

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

-----**RECENT MAJOR CHANGES**-----

-----**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-hyposensitive 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 Sanofi Pasteur Inc., 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**

Revised: [09/2016]

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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 for
5 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 *14 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 After removing the “flip-off” caps, cleanse the DTaP-IPV and ActHIB vial stoppers with a
47 suitable germicide. Do not remove the vial stoppers or metal seals holding them in place. Just
48 before use, thoroughly but gently shake the vial of DTaP-IPV component, withdraw the entire
49 liquid content and inject into the vial of the lyophilized ActHIB vaccine component. Gently swirl
50 the vial now containing Pentacel until a cloudy, uniform, white to off-white (yellow tinge)
51 suspension results.

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

55 Using a sterile needle and syringe and aseptic technique, withdraw and administer a single 0.5 mL
56 dose of Pentacel intramuscularly. Use a separate sterile needle and syringe for each injection.

57 Changing needles between withdrawing the vaccine from the vial and injecting it into a recipient
58 is not necessary unless the needle has been damaged or contaminated. Pentacel should be used
59 immediately after reconstitution. Refer to Figures 1, 2, 3, 4 and 5.

60

61 **Pentacel: Instructions for Reconstitution of ActHIB Vaccine Component with DTaP-IPV**
62 **Component**

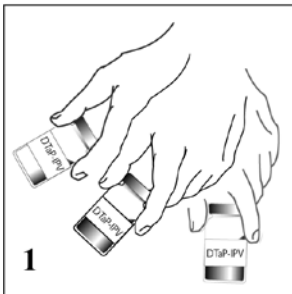


Figure 1
Gently shake the vial of DTaP-IPV component.

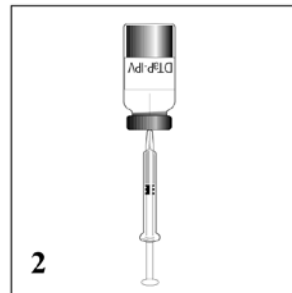


Figure 2
Withdraw the entire liquid content.

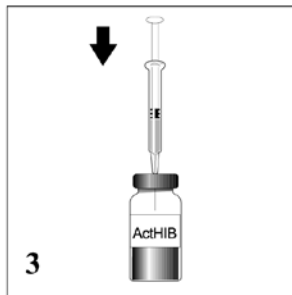


Figure 3
Insert the syringe needle through the stopper of the vial of lyophilized ActHIB vaccine component and inject the liquid into the vial.

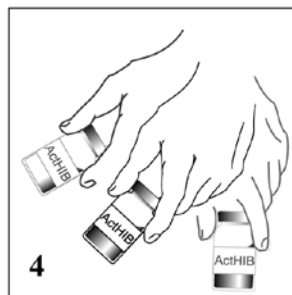


Figure 4
Swirl vial gently.

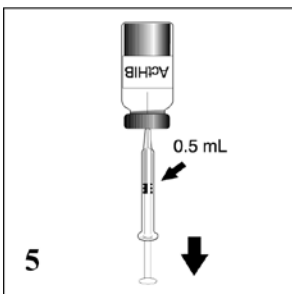


Figure 5
After reconstitution, immediately withdraw 0.5 mL of Pentacel vaccine and administer intramuscularly. Pentacel vaccine should be used immediately after reconstitution.

63

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

68 Do not administer this product intravenously or subcutaneously.

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

70 **3 DOSAGE FORMS AND STRENGTHS**

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

74 **4 CONTRAINDICATIONS**

75 **4.1 Hypersensitivity**

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

80 **4.2 Encephalopathy**

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

85 **4.3 Progressive Neurologic Disorder**

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

90 **5 WARNINGS AND PRECAUTIONS**

91 **5.1 Management of Acute Allergic Reactions**

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

94 **5.2 Adverse Reactions Following Prior Pertussis Vaccination**

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

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

103 **5.3 Guillain-Barré Syndrome and Brachial Neuritis**

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

108 **5.4 Infants and Children with a History of Previous Seizures**

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

113 **5.5 Limitations of Vaccine Effectiveness**

114 Vaccination with Pentacel may not protect all individuals.

115 **5.6 Altered Immunocompetence**

116 If Pentacel is administered to immunocompromised persons, including persons receiving
117 immunosuppressive therapy, the expected immune response may not be obtained. [See *Drug*
118 *Interactions* (7.2).]

