Mixed Sequences of DAPTACEL and other DTaP-containing Vaccines

## 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.

### DOSAGE FORMS AND STRENGTHS

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

### 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)
- 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).

### ADVERSE REACTIONS

Data are not available on the safety and effectiveness of using mixed sequences of DAPTACEL and other DTaP-containing Vaccines. Pentacel and VAXELIS contain twice the amount of detoxified pertussis toxin (PT) and four times the amount of filamentous hemagglutinin (FHA) as DAPTACEL. DAPTACEL may be used as any of the doses in a 5-dose DTaP series initiated with Pentacel or VAXELIS.

## HOW SUPPLIED/STORAGE AND HANDLING

DAPTACEL® may be used as any of the doses in a 5-dose DTaP series initiated with Pentacel or VAXELIS.

Data are not available on the safety and effectiveness of using mixed sequences of DAPTACEL and DTaP-containing vaccines from different manufacturers for successive doses of the DTaP vaccination series.

## PATIENT COUNSELING INFORMATION

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07/2022

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**FULL PRESCRIBING INFORMATION: CONTENTS**

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Immunization Series

2.2 Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

4.1 Hypersensitivity

4.2 Encephalopathy

4.3 Progressive Neurologic Disorder

5 WARNINGS AND PRECAUTIONS

5.1 Management of Acute Allergic Reactions

5.2 Adverse Reactions Following Prior Pertussis Vaccination

5.3 Guillain-Barré Syndrome and Brachial Neuritis

5.4 Infants and Children with a History of Previous Seizures

5.5 Limitations of Vaccine Effectiveness

5.6 Altered Immunocompetence

5.7 Apnea in Premature Infants

5.8 Syncope

6 ADVERSE REACTIONS

6.1 Data from Clinical Studies

6.2 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

7.2 Immunosuppressive Treatments

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 Diphtheria

14.2 Tetanus

14.3 Pertussis

14.4 Concomitantly Administered Vaccines

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed
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 ≥40.5°C (104.9°F) within 48 hours, not attributable to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode [HHSE]) within 48 hours.
- Persistent, inconsolable crying lasting ≥23 hours within 48 hours.
- Seizures with or without fever within 3 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. 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 avoid injury from fainting.

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-blinded 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 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 DT 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 DT.

### 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>Dose 1 (2 MONTHS) DAPTACEL N = 2,587</th>
<th>Dose 1 (2 MONTHS) DT N = 2,574</th>
<th>Dose 1 (2 MONTHS) DTP N = 2,102</th>
<th>Dose 2 (4 MONTHS) DAPTACEL N = 2,563</th>
<th>Dose 2 (4 MONTHS) DT N = 2,555</th>
<th>Dose 2 (4 MONTHS) DTP N = 2,040</th>
<th>Dose 3 (6 MONTHS) DAPTACEL N = 2,549</th>
<th>Dose 3 (6 MONTHS) DT N = 2,538</th>
<th>Dose 3 (6 MONTHS) DTP N = 2,001</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenderness (Any)</td>
<td>8.0†</td>
<td>8.4</td>
<td>59.5</td>
<td>10.1†</td>
<td>10.3</td>
<td>60.2</td>
<td>10.8</td>
<td>10.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Redness ≥2 cm</td>
<td>0.3†</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3†</td>
<td>0.8</td>
<td>5.1</td>
<td>3.7†</td>
<td>2.4</td>
<td>6.4</td>
</tr>
<tr>
<td>Swelling ≥2 cm</td>
<td>0.9†</td>
<td>0.7</td>
<td>10.6</td>
<td>1.6†</td>
<td>2.0</td>
<td>10.0</td>
<td>6.3†</td>
<td>3.9</td>
<td>10.5</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever ≥38.9°C (100.4°F)</td>
<td>7.8†</td>
<td>7.6</td>
<td>72.3</td>
<td>19.1†</td>
<td>18.4</td>
<td>74.3</td>
<td>23.6</td>
<td>22.1</td>
<td>65.1</td>
</tr>
<tr>
<td>Fretfulness§</td>
<td>32.3</td>
<td>33.0</td>
<td>82.1</td>
<td>39.6</td>
<td>39.8</td>
<td>85.4</td>
<td>35.9</td>
<td>37.7</td>
<td>73.0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>11.2†</td>
<td>10.3</td>
<td>39.2</td>
<td>9.1†</td>
<td>8.1</td>
<td>25.6</td>
<td>8.4†</td>
<td>7.7</td>
<td>17.5</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>32.7†</td>
<td>32.0</td>
<td>56.9</td>
<td>25.9†</td>
<td>25.6</td>
<td>50.6</td>
<td>18.9†</td>
<td>20.6</td>
<td>37.6</td>
</tr>
<tr>
<td>Crying ≥1 hour</td>
<td>1.7†</td>
<td>1.6</td>
<td>11.8</td>
<td>2.5†</td>
<td>2.7</td>
<td>9.3</td>
<td>1.2†</td>
<td>1.0</td>
<td>3.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6.9†</td>
<td>6.3</td>
<td>9.5</td>
<td>5.2‡</td>
<td>5.8</td>
<td>7.4</td>
<td>4.3</td>
<td>5.2</td>
<td>5.5</td>
</tr>
</tbody>
</table>

