

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

DAPTACEL (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed)

Suspension for Intramuscular Injection

Initial U.S. Approval: 2002

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

- DAPTACEL is a vaccine indicated for active immunization against diphtheria, tetanus and pertussis as a five dose series in infants and children 6 weeks through 6 years of age (prior to 7th birthday). (1)

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

- The five dose immunization series consists of a 0.5 mL intramuscular injection administered at 2, 4, 6 and 15-20 months of age, and at 4-6 years of age. (2.1, 2.2)

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

- Suspension for injection, supplied in single dose (0.5 mL) vials (3)

-----**CONTRAINDICATIONS**-----

- Severe allergic reaction (e.g. anaphylaxis) after a previous dose of any diphtheria toxoid, tetanus toxoid, or pertussis-containing vaccine, or any component of DAPTACEL. (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 DAPTACEL to persons with a history of:
 - fever $\geq 40.5^{\circ}\text{C}$ (105°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 DAPTACEL. (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 DAPTACEL 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 DAPTACEL, 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)
- Syncope (fainting) has been reported following vaccination with DAPTACEL. Procedures should be in place to prevent falling injury and manage syncopal reactions. (5.8)

-----**ADVERSE REACTIONS**-----

- Rates of adverse reactions varied by dose number, with systemic reactions most frequent following doses 1-3 and injection site reactions most frequent following doses 4 and 5. Systemic reactions that occurred in >50% of subjects following any dose included fussiness/irritability, inconsolable crying, and decreased activity/lethargy. Fever $\geq 38.0^{\circ}\text{C}$ occurred in 6-16% of US subjects, depending on dose number. Injection site reactions that occurred in >30% of subjects following any dose included tenderness, redness 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**-----

- In cases where DAPTACEL and Menactra are to be administered to children 4 through 6 years of age, the two vaccines should be administered concomitantly or Menactra should be administered prior to DAPTACEL. Administration of Menactra one month after DAPTACEL has been shown to reduce meningococcal antibody responses to Menactra. (7.1)
- Do not mix with any other vaccine in the same syringe or vial. (7.1)
- Immunosuppressive therapies may reduce the immune response to DAPTACEL. (7.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: [XX/201X]

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1 **FULL PRESCRIBING INFORMATION:**

2 **1 INDICATIONS AND USAGE**

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

6 **2 DOSAGE AND ADMINISTRATION**

7 **2.1 Immunization Series**

8 DAPTACEL is to be administered as a 5 dose series at 2, 4 and 6 months of age (at intervals of 6-
9 8 weeks), at 15-20 months of age and at 4-6 years of age. The first dose may be given as early as
10 6 weeks of age. Four doses of DAPTACEL constitute a primary immunization course for
11 pertussis. The fifth dose is a booster for pertussis immunization. Three doses of DAPTACEL
12 constitute a primary immunization course for diphtheria and tetanus. The fourth and fifth doses
13 are boosters for diphtheria and tetanus immunization. [See *Clinical Studies (14.1, 14.2, 14.3).*]

14 DAPTACEL should be used as the fifth dose of the DTaP series in children who initially received
15 4 doses of Pentacel® [(Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed,
16 Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) vaccine, Sanofi
17 Pasteur Limited]. Pentacel and DAPTACEL contain the same pertussis antigens, manufactured by
18 the same process, although Pentacel contains twice the amount of detoxified pertussis toxin (PT)
19 and four times the amount of filamentous hemagglutinin (FHA) as DAPTACEL.

20 Data are not available on the safety and effectiveness of using mixed sequences of DAPTACEL
21 and DTaP vaccines from different manufacturers for successive doses of the DTaP vaccination
22 series. DAPTACEL may be used to complete the immunization series in infants who have
23 received 1 or more doses of whole-cell pertussis DTP. However, the safety and efficacy of
24 DAPTACEL in such infants have not been fully demonstrated.

25 If a decision is made to withhold any recommended dose of pertussis vaccine, [see
26 *Contraindications (4.2), (4.3)* and *Warnings and Precautions (5.2)*], Diphtheria and Tetanus
27 Toxoids Adsorbed For Pediatric Use (DT) should be administered.

28 **2.2 Administration**

29 Parenteral drug products should be inspected visually for particulate matter and discoloration
30 prior to administration, whenever solution and container permit. If either of these conditions exist,
31 the product should not be administered.

32 After removing the “flip-off” cap, cleanse the vaccine vial stopper with a suitable germicide. Do
33 not remove either the rubber stopper or the metal seal holding it in place. Just before use, shake
34 the vial well, until a uniform, white, cloudy suspension results.

35 Using a sterile needle and syringe and aseptic technique, withdraw and administer a single 0.5 mL
36 dose of DAPTACEL intramuscularly. Use a separate sterile needle and syringe for each injection.
37 Changing needles between withdrawing the vaccine from the vial and injecting it into a recipient
38 is not necessary unless the needle has been damaged or contaminated. In infants younger than 1
39 year, the anterolateral aspect of the thigh provides the largest muscle and is the preferred site of
40 injection. In older children, the deltoid muscle is usually large enough for injection. The vaccine
41 should not be injected into the gluteal area or areas where there may be a major nerve trunk.

42 Do not administer this product intravenously or subcutaneously.

43 DAPTACEL should not be combined through reconstitution or mixed with any other vaccine.

44 **3 DOSAGE FORMS AND STRENGTHS**

45 DAPTACEL is a suspension for injection in 0.5 mL single dose vials. See *Description (11)* for a
46 complete listing of ingredients.

