DAPTACEL® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) Suspension for Intramuscular Injection

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)

DOSE 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)

DOSE 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 >40.5°C (105°F), hypotonic-hyporesponsive episode (HHE) or persistent, inconsolable crying lasting >3 hours within 48 hours after a previous pertussis-containing vaccine. (5.2)
  - seizures within 3 days after a previous pertussis-containing vaccine. (5.2)
- If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk for Guillain-Barré syndrome may be increased following 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 >38.0°C occurred in 6-16% of US subjects, depending on dose number. Injection site reactions that occurred in >50% 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.

CLINICAL STUDIES
- 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

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

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

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINdications

4.1 Hypersensitivity

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

4.2 Encephalopathy

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

4.3 Progressive Neurologic Disorder

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

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

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

5.2 Adverse Reactions Following Prior Pertussis Vaccination

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

- Temperature of ≥30.5°C (100°F) within 48 hours, not attributable to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode [HHE]) within 48 hours.
- Persistent, inconsolable crying lasting ≥23 hours within 48 hours.
- Seizures with or without fever within 5 days.

5.3 Guillain-Barré Syndrome and Brachial Neuritis

A review by the Institute of Medicine found evidence for a causal relation between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome. (1) 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.

5.4 Infants and Children with a History of Previous Seizures

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

5.5 Limitations of Vaccine Effectiveness

Vaccination with DAPTACEL may not protect all individuals.

5.6 Altered Immunocompetence

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

5.7 Apnea in Premature Infants

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.

5.8 Syncope

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

6 ADVERSE REACTIONS

6.1 Data from Clinical Studies

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

Approximately 18,000 doses of DAPTACEL have been administered to infants and children in 9 clinical studies. Of these, 3 doses of DAPTACEL were administered to 4,998 children, 4 doses of DAPTACEL were administered to 1,725 children, and 5 doses of DAPTACEL were administered to 465 children. A total of 889 children received 1 dose of DAPTACEL following 4 prior doses of Pentacel. In a randomized, double-blind pertussis vaccine efficacy trial, the Sweden I Efficacy Trial, conducted in Sweden during 1992-1995, the safety of DAPTACEL was compared with DT and a whole-cell pertussis DTP vaccine. A standard diary card was kept for 14 days after each dose and follow-up telephone calls were made 1 and 14 days after each injection. Telephone calls were made monthly to monitor the occurrence of severe events and/or hospitalizations for the 2 months after the last injection. There were fewer of the solicited common local and systemic reactions following DAPTACEL than following the whole-cell pertussis DTP vaccine. As shown in Table 1, the 2,587 infants who received DAPTACEL at 2, 4 and 6 months of age had similar rates of reactions within 24 hours as recipients of DT and significantly lower rates than infants receiving whole-cell pertussis DTP.

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

<table>
<thead>
<tr>
<th>EVENT</th>
<th>LOCAL</th>
<th>Dose 1 (2 MONTHS)</th>
<th>Dose 2 (4 MONTHS)</th>
<th>Dose 3 (6 MONTHS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DAPTACEL</td>
<td>DT</td>
<td>DTP</td>
<td>DAPTACEL</td>
</tr>
<tr>
<td>Local</td>
<td>N = 2,587</td>
<td>2,574</td>
<td>2,102</td>
<td>N = 2,563</td>
</tr>
<tr>
<td>Tenderness (Any)</td>
<td>8.0%</td>
<td>8.4%</td>
<td>59.5%</td>
<td>10.1%</td>
</tr>
<tr>
<td>Redness ≥2 cm</td>
<td>0.9%</td>
<td>0.7%</td>
<td>10.6%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Swelling ≥2 cm</td>
<td>0.7%</td>
<td>0.3%</td>
<td>6.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Systemic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever ≥38°C (100.4°F)</td>
<td>7.6%</td>
<td>7.6%</td>
<td>72.3%</td>
<td>19.1%</td>
</tr>
<tr>
<td>Fretfulness</td>
<td>32.3%</td>
<td>33.0%</td>
<td>82.1%</td>
<td>39.6%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>11.2%</td>
<td>10.3%</td>
<td>39.2%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>32.7%</td>
<td>32.0%</td>
<td>56.9%</td>
<td>25.5%</td>
</tr>
<tr>
<td>Crying ≥1 hour</td>
<td>1.7%</td>
<td>1.6%</td>
<td>11.8%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6.9%</td>
<td>6.3%</td>
<td>9.5%</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

