INDICATIONS AND USAGE

Pentacel is a vaccine indicated for active immunization against diphtheria, tetanus, pertussis, poliomyelitis and invasive disease due to Haemophilus influenzae type b. Pentacel is approved for use as a four dose series in children 6 weeks through 4 years of age (prior to 5th birthday). (1)

Dosage and Administration

The four dose immunization series consists of a 0.5 mL intramuscular injection, after reconstitution, administered at 2, 4, 6 and 15-18 months of age. (2.1)

Pentacel consists of a liquid vaccine component (DTaP-IPV component) and a lyophilized vaccine component (ActHIB vaccine). Reconstitute the ActHIB vaccine component with the DTaP-IPV component immediately before administration. (2.2)

Dosage Forms and Strengths

Suspension for injection (0.5 mL dose) supplied as a liquid vaccine component that is combined through reconstitution with a lyophilized vaccine component, both in single-dose vials. (3)

Contraindications

Severe allergic reaction (eg, anaphylaxis) after a previous dose of Pentacel, any ingredient of Pentacel, or any other diphtheria toxoid, tetanus toxoid, pertussis-containing vaccine, inactivated poliovirus vaccine or H. influenzae type b vaccine. (4.1)

Encephalopathy within 7 days of a previous pertussis-containing vaccine with no other identifiable cause. (4.2)

Progressive neurologic disorder until a treatment regimen has been established and the condition has stabilized. (4.3)

WARNINGS AND PRECAUTIONS

Carefully consider benefits and risks before administering Pentacel to persons with a history of:

- Fever ≥40.5°C (≥105°F), hypotonic-hyporesponsive episode (HHE) or persistent, inconsiderable crying lasting ≥3 hours within 48 hours after a previous pertussis-containing vaccine. (5.2)
- Seizures within 3 days after a previous pertussis-containing vaccine. (5.2)
- If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk for Guillain-Barré syndrome may be increased following Pentacel. (5.3)
- For infants and children with a history of previous seizures, an antipyretic may be administered (in the dosages recommended in its prescribing information) at the time of vaccination with Pentacel and for the next 24 hours. (5.4)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. The decision about when to administer an intramuscular vaccine, including Pentacel, to an infant born prematurely should be based on consideration of the individual infant’s medical status and the potential benefits and possible risks of vaccination. (5.7)

Adverse Reactions

Rates of adverse reactions varied by dose number. Systemic reactions that occurred in >50% of participants following any dose included fussiness/irritability and inconsiderable crying. Fever ≥38.0°C occurred in 6-16% of participants, depending on dose number. Injection site reactions that occurred in ≥30% of participants following any dose included tenderness and increase in arm circumference. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pharmacovigilance Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 and http://vaers.hhs.gov.

DRUG INTERACTIONS

Do not mix Pentacel or any of its components with any other vaccine or diluent. (7.1)

Immunosuppressive therapies may reduce the immune response to Pentacel. (7.2)

Urine antigen detection may not have definitive diagnostic value in suspected H. influenzae type b disease within one week following Pentacel. (7.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2019

FULL PRESCRIBING INFORMATION: CONTENTS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

6 ADVERSE REACTIONS

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

9 DESCRIPTION

10 CLINICAL PHARMACOLOGY

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14 HOW SUPPLIED/STORAGE AND HANDLING

15 PATIENT COUNSELING INFORMATION

FULL PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Pentacel® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine Suspension for Intramuscular Injection

Initial U.S. Approval: 2008

INDICATIONS AND USAGE

Pentacel is a vaccine indicated for active immunization against diphtheria, tetanus, pertussis, poliomyelitis and invasive disease due to Haemophilus influenzae type b. Pentacel is approved for use as a four dose series in children 6 weeks through 4 years of age (prior to 5th birthday). (1)

Dosage and Administration

The four dose immunization series consists of a 0.5 mL intramuscular injection, after reconstitution, administered at 2, 4, 6 and 15-18 months of age. (2.1)

Pentacel consists of a liquid vaccine component (DTaP-IPV component) and a lyophilized vaccine component (ActHIB vaccine). Reconstitute the ActHIB vaccine component with the DTaP-IPV component immediately before administration. (2.2)

Dosage Forms and Strengths

Suspension for injection (0.5 mL dose) supplied as a liquid vaccine component that is combined through reconstitution with a lyophilized vaccine component, both in single-dose vials. (3)

Contraindications

Severe allergic reaction (eg, anaphylaxis) after a previous dose of Pentacel, any ingredient of Pentacel, or any other diphtheria toxoid, tetanus toxoid, pertussis-containing vaccine, inactivated poliovirus vaccine or H. influenzae type b vaccine. (4.1)

Encephalopathy within 7 days of a previous pertussis-containing vaccine with no other identifiable cause. (4.2)

Progressive neurologic disorder until a treatment regimen has been established and the condition has stabilized. (4.3)

WARNINGS AND PRECAUTIONS

Carefully consider benefits and risks before administering Pentacel to persons with a history of:

- Fever ≥40.5°C (≥105°F), hypotonic-hyporesponsive episode (HHE) or persistent, inconsiderable crying lasting ≥3 hours within 48 hours after a previous pertussis-containing vaccine. (5.2)
- Seizures within 3 days after a previous pertussis-containing vaccine. (5.2)
- If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the risk for Guillain-Barré syndrome may be increased following Pentacel. (5.3)
- For infants and children with a history of previous seizures, an antipyretic may be administered (in the dosages recommended in its prescribing information) at the time of vaccination with Pentacel and for the next 24 hours. (5.4)
- Apnea following intramuscular vaccination has been observed in some infants born prematurely. The decision about when to administer an intramuscular vaccine, including Pentacel, to an infant born prematurely should be based on consideration of the individual infant’s medical status and the potential benefits and possible risks of vaccination. (5.7)

Adverse Reactions

Rates of adverse reactions varied by dose number. Systemic reactions that occurred in >50% of participants following any dose included fussiness/irritability and inconsiderable crying. Fever ≥38.0°C occurred in 6-16% of participants, depending on dose number. Injection site reactions that occurred in ≥30% of participants following any dose included tenderness and increase in arm circumference. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pharmacovigilance Department, Sanofi Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 at 1-800-822-2463 (1-800-VACCINE) or VAERS at 1-800-822-7967 and http://vaers.hhs.gov.

DRUG INTERACTIONS

Do not mix Pentacel or any of its components with any other vaccine or diluent. (7.1)

Immunosuppressive therapies may reduce the immune response to Pentacel. (7.2)

Urine antigen detection may not have definitive diagnostic value in suspected H. influenzae type b disease within one week following Pentacel. (7.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2019

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Pentacel® is a vaccine indicated for active immunization against diphtheria, tetanus, pertussis, poliomyelitis and invasive disease due to Haemophilus influenzae type b. Pentacel is approved for use as a four dose series in children 6 weeks through 4 years of age (prior to fifth birthday).

2 DOSAGE AND ADMINISTRATION

2.1 Immunization Series

Pentacel is to be administered as a 4 dose series at 2, 4, 6 and 15-18 months of age. The first dose may be given as early as 6 weeks of age. Four doses of Pentacel constitute a primary immunization course against pertussis. Three doses of Pentacel constitute a primary immunization course against diphtheria, tetanus, H. influenzae type b invasive disease, and poliomyelitis; the fourth dose is a booster for diphtheria, tetanus, H. influenzae type b invasive disease, and poliomyelitis immunizations [see Clinical Studies (14.1, 14.2, 14.3, 14.4, 14.5)].

Mixed Sequences of Pentacel and DTaP Vaccine

While Pentacel and DAPTACEL (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed [DTaP], Sanofi Pasteur Limited) vaccines contain the same pertussis antigens, manufactured by the same process, Pentacel contains twice the amount of detoxified pertussis toxin (PT) and four times the amount of filamentous hemagglutinin (FHA) as DAPTACEL. Pentacel may be used to complete the first 4 doses of the 5-dose DTaP series in infants and children who have received 1 or more doses of DAPTACEL and are also scheduled to receive the other antigens of Pentacel. However, data are not available on the safety and immunogenicity of such mixed sequences of Pentacel and DAPTACEL.
Mixed Sequences of Pentacel and Haemophilus b Conjugate Vaccine administered at ages 2, 4, 6, and 15-18 months, an additional booster dose of IPV vaccine must be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs.

5.5 Limitations of Vaccine Effectiveness

Vaccination with Pentacel may not protect all individuals.

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

The poliovirus component (poliovirus types 1, 2, and 3) of this formulation of Pentacel is grown in Vero cells [see Description (11)]. The clinical study data in this section were accrued with a Pentacel formulation in which the poliovirus component was grown in MRC-5 cells. The safety of Pentacel was evaluated in four clinical studies in which a total of 5,980 participants received at least one dose of Pentacel. In three of the studies, conducted in the US, a total of 4,198 participants were enrolled to receive four consecutive doses of Pentacel. In the fourth study, conducted in Canada, 1,782 participants previously vaccinated with three doses of Pentacel received a fourth dose. The vaccination schedules of Pentacel, Control vaccines, and concomitantly administered vaccines used in these studies are provided in Table 1.

Across the four studies, 50.8% of participants were female. Among participants in the three US studies, 64.5% were Caucasian, 9.2% were Black, 12.9% were Hispanic, 3.9% were Asian, and 3.5% were of other racial/ethnic groups. In the two Canadian studies, the racial/ethnic distribution of participants who received Pentacel and Control vaccines was similar. In the Canadian fourth dose study, 86.0% of participants were Caucasian, 1.9% were Black, 0.6% were Hispanic, 4.3% were Asian, 2.0% were East Indian, 0.5% were Native Indian, and 4.5% were of other racial/ethnic groups.