47 **4 CONTRAINDICATIONS**

48 **4.1 Hypersensitivity**

49 A severe allergic reaction (eg, anaphylaxis) after a previous dose of DAPTACEL or any other
50 tetanus toxoid, diphtheria toxoid, or pertussis-containing vaccine, or any other component of this
51 vaccine is a contraindication to administration of DAPTACEL. [See *Description (11)*.] Because
52 of uncertainty as to which component of the vaccine may be responsible, none of the components
53 should be administered. Alternatively, such individuals may be referred to an allergist for
54 evaluation if further immunizations are to be considered.

55 **4.2 Encephalopathy**

56 Encephalopathy (eg, coma, decreased level of consciousness, prolonged seizures) within 7 days of
57 a previous dose of a pertussis containing vaccine that is not attributable to another identifiable
58 cause is a contraindication to administration of any pertussis-containing vaccine, including
59 DAPTACEL.

60 **4.3 Progressive Neurologic Disorder**

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

65 **5 WARNINGS AND PRECAUTIONS**

66 **5.1 Management of Acute Allergic Reactions**

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

69 **5.2 Adverse Reactions Following Prior Pertussis Vaccination**

70 If any of the following events occur within the specified period after administration of a
71 whole-cell pertussis vaccine or a vaccine containing an acellular pertussis component, the
72 decision to administer DAPTACEL should be based on careful consideration of potential benefits
73 and possible risks. [See *Dosage and Administration (2.1)*.]

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

79 **5.3 Guillain-Barré Syndrome and Brachial Neuritis**

80 A review by the Institute of Medicine found evidence for a causal relation between tetanus toxoid
81 and both brachial neuritis and Guillain-Barré syndrome. (1) If Guillain-Barré syndrome occurred
82 within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk for Guillain-Barré
83 syndrome may be increased following DAPTACEL.

84 **5.4 Infants and Children with a History of Previous Seizures**

85 For infants or children with a history of previous seizures, an appropriate antipyretic may be
86 administered (in the dosage recommended in its prescribing information) at the time of
87 vaccination with a vaccine containing an acellular pertussis component (including DAPTACEL)
88 and for the following 24 hours, to reduce the possibility of post-vaccination fever.

89 **5.5 Limitations of Vaccine Effectiveness**

90 Vaccination with DAPTACEL may not protect all individuals.

91 **5.6 Altered Immunocompetence**

92 If DAPTACEL is administered to immunocompromised persons, including persons receiving
93 immunosuppressive therapy, the expected immune response may not be obtained. [See
94 *Immunosuppressive Treatments (7.2)*.]

95 **5.7 Apnea in Premature Infants**

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

100 **5.8 Syncope**

101 Syncope (fainting) has been reported following vaccination with DAPTACEL. Procedures should
102 be in place to prevent falling injury and manage syncopal reactions.

103 **6 ADVERSE REACTIONS**

104 **6.1 Data from Clinical Studies**

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

110 Approximately 18,000 doses of DAPTACEL have been administered to infants and children in 9
111 clinical studies. Of these, 3 doses of DAPTACEL were administered to 4,998 children, 4 doses of
112 DAPTACEL were administered to 1,725 children, and 5 doses of DAPTACEL were administered
113 to 485 children. A total of 989 children received 1 dose of DAPTACEL following 4 prior doses of
114 Pentacel.

115 In a randomized, double-blinded pertussis vaccine efficacy trial, the Sweden I Efficacy Trial,
116 conducted in Sweden during 1992-1995, the safety of DAPTACEL was compared with DT and a
117 whole-cell pertussis DTP vaccine. A standard diary card was kept for 14 days after each dose and
118 follow-up telephone calls were made 1 and 14 days after each injection. Telephone calls were
119 made monthly to monitor the occurrence of severe events and/or hospitalizations for the 2 months
120 after the last injection. There were fewer of the solicited common local and systemic reactions
121 following DAPTACEL than following the whole-cell pertussis DTP vaccine. As shown in Table

122 1, the 2,587 infants who received DAPTACEL at 2, 4 and 6 months of age had similar rates of
123 reactions within 24 hours as recipients of DT and significantly lower rates than infants receiving
124 whole-cell pertussis DTP.

125 **Table 1: Percentage of Infants from Sweden I Efficacy Trial with Local or Systemic**
 126 **Reactions within 24 Hours Post-Dose 1, 2 and 3 of DAPTACEL compared with**
 127 **DT and Whole-Cell Pertussis DTP Vaccines**

EVENT	Dose 1 (2 MONTHS)			Dose 2 (4 MONTHS)			Dose 3 (6 MONTHS)		
	DAPTACEL N = 2,587	DT N = 2,574	DTP N = 2,102	DAPTACEL N = 2,563	DT N = 2,555	DTP N = 2,040	DAPTACEL N = 2,549	DT N = 2,538	DTP N = 2,001
Local									
Tenderness (Any)	8.0*	8.4	59.5	10.1*	10.3	60.2	10.8*	10.0	50.0
Redness ≥2 cm	0.3*	0.3	6.0	1.0*	0.8	5.1	3.7*	2.4	6.4
Swelling ≥2 cm	0.9*	0.7	10.6	1.6*	2.0	10.0	6.3* [†]	3.9	10.5
Systemic									
Fever [‡] ≥38°C (100.4°F)	7.8*	7.6	72.3	19.1*	18.4	74.3	23.6*	22.1	65.1
Fretfulness [§]	32.3	33.0	82.1	39.6	39.8	85.4	35.9	37.7	73.0
Anorexia	11.2*	10.3	39.2	9.1*	8.1	25.6	8.4*	7.7	17.5
Drowsiness	32.7*	32.0	56.9	25.9*	25.6	50.6	18.9*	20.6	37.6
Crying ≥1 hour	1.7*	1.6	11.8	2.5*	2.7	9.3	1.2*	1.0	3.3
Vomiting	6.9*	6.3	9.5	5.2**	5.8	7.4	4.3	5.2	5.5