DT: Swedish National Biologics Laboratories
DTP: whole-cell pertussis DTP, Sanofi Pasteur Inc.
N = Number of evaluable subjects
*p<0.001: DAPTACEL versus whole-cell pertussis DTP
†p<0.0001: DAPTACEL versus DT
‡Rectal temperature
§Statistical comparisons were not made for this variable
**p<0.003: DAPTACEL versus whole-cell pertussis DTP
In the Sweden I Efficacy Trial, one case of whole limb swelling and generalized symptoms, with resolution within 24 hours, was observed following dose 2 of DAPTACEL. No episodes of anaphylaxis or encephalopathy were observed. No seizures were reported within 3 days of vaccination with DAPTACEL. Over the entire study period, 6 seizures were reported in the DAPTACEL group, 9 in the DT group and 3 in the whole-cell pertussis DT group, for overall rates of 2.3, 3.5 and 1.4 per 1,000 vaccinees, respectively. One case of infantile spasms was reported in the DAPTACEL group. There were no instances of invasive bacterial infection or death.

In a US study, children received 4 doses of DAPTACEL at 2, 4, 6 and 15-17 months of age. At 2 and 6 months of age, hepatitis B vaccine at 0 months of age. At 2 and 6 months of age, hepatitis B vaccine (recombinant) (Merck & Co., Inc.) was also administered concomitantly with Hib conjugate (tetanus toxoid conjugate) vaccine; or concomitantly with Hib conjugate (tetanus toxoid conjugate) vaccine, 7-valent pneumococcal conjugate vaccine, measles, mumps, rubella (MMR) vaccine (Merck & Co., Inc.), and varicella vaccine (Merck & Co., Inc.). In the fifth dose studies, DAPTACEL was administered concomitantly with IPV (all DAPTACEL-primed subjects and 47% of Pentacel-primed subjects) and MMR vaccine. In the US studies, the occurrence of solicited local and systemic adverse events listed in Table 3 was recorded daily by parents or guardians for Days 0-7 following vaccination. For Days 0 and 1 following the first three doses of DAPTACEL, signs and symptoms of HHE also were solicited. Periodic telephone calls were made to inquire about adverse events. Serious adverse events were monitored during the three studies, through 6 months following the last dose of DAPTACEL. The incidence and severity of selected solicited local and systemic adverse events that occurred within 3 days following each dose of DAPTACEL are shown in Table 3. The incidence of redness, tenderness and swelling at the DAPTACEL injection site increased with the fourth and fifth doses, with the highest rates reported after the fifth dose. The incidence of redness, tenderness and swelling at the DAPTACEL injection site was similarly increased when DAPTACEL was given as a fifth dose of DTaP vaccine in Pentacel-primed children.

In a separate study, a total of 989 children received DAPTACEL at 4-6 years of age following 4 prior doses of Pentacel in infancy (Pentacel-primed). In this fifth dose studies, DAPTACEL was administered concomitantly with IPV (all DAPTACEL-primed subjects and 47% of Pentacel-primed subjects) and MMR vaccine. The use of DAPTACEL as a fifth dose of DTaP vaccine was evaluated in 2 subsequent US clinical studies. In one study, a total of 485 children received DAPTACEL at 4-6 years of age following 4 prior doses of Pentacel in infancy (Pentacel-primed). In a separate study, a total of 989 children received DAPTACEL at 4-6 years of age following 4 prior doses of Pentacel in infancy (Pentacel-primed). The children included in these fifth dose studies were non-random subsets of participants from previous DAPTACEL or Pentacel studies. The subsets were representative of all children who received 4 doses of DAPTACEL or Pentacel in the earlier studies with regard to frequencies of solicited local and systemic adverse events following the fourth dose. In the US 4-dose DAPTACEL study, at 2, 4, and 6 months of age, DAPTACEL was administered concomitantly with Haemophilus influenzae type b (Hib) conjugate vaccine (tetanus toxoid conjugate) (Sanofi Pasteur SA), inactivated poliovirus vaccine (IPV) (Sanofi Pasteur SA), and 7-valent pneumococcal conjugate vaccine (Wyeth Pharmaceuticals Inc.). Infants had received the first dose of hepatitis B vaccine at 0 months of age. At 2 and 6 months of age, hepatitis B vaccine (recombinant) (Merck & Co., Inc.) was also administered concomitantly with DAPTACEL. Based on random assignment, the fourth dose of DAPTACEL was administered either alone; concomitantly with Hib conjugate (tetanus toxoid conjugate) vaccine; or concomitantly with Hib conjugate (tetanus toxoid conjugate) vaccine, 7-valent pneumococcal conjugate vaccine, measles, mumps, rubella (MMR) vaccine (Merck & Co., Inc.), and varicella vaccine (Merck & Co., Inc.). In the fifth dose studies, DAPTACEL was administered concomitantly with IPV (all DAPTACEL-primed subjects and 47% of Pentacel-primed subjects) and MMR vaccine.