DT: Swedish National Biosciences 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

§Statistical comparisons were not made for this variable

*p<0.003: DAPTACEL versus whole-cell pertussis DTP
The incidence of serious and less common selected systemic events in the Sweden I Efficacy Trial is summarized in Table 2.

<table>
<thead>
<tr>
<th>EVENT</th>
<th>Dose 1 (2 MONTHS) DAPTACEL N = 2,587</th>
<th>Dose 1 (2 MONTHS) DT N = 2,574</th>
<th>Dose 1 (2 MONTHS) DTP N = 2,102</th>
<th>Dose 2 (4 MONTHS) DAPTACEL N = 2,565</th>
<th>Dose 2 (4 MONTHS) DT N = 2,556</th>
<th>Dose 2 (4 MONTHS) DTP N = 2,040</th>
<th>Dose 3 (6 MONTHS) DAPTACEL N = 2,551</th>
<th>Dose 3 (6 MONTHS) DT N = 2,539</th>
<th>Dose 3 (6 MONTHS) DTP N = 2,002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal temperature ≥40°C (104°F) within 48 hours of vaccination</td>
<td>0.39</td>
<td>0.78</td>
<td>3.33</td>
<td>0</td>
<td>0.78</td>
<td>3.43</td>
<td>0.39</td>
<td>1.18</td>
<td>6.99</td>
</tr>
<tr>
<td>Hypotonic-hyporesponsive episode within 24 hours of vaccination</td>
<td>0</td>
<td>0</td>
<td>1.9</td>
<td>0</td>
<td>0</td>
<td>0.49</td>
<td>0.39</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Persistent crying ≥3 hours within 24 hours of vaccination</td>
<td>1.16</td>
<td>0</td>
<td>8.09</td>
<td>0.39</td>
<td>0.39</td>
<td>1.96</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Seizures within 72 hours of vaccination</td>
<td>0</td>
<td>0.39</td>
<td>0</td>
<td>0</td>
<td>0.39</td>
<td>0.49</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

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 DTP 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 massive bacterial infection or death.

In a US study, children received 4 doses of DAPTACEL at 2, 4, 6 and 15-17 months of age. A total of 1,454 children received DAPTACEL and were included in the safety analyses. Of these, 51.7% were female, 77.2% Caucasian, 6.3% Black, 6.5% Hispanic, 0.9% Asian and 9.1% other races. The use of DAPTACEL in infancy (DAPTACEL-primed) and in later childhood (Pentacel-primed) was explored.

In the US 4-dose DAPTACEL study, at 2, 4, 6 and 15-17 months of age, 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.