128 DT: Swedish National Biologics Laboratories
 129 DTP: whole-cell pertussis DTP, Sanofi Pasteur Inc.
 130 N = Number of evaluable subjects
 131 * p<0.001: DAPTACEL versus whole-cell pertussis DTP
 132 † p<0.0001: DAPTACEL versus DT
 133 ‡ Rectal temperature
 134 § Statistical comparisons were not made for this variable
 135 ** p<0.003: DAPTACEL versus whole-cell pertussis DTP

136 The incidence of serious and less common selected systemic events in the Sweden I Efficacy Trial
 137 is summarized in Table 2.

138 **Table 2: Selected Systemic Events: Rates Per 1,000 Doses after Vaccination at 2, 4 and 6**
139 **Months of Age in Sweden I Efficacy Trial**

EVENT	Dose 1 (2 MONTHS)			Dose 2 (4 MONTHS)			Dose 3 (6 MONTHS)		
	DAPTACEL N = 2,587	DT N = 2,574	DTP N = 2,102	DAPTACEL N = 2,565	DT N = 2,556	DTP N = 2,040	DAPTACEL N = 2,551	DT N = 2,539	DTP N = 2,002
Rectal temperature $\geq 40^{\circ}\text{C}$ (104°F) within 48 hours of vaccination	0.39	0.78	3.33	0	0.78	3.43	0.39	1.18	6.99
Hypotonic-hyporesponsive episode within 24 hours of vaccination	0	0	1.9	0	0	0.49	0.39	0	0
Persistent crying ≥ 3 hours within 24 hours of vaccination	1.16	0	8.09	0.39	0.39	1.96	0	0	1.0
Seizures within 72 hours of vaccination	0	0.39	0	0	0.39	0.49	0	0.39	0

140 DT: Swedish National Biologics Laboratories
141 DTP: whole-cell pertussis DTP, Sanofi Pasteur Inc.
142 N = Number of evaluable subjects

143 In the Sweden I Efficacy Trial, one case of whole limb swelling and generalized symptoms, with
144 resolution within 24 hours, was observed following dose 2 of DAPTACEL. No episodes of
145 anaphylaxis or encephalopathy were observed. No seizures were reported within 3 days of
146 vaccination with DAPTACEL. Over the entire study period, 6 seizures were reported in the
147 DAPTACEL group, 9 in the DT group and 3 in the whole-cell pertussis DTP group, for overall
148 rates of 2.3, 3.5 and 1.4 per 1,000 vaccinees, respectively. One case of infantile spasms was
149 reported in the DAPTACEL group. There were no instances of invasive bacterial infection or
150 death.

151 In a US study, children received 4 doses of DAPTACEL at 2, 4, 6 and 15-17 months of age. A
152 total of 1,454 children received DAPTACEL and were included in the safety analyses. Of these,
153 51.7% were female, 77.2% Caucasian, 6.3% Black, 6.5% Hispanic, 0.9% Asian and 9.1% other
154 races. The use of DAPTACEL as a fifth dose of DTaP vaccine was evaluated in 2 subsequent US
155 clinical studies. In one study, a total of 485 children received DAPTACEL at 4-6 years of age
156 following 4 prior doses of DAPTACEL in infancy (DAPTACEL-primed). In a separate study, a
157 total of 989 children received DAPTACEL at 4-6 years of age following 4 prior doses of Pentacel
158 in infancy (Pentacel-primed). The children included in these fifth dose studies were non-random
159 subsets of participants from previous DAPTACEL or Pentacel studies. The subsets were
160 representative of all children who received 4 doses of DAPTACEL or Pentacel in the earlier
161 studies with regard to frequencies of solicited local and systemic adverse events following the
162 fourth dose.

163 In the US 4-dose DAPTACEL study, at 2, 4, and 6 months of age, DAPTACEL was administered
164 concomitantly with *Haemophilus influenzae* type b (Hib) conjugate vaccine (tetanus toxoid
165 conjugate) (Sanofi Pasteur SA), inactivated poliovirus vaccine (IPV) (Sanofi Pasteur SA), and
166 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.). Infants had received the
167 first dose of hepatitis B vaccine at 0 months of age. At 2 and 6 months of age, hepatitis B vaccine
168 (recombinant) (Merck & Co., Inc.) was also administered concomitantly with DAPTACEL. Based
169 on random assignment, the fourth dose of DAPTACEL was administered either alone;
170 concomitantly with Hib conjugate (tetanus toxoid conjugate) vaccine; or concomitantly with Hib
171 conjugate (tetanus toxoid conjugate) vaccine, 7-valent pneumococcal conjugate vaccine, measles,
172 mumps, rubella (MMR) vaccine (Merck & Co., Inc.), and varicella vaccine (Merck & Co., Inc.).
173 In the fifth dose studies, DAPTACEL was administered concomitantly with IPV (all
174 DAPTACEL-primed subjects and 47% of Pentacel-primed subjects) and MMR vaccine.

175 In the US studies, the occurrence of solicited local and systemic adverse events listed in Table 3
176 was recorded daily by parents or guardians for Days 0-7 following vaccination. For Days 0 and 1
177 following the first three doses of DAPTACEL, signs and symptoms of HHE also were solicited.
178 Periodic telephone calls were made to inquire about adverse events. Serious adverse events were
179 monitored during the three studies, through 6 months following the last dose of DAPTACEL.

