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

RECENT MAJOR CHANGES

RECENT MAJOR CHANGES

- Pentacel is a vaccine indicated for active immunization against diphtheria, tetanus, pertussis, poliovirus 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)

INDICATIONS AND USAGE

- 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, 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 Pentacel. (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 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 inconsolable crying. Fever ≥38.0°C occurred in 6-16% of participants, depending on dose number. Injection site reactions that occurred in 2-3% of participants following any dose included tenderness and increase in arm circumference. (6.1)

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

DRUG INTERACTIONS

- Do not mix 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: [09/2016]

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2 DOSAGE AND ADMINISTRATION
 2.1 Immunization Series
 2.2 Administration
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 4.1 Hypersensitivity
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 4.3 Progressive Neurologic Disorder
5 WARNINGS AND PRECAUTIONS
 5.1 Management of Acute Allergic Reactions
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 5.3 Guillain-Barré Syndrome and Brachial Neuropathy
 5.4 Infants and Children with a History of Previous Seizures
 5.5 Limitations of Vaccine Effectiveness
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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 14 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 for successive doses of the primary DTaP series. Children who have completed a 4-dose series with Pentacel should receive a fifth dose of DTaP vaccine using DAPTACEL at 4-6 years of age. [1]

Data are not available on the safety and effectiveness of using mixed sequences of Pentacel and DTaP vaccine from different manufacturers.

Mixed Sequences of Pentacel and IPV Vaccine
Pentacel may be used in infants and children who have received 1 or more doses of another licensed IPV vaccine and are scheduled to receive the antigens of Pentacel. However, data are not available on the safety and immunogenicity of Pentacel in such infants and children. The Advisory Committee on Immunization Practices (ACIP) recommends that the final dose in the 4-dose IPV series be administered at age ≥4 years. [2] When Pentacel is administered at ages 2, 4, 6, and 15-18 months, an additional booster dose of IPV vaccine should be administered at 5 years, resulting in a 5-dose IPV series. [3]

Mixed Sequences of Pentacel and Haemophilus b Conjugate Vaccine
Pentacel may be used to complete the vaccination series in infants and children previously vaccinated with one or more doses of Haemophilus b Conjugate Vaccine (either separately administered or as part of another combination vaccine), who are also scheduled to receive the other antigens of Pentacel. However, data are not available on the safety and immunogenicity of Pentacel in such infants and children. If different brands of Haemophilus b Conjugate Vaccines are administered to complete the series, three primary immunizing doses are needed, followed by a booster dose.

2.2 Administration
The package contains a vial of the DTaP-IPV component and a vial of lyophilized ActHIB vaccine component.

After removing the "flip-off" cap, cleanse the DTaP-IPV and ActHIB vaccine vial stoppers with a suitable antiseptic. Do not remove the vial stoppers or metal seals holding them in place. Just before use, thoroughly but gently shake the vial of DTaP-IPV component, withdraw the entire liquid content, and inject the vial of the lyophilized ActHIB vaccine component. Gently swirl the vial now containing Pentacel until a cloudy, uniform, white to off-white (yellow tinge) suspension results.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If these conditions exist, Pentacel should not be administered.

Using a sterile needle and syringe and aseptic technique, withdraw and administer a single 0.5 mL dose of Pentacel intramuscularly. 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. Pentacel should be used immediately after reconstitution. Refer to Figures 1, 2, 3, 4, and 5.

Pentacel: Instructions for Reconstitution of ActHIB Vaccine Component with DTaP-IPV Component
Figure 1 Gently shake the vial of DTaP-IPV component.
Figure 2 Withdraw the entire liquid content.
Figure 3 Insert the syringe needle through the stopper of the vial of lyophilized ActHIB vaccine component and inject the liquid into the vial.
Figure 4 Swirl vial gently.
Figure 5 After reconstitution, immediately withdraw 0.5 mL of Pentacel vaccine and administer intramuscularly. Pentacel vaccine should be used immediately after reconstitution.