119 **5.7 Apnea in Premature Infants**

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

124 **6 ADVERSE REACTIONS**

125 **6.1 Data from Clinical Studies**

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

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

135 The safety of Pentacel was evaluated in four clinical studies in which a total of 5,980 participants
136 received at least one dose of Pentacel. In three of the studies, conducted in the US, a total of 4,198
137 participants were enrolled to receive four consecutive doses of Pentacel. In the fourth study,
138 conducted in Canada, 1,782 participants previously vaccinated with three doses of Pentacel
139 received a fourth dose. The vaccination schedules of Pentacel, Control vaccines, and
140 concomitantly administered vaccines used in these studies are provided in [Table 1](#).

141 Across the four studies, 50.8% of participants were female. Among participants in the three US
142 studies, 64.5% were Caucasian, 9.2% were Black, 12.9% were Hispanic, 3.9% were Asian, and
143 9.5% were of other racial/ethnic groups. In the two controlled studies, the racial/ethnic

144 distribution of participants who received Pentacel and Control vaccines was similar. In the
145 Canadian fourth dose study, 86.0% of participants were Caucasian, 1.9% were Black, 0.8% were
146 Hispanic, 4.3% were Asian, 2.0% were East Indian, 0.5% were Native Indian, and 4.5% were of
147 other racial/ethnic groups.

148 **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.

* PCV7 manufactured by Wyeth Laboratories.

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

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

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

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

150 **Solicited Adverse Reactions**

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

Table 2: Number (Percentage) of Children with Selected Solicited Adverse Reactions by Severity Occurring within 0-3 days 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

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

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

‡ 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%, 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 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%, respectively, for Pentacel vaccine, and 61.1%, 36.6%, 1.7% and 0.5%, respectively, for DAPTACEL + ActHIB.

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

158 **Hypotonic Hyporesponsive Episodes**

159 In Study P3T06, the diary cards included questions pertaining to HHEs. In Studies 494-01,
160 494-03, and 5A9908, a question about the occurrence of fainting or change in mental status was
161 asked during post-vaccination phone calls. Across these 4 studies, no HHEs, as defined in a report
162 of a US Public Health Service workshop (4) were reported among participants who received
163 Pentacel (N = 5,979), separately administered HCPDT + POLIOVAX + ActHIB (N = 1,032) or
164 separately administered DAPTACEL + IPOL + ActHIB (N = 1,455). Hypotonia not fulfilling
165 HHE criteria within 7 days following vaccination was reported in 4 participants after the
166 administration of Pentacel (1 on the same day as the 1st dose; 3 on the same day as the 3rd dose)
167 and in 1 participant after the administration of DAPTACEL + IPOL + ActHIB (4 days following
168 the 1st dose).

169 **Seizures**

170 Across Studies 494-01, 494-03, 5A9908 and P3T06, a total of 8 participants experienced a seizure
171 within 7 days following either Pentacel (4 participants; N = 4,197 for at least one of Doses 1-3; N
172 = 5,033 for Dose 4), separately administered HCPDT + POLIOVAX + ActHIB (3 participants; N
173 = 1,032 for at least one of Doses 1-3, N = 739 for Dose 4), separately administered DAPTACEL
174 + IPOL + ActHIB (1 participant; N = 1,455 for at least one of Doses 1-3), or separately
175 administered DAPTACEL + ActHIB (0 participants; N = 418 for Dose 4). Among the four
176 participants who experienced a seizure within 7 days following Pentacel, one participant in Study
177 494-01 had an afebrile seizure 6 days after the first dose, one participant in Study 494-01 had a
178 possible seizure the same day as the third dose, and two participants in Study 5A9908 had a
179 febrile seizure 2 and 4 days, respectively, after the fourth dose. Among the four participants who
180 experienced a seizure within 7 days following Control vaccines, one participant had an afebrile
181 seizure the same day as the first dose of DAPTACEL + IPOL + ActHIB, one participant had an
182 afebrile seizure the same day as the second dose of HCPDT + POLIOVAX + ActHIB, and two
183 participants had a febrile seizure 6 and 7 days, respectively, after the fourth dose of HCPDT +
184 POLIOVAX + ActHIB.

