

66 Pentacel is a suspension for injection (0.5 mL dose) supplied as a liquid vaccine component that is
67 combined through reconstitution with a lyophilized vaccine component, both in single-dose vials
68 [see *Dosage and Administration (2.2)* and *How Supplied/Storage and Handling (16)*].

69 **4 CONTRAINDICATIONS**

70 **4.1 Hypersensitivity**

71 A severe allergic reaction (eg, anaphylaxis) after a previous dose of Pentacel or any other
72 diphtheria toxoid, tetanus toxoid, or pertussis-containing vaccine, inactivated poliovirus vaccine
73 or *H. influenzae* type b vaccine, or any ingredient of this vaccine is a contraindication to
74 administration of Pentacel [see *Description (11)*].

75 **4.2 Encephalopathy**

76 Encephalopathy (eg, coma, decreased level of consciousness, prolonged seizures) within 7 days of
77 a previous dose of a pertussis containing vaccine that is not attributable to another identifiable
78 cause is a contraindication to administration of any pertussis-containing vaccine, including
79 Pentacel.

80 **4.3 Progressive Neurologic Disorder**

81 Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive
82 encephalopathy is a contraindication to administration of any pertussis-containing vaccine
83 including Pentacel. Pertussis vaccine should not be administered to individuals with such
84 conditions until a treatment regimen has been established and the condition has stabilized.

85 **5 WARNINGS AND PRECAUTIONS**

86 **5.1 Management of Acute Allergic Reactions**

87 Epinephrine hydrochloride solution (1:1,000) and other appropriate agents and equipment must be
88 available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs.

89 **5.2 Adverse Reactions Following Prior Pertussis Vaccination**

90 If any of the following events occur within the specified period after administration of a pertussis
91 vaccine, the decision to administer Pentacel should be based on careful consideration of potential
92 benefits and possible risks.

- 93 • Temperature of $\geq 40.5^{\circ}\text{C}$ ($\geq 105^{\circ}\text{F}$) within 48 hours, not attributable to another identifiable
94 cause.
- 95 • Collapse or shock-like state (hypotonic-hyporesponsive episode (HHE)) within 48 hours.
- 96 • Persistent, inconsolable crying lasting ≥ 3 hours within 48 hours.
- 97 • Seizures with or without fever within 3 days.

98 **5.3 Guillain-Barré Syndrome and Brachial Neuritis**

99 A review by the Institute of Medicine (IOM) found evidence for a causal relation between tetanus
100 toxoid and both brachial neuritis and Guillain-Barré syndrome. (3) If Guillain-Barré syndrome
101 occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk for
102 Guillain-Barré syndrome may be increased following Pentacel.

103 **5.4 Infants and Children with a History of Previous Seizures**

104 For infants or children with a history of previous seizures, an appropriate antipyretic may be
105 administered (in the dosage recommended in its prescribing information) at the time of
106 vaccination with a vaccine containing acellular pertussis antigens (including Pentacel) and for the
107 following 24 hours, to reduce the possibility of post-vaccination fever.

108 **5.5 Limitations of Vaccine Effectiveness**

109 Vaccination with Pentacel may not protect all individuals.

110 **5.6 Altered Immunocompetence**

111 If Pentacel is administered to immunocompromised persons, including persons receiving
112 immunosuppressive therapy, the expected immune response may not be obtained [see *Drug*
113 *Interactions* (7.2)].

114 **5.7 Apnea in Premature Infants**

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

119 **6 ADVERSE REACTIONS**

120 **6.1 Clinical Trials Experience**

121 Rates of adverse reactions varied by dose number. The most frequent (>50% of participants)
122 systemic reactions following any dose were fussiness/irritability and inconsolable crying. The
123 most frequent (>30% of participants) injection site reactions following any dose were tenderness
124 and increased circumference of the injected arm.

125 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
126 observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials
127 of another vaccine and may not reflect the rates observed in practice. The adverse reaction
128 information from clinical trials does, however, provide a basis for identifying the adverse events
129 that appear to be related to vaccine use and for approximating rates of those events.

130 The poliovirus component (poliovirus types 1, 2, and 3) of this formulation of Pentacel is grown
131 in Vero cells [see *Description* (11)]. The clinical study data in this section were accrued with a
132 Pentacel formulation in which the poliovirus component was grown in MRC-5 cells. The safety of
133 Pentacel was evaluated in four clinical studies in which a total of 5,980 participants received at
134 least one dose of Pentacel. In three of the studies, conducted in the US, a total of 4,198
135 participants were enrolled to receive four consecutive doses of Pentacel. In the fourth study,
136 conducted in Canada, 1,782 participants previously vaccinated with three doses of Pentacel
137 received a fourth dose. The vaccination schedules of Pentacel, Control vaccines, and
138 concomitantly administered vaccines used in these studies are provided in Table 1.

139 Across the four studies, 50.8% of participants were female. Among participants in the three US
140 studies, 64.5% were Caucasian, 9.2% were Black, 12.9% were Hispanic, 3.9% were Asian, and
141 9.5% were of other racial/ethnic groups. In the two controlled studies, the racial/ethnic
142 distribution of participants who received Pentacel and Control vaccines was similar. In the

143 Canadian fourth dose study, 86.0% of participants were Caucasian, 1.9% were Black, 0.8% were
144 Hispanic, 4.3% were Asian, 2.0% were East Indian, 0.5% were Native Indian, and 4.5% were of
145 other racial/ethnic groups.

146 **Table 1: Clinical Safety Studies of Pentacel: Vaccination Schedules**

Study	Pentacel	Control Vaccines	Concomitantly Administered Vaccines
494-01	2, 4, 6 and 15 months	HCPDT + POLIOVAX + ActHIB at 2, 4, 6, and 15 months	7-valent pneumococcal conjugate vaccine* (PCV7) at 2, 4, and 6 months in a subset of participants† Hepatitis B vaccine at 2 and 6 months‡
P3T06	2, 4, 6, and 15-16 months	DAPTACEL + IPOL + ActHIB at 2, 4, and 6 months; and DAPTACEL + ActHIB at 15-16 months	PCV7* at 2, 4, and 6 months Hepatitis B vaccine at 2 and 6 months‡
494-03	2, 4, 6, and 15-16 months	None	PCV7* at 2, 4, and 6 months in all participants; and at 15 months in a random subset of participants Hepatitis B vaccine at 2 and 6 months (if a dose was previously administered)‡ or at 2, 4, and 6 months (if no previous dose) Measles, mumps, rubella vaccine§ (MMR) and varicella§ vaccine at 12 or 15 months in random subsets of participants
5A9908	15-18 months¶	None	None

HCPDT: non-US licensed DTaP vaccine that is identical to the DTaP component of Pentacel.