180 The incidence and severity of selected solicited local and systemic adverse events that occurred
181 within 3 days following each dose of DAPTACEL are shown in Table 3. The incidence of
182 redness, tenderness and swelling at the DAPTACEL injection site increased with the fourth and
183 fifth doses, with the highest rates reported after the fifth dose. The incidence of redness,
184 tenderness and swelling at the DAPTACEL injection site was similarly increased when
185 DAPTACEL was given as a fifth dose of DTaP vaccine in Pentacel-primed children.

186 **Table 3: Number (Percentage) of Children from US Studies with Selected Solicited Local**
 187 **and Systemic Adverse Events by Severity Occurring Between 0 to 3 Days after**
 188 **Each Dose of DAPTACEL**

	Dose 1*	Dose 2*	Dose 3*	Dose 4*	Dose 5	
					DAPTACEL-primed*	Pentacel-primed*
	N = 1390-1406 %	N = 1346-1360 %	N = 1301-1312 %	N = 1118-1144 %	N = 473-481 %	N = 936-981 %
Injection Site Reactions (DAPTACEL injection site)						
Redness						
>5 mm	6.2	7.1	9.6	17.3	35.8	20.2
25 - 50 mm	0.6	0.5	1.9	6.3	10.4	6.8
>50 mm	0.4	0.1	0.0	3.1	15.8	6.6
Swelling						
>5 mm	4.0	4.0	6.5	11.7	23.9	12.0
25 - 50 mm	1.2	0.6	1.0	3.2	5.8	4.1
>50 mm	0.4	0.1	0.1	1.6	7.7	2.9
Tenderness†						
Any	48.8	38.2	40.9	49.5	61.5	50.0
Moderate	16.5	9.9	10.6	12.3	11.2	7.4
Severe	4.1	2.3	1.7	2.2	1.7	0.3
Increase in Arm Circumference‡						
>5 mm	-	-	-	30.1	38.3	28.6
20 - 40 mm				7.0	14.0	7.6
>40 mm				0.4	1.5	1.2
Interference with Normal Activity of the Arm§						
Any	-	-	-	-	20.4	8.8
Moderate					5.6	1.7
Severe					0.4	0.0
Systemic Reactions						
Fever**						
≥38.0°C	9.3	16.1	15.8	10.5	6.1	4.6
>38.5-39.5°C	1.5	3.9	4.8	2.7	2.1	2.0
>39.5°C	0.1	0.4	0.3	0.7	0.2	0.2
Decreased Activity/Lethargy††						
Any	51.1	37.4	33.2	25.3	21.0	12.6
Moderate	23.0	14.4	12.1	8.2	5.8	3.6
Severe	1.2	1.4	0.6	1.0	0.8	0.4
Inconsolable Crying‡‡						
Any	58.5	51.4	47.9	37.1	14.1	7.2
Moderate	14.2	12.6	10.8	7.7	3.5	1.9
Severe	2.2	3.4	1.4	1.5	0.4	0.3

	Dose 1*	Dose 2*	Dose 3*	Dose 4*	Dose 5	
					DAPTACEL-primed*	Pentacel-primed*
	N = 1390-1406 %	N = 1346-1360 %	N = 1301-1312 %	N = 1118-1144 %	N = 473-481 %	N = 936-981 %
Fussiness/Irritability§§						
Any	75.8	70.7	67.1	54.4	34.9	22.9
Moderate	27.7	25.0	22.0	16.3	7.5	5.3
Severe	5.6	5.5	4.3	3.9	0.4	0.5

- * In one U.S. study, children received four doses of DAPTACEL. A non-random subset of these children received a fifth dose of DAPTACEL in a subsequent study. A non-random subset of children previously vaccinated with 4 doses of Pentacel in previous clinical studies received a dose of DAPTACEL at 4-6 years of age as the fifth dose of DTaP vaccine in another clinical study.
- † Doses 1-4 - Moderate: subject cries when site is touched; Severe: subject cries when leg or arm is moved.
Dose 5 - Moderate: interfered with activities, but did not require medical care or absenteeism; Severe: incapacitating, unable to perform usual activities, may have/or required medical care or absenteeism.
- ‡ The circumference of the DAPTACEL-injected arm at the level of the axilla was monitored following the fourth and fifth doses only. Increase in arm circumference was calculated by subtracting the baseline circumference pre-vaccination (Day 0) from the circumference post-vaccination.
- § Moderate: decreased use of arm, but did not require medical care or absenteeism; Severe: incapacitating, refusal to move arm, may have/or required medical care or absenteeism.
- ** For Doses 1-3, 53.7% of temperatures were measured rectally, 45.1% were measured axillary, 1.0% were measured orally, and 0.1% were measured by an unspecified route. For Dose 4, 35.7% of temperatures were measured rectally, 62.3% were measured axillary, 1.5% were measured orally, and 0.5% were measured by an unspecified route. For Dose 5 in DAPTACEL-primed children, 0.2% of temperatures were measured rectally, 11.3% were measured axillary, and 88.4% were measured orally. For Dose 5 in Pentacel-primed children, 0.2% of temperatures were measured rectally, 0.5% were measured tympanically, 17% were measured axillary, and 81.7% were measured orally. Fever is based upon actual temperatures recorded with no adjustments to the measurement for route.
- †† Dose 1-4 - Moderate: interferes with and limits daily activity, less interactive; Severe: disabling (not interested in usual daily activity, subject cannot be coaxed to interact with caregiver).
Dose 5 - Moderate: interfered with activities, but did not require medical care or absenteeism;
Severe: incapacitating, unable to perform usual activities, may have/or required medical care or absenteeism.
- ‡‡ Doses 1-4 - Moderate: 1 to 3 hours inconsolable crying; Severe: >3 hours inconsolable crying.
Dose 5 - Moderate: interfered with activities, but did not require medical care or absenteeism;
Severe: incapacitating, unable to perform usual activities, may have/or required medical care or absenteeism.
- §§ Doses 1-4 - Moderate: Irritability for 1 to 3 hours; Severe: irritability for >3 hours.
Dose 5 - Moderate: interfered with activities, but did not require medical care or absenteeism;
Severe: incapacitating, unable to perform usual activities, may have/or required medical care or absenteeism.

