

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

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

Warnings & Precautions (5.8) XX/201X

-----**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.

-----**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**-----

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

14 DAPTACEL vaccine should be used as the fifth dose of the DTaP series in children who initially
15 received 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 vaccines contain the same pertussis antigens, manufactured
18 by the same process, although Pentacel vaccine contains twice the amount of detoxified pertussis toxin
19 (PT) and four times the amount of filamentous hemagglutinin (FHA) as DAPTACEL vaccine.

20 Data are not available on the safety and effectiveness of using mixed sequences of DAPTACEL
21 vaccine and DTaP vaccines from different manufacturers for successive doses of the DTaP
22 vaccination series. DAPTACEL vaccine may be used to complete the immunization series in infants
23 who have received 1 or more doses of whole-cell pertussis DTP. However, the safety and efficacy of
24 DAPTACEL vaccine 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 Toxoids
27 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 prior to
30 administration, whenever solution and container permit. If either of these conditions exist, the
31 product should not be administered.

32 After removing the “flip-off” cap, cleanse the vaccine vial stopper with a suitable germicide. Do not
33 remove either the rubber stopper or the metal seal holding it in place. Just before use, shake the vial
34 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 vaccine intramuscularly. Use a separate sterile needle and syringe for each
37 injection. Changing needles between withdrawing the vaccine from the vial and injecting it into a
38 recipient is not necessary unless the needle has been damaged or contaminated. In infants younger
39 than 1 year, the anterolateral aspect of the thigh provides the largest muscle and is the preferred site
40 of 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 vaccine should not be combined through reconstitution or mixed with any other
44 vaccine.

45 **3 DOSAGE FORMS AND STRENGTHS**

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

48 **4 CONTRAINDICATIONS**

49 **4.1 Hypersensitivity**

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

56 **4.2 Encephalopathy**

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

61 **4.3 Progressive Neurologic Disorder**

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

66 **5 WARNINGS AND PRECAUTIONS**

67 **5.1 Management of Acute Allergic Reactions**

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

70 **5.2 Adverse Reactions Following Prior Pertussis Vaccination**

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

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

80 **5.3 Guillain-Barré Syndrome and Brachial Neuritis**

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

85 **5.4 Infants and Children with a History of Previous Seizures**

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

90 **5.5 Limitations of Vaccine Effectiveness**

91 Vaccination with DAPTACEL vaccine may not protect all individuals.

92 **5.6 Altered Immunocompetence**

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

96 **5.7 Apnea in Premature Infants**

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

101 **5.8 Syncope**

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

104 **6 ADVERSE REACTIONS**

105 **6.1 Data from Clinical Studies**

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

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

116 In a randomized, double-blinded pertussis vaccine efficacy trial, the Sweden I Efficacy Trial,
117 conducted in Sweden during 1992-1995, the safety of DAPTACEL vaccine was compared with
118 DT and a whole-cell pertussis DTP vaccine. A standard diary card was kept for 14 days after each
119 dose and follow-up telephone calls were made 1 and 14 days after each injection. Telephone calls
120 were made monthly to monitor the occurrence of severe events and/or hospitalizations for the 2
121 months after the last injection. There were fewer of the solicited common local and systemic
122 reactions following DAPTACEL vaccine than following the whole-cell pertussis DTP vaccine. As
123 shown in Table 1, the 2,587 infants who received DAPTACEL vaccine at 2, 4 and 6 months of
124 age had similar rates of reactions within 24 hours as recipients of DT and significantly lower rates
125 than infants receiving whole-cell pertussis DTP.

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

| EVENT | Dose 1 (2 MONTHS) | | | Dose 2 (4 MONTHS) | | | Dose 3 (6 MONTHS) | | |
|------------------------------------------|----------------------------------|--------------------|---------------------|----------------------------------|--------------------|---------------------|----------------------------------|--------------------|---------------------|
| | DAPTACEL vaccine N = 2,587 | DT N = 2,574 | DTP N = 2,102 | DAPTACEL vaccine N = 2,563 | DT N = 2,555 | DTP N = 2,040 | DAPTACEL vaccine 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 |

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

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

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

| EVENT | Dose 1 (2 MONTHS) | | | Dose 2 (4 MONTHS) | | | Dose 3 (6 MONTHS) | | |
|-------------------------------------------------------------------------------------------------------|----------------------------------|--------------------|---------------------|----------------------------------|--------------------|---------------------|----------------------------------|--------------------|---------------------|
| | DAPTACEL vaccine N = 2,587 | DT N = 2,574 | DTP N = 2,102 | DAPTACEL vaccine N = 2,565 | DT N = 2,556 | DTP N = 2,040 | DAPTACEL vaccine 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 |

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

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

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

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

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

181 events were monitored during the three studies, through 6 months following the last dose of
182 DAPTACEL vaccine.