POLIOVAX: US licensed Poliovirus Vaccine Inactivated, Sanofi Pasteur Limited.

IPOL: US licensed Poliovirus Vaccine Inactivated, Sanofi Pasteur SA.

147 * PCV7 manufactured by Wyeth Laboratories.

148 † PCV7 was introduced after the study was initiated, and thus, administered concomitantly with Pentacel vaccine
149 in a subset of participants.

150 ‡ The first dose of hepatitis B vaccine (manufacturer not specified) was administered prior to study initiation, from
151 birth to 21 days of age. Subsequent doses were with hepatitis B vaccine manufactured by Merck and Co.

152 § MMR and varicella vaccines were both manufactured by Merck and Co.

153 ¶ Study participants previously had received three doses of Pentacel vaccine by 8 months of age.

154 Solicited Adverse Reactions

155 The incidence and severity of selected solicited injection site and systemic adverse reactions that
156 occurred within 3 days following each dose of Pentacel or Control vaccines in Study P3T06 is
157 shown in Table 2. Information on these reactions was recorded daily by parents or guardians on
158 diary cards. In Table 2, injection site reactions are reported for the Pentacel and DAPTACEL
159 injection sites.

160 **Table 2: Number (Percentage) of Children with Selected Solicited Adverse Reactions by Severity Occurring within 0-3 days**
161 **of Pentacel or Control Vaccines in Study P3T06**

Injection Site Reactions	Pentacel				DAPTACEL			
	Dose 1 N = 465-467 %	Dose 2 N = 451 %	Dose 3 N = 438-440 %	Dose 4 N = 387-396 %	Dose 1 N = 1,400-1,404 %	Dose 2 N = 1,358-1,359 %	Dose 3 N = 1,311-1,312 %	Dose 4 N = 376-380 %
Redness								
>5 mm	7.1	8.4	8.7	17.3	6.2	7.1	9.6	16.4
>25 mm	2.8	1.8	1.8	9.2	1.0	0.6	1.9	7.9
>50 mm	0.6	0.2	0.0	2.3	0.4	0.1	0.0	2.4
Swelling								
>5 mm	7.5	7.3	5.0	9.7	4.0	4.0	6.5	10.3
>25 mm	3.0	2.0	1.6	3.8	1.6	0.7	1.1	4.0
>50 mm	0.9	0.0	0.0	0.8	0.4	0.1	0.1	1.3
Tenderness*								
Any	47.5	39.2	42.7	56.1	48.8	38.2	40.9	51.1
Moderate or Severe	19.6	10.6	11.6	16.7	20.7	12.2	12.3	15.8
Severe	5.4	1.6	1.4	3.3	4.1	2.3	1.7	2.4
Increase in Arm Circumference								
>5 mm	–	–	–	33.6	–	–	–	30.6
>20 mm				4.7				6.9
>40 mm				0.5				0.8
Systemic Reactions	Pentacel				DAPTACEL + IPOL + ActHIB			DAPTACEL + ActHIB
	Dose 1 N = 466-467 %	Dose 2 N = 451-452 %	Dose 3 N = 435-440 %	Dose 4 N = 389-398 %	Dose 1 N = 1,390-1,406 %	Dose 2 N = 1,346-1,360 %	Dose 3 N = 1,301-1,312 %	Dose 4 N = 379-381 %
Fever^{†‡}								
≥38.0°C	5.8	10.9	16.3	13.4	9.3	16.1	15.8	8.7
>38.5°C	1.3	2.4	4.4	5.1	1.6	4.3	5.1	3.2
>39.5°C	0.4	0.0	0.7	0.3	0.1	0.4	0.3	0.8
Decreased Activity/Lethargy[§]								
Any	45.8	32.7	32.5	24.1	51.1	37.4	33.2	24.1
Moderate or Severe	22.9	12.4	12.7	9.8	24.3	15.8	12.7	9.2
Severe	2.1	0.7	0.2	2.5	1.2	1.4	0.6	0.3

Inconsolable Crying								
Any	59.3	49.8	47.3	35.9	58.5	51.4	47.9	36.2
≥1 hour	19.7	10.6	13.6	11.8	16.4	16.0	12.2	10.5
>3 hours	1.9	0.9	1.1	2.3	2.2	3.4	1.4	1.8
Fussiness/Irritability								
Any	76.9	71.2	68.0	53.5	75.8	70.7	67.1	53.8
≥1 hour	34.5	27.0	26.4	23.6	33.3	30.5	26.2	19.4
>3 hours	4.3	4.0	5.0	5.3	5.6	5.5	4.3	4.5

162 * Any: Mild, Moderate or Severe; Mild: subject whimpers when site is touched; Moderate: subject cries when site is touched; Severe: subject cries when leg
163 or arm is moved.

164 † Fever is based upon actual temperatures recorded with no adjustments to the measurement route.

165 ‡ Following Doses 1-3 combined, the proportion of temperature measurements that were taken by axillary, rectal or other routes, or not recorded were 46.0%,
166 53.0%, 1.0%, and 0% respectively, for Pentacel vaccine and 44.8%, 54.0%, 1.0%, and 0.1%, respectively, for DAPTACEL + IPOL + ActHIB. Following
167 Dose 4, the proportion of temperature measurements that were taken by axillary, rectal or other routes, or not recorded were 62.7%, 34.4%, 2.4% and 0.5%,
168 respectively, for Pentacel vaccine, and 61.1%, 36.6%, 1.7% and 0.5%, respectively, for DAPTACEL + ActHIB.

169 § Moderate: interferes with or limits usual daily activity; Severe: disabling, not interested in usual daily activity.

170 Hypotonic Hyporesponsive Episodes

171 In Study P3T06, the diary cards included questions pertaining to HHEs. In Studies 494-01,
172 494-03, and 5A9908, a question about the occurrence of fainting or change in mental status was
173 asked during post-vaccination phone calls. Across these 4 studies, no HHEs, as defined in a report
174 of a US Public Health Service workshop (4) were reported among participants who received
175 Pentacel (N = 5,979), separately administered HCPDT + POLIOVAX + ActHIB (N = 1,032) or
176 separately administered DAPTACEL + IPOL + ActHIB (N = 1,455). Hypotonia not fulfilling
177 HHE criteria within 7 days following vaccination was reported in 4 participants after the
178 administration of Pentacel (1 on the same day as the 1st dose; 3 on the same day as the 3rd dose)
179 and in 1 participant after the administration of DAPTACEL + IPOL + ActHIB (4 days following
180 the 1st dose).