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 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>EVENT</th>
<th>Dose 1* N = 1390–1406 %</th>
<th>Dose 2* N = 1346–1360 %</th>
<th>Dose 3* N = 1301–1312 %</th>
<th>Dose 4* N = 1116–1144 %</th>
<th>Dose 5 DAPTACEL-primed† N = 473–481 %</th>
<th>Dose 5 Pentacel-primed‡ N = 936–981 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection Site Reactions (DAPTACEL injection site)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Redness</td>
<td></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>
<td>20.2</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>
<td>6.8</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>
<td>6.6</td>
</tr>
<tr>
<td>Swelling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5 mm</td>
<td>4.0</td>
<td>4.0</td>
<td>6.5</td>
<td>11.7</td>
<td>23.9</td>
<td>12.0</td>
</tr>
<tr>
<td>25 – 50 mm</td>
<td>1.2</td>
<td>0.6</td>
<td>1.0</td>
<td>3.2</td>
<td>5.8</td>
<td>4.1</td>
</tr>
<tr>
<td>&gt;50 mm</td>
<td>0.4</td>
<td>0.1</td>
<td>0.1</td>
<td>1.6</td>
<td>7.7</td>
<td>2.9</td>
</tr>
<tr>
<td>Tenderness‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>48.8</td>
<td>38.2</td>
<td>40.9</td>
<td>49.5</td>
<td>61.5</td>
<td>50.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>16.5</td>
<td>9.9</td>
<td>10.6</td>
<td>12.3</td>
<td>11.2</td>
<td>7.4</td>
</tr>
<tr>
<td>Severe</td>
<td>4.1</td>
<td>2.3</td>
<td>1.7</td>
<td>2.2</td>
<td>1.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Increase in Arm Circumference‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5 mm</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>30.1</td>
<td>38.3</td>
<td>28.6</td>
</tr>
<tr>
<td>20 – 40 mm</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7.0</td>
<td>14.0</td>
<td>7.6</td>
</tr>
<tr>
<td>&gt;40 mm</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.4</td>
<td>1.5</td>
<td>1.2</td>
</tr>
</tbody>
</table>
### 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>Dose 1&lt;sup&gt;†&lt;/sup&gt; N = 1396–1406</th>
<th>Dose 2&lt;sup&gt;†&lt;/sup&gt; N = 1369–1360</th>
<th>Dose 3&lt;sup&gt;†&lt;/sup&gt; N = 1391–1312</th>
<th>Dose 4&lt;sup&gt;†&lt;/sup&gt; N = 1118–1144</th>
<th>Dose 5&lt;sup&gt;†&lt;/sup&gt; DAPTACEL-primed&lt;sup&gt;§&lt;/sup&gt; N = 473–481</th>
<th>Dose 5&lt;sup&gt;†&lt;/sup&gt; Pentacel-primed&lt;sup&gt;‡&lt;/sup&gt; N = 936–981</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interference with Normal Activity of the Arm</strong></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Any</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20.4</td>
<td>8.8</td>
</tr>
<tr>
<td>Moderate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Severe</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.4</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Systemic Reactions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fever</strong>&lt;sup&gt;Þ&lt;/sup&gt;</td>
<td>≥38.0°C</td>
<td>9.3</td>
<td>16.1</td>
<td>15.8</td>
<td>10.5</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>
</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>
</tr>
<tr>
<td><strong>Decreased Activity/Lethargy</strong>&lt;sup&gt;Ý&lt;/sup&gt;</td>
<td>Any</td>
<td>51.1</td>
<td>37.4</td>
<td>33.2</td>
<td>25.3</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>
</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>
</tr>
<tr>
<td><strong>Inconsolable Crying</strong>&lt;sup&gt;ß&lt;/sup&gt;</td>
<td>Any</td>
<td>58.5</td>
<td>51.4</td>
<td>47.9</td>
<td>37.1</td>
</tr>
<tr>
<td>Moderate</td>
<td>14.2</td>
<td>12.6</td>
<td>10.8</td>
<td>7.7</td>
<td>3.5</td>
</tr>
<tr>
<td>Severe</td>
<td>2.2</td>
<td>3.4</td>
<td>1.4</td>
<td>1.5</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Fussiness/Irritability</strong>&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Any</td>
<td>75.8</td>
<td>70.7</td>
<td>67.1</td>
<td>54.4</td>
</tr>
<tr>
<td>Moderate</td>
<td>27.7</td>
<td>25.0</td>
<td>22.0</td>
<td>16.3</td>
<td>7.5</td>
</tr>
<tr>
<td>Severe</td>
<td>5.6</td>
<td>5.5</td>
<td>4.3</td>
<td>3.9</td>
<td>0.4</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/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.