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

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

| | 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 vaccine 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 vaccine. A non-random subset of these children received a fifth dose of DAPTACEL vaccine in a subsequent study. A non-random subset of children previously vaccinated with 4 doses of Pentacel vaccine in previous clinical studies received a dose of DAPTACEL vaccine 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 vaccine-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.

192 In the US study in which children received 4 doses of DAPTACEL vaccine, of 1,454 subjects
193 who received DAPTACEL vaccine, 5 (0.3%) subjects experienced a seizure within 60 days
194 following any dose of DAPTACEL vaccine. One seizure occurred within 7 days post-vaccination:
195 an infant who experienced an afebrile seizure with apnea on the day of the first vaccination. Three
196 other cases of seizures occurred between 8 and 30 days post-vaccination. Of the seizures that
197 occurred within 60 days post-vaccination, 3 were associated with fever. In this study, there were
198 no reported cases of HHE following DAPTACEL vaccine. There was one death due to aspiration
199 222 days post-vaccination in a subject with ependymoma. Within 30 days following any dose of
200 DAPTACEL vaccine, 57 (3.9%) subjects reported at least one serious adverse event. During this
201 period, the most frequently reported serious adverse event was bronchiolitis, reported in 28
202 (1.9%) subjects. Other serious adverse events that occurred within 30 days following
203 DAPTACEL vaccine include three cases of pneumonia, two cases of meningitis and one case
204 each of sepsis, pertussis (post-dose 1), irritability and unresponsiveness.

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

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

221 were 4 additional cases of HHE in other studies using HCPDT vaccine for an overall rate of
222 33 (0.047%) in 69,525 doses.

223 **6.2 Data from Post-Marketing Experience**

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

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

- 231 • **Blood and lymphatic disorders**

- 232 Lymphadenopathy

- 233 • **Cardiac disorders**

- 234 Cyanosis

- 235 • **Gastro-intestinal disorders**

- 236 Nausea, diarrhea

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

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

- 240 • **Infections and infestations**

- 241 Injection site cellulitis, cellulitis, injection site abscess

- 242 • **Immune system disorders**

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

- 245 • **Nervous system disorders**

- 246 Convulsions: febrile convulsion, grand mal convulsion, partial seizures

- 247 HHE, hypotonia, somnolence, syncope

- 248 • **Psychiatric disorders**

- 249 Screaming

250 **7 DRUG INTERACTIONS**

251 **7.1 Concomitant Administration with Other Vaccines**

252 In clinical trials, DAPTACEL vaccine was administered concomitantly with one or more of the
253 following US licensed vaccines: Hib conjugate vaccine, IPV, hepatitis B vaccine, pneumococcal
254 conjugate vaccine, MMR vaccine, and varicella vaccine. [See *Adverse Reactions (6.1)* and
255 *Clinical Studies (14)*.] When DAPTACEL vaccine is given at the same time as another injectable
256 vaccine(s), the vaccines should be administered with different syringes and at different injection
257 sites.

258 **7.2 Immunosuppressive Treatments**

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

262

263 **8 USE IN SPECIFIC POPULATIONS**

264 **8.1 Pregnancy**

265 **Pregnancy Category C**

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

269 **8.4 Pediatric Use**

270 DAPTACEL vaccine is not indicated for infants below 6 weeks of age or children 7 years of age
271 or older. Safety and effectiveness of DAPTACEL vaccine in these age groups have not been
272 established.

273 **11 DESCRIPTION**

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

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

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

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

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

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

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

302 **12 CLINICAL PHARMACOLOGY**

303 **12.1 Mechanism of Action**

304 **Diphtheria**

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

310 **Tetanus**

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

316 **Pertussis**

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

320 **13 NON-CLINICAL TOXICOLOGY**

321 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

322 DAPTACEL vaccine has not been evaluated for carcinogenic or mutagenic potential or
323 impairment of fertility.

324 **14 CLINICAL STUDIES**

325 **14.1 Diphtheria**

326 In a US study in which children received 4 doses of DAPTACEL vaccine at 2, 4, 6 and 15-
327 17 months of age, after the third dose, 100% (N = 1,099) achieved diphtheria antitoxin levels of
328 ≥ 0.01 IU/mL and 98.5% achieved diphtheria antitoxin levels of ≥ 0.10 IU/mL. Among a random
329 subset of children who received the fourth dose of DAPTACEL vaccine at 15-16 months of age,
330 96.5% (N = 659) achieved diphtheria antitoxin levels of ≥ 1.0 IU/mL after the fourth dose.