### Table 1: Clinical Safety Studies of Pentacel: Vaccination Schedules

<table>
<thead>
<tr>
<th>Study</th>
<th>Pentacel</th>
<th>Control Vaccines</th>
<th>Concomitantly Administered Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>494-01</td>
<td>2, 4, 6 and 15 months</td>
<td>HCPDT + POLIVAX + ActHIB at 2, 4, 6, and 15 months</td>
<td>7-valent pneumococcal conjugate vaccine (PCV7) at 2, 4, and 6 months in a subset of participants³</td>
</tr>
</tbody>
</table>

- **Hepatitis B vaccine at 2 and 6 months³**
### Table 1: Clinical Safety Studies of Pentacel: Vaccination Schedules (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Pentacel Administered Vaccines</th>
<th>Control Vaccines</th>
<th>Concomitantly Administered Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P3T06</strong></td>
<td>2, 4, 6, and 15-16 months</td>
<td>DAPTACEL + IPOL + ActHIB at 2, 4, and 6 months; and DAPTACEL + ActHIB at 15-16 months</td>
<td>PCV7 at 2, 4, and 6 months; Hepatitis B vaccine at 2 and 6 months†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DAPTACEL + ActHIB at 15-16 months</td>
<td>§PCV7 manufactured by Wyeth Laboratories.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PCV7* at 2, 4, and 6 months in all participants; and at 15 months in a random subset of participants</td>
<td>†PCV7 was introduced after the study was initiated, and thus, administered concomitantly with Pentacel vaccine in a subset of participants.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatitis B vaccine at 2 and 6 months (if a dose was previously administered) or at 2, 4, and 6 months (if no previous dose)</td>
<td>‡The first dose of hepatitis B vaccine (manufacturer not specified) was administered prior to study initiation, from birth to 21 days of age. Subsequent doses were with hepatitis B vaccine manufactured by Merck and Co.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Measles, mumps, rubella vaccine§ (MMR) and varicella§ vaccine at 12 or 15 months in random subsets of participants</td>
<td>§MMR and varicella vaccines were both manufactured by Merck and Co.</td>
</tr>
<tr>
<td><strong>494-03</strong></td>
<td>2, 4, 6, and 15-16 months</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PCV7 at 2, 4, and 6 months in all participants; and at 15 months in a random subset of participants</td>
<td>$Study participants previously had received three doses of Pentacel vaccine by 8 months of age.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatitis B vaccine at 2 and 6 months (if a dose was previously administered) or at 2, 4, and 6 months (if no previous dose)</td>
<td>¶Study participants previously had received three doses of Pentacel vaccine by 8 months of age.</td>
</tr>
</tbody>
</table>

### Table 2: Number (Percentage) of Children with Selected Solicited Adverse Reactions by Severity Occurring within 0-3 days of Pentacel or Control Vaccines in Study P3T06

<table>
<thead>
<tr>
<th>Injection Site Reactions</th>
<th>Pentacel N = 465-467</th>
<th>Dose 1 %</th>
<th>Dose 2 N = 451</th>
<th>Dose 2 %</th>
<th>Dose 3 N = 438-440</th>
<th>Dose 3 %</th>
<th>Dose 4 N = 387-396</th>
<th>Dose 4 %</th>
<th>Dose 1 N = 1,400-1,404</th>
<th>Dose 1 %</th>
<th>Dose 2 N = 1,359-1,359</th>
<th>Dose 2 %</th>
<th>Dose 3 N = 1,311-1,312</th>
<th>Dose 3 %</th>
<th>Dose 4 N = 379-380</th>
<th>Dose 4 %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Redness</strong></td>
<td></td>
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<tr>
<td>&gt;5 mm</td>
<td>7.1</td>
<td>8.4</td>
<td>8.7</td>
<td>17.3</td>
<td>6.2</td>
<td>7.1</td>
<td>9.6</td>
<td>16.4</td>
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<tr>
<td>&gt;25 mm</td>
<td>2.8</td>
<td>1.8</td>
<td>1.8</td>
<td>9.2</td>
<td>1.0</td>
<td>0.6</td>
<td>1.9</td>
<td>7.9</td>
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<tr>
<td>&gt;50 mm</td>
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<td>0.2</td>
<td>0.0</td>
<td>2.3</td>
<td>0.4</td>
<td>0.1</td>
<td>0.0</td>
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<tr>
<td><strong>Swelling</strong></td>
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<td>5.0</td>
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<td>4.0</td>
<td>4.0</td>
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<tr>
<td>&gt;25 mm</td>
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<td>1.6</td>
<td>0.7</td>
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<td>4.0</td>
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<td>&gt;50 mm</td>
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<td><strong>Tenderness</strong></td>
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<tr>
<td>Any</td>
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<tr>
<td>Moderate or Severe</td>
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<td>&gt;39.5°C</td>
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<tr>
<td><strong>Decreased Activity/</strong></td>
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<td>Lethargy</td>
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</tbody>
</table>
In clinical trials, Pentacel was administered concomitantly with one or more of the following vaccines: hepatitis B vaccine, 7-valent pneumococcal conjugate vaccine, MMR and varicella vaccines [see Adverse Reactions (6) and Clinical Studies (14)]. If Pentacel is given at the same time as another reactogenic vaccine(s), the vaccine(s) should be administered with different syringes and at different injection sites.