185 **Serious Adverse Events**

186 In Study P3T06, within 30 days following any of Doses 1-3 of Pentacel or Control vaccines, 19 of
187 484 (3.9%) participants who received Pentacel and 50 of 1,455 (3.4%) participants who received
188 DAPTACEL + IPOL + ActHIB experienced a serious adverse event. Within 30 days following
189 Dose 4 of Pentacel or Control vaccines, 5 of 431 (1.2%) participants who received Pentacel and 4
190 of 418 (1.0%) participants who received DAPTACEL + ActHIB experienced a serious adverse
191 event. In Study 494-01, within 30 days following any of Doses 1-3 of Pentacel or Control
192 vaccines, 23 of 2,506 (0.9%) participants who received Pentacel and 11 of 1,032 (1.1%)
193 participants who received HCPDT + POLIOVAX + ActHIB experienced a serious adverse event.
194 Within 30 days following Dose 4 of Pentacel or Control vaccines, 6 of 1,862 (0.3%) participants
195 who received Pentacel and 2 of 739 (0.3%) participants who received HCPDT + POLIOVAX +
196 ActHIB experienced a serious adverse event.

197 Across Studies 494-01, 494-03 and P3T06, within 30 days following any of Doses 1-3 of Pentacel
198 or Control vaccines, overall, the most frequently reported serious adverse events were
199 bronchiolitis, dehydration, pneumonia and gastroenteritis. Across Studies 494-01, 494-03,
200 5A9908 and P3T06, within 30 days following Dose 4 of Pentacel or Control vaccines, overall, the
201 most frequently reported serious adverse events were dehydration, gastroenteritis, asthma, and
202 pneumonia.

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

208 A total of 5 deaths occurred during Studies 494-01, 494-03, 5A9908 and P3T06: 4 in children
209 who had received Pentacel (N = 5,979) and one in a participant who had received DAPTACEL +
210 IPOL + ActHIB (N = 1,455). There were no deaths reported in children who received HCPDT +
211 POLIOVAX + ActHIB (N = 1,032). Causes of death among children who received Pentacel were
212 asphyxia due to suffocation, head trauma, Sudden Infant Death syndrome, and neuroblastoma (8,

213 23, 52 and 256 days post-vaccination, respectively). One participant with ependymoma died
214 secondary to aspiration 222 days following DAPTACEL + IPOL + ActHIB.

215 **6.2 Data from Post-Marketing Experience**

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

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

- 223 • ***Cardiac disorders***

224 Cyanosis

- 225 • ***Gastrointestinal disorders***

226 Vomiting, diarrhea

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

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

- 231 • ***Immune system disorders***

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

- 233 • ***Infections and infestations***

234 Meningitis, rhinitis, viral infection

- 235 • ***Metabolism and nutrition disorders***
- 236 Decreased appetite

- 237 • ***Nervous system disorders***
- 238 Somnolence, HHE, depressed level of consciousness

- 239 • ***Psychiatric disorders***
- 240 Screaming

- 241 • ***Respiratory, thoracic and mediastinal disorders***
- 242 Apnea, cough

- 243 • ***Skin and subcutaneous tissue disorders***
- 244 Erythema, skin discoloration

- 245 • ***Vascular disorders***
- 246 Pallor

247 **7 DRUG INTERACTIONS**

248 **7.1 Concomitant Administration with Other Vaccines**

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

254 **7.2 Immunosuppressive Treatments**

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

258 **7.3 Drug/Laboratory Test Interactions**

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

262 **8 USE IN SPECIFIC POPULATIONS**

263 **8.1 Pregnancy**

264 **Pregnancy Category C**

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

268 **8.4 Pediatric Use**

269 The safety and effectiveness of Pentacel was established in the age group 6 weeks through 18
270 months on the basis of clinical studies. [See *Adverse Reactions (6.1)* and *Clinical Studies (14)*.]
271 The safety and effectiveness of Pentacel in the age group 19 months through 4 years is supported
272 by evidence in children 6 weeks through 18 months. The safety and effectiveness of Pentacel in
273 infants less than 6 weeks of age and in children 5 to 16 years of age have not been established.