181 Seizures

182 Across Studies 494-01, 494-03, 5A9908 and P3T06, a total of 8 participants experienced a seizure
183 within 7 days following either Pentacel (4 participants; N = 4,197 for at least one of Doses 1-3;
184 N = 5,033 for Dose 4), separately administered HCPDT + POLIOVAX + ActHIB (3 participants;
185 N = 1,032 for at least one of Doses 1-3, N = 739 for Dose 4), separately administered
186 DAPTACEL + IPOL + ActHIB (1 participant; N = 1,455 for at least one of Doses 1-3), or
187 separately administered DAPTACEL + ActHIB (0 participants; N = 418 for Dose 4). Among the
188 four participants who experienced a seizure within 7 days following Pentacel, one participant in
189 Study 494-01 had an afebrile seizure 6 days after the first dose, one participant in Study 494-01
190 had a possible seizure the same day as the third dose, and two participants in Study 5A9908 had a
191 febrile seizure 2 and 4 days, respectively, after the fourth dose. Among the four participants who
192 experienced a seizure within 7 days following Control vaccines, one participant had an afebrile
193 seizure the same day as the first dose of DAPTACEL + IPOL + ActHIB, one participant had an
194 afebrile seizure the same day as the second dose of HCPDT + POLIOVAX + ActHIB, and two
195 participants had a febrile seizure 6 and 7 days, respectively, after the fourth dose of HCPDT +
196 POLIOVAX + ActHIB.

197 Serious Adverse Events

198 In Study P3T06, within 30 days following any of Doses 1-3 of Pentacel or Control vaccines, 19 of
199 484 (3.9%) participants who received Pentacel and 50 of 1,455 (3.4%) participants who received
200 DAPTACEL + IPOL + ActHIB experienced a serious adverse event. Within 30 days following
201 Dose 4 of Pentacel or Control vaccines, 5 of 431 (1.2%) participants who received Pentacel and 4
202 of 418 (1.0%) participants who received DAPTACEL + ActHIB experienced a serious adverse
203 event. In Study 494-01, within 30 days following any of Doses 1-3 of Pentacel or Control
204 vaccines, 23 of 2,506 (0.9%) participants who received Pentacel and 11 of 1,032 (1.1%)
205 participants who received HCPDT + POLIOVAX + ActHIB experienced a serious adverse event.
206 Within 30 days following Dose 4 of Pentacel or Control vaccines, 6 of 1,862 (0.3%) participants
207 who received Pentacel and 2 of 739 (0.3%) participants who received HCPDT + POLIOVAX +
208 ActHIB experienced a serious adverse event.

209 Across Studies 494-01, 494-03 and P3T06, within 30 days following any of Doses 1-3 of Pentacel
210 or Control vaccines, overall, the most frequently reported serious adverse events were
211 bronchiolitis, dehydration, pneumonia and gastroenteritis. Across Studies 494-01, 494-03,
212 5A9908 and P3T06, within 30 days following Dose 4 of Pentacel or Control vaccines, overall, the

213 most frequently reported serious adverse events were dehydration, gastroenteritis, asthma, and
214 pneumonia.

215 Across Studies 494-01, 494-03, 5A9908 and P3T06, two cases of encephalopathy were reported,
216 both in participants who had received Pentacel (N = 5,979). One case occurred 30 days post-
217 vaccination and was secondary to cardiac arrest following cardiac surgery. One infant who had
218 onset of neurologic symptoms 8 days post-vaccination was subsequently found to have structural
219 cerebral abnormalities and was diagnosed with congenital encephalopathy.

220 A total of 5 deaths occurred during Studies 494-01, 494-03, 5A9908 and P3T06: 4 in children
221 who had received Pentacel (N = 5,979) and one in a participant who had received DAPTACEL +
222 IPOL + ActHIB (N = 1,455). There were no deaths reported in children who received HCPDT +
223 POLIOVAX + ActHIB (N = 1,032). Causes of death among children who received Pentacel were
224 asphyxia due to suffocation, head trauma, Sudden Infant Death syndrome, and neuroblastoma (8,
225 23, 52 and 256 days post-vaccination, respectively). One participant with ependymoma died
226 secondary to aspiration 222 days following DAPTACEL + IPOL + ActHIB.

227 **6.2 Data from Postmarketing Experience**

228 The following additional adverse events have been spontaneously reported during the
229 post-marketing use of Pentacel worldwide, since 1997. Between 1997 and 2007, Pentacel was
230 primarily used in Canada. Because these events are reported voluntarily from a population of
231 uncertain size, it may not be possible to reliably estimate their frequency or establish a causal
232 relationship to vaccine exposure.

233 The following adverse events were included based on one or more of the following factors:
234 severity, frequency of reporting, or strength of evidence for a causal relationship to Pentacel.

- 235 • ***Cardiac disorders***

236 Cyanosis

- 237 • ***Gastrointestinal disorders***

238 Vomiting, diarrhea

- 239 • ***General disorders and administration site conditions***

240 Injection site reactions (including inflammation, mass, abscess and sterile abscess),
241 extensive swelling of the injected limb (including swelling that involved adjacent joints),
242 vaccination failure/therapeutic response decreased (invasive *H. influenzae* type b disease)

- 243 • ***Immune system disorders***

244 Anaphylaxis/anaphylactic reaction, hypersensitivity (such as rash and urticaria)

- 245 • ***Infections and infestations***

246 Meningitis, rhinitis, viral infection

- 247 • ***Metabolism and nutrition disorders***

248 Decreased appetite

- 249 • ***Nervous system disorders***

250 Somnolence, HHE, depressed level of consciousness

- 251 • **Psychiatric disorders**
- 252 Screaming
- 253 • **Respiratory, thoracic and mediastinal disorders**
- 254 Apnea, cough
- 255 • **Skin and subcutaneous tissue disorders**
- 256 Erythema, skin discoloration
- 257 • **Vascular disorders**
- 258 Pallor

259 **7 DRUG INTERACTIONS**

260 **7.1 Concomitant Administration with Other Vaccines**

261 In clinical trials, Pentacel was administered concomitantly with one or more of the following US
262 licensed vaccines: hepatitis B vaccine, 7-valent pneumococcal conjugate vaccine, MMR and
263 varicella vaccines [see *Adverse Reactions (6)* and *Clinical Studies (14)*]. When Pentacel is given
264 at the same time as another injectable vaccine(s), the vaccine(s) should be administered with
265 different syringes and at different injection sites.