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

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

Serious Adverse Events

Hypotonia not fulfilling HHE criteria within 7 days following vaccination was reported in 4 participants after the administration of Pentacel (1 on the same day as the 1st dose; 3 on the same day as the 3rd dose) and in 1 participant after the administration of DAPTACEL + IPOL + ActHIB (4 days following the 1st dose).

Seizures

Across Studies 494-01, 494-03, S9A908 and P3T06, a total of 8 participants experienced a seizure within 7 days following either Pentacel (4 participants; N = 4,197 for at least one of Doses 1-3; N = 5,033 for Dose 4), separately administered HCPDT + POLIOVAX + ActHIB (3 participants; N = 1,032 for at least one of Doses 1-3, N = 739 for Dose 4) or separately administered DAPTACEL + IPOL + ActHIB (1 participant; N = 1,455). Within 7 days following vaccination, one participant who received Pentacel and 11 of 1,032 (1.1%) participants who received HCPDT + POLIOVAX + ActHIB experienced a serious adverse event. In Study 494-01, within 7 days following the first dose of Pentacel, one participant in Study 494-01 had a possible seizure within 3 days as the third dose, and two participants in Study S9A908 had a possible seizure within 3 days as the third dose.

Serious Adverse Events

In Study P3T06, within 30 days following any of Doses 1-3 of Pentacel or Control vaccines, 19 of 484 (3.9%) participants who received Pentacel and 50 of 1,455 (3.4%) participants who received DAPTACEL + IPOL + ActHIB experienced a serious adverse event. Within 30 days following Dose 4 of Pentacel or Control vaccines, 4 of 418 (1.0%) participants who received DAPTACEL + IPOL + ActHIB experienced a serious adverse event. In Study 494-01, within 30 days following any of Doses 1-3 of Pentacel or Control vaccines, 32 of 2,376 (1.3%) participants who received Pentacel and 15 of 1,455 (1.0%) participants who received DAPTACEL + IPOL + ActHIB experienced a serious adverse event. In Study 494-01, within 30 days following any of Doses 1-3 of Control vaccines, 5 of 431 (1.2%) participants who received Pentacel and 4 of 418 (1.0%) participants who received DAPTACEL + IPOL + ActHIB experienced a serious adverse event. Within 30 days following Dose 4 of Pentacel or Control vaccines, 2 of 1,862 (0.3%) participants who received Pentacel and 2 of 739 (0.3%) participants who received HCPDT + POLIOVAX + ActHIB experienced a serious adverse event.

Serious Adverse Events

In Study P3T06, within 30 days following any of Doses 1-3 of Pentacel or Control vaccines, overall, the most frequently reported serious adverse events were bronchitis, dehydration, pneumonia and gastroenteritis. Across Studies 494-01, 494-03, S9A908 and P3T06, 4 of 30 days following Dose 4 of Pentacel or Control vaccines, 5 of 431 (1.2%) participants who received Pentacel and 4 of 418 (1.0%) participants who received DAPTACEL + IPOL + ActHIB experienced a serious adverse event. Within 30 days following the first dose of Pentacel or Control vaccines, overall, the most frequently reported serious adverse events were dehydration, gastroenteritis, asthma, and pneumonia.

Across Studies 494-01, 494-03, S9A908 and P3T06, two cases of encephalopathy were reported, both in participants who had received DAPTACEL + IPOL + ActHIB (N = 1,455). There were no deaths reported in children who received HCPDT + POLIOVAX + ActHIB (N = 1,032). Causes of deaths among children who received Pentacel were asphyxia due to suffocation, head trauma, Sudden Infant Death syndrome, and neuroblastoma (8, 23, 52 and 256 days post-vaccination, respectively). One participant with ependymoma died secondary to aspiration 22 days following DAPTACEL + IPOL + ActHIB.

6.2 Data from Postmarketing Experience

The following additional adverse events have been spontaneously reported during the postmarketing use of Pentacel worldwide, since 1997. Between 1997 and 2007, Pentacel was primarily used in Canada. 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 Pentacel.

- **Cardiac disorders**
  - Cynosis

- **Gastrointestinal disorders**
  - Vomiting, diarrhea

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

- **Immunologic disorders**
  - Anaphylaxis/anaphylactic reaction, hypersensitivity (such as rash and urticaria)
  - Infections and infestations
  - Meningitis, encephalitis, virus infection

- **Metabolism and nutrition disorders**
  - Decreased appetite

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

- **Psychiatric disorders**
  - Screaming

- **Respiratory, thoracic and mediastinal disorders**
  - Apnea, cough

- **Skin and subcutaneous tissue disorders**
  - Erythema, skin discoloration

- **Vascular disorders**

7. **DRUG INTERACTIONS**

7.1 Concomitant Administration with Other Vaccines

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

7.2 Immunosuppressive Treatments

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

7.3 Drug/Laboratory Test Interactions

Antigenaemia has been detected in some instances following receipt of ActHIB. Urine antigen detection may not have definite diagnostic value in suspected H. influenzae type b disease within one week following receipt of Pentacel.

8. USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The safety and effectiveness of Pentacel was established in the age group 6 weeks through 18 months as defined in a report of a US Public Health Service workshop (4) were reported among participants who received Pentacel (N = 5,979), separately administered HCPDT + POLIOVAX + ActHIB (N = 1,032) or separately administered DAPTACEL + IPOL + ActHIB (N = 1,455). Among the four participants who experienced a seizure within 7 days following Pentacel, one participant in Study 494-01 had an afebrile seizure 6 days after the first dose, one participant in Study 494-01 had a possible seizure within 3 days as the third dose, and two participants in Study S9A908 had a possible seizure 2 and 4 days, respectively, after the fourth dose. Among the four participants who experienced a seizure within 7 days following Control vaccines, one participant had an afebrile seizure within 3 days as the first dose of DAPTACEL + IPOL + ActHIB, one participant had an afebrile seizure within 3 days as the second dose of HCPDT + POLIOVAX + ActHIB, and two participants had a possible seizure 6 and 7 days, respectively, after the fourth dose of HCPDT + POLIOVAX + ActHIB.

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

рубашка
sulfate, \( \text{H. influenzae} \) type b polysaccharide vaccine in Finland, (16) a post-vaccination anti-PRP level of 0.15 mcg/mL has been accepted as a minimal protective level. Data from an efficacy study with \( \text{H. influenzae} \) type b polysaccharide vaccine in Finland indicate that a level >1.0 mcg/mL 3 weeks after vaccination predicts protection through a subsequent one-year period. (17) (18) These levels have been used to evaluate the effectiveness of Haemophilus b Conjugate Vaccines, including the ActHIB component of Pentacel. 13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Pentacel has not been evaluated for carcinogenic or mutagenic potential or impairment of fertility.

14 CLINICAL STUDIES The efficacy of Pentacel is based on the immunogenicity of the individual antigens compared to separately administered vaccines. The polysaccharide component (poliovirus types 1, 2, and 3) of this formulation of Pentacel is grown in Vero cells (see Description (11)). The clinical study data in this section were accrued with a Pentacel formulation in which the polysaccharide component was grown in MRC-5 cells. The polysaccharide component of the two Pentacel formulations are analytically comparable. Serological correlates of protection exist for diphtheria, tetanus, poliomyelitis, and invasive disease due to \( \text{H. influenzae} \) type b [see Clinical Pharmacology (12.1)]. The efficacy against pertussis, for which there is no well-established serological correlate of protection, was based, in part, on a comparison of pertussis immune responses following Pentacel in US children to responses following DAPTACEL (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DTap) manufactured by Sanofi Pasteur Limited) in an efficacy study conducted in Sweden (Sweden I Efficacy Trial). While Pentacel and DAPTACEL contain the same pertussis antigens, manufactured by the same process, Pentacel contains twice as much detoxified PT and four times as much FHA as DAPTACEL.

14.1 Diphtheria The proportions of participants achieving diphtheria antitoxin seroprotective levels one month following three and four doses of Pentacel or DAPTACEL in Study P3T06 are provided in Table 3.

14.2 Tetanus The proportions of participants achieving tetanus antitoxoid seroprotective levels one month following three and four doses of Pentacel or DAPTACEL in Study P3T06 are provided in Table 3.

Table 3: Study P3T06 Diphtheria Antitoxin and Tetanus Antitoxoid Responses One Month Following Dose 3 and Dose 4 of Pentacel or DAPTACEL + IPOL + ActHIB in US Children Vaccinated at 2, 4, 6, and 15-16 Months of Age

<table>
<thead>
<tr>
<th>Post-Dose 3</th>
<th>N = 331-345</th>
<th>N = 1,037-1,099</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria Antitoxin</td>
<td>100.0%</td>
<td>98.8%</td>
</tr>
<tr>
<td>≥ 0.01 IU/mL</td>
<td>99.0%</td>
<td>97.5%</td>
</tr>
<tr>
<td>≥ 0.010 IU/mL</td>
<td>97.9%</td>
<td>96.5%</td>
</tr>
<tr>
<td>Tetanus Antitoxoid</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>≥ 0.010 IU/mL</td>
<td>99.7%</td>
<td>99.3%</td>
</tr>
<tr>
<td>≥ 0.01 IU/mL</td>
<td>99.7%</td>
<td>99.3%</td>
</tr>
</tbody>
</table>

Per Protocol Immunogenicity population.

Seroprotection rate following Pentacel vaccine is not inferior to DAPTACEL vaccine (upper limit of 90% CI of the difference DAPTACEL – Pentacel = <10%) (Non-inferiority criteria were not pre-specified).

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

14.3 Pertussis In a clinical pertussis vaccine efficacy study conducted in Sweden during 1992-1995 (Sweden I Efficacy Trial), 2,587 infants received DAPTACEL and 2,574 infants received a non-US licensed DT vaccine as placebo at 2, 4, and 6 months of age. (1) The mean length of follow-up was 2 years after the third dose of vaccine. The protective efficacy of DAPTACEL against pertussis after 3 doses of vaccine 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% CI 80.1%, 88.6%). The protective efficacy of DAPTACEL against mild pertussis (≥1 day of cough with laboratory confirmation) was 77.9% (95% CI 72.6%, 82.2%). Protection against pertussis by Pentacel was sustained for the 2-year follow-up period.