331 **14.2 Tetanus**

332 In a US study in which children received 4 doses of DAPTACEL vaccine at 2, 4, 6 and
333 15-17 months of age, after the third dose, 100% (N = 1,037) achieved tetanus antitoxin levels of
334 ≥ 0.10 IU/mL. Among a random subset of children who received the fourth dose of DAPTACEL
335 vaccine at 15-16 months of age, 98.8% (N = 681) achieved tetanus antitoxin levels of ≥ 1.0 IU/mL
336 after the fourth dose.

337 **14.3 Pertussis**

338 A randomized, double-blinded, placebo-controlled efficacy and safety study was conducted in
339 Sweden during 1992-1995 (Sweden I Efficacy Trial) under the sponsorship of the National
340 Institute of Allergy and Infectious Diseases. A total of 9,829 infants received 1 of 4 vaccines:
341 DAPTACEL vaccine (N = 2,587); another investigational acellular pertussis vaccine (N = 2,566);
342 whole-cell pertussis DTP vaccine (N = 2,102); or DT vaccine as placebo (Swedish National
343 Bacteriological Laboratory, N = 2,574). Infants were immunized at 2, 4 and 6 months of age. The
344 mean length of follow-up was 2 years after the third dose of vaccine. The protective efficacy of

345 DAPTACEL vaccine against pertussis after 3 doses using the World Health Organization (WHO)
346 case definition (≥ 21 consecutive days of paroxysmal cough with culture or serologic confirmation
347 or epidemiologic link to a confirmed case) was 84.9% (95% confidence interval [CI] 80.1 to
348 88.6). The protective efficacy of DAPTACEL vaccine against mild pertussis (≥ 1 day of cough
349 with laboratory confirmation) was 77.9% (95% CI 72.6 to 82.2). Protection against pertussis by
350 DAPTACEL vaccine was sustained for the 2-year follow-up period.

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

369 14.4 Concomitantly Administered Vaccines

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

375 In the US study in which infants received DAPTACEL vaccine concomitantly with Hib conjugate
376 (tetanus toxoid conjugate) vaccine, IPV, 7-valent pneumococcal conjugate vaccine, and hepatitis
377 B vaccine [see *Adverse Reactions (6.1)*], at 7 months of age, 100.0% of subjects (N = 1,050-
378 1,097) had protective neutralizing antibody levels ($\geq 1:8$ 1/dil) for poliovirus types 1, 2 and 3; and
379 92.4% (N = 998) achieved anti-hepatitis B surface antigen levels ≥ 10.0 mIU/mL. Although there
380 is no established serologic correlate of protection for any of the pneumococcal serotypes, at
381 7 months of age 91.3%-98.9% (N = 1,027-1,029) achieved anti-pneumococcal polysaccharide
382 levels ≥ 0.5 mcg/mL for serotypes 4, 9V, 14, 18C, 19F and 23F and 80.7% (N = 1,027) achieved
383 an anti-pneumococcal polysaccharide level ≥ 0.5 mcg/mL for serotype 6B. The mumps
384 seroresponse rate was lower when DAPTACEL vaccine was administered concomitantly (86.6%;
385 N = 307) vs. non-concomitantly (90.1%; N = 312) with the first dose of MMR vaccine [upper
386 limit of 90% confidence interval for difference in rates (non-concomitant minus concomitant)
387 $>5\%$]. There was no evidence for interference in the immune response to the measles, rubella, and
388 varicella antigens or to the fourth dose of the 7-valent pneumococcal conjugate vaccine with
389 concomitant administration of DAPTACEL vaccine.

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409

410

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

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

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

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

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

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

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

420 **17 PATIENT COUNSELING INFORMATION**

421 Before administration of DAPTACEL vaccine, health-care personnel should inform the parent or
422 guardian of the benefits and risks of the vaccine and the importance of completing the
423 immunization series unless a contraindication to further immunization exists.

424 The health-care provider should inform the parent or guardian about the potential for adverse
425 reactions that have been temporally associated with DAPTACEL vaccine and other vaccines
426 containing similar components. The health-care provider should provide the Vaccine Information
427 Statements (VIS) which are required by the National Childhood Vaccine Injury Act of 1986 to be
428 given with each immunization. The parent or guardian should be instructed to report adverse
429 reactions to their health-care provider.

430

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432 **Sanofi Pasteur Limited**

433 Toronto Ontario Canada

434 Distributed by:

435 **Sanofi Pasteur Inc.**

436 Swiftwater PA 18370 USA

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

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