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. Pentacel should not be mixed in the same syringe with other parenteral products.

3 DOSAGE FORMS AND STRENGTHS
Pentacel is a 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. [See Dosage and Administration (3.2) and How Supplied/Storage and Handling (16).]

4 CONTRAINDICATIONS
4.1 Hypersensitivity
A severe allergic reaction (eg, anaphylaxis) after a previous dose of Pentacel or any other diptheria toxoid, tetanus toxoid, or pertussis-containing vaccine, inactivated poliovirus vaccine or H. influenzae type b vaccine, or any ingredient of this vaccine is a contraindication to administration of any pertussis-containing vaccine, including Pentacel.

4.2 Encephalopathy
Encephalopathy (eg, 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 Pentacel.

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 Pentacel. 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 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 pertussis vaccine, the decision to administer Pentacel should be based on careful consideration of potential benefits and possible risks:

- Temperature of ≥40.5°C (≥105°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 ≥3 hours within 48 hours.
- Seizures with or without fever within 3 days.

5.3 Guillain-Barre Syndrome and Brachial Neuritis
A review by the Institute of Medicine (IOM) found evidence for a causal relation between tetanus toxoid and both brachial neuritis and Guillain-Barré syndrome. [3] 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.

5.4 Infants and Children with a History of Previous Seizures
Infants or children with a history of previous seizures, an appropriate antiepileptic may be administered (in the dosage recommended in its prescribing information) at the time of vaccination with a vaccine containing acellular pertussis antigens (including Pentacel) and for the following 24 hours, to reduce the possibility of post-vaccination fever.

5.5 Limitations of Vaccine Effectiveness
Vaccination with Pentacel may not protect all individuals.

5.6 Altered Immunocompetence
If Pentacel is administered to immunocompromised persons, including persons receiving immunosuppressive therapy, the expected immune response may not be obtained. [See Drug Interactions (7.2).]

5.7 Apexis in Premature Infants
Apexis 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.

6 ADVERSE REACTIONS
6.1 Data from Clinical Studies
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 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, 1,762 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, 84.5% were Caucasian, 9.2% were Black, 12.9% were Hispanic, 3.9% were Asian, and 9.5% were of other racial/ethnic groups. In the two controlled 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, 0.8% 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 Control Vaccines</th>
<th>Concomitantly Administered Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>494-01</td>
<td>DAPT ACEL + IPOL + ActHIB</td>
<td>DAPT ACEL + IPOL + ActHIB, PCV7 (PCV7 at doses 1-3; N = 533)</td>
</tr>
<tr>
<td>494-03</td>
<td>DAPT ACEL + IPOL + ActHIB</td>
<td>DAPT ACEL + IPOL + ActHIB, PCV7 (PCV7 at 2, 4, and 6 doses; N = 435)</td>
</tr>
<tr>
<td>5A9908</td>
<td>DAPTACEL + IPOL + ActHIB</td>
<td>DAPTACEL + IPOL + ActHIB, PCV7 (PCV7 at 2, 4, and 6 doses; N = 533)</td>
</tr>
</tbody>
</table>