274 **11 DESCRIPTION**

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

282 Each 0.5 mL dose contains 15 Lf diphtheria toxoid, 5 Lf tetanus toxoid, acellular pertussis
283 antigens [20 mcg detoxified pertussis toxin (PT), 20 mcg filamentous hemagglutinin (FHA),
284 3 mcg pertactin (PRN), 5 mcg fimbriae types 2 and 3 (FIM)], inactivated polioviruses
285 [40 D-antigen units (DU) Type 1 (Mahoney), 8 DU Type 2 (MEF-1), 32 DU Type 3 (Saukett)]
286 and 10 mcg PRP of *H. influenzae* type b covalently bound to 24 mcg of tetanus toxoid (PRP-T).

287 Other ingredients per 0.5 mL dose include 1.5 mg aluminum phosphate (0.33 mg aluminum) as
288 the adjuvant, polysorbate 80 (approximately 10 ppm by calculation), 42.5 mg sucrose, ≤5 mcg
289 residual formaldehyde, <50 ng residual glutaraldehyde, ≤50 ng residual bovine serum albumin,
290 3.3 mg (0.6% v/v) 2-phenoxyethanol (not as a preservative), <4 pg of neomycin and <4 pg
291 polymyxin B sulfate.

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

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

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

306 Poliovirus Type 1, Type 2 and Type 3 are each grown in separate cultures of MRC-5 cells, a line
307 of normal human diploid cells, by the microcarrier method. (9) (10) The cells are grown in CMRL
308 (Connaught Medical Research Laboratories) 1969 medium, supplemented with calf serum. For
309 viral growth, the culture medium is replaced by Medium 199, without calf serum. After
310 clarification and filtration, the viral suspensions are concentrated by ultrafiltration, and purified by
311 liquid chromatography steps. The monovalent viral suspensions are inactivated with
312 formaldehyde. Monovalent concentrates of each inactivated poliovirus are combined to produce a
313 trivalent poliovirus concentrate.

314 The adsorbed diphtheria, tetanus and acellular pertussis antigens are combined with aluminum
315 phosphate (as adjuvant), 2-phenoxyethanol (not as a preservative) and water for injection, into an
316 intermediate concentrate. The trivalent poliovirus concentrate is added and the DTaP-IPV
317 component is diluted to its final concentration. The DTaP-IPV component does not contain a
318 preservative.

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

324 PRP, a high molecular weight polymer, is prepared from the *Haemophilus influenzae* type b strain
325 1482 grown in a semi-synthetic medium. (11) The tetanus toxoid for conjugation to PRP is
326 prepared by ammonium sulfate purification, and formalin inactivation of the toxin from cultures
327 of *Clostridium tetani* (Harvard strain) grown in a modified Mueller and Miller medium. (12) The
328 toxoid is filter sterilized prior to the conjugation process. The ActHIB component does not
329 contain a preservative. Potency of the ActHIB component is specified on each lot by limits on the
330 content of PRP polysaccharide and protein per dose and the proportion of polysaccharide and
331 protein that is characterized as high molecular weight conjugate.

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

334 **12 CLINICAL PHARMACOLOGY**

335 **12.1 Mechanism of Action**

336 **Diphtheria**

337 Diphtheria is an acute toxin-mediated disease caused by toxigenic strains of *C. diphtheriae*.
338 Protection against disease is due to the development of neutralizing antibodies to diphtheria toxin.
339 A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of
340 protection. Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective. (13) Levels
341 of 1.0 IU/mL have been associated with long-term protection. (14)

342 **Tetanus**

343 Tetanus is an acute disease caused by an extremely potent neurotoxin produced by *C. tetani*.
344 Protection against disease is due to the development of neutralizing antibodies to tetanus toxin. A
345 serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assay is
346 considered the minimum protective level. (13) (15) A tetanus antitoxoid level ≥ 0.1 IU/mL as
347 measured by the ELISA used in clinical studies of Pentacel is considered protective.