266 **7.2 Immunosuppressive Treatments**

267 Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic
268 drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune
269 response to Pentacel [see *Warnings and Precautions (5.6)*].

270 **7.3 Drug/Laboratory Test Interactions**

271 Antigenuria has been detected in some instances following receipt of ActHIB. Urine antigen
272 detection may not have definite diagnostic value in suspected *H. influenzae* type b disease within
273 one week following receipt of Pentacel. (5)

274 **8 USE IN SPECIFIC POPULATIONS**

275 **8.4 Pediatric Use**

276 The safety and effectiveness of Pentacel was established in the age group 6 weeks through 18
277 months on the basis of clinical studies [see *Clinical Trials Experience (6.1)* and *Clinical Studies*
278 *(14)*]. The safety and effectiveness of Pentacel in the age group 19 months through 4 years is
279 supported by evidence in children 6 weeks through 18 months. The safety and effectiveness of
280 Pentacel in infants less than 6 weeks of age and in children 5 to 16 years of age have not been
281 established.

282 **11 DESCRIPTION**

283 Pentacel consists of a Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and
284 Inactivated Poliovirus (DTaP-IPV) component and an ActHIB® component combined through
285 reconstitution for intramuscular injection. ActHIB (Haemophilus b Conjugate Vaccine [Tetanus
286 Toxoid Conjugate]), consists of *H. influenzae* type b capsular polysaccharide
287 (polyribosyl-ribitol-phosphate [PRP]) covalently bound to tetanus toxoid (PRP-T). The DTaP-
288 IPV component is supplied as a sterile liquid used to reconstitute the lyophilized ActHIB
289 component to form Pentacel. Pentacel is a uniform, cloudy, white to off-white (yellow tinge)
290 suspension.

291 Each 0.5 mL dose contains 15 Lf diphtheria toxoid, 5 Lf tetanus toxoid, acellular pertussis
292 antigens [20 mcg detoxified pertussis toxin (PT), 20 mcg filamentous hemagglutinin (FHA),
293 3 mcg pertactin (PRN), 5 mcg fimbriae types 2 and 3 (FIM)], inactivated polioviruses
294 [29 D-antigen units (DU) Type 1 (Mahoney), 7 DU Type 2 (MEF-1), 26 DU Type 3 (Saukett)]
295 and 10 mcg PRP of *H. influenzae* type b covalently bound to 24 mcg of tetanus toxoid (PRP-T).

296 Other ingredients per 0.5 mL dose include 1.5 mg aluminum phosphate (0.33 mg aluminum) as
297 the adjuvant, <8.1 mcg polysorbate 80, 3.3 mg (0.6% v/v) 2-phenoxyethanol (not as a
298 preservative), 42.5 mg sucrose, 2 mcg to 7 mcg residual formaldehyde, <50 ng residual
299 glutaraldehyde, ≤10 ng residual bovine serum albumin, <0.0001 pg streptomycin sulphate, <0.01
300 pg of neomycin and <0.000001 pg polymyxin B sulphate.

301 *Corynebacterium diphtheriae* is grown in modified Mueller's growth medium. (6) After
302 purification by ammonium sulfate fractionation, the diphtheria toxin is detoxified with
303 formaldehyde and diafiltered.

304 *Clostridium tetani* is grown in modified Mueller-Miller casamino acid medium without beef
305 heart infusion. (7) Tetanus toxin is detoxified with formaldehyde and purified by ammonium
306 sulfate fractionation and diafiltration. Diphtheria and tetanus toxoids are individually adsorbed
307 onto aluminum phosphate.

308 The acellular pertussis vaccine antigens are produced from *Bordetella pertussis* cultures grown
309 in Stainer-Scholte medium (8) modified by the addition of casamino acids and dimethyl-beta-
310 cyclodextrin. PT, FHA and PRN are isolated separately from the supernatant culture medium.
311 FIM are extracted and copurified from the bacterial cells. The pertussis antigens are purified by
312 sequential filtration, salt-precipitation, ultrafiltration and chromatography. PT is detoxified with
313 glutaraldehyde. FHA is treated with formaldehyde and the residual aldehydes are removed by
314 ultrafiltration. The individual antigens are adsorbed separately onto aluminum phosphate.

315 The Type 1, Type 2, and Type 3 polioviruses are individually grown in Vero cells (a continuous
316 line of monkey kidney cells). Prior to viral propagation, the cells are grown in Iscove's medium,
317 supplemented with calf serum. For viral propagation, the culture medium is replaced by M199
318 medium without calf serum. The viral harvests are concentrated and purified, then inactivated
319 with formaldehyde to produce monovalent suspensions of each serotype. Specified quantities of
320 monovalent suspensions of each serotype are mixed to produce the trivalent poliovirus
321 concentrate. The adsorbed diphtheria, tetanus and acellular pertussis antigens are combined with
322 aluminum phosphate (as adjuvant), 2-phenoxyethanol (not as a preservative) and water for

323 injection, into an intermediate concentrate. The trivalent poliovirus concentrate is added and the
324 DTaP-IPV component is diluted to its final concentration. The DTaP-IPV component does not
325 contain a preservative.

326 Both diphtheria and tetanus toxoids induce at least 2 neutralizing units per mL in the guinea pig
327 potency test. The potency of the acellular pertussis antigens is evaluated by the antibody
328 response of immunized mice to detoxified PT, FHA, PRN and FIM as measured by enzyme-
329 linked immunosorbent assay (ELISA). The potency of inactivated poliovirus antigens is
330 determined by measuring antibody-mediated neutralization of poliovirus in sera from immunized
331 rats.

332 PRP, a high molecular weight polymer, is prepared from the *Haemophilus influenzae* type b
333 strain 1482 grown in a semi-synthetic medium. (9) The tetanus toxoid for conjugation to PRP is
334 prepared by ammonium sulfate purification, and formalin inactivation of the toxin from cultures
335 of *Clostridium tetani* (Harvard strain) grown in a modified Mueller and Miller medium. (10) The
336 toxoid is filter sterilized prior to the conjugation process. The ActHIB component does not
337 contain a preservative. Potency of the ActHIB component is specified on each lot by limits on
338 the content of PRP polysaccharide and protein per dose and the proportion of polysaccharide and
339 protein that is characterized as high molecular weight conjugate.