**Table 2: Number (Percentage) of Children with Selected Solicited Adverse Reactions by 24 hours post-vaccination.**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Redness</td>
<td>7.1</td>
<td>8.4</td>
<td>8.7</td>
<td>6.2</td>
<td>7.1</td>
</tr>
<tr>
<td></td>
<td>25 mm</td>
<td>28.2</td>
<td>21.7</td>
<td>20.3</td>
<td>23.1</td>
</tr>
<tr>
<td></td>
<td>50 mm</td>
<td>6.6</td>
<td>0.2</td>
<td>0.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Swelling</td>
<td>7.0</td>
<td>7.3</td>
<td>5.0</td>
<td>9.7</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>&gt;5 mm</td>
<td>2.0</td>
<td>1.6</td>
<td>0.8</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>50 mm</td>
<td>0.9</td>
<td>0.0</td>
<td>0.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Tenderness</td>
<td>47.5</td>
<td>39.2</td>
<td>42.7</td>
<td>56.1</td>
<td>48.8</td>
</tr>
<tr>
<td></td>
<td>&gt;5 mm</td>
<td>20.0</td>
<td>1.6</td>
<td>0.8</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>50 mm</td>
<td>3.6</td>
<td>4.7</td>
<td>0.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Increase in Arm Circumference</td>
<td>5.4</td>
<td>1.6</td>
<td>1.4</td>
<td>3.3</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>&gt;20 mm</td>
<td>0.5</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>&gt;40 mm</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fever</td>
<td>5.5</td>
<td>10.9</td>
<td>16.3</td>
<td>13.4</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td>&gt;38.0°C</td>
<td>10.9</td>
<td>16.3</td>
<td>13.4</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td>&gt;38.5°C</td>
<td>2.4</td>
<td>4.4</td>
<td>5.1</td>
<td>4.3</td>
</tr>
<tr>
<td>Decreased Activity/Lethargy</td>
<td>45.8</td>
<td>32.7</td>
<td>32.5</td>
<td>24.1</td>
<td>51.1</td>
</tr>
<tr>
<td></td>
<td>&gt;20 mm</td>
<td>12.4</td>
<td>12.7</td>
<td>9.8</td>
<td>24.3</td>
</tr>
<tr>
<td></td>
<td>&gt;40 mm</td>
<td>2.1</td>
<td>0.7</td>
<td>0.2</td>
<td>1.2</td>
</tr>
</tbody>
</table>

**Fussiness/ Irritability**

| >1 hour | 5.4 | 4.0 | 5.0 | 5.3 | 4.0 |
| >3 hours| 1.9 | 0.9 | 1.1 | 2.3 | 2.2 |

**Table 3: Solicited Injection Site and Systemic Reactions Following Doses 1-3 and Dose 4 of Pentacel or Control Vaccines.**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotonicity</td>
<td>76.9</td>
<td>71.2</td>
<td>68.0</td>
<td>53.5</td>
<td>75.8</td>
</tr>
<tr>
<td></td>
<td>&gt;1 hour</td>
<td>34.5</td>
<td>27.0</td>
<td>26.4</td>
<td>23.6</td>
</tr>
<tr>
<td></td>
<td>&gt;3 hours</td>
<td>19.7</td>
<td>10.6</td>
<td>13.6</td>
<td>11.8</td>
</tr>
<tr>
<td></td>
<td>&gt;4 hours</td>
<td>1.9</td>
<td>0.9</td>
<td>1.1</td>
<td>2.3</td>
</tr>
</tbody>
</table>

**Table 4: Seizures Following Doses 1-3 and Dose 4 of Pentacel or Control Vaccines.**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fainting</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Crying</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Irritability</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Table 5: Hypotonicity Following Doses 1-3 and Dose 4 of Pentacel or Control Vaccines.**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fainting</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Crying</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Irritability</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>
• Cardiac disorders
• 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)
• Immune system disorders
  • Anaphylaxis/anaphylactic reaction, hypersensitivity (such as rash and urticaria)
• Infections and infestations
  • Meningitis, rhinitis, viral infection
• Metabolism and nutrition disorders
  • Decreased appetite
• Nervous system disorders
  • Somnolence, HIE, depressed level of consciousness
• Psychiatric disorders
  • Sclerosis
• Respiratory, thoracic and mediastinal disorders
  • Aspira, cough
• Skin and subcutaneous tissue disorders
  • Erythema, skin discoloration
• Vascular disorders
  • Palor
7 DRUG INTERACTIONS
7.1 Concomitant Administration with Other Vaccines
In clinical trials, Pentacel was administered concomitantly with one or more of the following US licensed 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 injectable vaccine(s), the vaccine(s) should be administered with different syringes and at different injection sites.