189 In the US study in which children received 4 doses of DAPTACEL, of 1,454 subjects who
190 received DAPTACEL, 5 (0.3%) subjects experienced a seizure within 60 days following any dose
191 of DAPTACEL. One seizure occurred within 7 days post-vaccination: an infant who experienced
192 an afebrile seizure with apnea on the day of the first vaccination. Three other cases of seizures
193 occurred between 8 and 30 days post-vaccination. Of the seizures that occurred within 60 days
194 post-vaccination, 3 were associated with fever. In this study, there were no reported cases of HHE
195 following DAPTACEL. There was one death due to aspiration 222 days post-vaccination in a
196 subject with ependymoma. Within 30 days following any dose of DAPTACEL, 57 (3.9%)
197 subjects reported at least one serious adverse event. During this period, the most frequently
198 reported serious adverse event was bronchiolitis, reported in 28 (1.9%) subjects. Other serious
199 adverse events that occurred within 30 days following DAPTACEL include three cases of
200 pneumonia, two cases of meningitis and one case each of sepsis, pertussis (post-dose 1),
201 irritability and unresponsiveness.

202 In the US study in which DAPTACEL was administered as a fifth DTaP dose in DAPTACEL-
203 primed subjects, within 30 days following the fifth consecutive dose of DAPTACEL, 1 (0.2%)
204 subject reported 2 serious adverse events (bronchospasm and hypoxia). In the US study in which
205 DAPTACEL was administered as a fifth DTaP dose in Pentacel-primed subjects, within 30 days
206 following DAPTACEL, 4 (0.4%) subjects reported one or more serious adverse events (asthma
207 and pneumonia; idiopathic thrombocytopenic purpura; vomiting; cellulitis not at the injection
208 site). In these two studies, there were no reports of seizures within 30 days following DAPTACEL
209 in either the DAPTACEL-primed subjects or Pentacel-primed subjects.

210 In another study (Sweden II Efficacy Trial), 3 DTaP vaccines and a whole-cell pertussis DTP
211 vaccine, none of which are licensed in the US, were evaluated to assess relative safety and
212 efficacy. This study included HCPDT, a vaccine made of the same components as DAPTACEL
213 but containing twice the amount of detoxified PT and four times the amount of FHA (20 mcg
214 detoxified PT and 20 mcg FHA). HHE was observed following 29 (0.047%) of 61,220 doses of
215 HCPDT; 16 (0.026%) of 61,219 doses of an acellular pertussis vaccine made by another
216 manufacturer; and 34 (0.056%) of 60,792 doses of a whole-cell pertussis DTP vaccine. There
217 were 4 additional cases of HHE in other studies using HCPDT vaccine for an overall rate of
218 33 (0.047%) in 69,525 doses.

219 In a randomized, parallel-group, US multi-center clinical trial conducted in children 4 through 6
220 years of age, DAPTACEL was administered as follows: concomitantly with IPV (Sanofi Pasteur
221 SA) followed 30 days later by Menactra® [Meningococcal (Groups A, C, Y and W-135)
222 Polysaccharide Diphtheria Toxoid Conjugate vaccine, Sanofi Pasteur Inc.] [Group A];
223 concomitantly with Menactra followed 30 days later by IPV [Group B]; or 30 days after
224 concomitant administration of Menactra and IPV [Group C]. Solicited injection site and systemic
225 reactions were recorded in a diary card for 7 consecutive days after each vaccination. For all study
226 groups, the most frequently reported solicited local reaction at the DAPTACEL injection site was
227 pain: 71.7%, 69.4% and 52.1% of subjects in Groups A, B and C, respectively. For all study
228 groups, the most frequently reported systemic reaction after DAPTACEL vaccination was
229 myalgia: 46.2%, 37.3% and 25.8% of subjects in Groups A, B and C, respectively. Fever >39.5°C
230 occurred at <1.0% in all groups.

231

232 **6.2 Data from Post-Marketing Experience**

233 The following adverse events have been spontaneously reported during the post-marketing use of
234 DAPTACEL in the US and other countries. Because these events are reported voluntarily from a
235 population of uncertain size, it may not be possible to reliably estimate their frequency or
236 establish a causal relationship to vaccine exposure.

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

- 239 • **Blood and lymphatic disorders**

- 240 Lymphadenopathy

- 241 • **Cardiac disorders**

- 242 Cyanosis

- 243 • **Gastro-intestinal disorders**

244 Nausea, diarrhea

245 • **General disorders and administration site conditions**

246 Local reactions: injection site pain, injection site rash, injection site nodule, injection site
247 mass, extensive swelling of injected limb (including swelling that involves adjacent joints).