12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action

Diphtheria is an acute toxin-mediated disease caused by toxigenic strains of \( \text{C. diphtheriae} \). 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 a protective level. (10) Levels of 1.0 IU/mL have been associated with long-term protection.

Tetanus Tetanus is an acute disease caused by an extremely potent neurotoxin produced by \( \text{C. tetani} \). Protection against disease is due to the development of neutralizing antibodies to tetanus toxin. A serum tetanus antitoxoid level ≥0.1 IU/mL is measured by the ELISA used in clinical studies of Pentacel is considered protective.

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

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

Invasive Disease Due to \( \text{H. influenzae} \) Type b \( \text{H. influenzae} \) type b can cause invasive disease such as meningitis and sepsis. Anti-PRP antibody has been shown to correlate with protection against invasive disease due to \( \text{H. influenzae} \) type b.
Based on comparisons of the immune responses to DAPTACEL in US infants (Post-Dose 3) and Canadian children (Post-Dose 4) relative to infants who participated in the Sweden I Efficacy Trial, it was concluded that 4 doses of DAPTACEL were needed for primary immunization against pertussis in US children. (1)

In a serology bridging analysis, immune responses to FHA, PRN and FIM in a subset of infants who received three doses of DAPTACEL in the Sweden I Efficacy Trial were compared to the Post-Dose 3 and Post-Dose 4 responses in a subset of US children from Study 494-01 who received Pentacel (Table 4). Available sera from infants who received DAPTACEL in the Sweden I Efficacy Trial and sera from children who received PCV7 concomitantly with the first three doses of Pentacel in Study 494-01 (Table 1) were assayed in parallel. Data on levels of antibody to PT using an adequately specific assay were not available for this serology bridging analysis. Geometric mean antibody concentrations (GMCS) and seroconversion rates for antibodies to FHA, PRN and FIM one month following Dose 3 of DAPTACEL in the subset of infants from the Sweden I Efficacy Trial and one month following Dose 3 and Dose 4 of Pentacel in a subset of infants from US Study 494-01 are presented in Table 4. Seroconversion was defined as 4-fold rise in antibody level (Post-Dose 3/Pre-Dose 1 or Post-Dose 4/Pre-Dose 1). For anti-FHA and anti-FIM, the non-inferiority criteria were met for seroconversion rates, and for anti-FHA, anti-PRN, and anti-FIM, the non-inferiority criteria were met for GMCs, following Dose 4 of Pentacel relative to Dose 3 of DAPTACEL. The non-inferiority criteria for anti-PRN seroconversion following Dose 4 of Pentacel relative to Dose 3 of DAPTACEL was not met (upper limit of 95% CI for difference in rate (DAPTACEL minus Pentacel) = 13.24%). Whether the lower anti-PRN seroconversion rate following Dose 4 of Pentacel in US children relative to Dose 3 of DAPTACEL in Swedish infants correlates with diminished efficacy of Pentacel against pertussis is unknown.

Table 4: FHA, PRN and FIM Antibody Responses One Month Following Dose 3 of DAPTACEL in a Subset of Infants Vaccinated at 2, 4, and 6 Months of Age in the Sweden I Efficacy Trial and One Month Following Dose 3 and Dose 4 of Pentacel in a Subset of Infants Vaccinated at 2, 4, 6, and 15-16 Months of Age in US Study 494-01

<table>
<thead>
<tr>
<th></th>
<th>Post-Dose 3 DAPTACEL</th>
<th>Post-Dose 3 DAPTACEL + IPOL + ActHIB</th>
<th>Post-Dose 4 Pentacel</th>
<th>Post-Dose 4 DAPTACEL + ActHIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-FHA % achieving 4-fold rise</td>
<td>68.8%</td>
<td>40.70%</td>
<td>79.8%</td>
<td>91.7%</td>
</tr>
<tr>
<td>GMC (EU/mL)</td>
<td>70.71</td>
<td>71.46</td>
<td>128.95%</td>
<td></td>
</tr>
<tr>
<td>Anti-PRN % achieving 4-fold rise</td>
<td>98.8%</td>
<td>111.26%</td>
<td>74.4%</td>
<td>89.2%</td>
</tr>
<tr>
<td>GMC (EU/mL)</td>
<td>38.11</td>
<td>38.11</td>
<td>90.85%</td>
<td></td>
</tr>
<tr>
<td>Anti-FIM % achieving 4-fold rise</td>
<td>86.3%</td>
<td>339.31%</td>
<td>86.5%</td>
<td>91.5%</td>
</tr>
<tr>
<td>GMC (EU/mL)</td>
<td>265.02</td>
<td>265.02</td>
<td>506.57%</td>
<td></td>
</tr>
</tbody>
</table>