348 **Pertussis**

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

352 **Poliomyelitis**

353 Polioviruses, of which there are three serotypes (Types 1, 2, and 3) are enteroviruses. The
354 presence of poliovirus type-specific neutralizing antibodies has been correlated with protection
355 against poliomyelitis. (16)

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

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

359 Based on data from passive antibody studies (17) and an efficacy study with *H. influenzae* type b
360 polysaccharide vaccine in Finland, (18) a post-vaccination anti-PRP level of 0.15 mcg/mL has
361 been accepted as a minimal protective level. Data from an efficacy study with *H. influenzae* type
362 b polysaccharide vaccine in Finland indicate that a level >1.0 mcg/mL 3 weeks after vaccination
363 predicts protection through a subsequent one-year period. (19) (20) These levels have been used
364 to evaluate the effectiveness of Haemophilus b Conjugate Vaccines, including the ActHIB
365 component of Pentacel.

366 **13 NON-CLINICAL TOXICOLOGY**

367 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

369 **14 CLINICAL STUDIES**

370 The efficacy of Pentacel is based on the immunogenicity of the individual antigens compared to
371 separately administered vaccines. Serological correlates of protection exist for diphtheria, tetanus,
372 poliomyelitis, and invasive disease due to *H. influenzae* type b. [See *Clinical Pharmacology*
373 (12.1).] The efficacy against pertussis, for which there is no well established serological correlate
374 of protection, was based, in part, on a comparison of pertussis immune responses following
375 Pentacel in US children to responses following DAPTACEL (Diphtheria and Tetanus Toxoids
376 and Acellular Pertussis Vaccine Adsorbed (DTaP) manufactured by Sanofi Pasteur Limited) in an
377 efficacy study conducted in Sweden (Sweden I Efficacy Trial). While Pentacel and DAPTACEL
378 contain the same pertussis antigens, manufactured by the same process, Pentacel contains twice as
379 much detoxified PT and four times as much FHA as DAPTACEL.

380 Immune responses to Pentacel were evaluated in four US studies: Studies 494-01, P3T06, 494-03,
381 and M5A10. The vaccination schedules of Pentacel, Control vaccines, and concomitantly
382 administered vaccines used in Studies 494-01, P3T06, and 494-03 are provided in [Table 1](#). [See
383 *Adverse Reactions* (6.1).] In Study M5A10, participants were randomized to receive Pentacel or
384 separately administered DAPTACEL, IPOL, and ActHIB at 2, 4, and 6 months of age. 7-valent
385 pneumococcal conjugate (PCV7, Wyeth Pharmaceuticals Inc.) at 2, 4, and 6 months of age, and
386 Hepatitis B vaccine (Merck and Co. or GlaxoSmithKline Biologicals) at 2 and 6 months of age,
387 were administered concomitantly with Pentacel or Control vaccines.

388 **14.1 Diphtheria**

389 The proportions of participants achieving diphtheria antitoxin seroprotective levels one month
390 following three and four doses of Pentacel or DAPTACEL in Study P3T06 are provided in [Table](#)
391 [3](#).

392 **14.2 Tetanus**

393 The proportions of participants achieving tetanus antitoxoid seroprotective levels one month
394 following three and four doses of Pentacel or DAPTACEL in Study P3T06 are provided in [Table](#)
395 [3](#).

396 **Table 3: Study P3T06 Diphtheria Antitoxin and Tetanus Antitoxoid Responses One Month**
 397 **Following Dose 3 and Dose 4 of Pentacel or DAPTACEL + IPOL + ActHIB in US Children**
 398 **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%

Per Protocol Immunogenicity population.