340 The vial stoppers for the DTaP-IPV and ActHIB components of Pentacel are not made with
341 natural rubber latex.

342 **12 CLINICAL PHARMACOLOGY**

343 **12.1 Mechanism of Action**

344 Diphtheria

345 Diphtheria is an acute toxin-mediated disease caused by toxigenic strains of *C. diphtheriae*.
346 Protection against disease is due to the development of neutralizing antibodies to diphtheria
347 toxin. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree
348 of protection. Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective. (11)
349 Levels of 1.0 IU/mL have been associated with long-term protection. (12)

350 Tetanus

351 Tetanus is an acute disease caused by an extremely potent neurotoxin produced by *C. tetani*.
352 Protection against disease is due to the development of neutralizing antibodies to tetanus toxin. A
353 serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assay is
354 considered the minimum protective level. (11) (13) A tetanus antitoxoid level ≥ 0.1 IU/mL as
355 measured by the ELISA used in clinical studies of Pentacel is considered protective.

356 Pertussis

357 Pertussis (whooping cough) is a respiratory disease caused by *B. pertussis*. This Gram-negative
358 coccobacillus produces a variety of biologically active components, though their role in either
359 the pathogenesis of, or immunity to, pertussis has not been clearly defined.

360 Poliomyelitis

361 Polioviruses, of which there are three serotypes (Types 1, 2, and 3) are enteroviruses. The
362 presence of poliovirus type-specific neutralizing antibodies has been correlated with protection
363 against poliomyelitis. (14)

364 Invasive Disease Due to *H. influenzae* Type b

365 *H. influenzae* type b can cause invasive disease such as meningitis and sepsis. Anti-PRP antibody
366 has been shown to correlate with protection against invasive disease due to *H. influenzae* type b.

367 Based on data from passive antibody studies (15) and an efficacy study with *H. influenzae* type b
368 polysaccharide vaccine in Finland, (16) a post-vaccination anti-PRP level of 0.15 mcg/mL has
369 been accepted as a minimal protective level. Data from an efficacy study with *H. influenzae* type
370 b polysaccharide vaccine in Finland indicate that a level >1.0 mcg/mL 3 weeks after vaccination
371 predicts protection through a subsequent one-year period. (17) (18) These levels have been used
372 to evaluate the effectiveness of Haemophilus b Conjugate Vaccines, including the ActHIB
373 component of Pentacel.

374 **13 NONCLINICAL TOXICOLOGY**

375 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

376 Pentacel has not been evaluated for carcinogenic or mutagenic potential or impairment of
377 fertility.

378 **14 CLINICAL STUDIES**

379 The efficacy of Pentacel is based on the immunogenicity of the individual antigens compared to
380 separately administered vaccines. The poliovirus component (poliovirus types 1, 2 and 3) of this
381 formulation of Pentacel is grown in Vero cells [see *Description (11)*]. The clinical study data in
382 this section were accrued with a Pentacel formulation in which the poliovirus component was
383 grown in MRC-5 cells. The poliovirus component of the two Pentacel formulations are
384 analytically comparable. Serological correlates of protection exist for diphtheria, tetanus,
385 poliomyelitis, and invasive disease due to *H. influenzae* type b [see *Clinical Pharmacology*
386 *(12.1)*]. The efficacy against pertussis, for which there is no well-established serological
387 correlate of protection, was based, in part, on a comparison of pertussis immune responses
388 following Pentacel in US children to responses following DAPTACEL (Diphtheria and Tetanus
389 Toxoids and Acellular Pertussis Vaccine Adsorbed (DTaP) manufactured by Sanofi Pasteur
390 Limited) in an efficacy study conducted in Sweden (Sweden I Efficacy Trial). While Pentacel
391 and DAPTACEL contain the same pertussis antigens, manufactured by the same process,
392 Pentacel contains twice as much detoxified PT and four times as much FHA as DAPTACEL.

393 Immune responses to Pentacel were evaluated in four US studies: Studies 494-01, P3T06, 494-
394 03, and M5A10. The vaccination schedules of Pentacel, Control vaccines, and concomitantly
395 administered vaccines used in Studies 494-01, P3T06, and 494-03 are provided in Table 1 [see

396 *Clinical Trials Experience (6.1)*]. In Study M5A10, participants were randomized to receive
397 Pentacel or separately administered DAPTACEL, IPOL, and ActHIB at 2, 4, and 6 months of
398 age. 7-valent pneumococcal conjugate (PCV7, Wyeth Pharmaceuticals Inc.) at 2, 4, and 6
399 months of age, and Hepatitis B vaccine (Merck and Co. or GlaxoSmithKline Biologicals) at 2
400 and 6 months of age, were administered concomitantly with Pentacel or Control vaccines.

401 **14.1 Diphtheria**

402 The proportions of participants achieving diphtheria antitoxin seroprotective levels one month
403 following three and four doses of Pentacel or DAPTACEL in Study P3T06 are provided in
404 Table 3.

405 **14.2 Tetanus**

406 The proportions of participants achieving tetanus antitoxoid seroprotective levels one month
407 following three and four doses of Pentacel or DAPTACEL in Study P3T06 are provided in Table
408 3.

409 **Table 3: Study P3T06 Diphtheria Antitoxin and Tetanus Antitoxoid Responses One Month**
410 **Following Dose 3 and Dose 4 of Pentacel or DAPTACEL + IPOL + ActHIB in US Children**
411 **Vaccinated at 2, 4, 6, and 15-16 Months of Age**

	Pentacel	DAPTACEL + IPOL + ActHIB
Post-Dose 3	N = 331-345	N = 1,037-1,099
Diphtheria Antitoxin % ≥0.01 IU/mL* % ≥0.10 IU/mL†	100.0% 98.8%	100.0% 98.5%
Tetanus Antitoxoid % ≥0.10 IU/mL†	99.7%	100.0%
Post-Dose 4	N = 341-352	N = 328-334
Diphtheria Antitoxin % ≥0.10 IU/mL* % ≥1.0 IU/mL†	100.0% 96.5%	100.0% 95.7%
Tetanus Antitoxoid % ≥0.10 IU/mL* % ≥1.0 IU/mL‡	100.0% 92.9%	100.0% 99.4%

412 Per Protocol Immunogenicity population.

413 * Seroprotection rate following Pentacel vaccine is not inferior to DAPTACEL vaccine (upper limit of 90% CI of
414 the difference DAPTACEL – Pentacel is <10%).

415 † Non-inferiority criteria were not pre-specified.

416 ‡ With the ELISA used in this study, a tetanus antitoxoid level of 1.0 IU/mL is 10 times the protective level.