In a separate study, Study P3T06, US infants were randomized to receive either Pentacel or DAPTACEL + IPOL + ActHIB at 2, 4, 6, and 15-16 months of age (Table 1). The pertussis immune responses (GMCS and seroconversion rates) one month following the third and fourth doses were compared between the two groups (Table 5). Seroconversion was defined as a 4-fold rise in antibody level (Post-Dose 3/Pre-Dose 1 or Post-Dose 4/Pre-Dose 1). Data on anti-PT responses obtained from an adequately specific assay were available on only a non-random subset of study participants. The subset of study participants was representative of all study participants with regard to Pre-Dose 1, Post-Dose 3 and Post-Dose 4 GMCs of antibodies to FHA, PRN and FIM. For each of the pertussis antigens, non-inferiority criteria were met for seroconversion rates and GMCS following Dose 3 of Pentacel relative to Dose 3 of DAPTACEL. Following Dose 4 of Pentacel relative to Dose 4 of DAPTACEL, non-inferiority criteria were met for all comparisons except for anti-PT GMCs (upper limit of 95% CI for ratio of GMCS (DAPTACEL/Pentacel) = 2.25). Whether the lower anti-PRN GMC following Dose 4 of Pentacel relative to Dose 4 of DAPTACEL in US children correlates with diminished efficacy of Pentacel against pertussis is unknown.

Table 5: Pertussis Antibody Responses One Month Following Doses 3 and 4 of Pentacel or DAPTACEL + IPOL + ActHIB in US Infants Vaccinated at 2, 4, 6, and 15-16 Months of Age in Study P3T08

<table>
<thead>
<tr>
<th></th>
<th>Post-Dose 3 Pentacel</th>
<th>Post-Dose 3 DAPTACEL + IPOL + ActHIB</th>
<th>Post-Dose 4 Pentacel</th>
<th>Post-Dose 4 DAPTACEL + ActHIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-PT % achieving 4-fold rise</td>
<td>95.8%</td>
<td>102.62%</td>
<td>87.3%</td>
<td>93.8%</td>
</tr>
<tr>
<td>GMC (EU/mL)</td>
<td>61.88</td>
<td>61.88</td>
<td>107.89%</td>
<td>100.29</td>
</tr>
<tr>
<td>Anti-FHA % achieving 4-fold rise</td>
<td>81.9%</td>
<td>73.68%</td>
<td>60.9%</td>
<td>79.3%</td>
</tr>
<tr>
<td>GMC (EU/mL)</td>
<td>29.22</td>
<td>29.22</td>
<td>107.94%</td>
<td>64.02</td>
</tr>
<tr>
<td>Anti-PRN % achieving 4-fold rise</td>
<td>74.2%</td>
<td>36.05%</td>
<td>75.4%</td>
<td>98.3%</td>
</tr>
<tr>
<td>GMC (EU/mL)</td>
<td>43.25</td>
<td>43.25</td>
<td>93.59%</td>
<td>186.07</td>
</tr>
<tr>
<td>Anti-FIM % achieving 4-fold rise</td>
<td>91.7%</td>
<td>268.15%</td>
<td>86.3%</td>
<td>91.6%</td>
</tr>
<tr>
<td>GMC (EU/mL)</td>
<td>267.18</td>
<td>267.18</td>
<td>553.39%</td>
<td>513.54</td>
</tr>
</tbody>
</table>

14.4 Poliomyelitis

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

In Study 494-01 (Table 1), in which infants were randomized to receive Pentacel or HCPTD + POLIOVAX + ActHIB, GMTs (1/dil) of antibodies to Poliovirus types 1, 2, and 3 one month following Dose 4 of Pentacel (N = 851-857) were 2,304, 4,178, and 4,415, respectively, and one month following Dose 4 of POLIOVAX (N = 284-297) were 2,230, 2,840, and 3,300, respectively.

14.5 Invasive Disease due to H. Influenzae Type b

Anti-PRP seroprotection rates and GMCS one month following Dose 3 of Pentacel or separately administered ActHIB in studies 494-01, P3T06, and M5A10 are presented in Table 6. In Study 494-01, non-inferiority criteria were not met for the proportion of participants who achieved an anti-PRP level ≥1.0 mcg/mL and for anti-PRP GMCS following Pentacel compared with separately administered ActHIB. In each of Studies P3T06 and M5A10, the non-inferiority criterion was met for the proportion of participants who achieved an anti-PRP level ≥1.0 mcg/mL following Pentacel compared with separately administered ActHIB. In Study M5A10, the non-inferiority criterion was met for anti-PRP GMCS following Pentacel compared with separately administered ActHIB.
Table 6: Anti-PRP Seroprotection Rates and GMCs One Month Following Three Doses of Pentacel or Separate DTP + IPV + ActHIB Administered at 2, 4, and 6 Months of Age in Studies 494-01, P3T06, and MSA10