248 • **Infections and infestations**

249 Injection site cellulitis, cellulitis, injection site abscess

250 • **Immune system disorders**

251 Hypersensitivity, allergic reaction, anaphylactic reaction (edema, face edema, swelling face,
252 pruritus, rash generalized) and other types of rash (erythematous, macular, maculo-papular)

253 • **Nervous system disorders**

254 Convulsions: febrile convulsion, grand mal convulsion, partial seizures

255 HHE, hypotonia, somnolence, syncope

256 • **Psychiatric disorders**

257 Screaming

258

259 **7 DRUG INTERACTIONS**

260 **7.1 Concomitant Administration with Other Vaccines**

261 In clinical trials, DAPTACEL was administered concomitantly with one or more of the following
262 US licensed vaccines: Hib conjugate vaccine, IPV, hepatitis B vaccine, pneumococcal conjugate
263 vaccine, Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid
264 Conjugate vaccine, MMR vaccine, and varicella vaccine. [See *Adverse Reactions (6.1)* and
265 *Clinical Studies (14.4)*.] When DAPTACEL is given at the same time as another injectable
266 vaccine(s), the vaccines should be administered with different syringes and at different injection
267 sites.

268 In cases where DAPTACEL and Menactra are to be administered to children 4 through 6 years of
269 age, the two vaccines should be administered concomitantly or Menactra should be administered
270 prior to DAPTACEL. Administration of Menactra one month after DAPTACEL has been shown
271 to reduce meningococcal antibody responses to Menactra. [See *Adverse Reactions (6.1)* and
272 *Clinical Studies (14.4)*.]

273 **7.2 Immunosuppressive Treatments**

274 Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic
275 drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune
276 response to DAPTACEL.

277 **8 USE IN SPECIFIC POPULATIONS**

278 **8.1 Pregnancy**

279 DAPTACEL is not approved for use in individuals 7 years of age and older. Human or animal
280 data are not available to assess vaccine-associated risks in pregnancy.

281 **8.2 Lactation**

282 DAPTACEL is not approved for use in individuals 7 years of age and older. Human or animal
283 data are not available to assess the impact of DAPTACEL on milk production, its presence in
284 breast milk, or its effects on the breastfed infant.

285 **8.4 Pediatric Use**

286 DAPTACEL is not indicated for use in infants below 6 weeks of age or children 7 years of age or
287 older. Safety and effectiveness of DAPTACEL in these age groups have not been established.

288 **11 DESCRIPTION**

289 DAPTACEL is a sterile isotonic suspension of pertussis antigens and diphtheria and tetanus
290 toxoids adsorbed on aluminum phosphate, for intramuscular injection.

291 Each 0.5 mL dose contains 15 Lf diphtheria toxoid, 5 Lf tetanus toxoid and acellular pertussis
292 antigens [10 mcg detoxified pertussis toxin (PT), 5 mcg filamentous hemagglutinin (FHA), 3 mcg
293 pertactin (PRN), and 5 mcg fimbriae types 2 and 3 (FIM)].

294 Other ingredients per 0.5 mL dose include 1.5 mg aluminum phosphate (0.33 mg of aluminum) as
295 the adjuvant, ≤5 mcg residual formaldehyde, <50 ng residual glutaraldehyde and 3.3 mg (0.6%
296 v/v) 2-phenoxyethanol (not as a preservative).

297 The acellular pertussis vaccine components are produced from *Bordetella pertussis* cultures
298 grown in Stainer-Scholte medium (2) modified by the addition of casamino acids and
299 dimethyl-beta-cyclodextrin. PT, FHA and PRN are isolated separately from the supernatant
300 culture medium. The FIM components are extracted and co-purified from the bacterial cells. The
301 pertussis antigens are purified by sequential filtration, salt-precipitation, ultrafiltration and
302 chromatography. PT is detoxified with glutaraldehyde. FHA is treated with formaldehyde, and the
303 residual aldehydes are removed by ultrafiltration. The individual antigens are adsorbed separately
304 onto aluminum phosphate.

305 *Corynebacterium diphtheriae* is grown in modified Mueller's growth medium. (3) After
306 purification by ammonium sulfate fractionation, diphtheria toxin is detoxified with formaldehyde
307 and diafiltered. *Clostridium tetani* is grown in modified Mueller-Miller casamino acid medium
308 without beef heart infusion. (4) Tetanus toxin is detoxified with formaldehyde and purified by
309 ammonium sulfate fractionation and diafiltration. Diphtheria and tetanus toxoids are individually
310 adsorbed onto aluminum phosphate.

311 The adsorbed diphtheria, tetanus and acellular pertussis components are combined with aluminum
312 phosphate (as adjuvant), 2-phenoxyethanol (not as a preservative) and water for injection.

313 Both diphtheria and tetanus toxoids induce at least 2 units of antitoxin per mL in the guinea pig
314 potency test. The potency of the acellular pertussis vaccine components is determined by the
315 antibody response of immunized mice to detoxified PT, FHA, PRN and FIM as measured by
316 enzyme-linked immunosorbent assay (ELISA).

317 **12 CLINICAL PHARMACOLOGY**

318 **12.1 Mechanism of Action**

319 **Diphtheria**

320 Diphtheria is an acute toxin-mediated disease caused by toxigenic strains of *C diphtheriae*.
321 Protection against disease is due to the development of neutralizing antibodies to diphtheria toxin.
322 A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of
323 protection. Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective. (5) Levels
324 of 1.0 IU/mL have been associated with long-term protection. (6)

325 **Tetanus**

326 Tetanus is an acute disease caused by an extremely potent neurotoxin produced by *C tetani*.
327 Protection against disease is due to the development of neutralizing antibodies to tetanus toxin. A
328 serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assay is
329 considered the minimum protective level. (5) (7) A tetanus antitoxin level ≥ 0.1 IU/mL as
330 measured by the ELISA used in clinical studies of DAPTACEL is considered protective.