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

<table>
<thead>
<tr>
<th>EVENT</th>
<th>Dose 1 (2 MONTHS)</th>
<th>Dose 2 (4 MONTHS)</th>
<th>Dose 3 (6 MONTHS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DAPTACEL N = 2,587</td>
<td>DTP N = 2,574</td>
<td>DAPTACEL N = 2,565</td>
</tr>
<tr>
<td>Rectal temperature &gt;40°C (104°F) within 48 hours of vaccination</td>
<td>0.39</td>
<td>0.78</td>
<td>3.33</td>
</tr>
<tr>
<td>Hypotonic-hypo-responsive episode within 24 hours of vaccination</td>
<td>0</td>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>Persistent crying &gt;3 hours within 24 hours of vaccination</td>
<td>1.16</td>
<td>0</td>
<td>6.09</td>
</tr>
<tr>
<td>Seizures within 72 hours of vaccination</td>
<td>0</td>
<td>0.39</td>
<td>0</td>
</tr>
</tbody>
</table>

DT: Swedish National Biologics Laboratories
DTP: whole-cell pertussis DTP, Sanofi Pasteur Inc.

N = Number of evaluable subjects

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

<table>
<thead>
<tr>
<th>Injection Site Reactions (DAPTACEL injection site)</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
<th>Dose 4</th>
<th>Dose 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5 mm</td>
<td>6.2</td>
<td>7.1</td>
<td>9.6</td>
<td>17.3</td>
<td>35.8</td>
</tr>
<tr>
<td>25 - 50 mm</td>
<td>0.6</td>
<td>0.5</td>
<td>1.9</td>
<td>6.3</td>
<td>10.4</td>
</tr>
<tr>
<td>&gt;50 mm</td>
<td>0.4</td>
<td>0.1</td>
<td>0.0</td>
<td>3.1</td>
<td>15.8</td>
</tr>
</tbody>
</table>

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   | 26.8   |
| 20 - 40 mm                                        | -      | -      | -      | 7.0    | 14.0   | 7.6    |
| >40 mm                                            | -      | -      | -      | 0.4    | 1.5    | 1.2    |
In the US study in which children received 4 doses of DAPTACEL, 1,454 subjects who received DAPTACEL, 5 (0.3%) subjects experienced a seizure within 60 days following any dose of DAPTACEL. One seizure occurred within 7 days post-vaccination: an infant who experienced an afebrile seizure with apnea on the day of the first vaccination. Three other cases of seizures occurred between 8 and 30 days post-vaccination. Of the seizures that occurred within 60 days post-vaccination, 3 were associated with DAPTACEL administration on Day 1, and one was associated with DAPTACEL administration on Day 7. One seizure occurred within 7 days post-vaccination: an infant who experienced an afebrile seizure with apnea on the day of the first vaccination. Three other cases of seizures occurred between 8 and 30 days post-vaccination. Of the seizures that occurred within 60 days post-vaccination, 3 were associated with DAPTACEL administration on Day 1, and one was associated with DAPTACEL administration on Day 7. One seizure occurred within 7 days post-vaccination: an infant who experienced an afebrile seizure with apnea on the day of the first vaccination. Three other cases of seizures occurred between 8 and 30 days post-vaccination. Of the seizures that occurred within 60 days post-vaccination, 3 were associated with DAPTACEL administration on Day 1, and one was associated with DAPTACEL administration on Day 7.