¶Dose 5: Moderate: interfered with activities, but did not require medical care or absenteeism; Severe: incapacitating, unable to perform usual activities, may have/required medical care or absenteeism.

þFor 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.

ßDose 5: Moderate: interfered with activities, but did not require medical care or absenteeism; Severe: incapacitating, unable to perform usual activities, may have/required medical care or absenteeism.

††Doses 1–4: Moderate: interfered with activities, but did not require medical care or absenteeism; Severe: incapacitating, unable to perform usual activities, may have/required medical care or absenteeism.

†††Doses 1–4: Moderate: interfered with activities, but did not require medical care or absenteeism; Severe: incapacitating, unable to perform usual activities, may have/required medical care or absenteeism.

†‡Doses 1–4: Moderate: interfered with activities, but did not require medical care or absenteeism; Severe: incapacitating, unable to perform usual activities, may have/required medical care or absenteeism.

†††Doses 1–4: Moderate: interfered with activities, but did not require medical care or absenteeism; Severe: incapacitating, unable to perform usual activities, may have/required medical care or absenteeism.

In the 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 in an infant who experienced an afebrile seizure with apnea on the day of the first vaccination. Three other cases of seizures occurred between 9 and 30 days post-vaccination. Of the seizures that occurred within 60 days post-vaccination, 3 were associated with fever. In this study, there were no reported cases of HHE following DAPTACEL. There was one death due to aspiration 222 days post-vaccination in a subject with spina bifida. Within 30 days following any dose of DAPTACEL, 57 (3.9%) subjects reported at least one serious adverse event. During this period, the most frequently reported serious adverse event was bronchitis, reported in 28 (1.9%) subjects. Other serious adverse events that occurred within 30 days following DAPTACEL include three cases of pneumonia, two cases of meningitis and one each of sepsis, pertussis (post-dose 1), irritability and unresponsiveness.

In the US study in which children received 4 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.

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

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 (Sanofi Pasteur SA) followed 30 days later by Menactra® (Meningococcal [Groups A, C, Y and W-135] Polysaccharide Diphtheria Toxoid Conjugate vaccine, Sanofi Pasteur Inc.) [Group A]; concomitantly with Menactra followed 30 days later by 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 solicited local reaction at the DAPTACEL injection site was pain: 71.7%, 69.4% and 52.1% 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 Postmarketing Experience

The following adverse events have been spontaneously reported during the postmarketing 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. The following adverse events were included based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to DAPTACEL.
• Blood and lymphatic disorders
  - Lymphadenopathy
• Cardiac disorders
  - Cyanosis
• Gastro-intestinal disorders
  - Nausea, vomiting
• General disorders and administration site conditions
  - Local reactions: injection site pain, injection site rash, injection site nodule, injection site mass, extensive swelling of injected limb (including swelling that involves adjacent joints).
• Infections and infestations
  - Injection site cellulitis, injection site abscess
• Immune system disorders
  - Hypersensitivity, allergic reaction, anaphylactic reaction (edema, face edema, swelling face, pruritus, rash generalized and/or other types of rash (erythematous, macular, maculopapular)
• Nervous system disorders
  - Convulsions: febrile convulsion, grand mal convulsion, partial seizures
• Psychiatric disorders