331 **Pertussis**

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

335 **13 NON-CLINICAL TOXICOLOGY**

336 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

337 DAPTACEL has not been evaluated for carcinogenic or mutagenic potential or impairment of
338 fertility.

339 **14 CLINICAL STUDIES**

340 **14.1 Diphtheria**

341 In a US study in which children received 4 doses of DAPTACEL at 2, 4, 6 and 15-17 months of
342 age, after the third dose, 100% (N = 1,099) achieved diphtheria antitoxin levels of ≥ 0.01 IU/mL
343 and 98.5% achieved diphtheria antitoxin levels of ≥ 0.10 IU/mL. Among a random subset of
344 children who received the fourth dose of DAPTACEL at 15-16 months of age, 96.5% (N = 659)
345 achieved diphtheria antitoxin levels of ≥ 1.0 IU/mL after the fourth dose.

346 **14.2 Tetanus**

347 In a US study in which children received 4 doses of DAPTACEL at 2, 4, 6 and 15-17 months of
348 age, after the third dose, 100% (N = 1,037) achieved tetanus antitoxin levels of ≥ 0.10 IU/mL.
349 Among a random subset of children who received the fourth dose of DAPTACEL at 15-16
350 months of age, 98.8% (N = 681) achieved tetanus antitoxin levels of ≥ 1.0 IU/mL after the fourth
351 dose.

352 **14.3 Pertussis**

353 A randomized, double-blinded, placebo-controlled efficacy and safety study was conducted in
354 Sweden during 1992-1995 (Sweden I Efficacy Trial) under the sponsorship of the National
355 Institute of Allergy and Infectious Diseases. A total of 9,829 infants received 1 of 4 vaccines:
356 DAPTACEL (N = 2,587); another investigational acellular pertussis vaccine (N = 2,566); whole-
357 cell pertussis DTP vaccine (N = 2,102); or DT vaccine as placebo (Swedish National
358 Bacteriological Laboratory, N = 2,574). Infants were immunized at 2, 4 and 6 months of age. The
359 mean length of follow-up was 2 years after the third dose of vaccine. The protective efficacy of
360 DAPTACEL against pertussis after 3 doses using the World Health Organization (WHO) case

361 definition (≥ 21 consecutive days of paroxysmal cough with culture or serologic confirmation or
362 epidemiologic link to a confirmed case) was 84.9% (95% confidence interval [CI] 80.1 to 88.6).
363 The protective efficacy of DAPTACEL against mild pertussis (≥ 1 day of cough with laboratory
364 confirmation) was 77.9% (95% CI 72.6 to 82.2). Protection against pertussis by DAPTACEL was
365 sustained for the 2-year follow-up period.

366 In order to assess the antibody response to the pertussis antigens of DAPTACEL in the US
367 population, 2 lots of DAPTACEL, including the lot used in the Sweden I Efficacy Trial, were
368 administered to US infants in the US Bridging Study. In this study, antibody responses following
369 3 doses of DAPTACEL given to US children at 2, 4 and 6 months of age were compared to those
370 from a subset of the infants enrolled in the Sweden I Efficacy Trial. Assays were performed in
371 parallel on the available sera from the US and Swedish infants. Antibody responses to all the
372 antigens were similar except for those to the PRN component. For both lots of DAPTACEL, the
373 geometric mean concentration (GMC) and percent response to PRN in US infants (Lot 006, N
374 = 107; Lot 009, N = 108) were significantly lower after 3 doses of vaccine than in Swedish infants
375 (N = 83). In separate US and Canadian studies in which children received DAPTACEL at 2, 4 and
376 6 months of age, with a fourth dose at either 17-20 months (Canadian study) or 15-16 months
377 (random subset from US study) of age, antibody responses to each pertussis antigen following the
378 fourth dose (Canadian study N = 275; US study N = 237-347) were at least as high as those seen
379 in the Swedish infants after 3 doses. While a serologic correlate of protection for pertussis has not
380 been established, the antibody response to all antigens in North American infants after 4 doses of
381 DAPTACEL at 2, 4, 6 and 15-20 months of age was comparable to that achieved in Swedish
382 infants in whom efficacy was demonstrated after 3 doses of DAPTACEL at 2, 4 and 6 months of
383 age.

384 **14.4 Concomitantly Administered Vaccines**

385 In the US Bridging study, DAPTACEL was given concomitantly with Hib conjugate vaccine
386 (Sanofi Pasteur SA) according to local practices. Anti-PRP immune response was evaluated in
387 261 infants who received 3 doses of Hib conjugate vaccine. One month after the third dose, 96.9%
388 achieved anti-PRP antibody levels of at least 0.15 mcg/mL and 82.7% achieved antibody levels of
389 at least 1.0 mcg/mL.

390 In the US study in which infants received DAPTACEL concomitantly with Hib conjugate (tetanus
391 toxoid conjugate) vaccine, IPV, 7-valent pneumococcal conjugate vaccine, and hepatitis B
392 vaccine [see *Adverse Reactions (6.1)*], at 7 months of age, 100.0% of subjects (N = 1,050-1,097)
393 had protective neutralizing antibody levels ($\geq 1:8$ 1/dil) for poliovirus types 1, 2 and 3; and 92.4%
394 (N = 998) achieved anti-hepatitis B surface antigen levels ≥ 10.0 mIU/mL. Although there is no
395 established serologic correlate of protection for any of the pneumococcal serotypes, at 7 months
396 of age 91.3%-98.9% (N = 1,027-1,029) achieved anti-pneumococcal polysaccharide levels ≥ 0.5
397 mcg/mL for serotypes 4, 9V, 14, 18C, 19F and 23F and 80.7% (N = 1,027) achieved an anti-
398 pneumococcal polysaccharide level ≥ 0.5 mcg/mL for serotype 6B. The mumps seroresponse rate
399 was lower when DAPTACEL was administered concomitantly (86.6%; N = 307) vs.
400 non-concomitantly (90.1%; N = 312) with the first dose of MMR vaccine [upper limit of 90%
401 confidence interval for difference in rates (non-concomitant minus concomitant) $>5\%$]. There was
402 no evidence for interference in the immune response to the measles, rubella, and varicella
403 antigens or to the fourth dose of the 7-valent pneumococcal conjugate vaccine with concomitant
404 administration of DAPTACEL.