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

<table>
<thead>
<tr>
<th>Severity</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
<th>Dose 4</th>
<th>Dose 5</th>
<th>DAPTACEL-primed</th>
<th>Pentacel-primed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 1390-1406 %</td>
<td>N = 1346-1360 %</td>
<td>N = 1301-1312 %</td>
<td>N = 1118-1144 %</td>
<td>N = 473-481 %</td>
<td>N = 936-961 %</td>
<td></td>
</tr>
<tr>
<td><strong>Interference with Normal Activity of the Arm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Any</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20.4</td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5.6</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.4</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td><strong>Systemic Reactions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥38.0°C</td>
<td>9.3</td>
<td>16.1</td>
<td>15.8</td>
<td>10.5</td>
<td>6.1</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>&gt;38.5-39.5°C</td>
<td>1.5</td>
<td>3.9</td>
<td>4.8</td>
<td>2.7</td>
<td>2.1</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>&gt;39.5°C</td>
<td>0.1</td>
<td>0.4</td>
<td>0.3</td>
<td>0.7</td>
<td>0.2</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td><strong>Decreased Activity/Lethargy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>51.1</td>
<td>37.4</td>
<td>33.2</td>
<td>25.3</td>
<td>21.0</td>
<td>12.6</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>23.0</td>
<td>14.4</td>
<td>12.1</td>
<td>8.2</td>
<td>5.8</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>1.2</td>
<td>1.4</td>
<td>0.6</td>
<td>1.0</td>
<td>0.8</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td><strong>Inconsonable Crying</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>3.4</td>
<td>1.4</td>
<td>1.5</td>
<td>0.4</td>
<td>0.3</td>
<td></td>
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<tr>
<td><strong>Fussiness/Irritability</strong></td>
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<tr>
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<tr>
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<td>25.0</td>
<td>22.0</td>
<td>16.3</td>
<td>7.5</td>
<td>5.3</td>
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<tr>
<td>Severe</td>
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<td>5.5</td>
<td>4.3</td>
<td>3.9</td>
<td>0.4</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

*In one US 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 Pentacel-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 axillary, and 99.5% 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: 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.

In a randomized, parallel-group, US multicenter clinical trial conducted in children 4 through 6 years of age, DAPTACEL was administered as follows: concomitantly with IPV [Group B]; or 30 days after concomitant administration of Menactra and IPV [Group C]. Solicited injection site and systemic reactions were recorded in a diary card for 7 consecutive days after each vaccination. For all study groups, the most frequently reported systemic reaction after DAPTACEL vaccination was myalgia: 46.2%, 37.3% and 25.8% of subjects in Groups A, B and C, respectively. For all study groups, the most frequently reported systemic reaction after DAPTACEL vaccination was myalgia: 46.2%, 37.3% and 25.8% of subjects in Groups A, B and C, respectively. Fever >39.5°C occurred at <1.0% in all groups.

**6.2 Data from Post-Marketing Experience**

The following adverse events have been spontaneously reported during the post-marketing use of DAPTACEL in the US and other countries. Because these events are reported voluntarily from a population of uncertain size, it may not be possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.
against disease is due to the development of neutralizing antibodies to tetanus toxin. A serum tetanus antitoxin level of 0.1 IU/mL is considered protective.

### 11 NON-CLINICAL TOXICOLOGY

11.1 Mechanism of Action

Diphtheria

Diphtheria is an acute toxin-mediated disease caused by toxicogenic strains of C. diphteriae. Protection against disease is due to the development of neutralizing antibodies to diphtheria toxin. A serum diphtheria antitoxin level of 0.01 IU/mL is the lowest level giving some degree of protection. Antitoxin levels of at least 0.1 IU/mL have been associated with long-term protection. (6)

Tetanus

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

### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Diphtheria

Diphtheria is caused by the Gram-negative bacillus C. diphteriae. The bacillus produces a variety of toxins and enzymes through their role in either the pathogenesis of, or immunity to, pertussis has not been clearly defined.