417 **14.3 Pertussis**

418 In a clinical pertussis vaccine efficacy study conducted in Sweden during 1992-1995
419 (Sweden I Efficacy Trial), 2,587 infants received DAPTACEL and 2,574 infants received a non-
420 US licensed DT vaccine as placebo at 2, 4, and 6 months of age. (1) The mean length of follow-
421 up was 2 years after the third dose of vaccine. The protective efficacy of DAPTACEL against
422 pertussis after 3 doses of vaccine using the World Health Organization (WHO) case
423 definition (≥ 21 consecutive days of paroxysmal cough with culture or serologic confirmation or
424 epidemiologic link to a confirmed case) was 84.9% (95% confidence interval [CI] 80.1%,
425 88.6%). The protective efficacy of DAPTACEL against mild pertussis (≥ 1 day of cough with
426 laboratory confirmation) was 77.9% (95% CI 72.6%, 82.2%). Protection against pertussis by
427 DAPTACEL was sustained for the 2-year follow-up period.

428 Based on comparisons of the immune responses to DAPTACEL in US infants (Post-Dose 3) and
429 Canadian children (Post-Dose 4) relative to infants who participated in the Sweden I Efficacy
430 Trial, it was concluded that 4 doses of DAPTACEL were needed for primary immunization
431 against pertussis in US children. (1)

432 In a serology bridging analysis, immune responses to FHA, PRN and FIM in a subset of infants
433 who received three doses of DAPTACEL in the Sweden I Efficacy Trial were compared to the
434 Post-Dose 3 and Post-Dose 4 responses in a subset of US children from Study 494-01 who
435 received Pentacel (Table 4). Available stored sera from infants who received DAPTACEL in the
436 Sweden I Efficacy Trial and sera from children who received PCV7 concomitantly with the first
437 three doses of Pentacel in Study 494-01 (Table 1) were assayed in parallel. Data on levels of
438 antibody to PT using an adequately specific assay were not available for this serology bridging
439 analysis.

440 Geometric mean antibody concentrations (GMCs) and seroconversion rates for antibodies to
441 FHA, PRN and FIM one month following Dose 3 of DAPTACEL in the subset of infants from
442 the Sweden I Efficacy Trial and one month following Dose 3 and Dose 4 of Pentacel in a subset
443 of infants from US Study 494-01 are presented in Table 4. Seroconversion was defined as 4-fold
444 rise in antibody level (Post-Dose 3/Pre-Dose 1 or Post-Dose 4/Pre-Dose 1). For anti-FHA and
445 anti-FIM, the non-inferiority criteria were met for seroconversion rates, and for anti-FHA, anti-
446 PRN, and anti-FIM, the non-inferiority criteria were met for GMCs, following Dose 4 of
447 Pentacel relative to Dose 3 of DAPTACEL. The non-inferiority criterion for anti-PRN
448 seroconversion following Dose 4 of Pentacel relative to Dose 3 of DAPTACEL was not met
449 [upper limit of 95% CI for difference in rate (DAPTACEL minus Pentacel) = 13.24%]. Whether
450 the lower anti-PRN seroconversion rate following Dose 4 of Pentacel in US children relative to
451 Dose 3 of DAPTACEL in Swedish infants correlates with diminished efficacy of Pentacel
452 against pertussis is unknown.

453

454 **Table 4: FHA, PRN and FIM Antibody Responses One Month Following Dose 3 of**
 455 **DAPTACEL in a Subset of Infants Vaccinated at 2, 4, and 6 Months of Age in the Sweden I**
 456 **Efficacy Trial and One Month Following Dose 3 and Dose 4 of Pentacel in a Subset of**
 457 **Infants Vaccinated at 2, 4, 6, and 15-16 Months of Age in US Study 494-01**

	Post-Dose 3 DAPTACEL Sweden I Efficacy Trial N = 80	Post-Dose 3 Pentacel* US Study 494-01 N = 730-995	Post-Dose 4 Pentacel† US Study 494-01 N = 507-554
Anti-FHA			
% achieving 4-fold rise‡	68.8	79.8	91.7§
GMC (EU/mL)	40.70	71.46	129.85§
Anti-PRN			
% achieving 4-fold rise‡	98.8	74.4	89.2¶
GMC (EU/mL)	111.26	38.11	90.82§
Anti-FIM			
% achieving 4-fold rise‡	86.3	86.5	91.5§
GMC (EU/mL)	339.31	265.02	506.57§

Analyzed sera were from subsets of the Per Protocol Immunogenicity populations in each study.

Data on anti-PT levels using an adequately specific assay were not available.

458 * Non-inferiority criteria were not pre-specified for the comparisons of immune responses to Pentacel vaccine
 459 Post-Dose 3 vs. DAPTACEL vaccine Post-Dose 3.

460 † Pre-specified non-inferiority analyses compared immune responses to Pentacel vaccine Post-Dose 4 vs.
 461 DAPTACEL vaccine Post-Dose 3.

462 ‡ Fold rise was calculated as Post-Dose 3/Pre-Dose 1 antibody level or Post-Dose 4/Pre-Dose 1 antibody level.

463 § Percent achieving 4-fold rise or GMC Post-Dose 4 Pentacel vaccine is not inferior to Post-Dose 3 DAPTACEL
 464 vaccine [upper limit of 95% CI for difference in rates (DAPTACEL minus Pentacel) <10% and upper limit of
 465 90% CI for GMC ratio (DAPTACEL/Pentacel) <1.5].

466 ¶ Non-inferiority criterion is not met for percent achieving 4-fold rise in anti-PRN Post-Dose 4 Pentacel vaccine
 467 relative to Post-Dose 3 DAPTACEL vaccine [upper limit of 95% CI for difference in rates (DAPTACEL minus
 468 Pentacel) = 13.24%, exceeds the non-inferiority criterion of <10%].

469 In a separate study, Study P3T06, US infants were randomized to receive either Pentacel or
 470 DAPTACEL + IPOL + ActHIB at 2, 4, 6, and 15-16 months of age (Table 1). The pertussis
 471 immune responses (GMCs and seroconversion rates) one month following the third and fourth
 472 doses were compared between the two groups (Table 5). Seroconversion was defined as a 4-fold
 473 rise in antibody level (Post-Dose 3/Pre-Dose 1 or Post-Dose 4/Pre-Dose 1). Data on anti-PT
 474 responses obtained from an adequately specific assay were available on only a non-random
 475 subset of study participants. The subset of study participants was representative of all study
 476 participants with regard to Pre-Dose 1, Post-Dose 3 and Post-Dose 4 GMCs of antibodies to
 477 FHA, PRN and FIM. For each of the pertussis antigens, non-inferiority criteria were met for
 478 seroconversion rates and GMCs following Dose 3 of Pentacel relative to Dose 3 of DAPTACEL.
 479 Following Dose 4 of Pentacel relative to Dose 4 of DAPTACEL, non-inferiority criteria were
 480 met for all comparisons except for anti-PRN GMCs [upper limit of 90% CI for ratio of GMCs
 481 (DAPTACEL/Pentacel) = 2.25]. Whether the lower anti-PRN GMC following Dose 4 of
 482 Pentacel relative to Dose 4 of DAPTACEL in US children correlates with diminished efficacy of
 483 Pentacel against pertussis is unknown.