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

† Non-inferiority criteria were not pre-specified.

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

399

400 **14.3 Pertussis**

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

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

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

423 Geometric mean antibody concentrations (GMCs) and seroconversion rates for antibodies to
424 FHA, PRN and FIM one month following Dose 3 of DAPTACEL in the subset of infants from the
425 Sweden I Efficacy Trial and one month following Dose 3 and Dose 4 of Pentacel in a subset of
426 infants from US Study 494-01 are presented in Table 4. Seroconversion was defined as 4-fold rise
427 in antibody level (Post-Dose 3/Pre-Dose 1 or Post-Dose 4/Pre-Dose 1). For anti-FHA and anti-
428 FIM, the non-inferiority criteria were met for seroconversion rates, and for anti-FHA, anti-PRN,

429 and anti-FIM, the non-inferiority criteria were met for GMCs, following Dose 4 of Pentacel
430 relative to Dose 3 of DAPTACEL. The non-inferiority criterion for anti-PRN seroconversion
431 following Dose 4 of Pentacel relative to Dose 3 of DAPTACEL was not met [upper limit of 95%
432 CI for difference in rate (DAPTACEL minus Pentacel) = 13.24%]. Whether the lower anti-PRN
433 seroconversion rate following Dose 4 of Pentacel in US children relative to Dose 3 of
434 DAPTACEL in Swedish infants correlates with diminished efficacy of Pentacel against pertussis
435 is unknown.

436 **Table 4: FHA, PRN and FIM Antibody Responses One Month Following Dose 3 of**
 437 **DAPTACEL in a Subset of Infants Vaccinated at 2, 4, and 6 Months of Age in the Sweden I**
 438 **Efficacy Trial and One Month Following Dose 3 and Dose 4 of Pentacel in a Subset of**
 439 **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.

- * Non-inferiority criteria were not pre-specified for the comparisons of immune responses to Pentacel vaccine Post-Dose 3 vs. DAPTACEL vaccine Post-Dose 3.
- † Pre-specified non-inferiority analyses compared immune responses to Pentacel vaccine Post-Dose 4 vs. DAPTACEL vaccine Post-Dose 3.
- ‡ Fold rise was calculated as Post-Dose 3/Pre-Dose 1 antibody level or Post-Dose 4/Pre-Dose 1 antibody level.
- § Percent achieving 4-fold rise or GMC Post-Dose 4 Pentacel vaccine is not inferior to Post-Dose 3 DAPTACEL vaccine [upper limit of 95% CI for difference in rates (DAPTACEL minus Pentacel) <10% and upper limit of 90% CI for GMC ratio (DAPTACEL/Pentacel) <1.5].
- ** Non-inferiority criterion is not met for percent achieving 4-fold rise in anti-PRN Post-Dose 4 Pentacel vaccine relative to Post-Dose 3 DAPTACEL vaccine [upper limit of 95% CI for difference in rates (DAPTACEL minus Pentacel) = 13.24%, exceeds the non-inferiority criterion of <10%].

440 In a separate study, Study P3T06, US infants were randomized to receive either Pentacel or
441 DAPTACEL + IPOL + ActHIB at 2, 4, 6, and 15-16 months of age (Table 1). The pertussis
442 immune responses (GMCs and seroconversion rates) one month following the third and fourth
443 doses were compared between the two groups (Table 5). Seroconversion was defined as a 4-fold
444 rise in antibody level (Post-Dose 3/Pre-Dose 1 or Post-Dose 4/Pre-Dose 1). Data on anti-PT
445 responses obtained from an adequately specific assay were available on only a non-random subset
446 of study participants. The subset of study participants was representative of all study participants
447 with regard to Pre-Dose 1, Post-Dose 3 and Post-Dose 4 GMCs of antibodies to FHA, PRN and
448 FIM. For each of the pertussis antigens, non-inferiority criteria were met for seroconversion rates
449 and GMCs following Dose 3 of Pentacel relative to Dose 3 of DAPTACEL. Following Dose 4 of
450 Pentacel relative to Dose 4 of DAPTACEL, non-inferiority criteria were met for all comparisons
451 except for anti-PRN GMCs [upper limit of 90% CI for ratio of GMCs (DAPTACEL/Pentacel) =
452 2.25]. Whether the lower anti-PRN GMC following Dose 4 of Pentacel relative to Dose 4 of
453 DAPTACEL in US children correlates with diminished efficacy of Pentacel against pertussis is
454 unknown.