### 14 STUDIES

14.1 Diphtheria

In a US study in which children received 4 doses of DAPTACEL at 2, 4, 6, and 15-17 months of age, after the third dose, 100% (N = 1,069) achieved diphtheria antitoxin levels of ≥0.1 IU/mL, 98.5% achieved diphtheria antitoxin levels of ≥0.10 IU/mL. Among a random subset of children who received the fourth dose of DAPTACEL at 15-16 months of age, 96.5% (N = 659) achieved diphtheria antitoxin levels of ≥0.10 IU/mL after the fourth dose.

14.2 Tetanus

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

14.3 Pertussis

A randomized, double-blind, placebo-controlled efficacy and safety study was conducted in Sweden during 1992-1995 (Sweden I Efficacy Trial) under the sponsorship of the National Institute of Allergy and Infectious Diseases. A total of 9,829 infants received 1 of 4 vaccines: DAPTACEL; another investigational acellular pertussis vaccine (N = 2,566); whole-cell pertussis DT vaccine (N = 2,102); or DT vaccine as placebo (Swedish National Bacteriological Laboratory, N = 2,574). Infants were immunized at 2, 4, and 6 months of age. The mean length of follow-up was 2 years after the third dose. The protective efficacy of DAPTACEL against pertussis after 5 doses using the World Health Organization (WHO) case definition (≥21 consecutive days of paroxysmal cough with culture or serologic confirmation or epidemiologic link to a confirmed case) was 84.9% (95% confidence interval [CI] 80.1 to 88.6). The protective efficacy of DAPTACEL against mild pertussis (≥1 day of cough with laboratory confirmation) was 77.9% (95% CI 72.6 to 82.2). Protection against pertussis by DAPTACEL was sustained for the 2-year follow-up period.

In order to assess the antibody response to the pertussis antigens of DAPTACEL in the US population, 2 lots of DAPTACEL, including the lot used in the Sweden I Efficacy Trial, were administered to US infants in an US Bridging Study. In this study, antibody responses following 3 doses of DAPTACEL given to US children at 2, 4 and 6 months of age were compared to those from a subset of the infants enrolled in the Sweden I Efficacy Trial. Assays were performed in parallel on the available sera from the US and Swedish infants. Antibody responses to all the antigens were similar except for those to the monovalent component. For both lots of DAPTACEL, the geometric mean concentration (GMC) and percent response to PRN in US infants (Lot 006, N = 107; Lot 009, N = 108) were significantly lower after 3 doses of vaccine than in Swedish infants (N = 83). In separate US and Canadian studies in which children received DAPTACEL at 2, 4, 6 and 12 months of age, with a fourth dose at either 17-20 months of age (US) or 15-16 months of age (Canada) and a random subset of children were given DAPTACEL at the fourth dose, the antibody responses to each pertussis antigen following the fourth dose (Canadian study, N = 275; US study N = 237-347) were at least as high as those seen in the Swedish infants after 3 doses. While a serologic correlate of protection for pertussis has not been established, the antibody response to all antigens in North American infants after 4 doses of DAPTACEL at 2, 4, 6 and 15-20 months of age was comparable to that achieved in Swedish infants in whom efficacy was demonstrated after 3 doses of DAPTACEL at 2, 4 and 6 months of age.
15 REFERENCES


5 Department of Health and Human Services, Food and Drug Administration. Biological products; bacterial vaccines and toxoids; implementation of efficacy review; proposed rule. Federal Register 1985;50(240):51002-117.


16 HOW SUPPLIED/STORAGE AND HANDLING

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

DAPTACEL is supplied in a single-dose vial (NDC No. 49281-286-58):
- in packages of 1 vial: NDC No. 49281-286-01;
- in packages of 5 vials: NDC No. 49281-286-05;
- in packages of 10 vials: NDC No. 49281-286-10.

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

17 PATIENT COUNSELING INFORMATION

Inform the parent or guardian of the following:
- The potential benefits and risks of immunization with DAPTACEL.
- The common adverse reactions that have occurred following administration of DAPTACEL or other vaccines containing similar components.
- Other adverse reactions can occur. Call healthcare provider with any adverse reactions of concern.

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

Manufactured by:
Sanofi Pasteur Limited
Toronto Ontario Canada

Distributed by:
Sanofi Pasteur Inc.
Swiftwater PA 18370 USA


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R11-0220 USA

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