7.2 Immunosuppressive Treatments
Immunosuppressive therapies, including irradiation, antimetabolites, 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
Antigenuena has been detected in some instances following receipt of AChIB. Urine antigen detection may not have definite diagnostic value in suspected H. influenzae type b disease within one week following receipt of Pentacel. (5)

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C
Animal reproduction studies have not been conducted with Pentacel. It is also not known whether Pentacel can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity.

8.4 Pediatric Use
The safety and effectiveness of Pentacel was established in the age group 6 weeks through 18 months on the basis of clinical studies. [See Adverse Reactions (6.1) and Clinical Studies (14).] The safety and effectiveness of Pentacel in the age group 19 months through 4 years is supported by the results of clinical studies. [See 8.4.] The safety and effectiveness of Pentacel in infants 6 weeks through 18 months. 

8.5 Geriatric Use
No special precautions are necessary when Pentacel is administered to geriatric patients.

8.6 Female and Male Reproduction
Pentacel has not been evaluated for carcinogenic or mutagenic potential or impairment of fertility.

9.4 Additional Information
Other ingredients per 0.5 mL dose include 1.5 mg aluminum phosphate (0.33 mg aluminum) as the adjuvant, polysorbate 80 (approximately 10 ppm by calculation), 42.5 mg sucrose, ≤5 mg residual formaldehyde, ≤50 ng residual glutaraldehyde, ≤50 ng residual bovine serum albumin, ≤3 mg (0.05% v/v) 2-phenoxethanol (not as a preservative), ≤4 µg of neomycin and ≤4 µg polymyxin B sulfate. Corynebacterium diphtheriae is grown in modified Mueller’s growth medium. (6) After purification by ammonium sulfate fractionation, the diphtheria toxin is detoxified with formaldehyde and dithiothreitol. Clostridium tetani is grown in modified Mueller-Hinton casamino acid medium without beef heart infusion. (7) Tetanus toxin is modified with formaldehyde and purified by ammonium sulfate fractionation and diafiltration. Diphtheria and tetanus toxoids are individually adsorbed onto aluminum phosphate.

The acellular pertussis vaccine antigens are produced from Bordetella pertussis cultures grown in Stainer-Schroetter medium (8) modified by the addition of casamino acids and dimethyl-beta-cyclodextrin. PT, FHA and PRN are isolated separately from the supernatant culture medium. FIM are extracted and copurified from the bacterial cells. The pertussis antigens are purified by sequential filtration, salt-precipitation, ultrafiltration and chromatography. PT is detoxified with glutaraldehyde, FHA is treated with formaldehyde and the residual aldehydes are removed by ultrafiltration. The individual antigens are adsorbed separately onto aluminum phosphate.
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.

9 IMMUNOBIOLOGY
Vaccines stimulate an immune response that can be demonstrated by antibody production, cell-mediated immunity, and cell-mediated cytotoxicity.

10 CLINICAL PHARMACOLOGY
10.1 Mechanism of Action
Diphtheria
Diphtheria is an acute toxin-mediated disease caused by toxigenic strains of 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 some degree of protection. Antitoxin levels of at least 0.1 IU/mL are generally regarded as protective. (13) Levels of 1.0 IU/mL have been associated with long-term protection. (14)

10.2 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 0.01 IU/mL is measured by neutralization assay is considered the minimal protective level. (13) A serum tetanus toxoid level ≥0.1 IU/mL, as measured by the ELISA used in clinical studies of Pentacel is considered protective.