455 **Table 5: Pertussis Antibody Responses One Month Following Doses 3 and 4 of Pentacel or**
456 **DAPTACEL + IPOL + ActHIB in US Infants Vaccinated at 2, 4, 6, and 15-16 Months of Age**
457 **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

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

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

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

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

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

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

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

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

458

459 **14.4 Poliomyelitis**

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

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

470 **14.5 Invasive Disease due to *H. Influenzae* Type b**

471 Anti-PRP seroprotection rates and GMCs one month following Dose 3 of Pentacel-or separately
472 administered ActHIB in studies 494-01, P3T06, and M5A10 are presented in Table 6. In Study
473 494-01, non-inferiority criteria were not met for the proportion of participants who achieved an
474 anti-PRP level ≥ 1.0 mcg/mL and for anti-PRP GMCs following Pentacel compared with
475 separately administered ActHIB. In each of Studies P3T06 and M5A10, the non-inferiority
476 criterion was met for the proportion of participants who achieved an anti-PRP level ≥ 1.0 mcg/mL
477 following Pentacel compared with separately administered ActHIB. In Study M5A10, the non-
478 inferiority criterion was met for anti-PRP GMCs following Pentacel compared with separately
479 administered ActHIB.

480

481 **Table 6: Anti-PRP Seroprotection Rates and GMCs One Month Following Three Doses of**
 482 **Pentacel-or Separate DTaP + IPV + ActHIB Administered at 2, 4, and 6 Months of Age in**
 483 **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.

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

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

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

§ Non-inferiority criterion not pre-specified.

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

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

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

489 In Study P3T06, at 15 months of age prior to receipt of Dose 4 of study vaccines, 65.4% of
490 Pentacel recipients (N = 335) and 60.7% of separately administered ActHIB recipients (N = 323)
491 had an anti-PRP level ≥ 0.15 mcg/mL. Following Dose 4 of study vaccines, 97.8% of Pentacel
492 recipients (N = 361) and 95.9% of separately administered ActHIB recipients (N = 340) had an
493 anti-PRP level ≥ 1.0 mcg/mL.

494 **14.6 Concomitantly Administered Vaccines**

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

501 In Study 494-03, (Table 1) there was no evidence for interference in the immune response to the
502 fourth dose of PCV7 (percent of participants with antibody levels ≥ 0.15 mcg/mL and ≥ 0.5
503 mcg/mL and GMCs to each serotype) administered at 15 months of age concomitantly with
504 Pentacel (N = 155) relative to this vaccine administered concomitantly with MMR and varicella
505 vaccines (N = 158). There was no evidence for interference in the immune response to MMR and
506 varicella vaccines (percent of participants with pre-specified seroresponse level) administered at
507 15 months of age concomitantly with Pentacel (N = 154) relative to these vaccines administered
508 concomitantly with PCV7 (N = 144). The immune responses to MMR, varicella vaccine and the
509 fourth dose of PCV7 were evaluated one month post-vaccination.

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560 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

563 5 Dose Package (NDC No. 49281-510-05) containing 5 vials of DTaP-IPV component (NDC No.
564 49281-560-05) to be used to reconstitute 5 single dose vials of lyophilized ActHIB vaccine
565 component (NDC No. 49281-545-15).

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

568 Pentacel should be used immediately after reconstitution.

569 **17 PATIENT COUNSELING INFORMATION**

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

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

579 Manufactured by:

580 **Sanofi Pasteur Limited**

581 Toronto Ontario Canada

582 and **Sanofi Pasteur SA**

583 Lyon France

584 Distributed by:

585 **Sanofi Pasteur Inc.**

586 Swiftwater PA 18370 USA

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