<table>
<thead>
<tr>
<th>Study 494-01</th>
<th>Pentacel</th>
<th>HCPDT + POLIOVAX + ActHIB</th>
<th>N = 401</th>
</tr>
</thead>
<tbody>
<tr>
<td>% achieving anti-PRP ≥0.15 mcg/mL</td>
<td>95.4†</td>
<td>98.3</td>
<td></td>
</tr>
<tr>
<td>% achieving anti-PRP ≥1.0 mcg/mL</td>
<td>79.1†</td>
<td>88.8</td>
<td></td>
</tr>
<tr>
<td>Anti-PRP GMC (mcg/mL)</td>
<td>3.19†</td>
<td>6.23</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study P3T06</th>
<th>Pentacel</th>
<th>DAPTACEL + IPOL + ActHIB</th>
<th>N = 1,128</th>
</tr>
</thead>
<tbody>
<tr>
<td>% achieving anti-PRP ≥0.15 mcg/mL</td>
<td>92.3</td>
<td>93.3</td>
<td></td>
</tr>
<tr>
<td>% achieving anti-PRP ≥1.0 mcg/mL</td>
<td>72.1†</td>
<td>70.8</td>
<td></td>
</tr>
<tr>
<td>Anti-PRP GMC (mcg/mL)</td>
<td>2.31†</td>
<td>2.29</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study MSA10</th>
<th>Pentacel</th>
<th>DAPTACEL + IPOL + ActHIB</th>
<th>N = 421</th>
</tr>
</thead>
<tbody>
<tr>
<td>% achieving anti-PRP ≥0.15 mcg/mL</td>
<td>93.8†</td>
<td>90.3</td>
<td></td>
</tr>
<tr>
<td>% achieving anti-PRP ≥1.0 mcg/mL</td>
<td>75.1†</td>
<td>74.8</td>
<td></td>
</tr>
<tr>
<td>Anti-PRP GMC (mcg/mL)</td>
<td>2.52†</td>
<td>2.38</td>
<td></td>
</tr>
</tbody>
</table>

Per Protocol Immunogenicity population for all studies.

‡Non-inferiority criterion not met for GMC following Pentacel vaccine relative to ActHIB vaccine [upper limit of 90% CI for difference in rates (ActHIB minus Pentacel) <10%].

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

Per Protocol immunogenicity population for all studies.

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

§Non-inferiority criterion not pre-specified.

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

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

In Study 494-01, at 15 months of age prior to receipt of Dose 4 of study vaccines, 68.6% of Pentacel recipients (N = 829) and 80.8% of separately administered ActHIB recipients (N = 291) had an anti-PRP level ≥0.15 mcg/mL. Following Dose 4 of study vaccines, 99.2% of Pentacel recipients (N = 874) and 99.0% of separately administered ActHIB recipients (N = 335) had an anti-PRP level ≥1.0 mcg/mL. Following Dose 4 of study vaccines, 97.8% of Pentacel recipients (N = 361) and 95.4% of separately administered ActHIB recipients (N = 340) had an anti-PRP level ≥1.0 mcg/mL.

14.8 Concomitantly Administered Vaccines

In Study P3T06, there was no evidence for reduced antibody responses to hepatitis B vaccine (percent of participants with anti-HBsAg ≥10 mIU/mL and GMCs) or PCV7 (percent of participants with antibody levels ≥0.15 mcg/mL and ≥0.5 mcg/mL) and GMCS to each serotype administered concomitantly with Pentacel (N = 401).

In Study MSA10, there was no evidence for reduced antibody responses to hepatitis B vaccine and PCV7 were evaluated one month following the third dose.

In Study 494-03, there was no evidence for interference in the immune response to the fourth dose of PCV7 (percent of participants with antibody levels ≥0.15 mcg/mL and ≥0.5 mcg/mL) and GMCs to each serotype administered concomitantly with Pentacel (N = 325-326) relative to these vaccines administered concomitantly with ActHIB vaccine (N = 998-1,029). The immune responses to hepatitis B vaccine and PCV7 were evaluated one month following the third dose.

In Study P3T06, there was no evidence for interference in the immune response to the fourth dose of PCV7 (percent of participants with antibody levels ≥0.15 mcg/mL and ≥0.5 mcg/mL) and GMCs to each serotype administered concomitantly with Pentacel (N = 155) relative to this vaccine administered concomitantly with MMR and varicella vaccines (N = 158). There was no evidence for interference in the immune response to MMR and varicella vaccines (percent of participants with pre-specified seroresponse level) administered at 15 months of age concomitantly with Pentacel (N = 154) relative to these vaccines administered concomitantly with PCV7 (N = 144). The immune responses to MMR, varicella vaccine and the fourth dose of PCV7 were evaluated one month post-vaccination.

15 REFERENCES

1. DAPTACEL® [full prescribing information]. Toronto, ON: Sanofi Pasteur; 2016.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

The vials stoppers for the DTPa-IPV and ActHIB vaccine components of Pentacel are not made with natural rubber latex.

5 Package (NDC No. 49281-511-05) containing 5 vials of DTPa-IPV component (NDC No. 49281-561-01) to be used to reconstitute 5 single-dose vials of lypoHfct ActHIB vaccine component (NDC No. 49281-544-58).

16.2 Storage and Handling

Pentacel 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

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

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