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

10.4 Poliomyelitis
Poliomiruses, 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. (16)

10.5 Invasive Disease Due to H. influenzae Type b
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 H. influenzae type b. Based on data from passive antibody studies (17) and an efficacy study with H. influenzae type b polysaccharide vaccine in Finland, (18) a post-vaccination anti-PRP antibody level of 0.15 mcg/mL has been accepted as a minimal protective level. Data from an efficacy study with 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. (19) (20) These levels have been used to evaluate the effectiveness of Haemophilus b Conjugate Vaccines, including the ActHIB component of Pentacel. (18)

11 DESCRIPTION
Pentacel consists of a Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus (DTaP-IPV) component and an Acellular Pertussis Adsorbed and Inactivated Poliovirus (DAPTACEL) component. The DTaP-IPV component contains PT, FHA, PRN, 5 mcg fimbriae types 2 and 3 (FIM), inactivated polioviruses [40 D-antigen units (DU) type 1 (Mahoney), 8 DU type 2 (MEF-1), 32 DU type 3 (Saulkett] and 10 mcg PRP of H. influenzae type b covalently bound to 24 mcg of tetanus toxoid (PRP-T).

Other ingredients per 0.5 mL dose include 1.5 mg aluminum phosphate (0.33 mg aluminum) as the adjuvant, polysorbate 80 (approximately 10 ppm by calculation), 42.5 mg sucrose, ≤5 mg residual formaldehyde, ≤50 ng residual glutaraldehyde, ≤50 ng residual bovine serum albumin, ≤3 mg (0.05% v/v) 2-phenoxethanol (not as a preservative), ≤4 µg of neomycin and ≤4 µg polymyxin B sulfate. C. diphtheriae is grown in modified Mueller’s growth medium. (6) After purification by ammonium sulfate fractionation, the diphtheria toxin is detoxified with formaldehyde and dithiothreitol. Clostridium tetani is grown in modified Mueller-Hinton casamino acid medium without beef heart infusion. (7) Tetanus toxin is modified with formaldehyde and purified by ammonium sulfate fractionation and diafiltration. Diphtheria and tetanus toxoids are individually adsorbed onto aluminum phosphate.

The acellular pertussis vaccine antigens are produced from Bordetella pertussis cultures grown in Stainer-Schroetter medium (8) modified by the addition of casamino acids and dimethyl-beta-cyclodextrin. PT, FHA and PRN are isolated separately from the supernatant culture medium. FIM are extracted and copurified from the bacterial cells. The pertussis antigens are purified by sequential filtration, salt-precipitation, ultrafiltration and chromatography. PT is detoxified with glutaraldehyde, FHA is treated with formaldehyde and the residual aldehydes are removed by ultrafiltration. The individual antigens are adsorbed separately onto aluminum phosphate.
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. Immune responses to Pentacel were evaluated in four US studies: Studies 494-01, P3T06, 494-03, and MSA10. The vaccination schedules of Pentacel, Control vaccines, and concomitantly administered vaccines used in Studies 494-01, P3T06, and 494-03 are provided in Table 1. (See 8.5.)

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14.3 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 are provided in 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 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>Serum Type</th>
<th>Post-Dose 3</th>
<th>Post-Dose 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria Antitoxin</td>
<td>% achieving 4-fold rise</td>
<td>% achieving 4-fold rise</td>
</tr>
<tr>
<td>% ≥0.1 IU/mL</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>% &lt;0.1 IU/mL</td>
<td>98.8%</td>
<td>98.8%</td>
</tr>
<tr>
<td>Tetanus Antitoxoid</td>
<td>% achieving 4-fold rise</td>
<td>% achieving 4-fold rise</td>
</tr>
<tr>
<td>% ≥0.1 IU/mL</td>
<td>99.7%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

14.3 Pertussis

In a separate study, Study P3T06, US infants were randomized to receive either Pentacel or DAPTACEL + IPOL + ActHIB in the subset of infants who received DAPTACEL in the Sweden I Efficacy Trial and one month following Dose 3 and Dose 4 of Pentacel in a subset of infants from Study P3T06. In Study 494-01 (Table 4), in which infants were randomized to receive either Pentacel or HCPDT at 2, 4, and 6 months of age, 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-PRN 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 set for seroconversion rates and GMCs following Dose 3 DAPTACEL vaccine relative to Dose 3 Pentacel vaccine. The non-inferiority criteria were met for all comparisons except for anti-PRN GMCs (upper limit of 90% 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 + IPOL + ActHIB in US Infants Vaccinated at 2, 4, 6, and 15-16 Months of Age in Study P3T06