484 **Table 5: Pertussis Antibody Responses One Month Following Doses 3 and 4 of Pentacel or**
 485 **DAPTACEL + IPOL + ActHIB in US Infants Vaccinated at 2, 4, 6, and 15-16 Months of**
 486 **Age in Study P3T06**

	Post-Dose 3 Pentacel	Post-Dose 3 DAPTACEL + IPOL + ActHIB	Post-Dose 4 Pentacel	Post-Dose 4 DAPTACEL + ActHIB
	N = 143	N = 481-485	N = 113	N = 127-128
Anti-PT % achieving 4-fold rise* GMC (EU/mL)	95.8 [†] 102.62 [†]	87.3 61.88	93.8 [‡] 107.89 [‡]	91.3 100.29
	N = 218-318	N = 714-1,016	N = 230-367	N = 237-347
Anti-FHA % achieving 4-fold rise* GMC (EU/mL)	81.9 [§] 73.68 [§]	60.9 29.22	88.4 [¶] 107.94 [¶]	79.3 64.02
Anti-PRN % achieving 4-fold rise* GMC (EU/mL)	74.2 [§] 36.05 [§]	75.4 43.25	92.7 [¶] 93.59 [#]	98.3 186.07
Anti-FIM % achieving 4-fold rise* GMC (EU/mL)	91.7 [§] 268.15 [§]	86.3 267.18	93.5 [¶] 553.39 [¶]	91.6 513.54

487 Per Protocol Immunogenicity population for anti-FHA, anti-PRN, and anti-FIM.

488 Non-random subset of per Protocol Immunogenicity population for anti-PT. See text for further
 489 information on the subset evaluated.

490 * Fold rise was calculated as Post-Dose 3/Pre-Dose 1 antibody level or Post-Dose 4/Pre-Dose 1 antibody level.

491 † Percent achieving 4-fold rise or GMC Post-Dose 3 Pentacel vaccine not inferior to Post-Dose 3 DAPTACEL
 492 vaccine [upper limit of 95% CI for GMC ratio (DAPTACEL/Pentacel) <1.5 and upper limit of 95% CI for
 493 differences in rates (DAPTACEL minus Pentacel) <10%].

494 ‡ Percent achieving 4-fold rise or GMC Post-Dose 4 Pentacel vaccine not inferior to Post-Dose 4 DAPTACEL
 495 vaccine [upper limit of 95% CI for GMC ratio (DAPTACEL/Pentacel) <1.5 and upper limit of 95% CI for
 496 differences in rates (DAPTACEL minus Pentacel) <10%].

497 § Percent achieving 4-fold rise or GMC Post-Dose 3 Pentacel vaccine not inferior to Post-Dose 3 DAPTACEL
 498 vaccine [upper limit of 90% CI for GMC ratio (DAPTACEL/Pentacel) <1.5 and upper limit of 90% CI for
 499 differences in rates (DAPTACEL minus Pentacel) <10%].

500 ¶ Percent achieving 4-fold rise or GMC Post-Dose 4 Pentacel vaccine not inferior to Post-Dose 4 DAPTACEL
 501 vaccine [upper limit of 90% CI for GMC ratio (DAPTACEL/Pentacel) <1.5 and upper limit of 90% CI for
 502 differences in rates (DAPTACEL minus Pentacel) <10%].

503 # Non-inferiority criterion is not met for GMC Post-Dose 4 Pentacel vaccine relative to Post-Dose 4 DAPTACEL
 504 vaccine [upper limit of 90% CI for GMC ratio (DAPTACEL/Pentacel) = 2.25, which exceeds the non-
 505 inferiority criterion of <1.5].

506 **14.4 Poliomyelitis**

507 In Study P3T06 (Table 1), in which infants were randomized to receive the first three doses of
508 Pentacel or DAPTACEL + IPOL + ActHIB at 2, 4, and 6 months of age, one month following
509 the third dose of study vaccines, $\geq 99.4\%$ of participants in both groups
510 (Pentacel: N = 338-350), (DAPTACEL + IPOL + ActHIB: N = 1,050-1,097) achieved
511 neutralizing antibody levels of $\geq 1:8$ for Poliovirus types 1, 2, and 3.

512 In Study 494-01 (Table 1), in which infants were randomized to receive Pentacel or HCPDT +
513 POLIOVAX + ActHIB, GMTs (1/dil) of antibodies to Poliovirus types 1, 2, and 3 one month
514 following Dose 4 of Pentacel (N = 851-857) were 2,304, 4,178, and 4,415, respectively, and one
515 month following Dose 4 of POLIOVAX (N = 284-287) were 2,330, 2,840, and 3,300,
516 respectively.

517 **14.5 Invasive Disease due to *H. Influenzae* Type b**

518 Anti-PRP seroprotection rates and GMCs one month following Dose 3 of Pentacel or separately
519 administered ActHIB in studies 494-01, P3T06, and M5A10 are presented in Table 6. In Study
520 494-01, non-inferiority criteria were not met for the proportion of participants who achieved an
521 anti-PRP level ≥ 1.0 mcg/mL and for anti-PRP GMCs following Pentacel compared with
522 separately administered ActHIB. In each of Studies P3T06 and M5A10, the non-inferiority
523 criterion was met for the proportion of participants who achieved an anti-PRP level ≥ 1.0
524 mcg/mL following Pentacel compared with separately administered ActHIB. In Study M5A10,
525 the non-inferiority criterion was met for anti-PRP GMCs following Pentacel compared with
526 separately administered ActHIB.