7 DRUG INTERACTIONS
7.1 Concomitant Administration with Other Vaccines
In clinical trials, DAPTACEL was administered concomitantly with one or more of the following US licensed vaccines: Hib conjugate vaccine, IPV, hepatitis B vaccine, pneumococcal conjugate vaccine, Meningococcal (Groups A, C, Y, and W-135) Polysaccharide Diphtheria Toxoid Conjugate vaccine, MMR vaccine, and varicella vaccine. [See Adverse Reactions (6.1) and Clinical Studies (14.4)]. When DAPTACEL was co-administered (i.e., same time) with one or more of the following vaccines: Acellular pertussis vaccine, DTaP [Triacellular pertussis vaccine (Diphtheria and tetanus), 3 dose series (14.4)]. In a study of DAPTACEL in healthy adults, the antibody response to tetanus toxoid was non-inferior when DAPTACEL was administered concomitantly with Menactra [Menomeningococcal (Groups A, C, Y, and W-135) Polysaccharide Vaccine] and a dose of IPXPlan [Inactivated polio vaccine]. The antibody response to tetanus toxoid was non-inferior when DAPTACEL was administered concomitantly with Menactra [Menomeningococcal (Groups A, C, Y, and W-135) Polysaccharide Vaccine] and a dose of IPXPlan [Inactivated polio vaccine]. The antibody response to tetanus toxoid was non-inferior when DAPTACEL was administered concomitantly with Menactra [Menomeningococcal (Groups A, C, Y, and W-135) Polysaccharide Vaccine] and a dose of IPXPlan [Inactivated polio vaccine]. The antibody response to tetanus toxoid was non-inferior when DAPTACEL was administered concomitantly with Menactra [Menomeningococcal (Groups A, C, Y, and W-135) Polysaccharide Vaccine].

7.2 Immunosuppressive Treatments
Immunosuppressive therapies, including irradiation, immunosuppressive agents, corticosteroids (used in greater than physiologic doses), may reduce the immune response to DAPTACEL.

8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use
DAPTACEL is not indicated for use in infants below 6 weeks of age or children 7 years of age or older. Safety and effectiveness of DAPTACEL in these age groups have not been established.

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

Each 0.5 mL dose contains 15 µg diphtheria toxoid, 5 µg tetanus toxoid and acellular pertussis antigens [100 mcg detoxified pertussis toxin (PT), 5 mcg filamentous hemagglutinin (FHA), 3 mg pertactin (PRN), and 5 mcg fimbriae types 2 and 3 (FIM)] (IPXPlan, NIPXPlan) [Streptococcus pneumoniae]. Other antigens may be added, such as 1.5 mg aluminum phosphate (0.33 mg of aluminum) as the adjuvant, ±5 mcg residual formaldehyde, <50 ng residual gludurahaldey and 3.3 mg (0.6% v/v) 2-phenoxyethanol (not as a preservative).

The acellular pertussis vaccine components are produced from Bordetella pertussis cultures grown in Stainer-Scholte medium. (3) After purification by diafi ation. Diphtheria and tetanus toxoids are individually adsorbed onto aluminum phosphate. (14.4)

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Diphtheria
Diphtheria toxoid is the antigenic component of DAPTACEL. Diphtheria toxoid is toxoidized and adsorbed to aluminum phosphate. (14.4)

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 toxoid. A serum tetanus antitoxin level of at least 0.1 IU/mL is considered the minimum protective level. (5) A tetanus antitoxin level ≥0.1 IU/mL, as measured by the ELISA used in clinical studies of DAPTACEL is considered protective.

Pertussis
Pertussis (whooping cough) is a respiratory disease caused by B. pertussis. This Gram-negative cocccobacillus produces a variety of biologically active components, though their role in either the pathogenesis, or immune response has not been clearly defined.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
DAPTACEL has not been evaluated for carcinogenic or mutagenic potential or impairment of fertility.
C, and W-135 were non-inferior to those observed when Menactra (and IPV) were administered [Group C]. The non-inferiority criterion was marginally missed for meningococcal serogroup Y. [See Drug Interactions (7.1)].

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.
8 VAXELIS® [full prescribing information]. Toronto, ON: MSP Vaccine Company.

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

US Patents: 4500639, 4687738, 4784589, 4997915, 5441159, 5687787, 5877298.

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