405 In a randomized, parallel-group, US multi-center clinical trial conducted in children 4 through 6
406 years of age, DAPTACEL was administered as follows: concomitantly with IPV (Sanofi Pasteur
407 SA) followed 30 days later by Menactra [Group A]; concomitantly with Menactra followed 30
408 days later by IPV [Group B]; or 30 days after concomitant administration of Menactra and IPV
409 [Group C]. Sera were obtained approximately 30 days after each respective vaccination. When
410 DAPTACEL was administered concomitantly with Menactra [Group B], antibody responses to
411 PT, FHA and PRN (GMC), tetanus (% participants with antibody concentrations ≥ 1.0 IU/mL),
412 and diphtheria (% participants with antibody concentrations ≥ 1.0 IU/mL) were non-inferior to

413 those observed when DAPTACEL (and IPV) were administered [Group A]. The anti-FIM GMCs
414 were marginally lower when DAPTACEL and Menactra were administered concomitantly but the
415 clinical significance is unknown because there are no established serological correlates of
416 protection for pertussis. When DAPTACEL (and IPV) were administered 30 days prior to
417 Menactra [Group A], significantly lower serum-bactericidal assay-human complement (SBA-H)
418 GMTs to all 4 meningococcal serogroups were observed compared to when Menactra (and IPV)
419 were administered 30 days prior to DAPTACEL [Group C]. When DAPTACEL was administered
420 concomitantly with Menactra [Group B], SBA-H GMTs to meningococcal serogroups A, C, and
421 W-135 were non-inferior to those observed when Menactra (and IPV) were administered [Group
422 C]. The non-inferiority criterion was marginally missed for meningococcal serogroup Y. [See
423 *Drug Interactions (7.1).*]

424 **15 REFERENCES**

425

- 426 1 Stratton KR, et al. editors. Adverse events associated with childhood vaccines; evidence
427 bearing on causality. Washington D.C.: National Academy Press. 1994. p. 67-117.
- 428 2 Stainer DW, Scholte MJ. A simple chemically defined medium for the production of phase I
429 Bordetella pertussis. J Gen Microbiol 1970;63:211-20.
- 430 3 Stainer DW. Production of diphtheria toxin. In: Manclark CR, editor. Proceedings of an
431 informal consultation on the World Health Organization requirements for diphtheria,
432 tetanus, pertussis and combined vaccines. United States Public Health Service, Bethesda,
433 MD. DHHS 91-1174. 1991. p. 7-11.
- 434 4 Mueller JH, Miller PA. Variable factors influencing the production of tetanus toxin. J
435 Bacteriol 1954;67(3):271-7.
- 436 5 Department of Health and Human Services, Food and Drug Administration. Biological
437 products; bacterial vaccines and toxoids; implementation of efficacy review; proposed rule.
438 Federal Register 1985;50(240):51002-117.
- 439 6 Wharton M, et al. Diphtheria Toxoid. In: Plotkin SA, Orenstein WA, editors. Vaccines. 4th
440 ed. Philadelphia, PA: W. B. Saunders 2004 p. 211-28.
- 441 7 Wassilak SGF, et al. Tetanus Toxoid. In: Plotkin SA, Orenstein WA, editors. Vaccines. 4th
442 ed. Philadelphia, PA: W. B. Saunders 2004 p. 745-81.

443

444

445 **16 HOW SUPPLIED/STORAGE AND HANDLING**

446 The vial stopper for this product is not made with natural rubber latex.

447 DAPTACEL is supplied in a single dose vial (NDC No. 49281-286-58):

448 in packages of 1 vial: NDC No. 49281-286-01;

449 in packages of 5 vials: NDC No. 49281-286-05;

450 in packages of 10 vials: NDC No. 49281-286-10.

451 DAPTACEL should be stored at 2° to 8°C (35° to 46°F). DO NOT FREEZE. Product which has
452 been exposed to freezing should not be used. Do not use after expiration date shown on the label.

453 **17 PATIENT COUNSELING INFORMATION**

454 Inform the parent or guardian of the following:

- 455 • The potential benefits and risks of immunization with DAPTACEL.
- 456 • The common adverse reactions that have occurred following administration of DAPTACEL or
457 other vaccines containing similar components.
- 458 • Other adverse reactions can occur. Call healthcare provider with any adverse reactions of
459 concern.

460 Provide the Vaccine Information Statements (VIS), which are required by the National Childhood
461 Vaccine Injury Act of 1986.

462 Manufactured by:

463 **Sanofi Pasteur Limited**

464 Toronto Ontario Canada

465 Distributed by:

466 **Sanofi Pasteur Inc.**

467 Swiftwater PA 18370 USA

468 US Patents: 4500639, 4687738, 4784589, 4997915, 5444159, 5667787, 5877298.

469 DAPTACEL® is a registered trademark of Sanofi Pasteur Limited.

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