527

528 **Table 6: Anti-PRP Seroprotection Rates and GMCs One Month Following Three Doses of**
529 **Pentacel or Separate DTaP + IPV + ActHIB Administered at 2, 4, and 6 Months of Age in**
530 **Studies 494-01, P3T06, and M5A10**

	Study 494-01	
	Pentacel N = 1,127	HCPDT + POLIOVAX + ActHIB N = 401
% achieving anti-PRP ≥ 0.15 mcg/mL	95.4*	98.3
% achieving anti-PRP ≥ 1.0 mcg/mL	79.1 [†]	88.8
Anti-PRP GMC (mcg/mL)	3.19 [‡]	6.23
	Study P3T06	
	Pentacel N = 365	DAPTACEL + IPOL + ActHIB N = 1,128
% achieving anti-PRP ≥ 0.15 mcg/mL	92.3*	93.3
% achieving anti-PRP ≥ 1.0 mcg/mL	72.1*	70.8
Anti-PRP GMC (mcg/mL)	2.31 [§]	2.29
	Study M5A10	
	Pentacel N = 826	DAPTACEL + IPOL + ActHIB N = 421
% achieving anti-PRP ≥ 0.15 mcg/mL	93.8 [¶]	90.3
% achieving anti-PRP ≥ 1.0 mcg/mL	75.1 [¶]	74.8
Anti-PRP GMC (mcg/mL)	2.52 [#]	2.38

Per Protocol Immunogenicity population for all studies.

IPV indicates Poliovirus Vaccine Inactivated.

531 * Percent achieving specified level following Pentacel vaccine not inferior to ActHIB vaccine [upper limit of 90%
532 CI for difference in rates (ActHIB minus Pentacel) <10%].

533 [†] Non-inferiority criterion not met for percent achieving anti-PRP ≥ 1.0 mcg/mL following Pentacel vaccine
534 relative to ActHIB vaccine [upper limit of 90% CI for difference in rates (ActHIB minus Pentacel), 12.9%,
535 exceeds the non-inferiority criterion <10%].

536 [‡] Non-inferiority criterion not met for GMC following Pentacel vaccine relative to ActHIB vaccine [upper limit
537 of 90% CI of GMC ratio (ActHIB/Pentacel), 2.26, exceeds the non-inferiority criterion <1.5].

538 [§] Non-inferiority criterion not pre-specified.

539 [¶] Percent achieving specified level following Pentacel vaccine not inferior to ActHIB vaccine [upper limit of 95%
540 CI for difference in rates (ActHIB minus Pentacel) <10%].

541 [#] GMC following Pentacel vaccine not inferior to ActHIB vaccine [upper limit of 90% CI of GMC ratio
542 (ActHIB/Pentacel) <1.5].

543 In Study 494-01, at 15 months of age prior to receipt of Dose 4 of study vaccines, 68.6% of
544 Pentacel recipients (N = 829) and 80.8% of separately administered ActHIB recipients (N = 276)
545 had an anti-PRP level ≥ 0.15 mcg/mL. Following Dose 4 of study vaccines, 98.2% of Pentacel
546 recipients (N = 874) and 99.0% of separately administered ActHIB recipients (N = 291) had an
547 anti-PRP level ≥ 1.0 mcg/mL.

548 In Study P3T06, at 15 months of age prior to receipt of Dose 4 of study vaccines, 65.4% of
549 Pentacel recipients (N = 335) and 60.7% of separately administered ActHIB recipients (N = 323)

550 had an anti-PRP level ≥ 0.15 mcg/mL. Following Dose 4 of study vaccines, 97.8% of Pentacel
551 recipients (N = 361) and 95.9% of separately administered ActHIB recipients (N = 340) had an
552 anti-PRP level ≥ 1.0 mcg/mL.

553 **14.6 Concomitantly Administered Vaccines**

554 In Study P3T06, (Table 1) there was no evidence for reduced antibody responses to hepatitis B
555 vaccine (percent of participants with anti-HBsAg ≥ 10 mIU/mL and GMCs) or PCV7 (percent of
556 participants with antibody levels ≥ 0.15 mcg/mL and ≥ 0.5 mcg/mL and GMCs to each serotype)
557 administered concomitantly with Pentacel (N = 321-325) relative to these vaccines administered
558 concomitantly with DAPTACEL + IPOL + ActHIB (N = 998-1,029). The immune responses to
559 hepatitis B vaccine and PCV7 were evaluated one month following the third dose.

560 In Study 494-03, (Table 1) there was no evidence for interference in the immune response to the
561 fourth dose of PCV7 (percent of participants with antibody levels ≥ 0.15 mcg/mL and ≥ 0.5
562 mcg/mL and GMCs to each serotype) administered at 15 months of age concomitantly with
563 Pentacel (N = 155) relative to this vaccine administered concomitantly with MMR and varicella
564 vaccines (N = 158). There was no evidence for interference in the immune response to MMR and
565 varicella vaccines (percent of participants with pre-specified seroresponse level) administered at
566 15 months of age concomitantly with Pentacel (N = 154) relative to these vaccines administered
567 concomitantly with PCV7 (N = 144). The immune responses to MMR, varicella vaccine and the
568 fourth dose of PCV7 were evaluated one month post-vaccination.

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613 **16 HOW SUPPLIED/STORAGE AND HANDLING**

614 **16.1 How Supplied**

615 The vial stoppers for the DTaP-IPV and ActHIB vaccine components of Pentacel are not made
616 with natural rubber latex.

617 5 Dose Package (NDC No. 49281-511-05) containing 5 vials of DTaP-IPV component (NDC
618 No. 49281-561-01) to be used to reconstitute 5 single-dose vials of lyophilized ActHIB vaccine
619 component (NDC No. 49281-544-58).

620

621 **16.2 Storage and Handling**

622 Pentacel should be stored at 2° to 8°C (35° to 46°F). Do not freeze. Product which has been
623 exposed to freezing should not be used. Do not use after expiration date shown on the label.

624 **17 PATIENT COUNSELING INFORMATION**

625 Before administration of Pentacel, health-care personnel should inform the parent or guardian of
626 the benefits and risks of the vaccine and the importance of completing the immunization series
627 unless a contraindication to further immunization exists.

628 The health-care provider should inform the parent or guardian about the potential for adverse
629 reactions that have been temporally associated with Pentacel or other vaccines containing similar
630 ingredients. The health-care provider should provide the Vaccine Information Statements (VIS)
631 which are required by the National Childhood Vaccine Injury Act of 1986 to be given with each
632 immunization. The parent or guardian should be instructed to report adverse reactions to their
633 health-care provider.

634 Manufactured by:
635 **Sanofi Pasteur Limited**
636 Toronto Ontario Canada

637 and **Sanofi Pasteur SA**
638 Marcy L'Etoile France

639 Distributed by:
640 **Sanofi Pasteur Inc.**
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