<table>
<thead>
<tr>
<th>Serum Type</th>
<th>Post-Dose 3</th>
<th>Post-Dose 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-FHA</td>
<td>% achieving 4-fold rise</td>
<td>% achieving 4-fold rise</td>
</tr>
<tr>
<td>GMC (EU/mL)</td>
<td>95.81</td>
<td>91.3</td>
</tr>
<tr>
<td>Anti-PRN</td>
<td>% achieving 4-fold rise</td>
<td>% achieving 4-fold rise</td>
</tr>
<tr>
<td>GMC (EU/mL)</td>
<td>73.65</td>
<td>64.02</td>
</tr>
</tbody>
</table>
months following Dose 4 of POLIOVAX (N = 284-287) were 2,330, 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 MSA10 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 MSA10, 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 MSA10, 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 DTap + IPV + ActHIB Administered at 2, 4, and 6 Months of Age in Studies 494-01, P3T06, and MSA10

<table>
<thead>
<tr>
<th>Study</th>
<th>Pentacel</th>
<th>HC/DT + POLIOVAX + ActHIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>% achieving anti-PRP ≥1.0 mcg/mL</td>
<td>% achieving anti-PRP ≥1.0 mcg/mL</td>
</tr>
<tr>
<td>N = 686</td>
<td>93.3*</td>
<td>93.3</td>
</tr>
<tr>
<td>N = 356</td>
<td>72.1*</td>
<td>70.8</td>
</tr>
<tr>
<td>N = 401</td>
<td>79.1</td>
<td>88.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Pentacel</th>
<th>DAPTACEL + IPOL + ActHIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 686</td>
<td>% achieving anti-PRP ≥1.0 mcg/mL</td>
<td>GMC (mcg/mL)</td>
</tr>
<tr>
<td>N = 356</td>
<td>72.1*</td>
<td>2.31</td>
</tr>
<tr>
<td>N = 401</td>
<td>79.1*</td>
<td>2.29</td>
</tr>
</tbody>
</table>

Study 494-01

- Anti-PRP seroprotection rates and GMCs one month following Dose 4 of study vaccines, 68.6% of Pentacel recipients (N = 829) and 50.8% of separately administered ActHIB recipients (N = 276) had an anti-PRP level ≥0.15 mcg/mL. Following Dose 4 of study vaccines, 98.2% of Pentacel recipients (N = 874) and 99.0% of separately administered ActHIB recipients (N = 291) had an anti-PRP level ≥1.0 mcg/mL.

- In Study P3T06, 15 months of age prior to receipt of Dose 4 of study vaccines, 65.4% of Pentacel recipients (N = 335) and 60.7% of separately administered ActHIB recipients (N = 323) had an anti-PRP level ≥0.15 mcg/mL. Following Dose 4 of study vaccines, 97.8% of Pentacel recipients (N = 361) and 95.9% of separately administered ActHIB recipients (N = 340) had an anti-PRP level ≥1.0 mcg/mL.

- In Study P7T06, 15 months of age prior to receipt of Dose 4 of study vaccines, 65.4% of Pentacel recipients (N = 335) and 60.7% of separately administered ActHIB recipients (N = 323) had an anti-PRP level ≥0.15 mcg/mL. Following Dose 4 of study vaccines, 97.8% of Pentacel recipients (N = 361) and 95.9% of separately administered ActHIB recipients (N = 340) had an anti-PRP level ≥1.0 mcg/mL.

14.6 Concomitantly Administered Vaccines

In Study P7T06, (Table 1) 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 = 321-325) relative to these vaccines administered at 15 months of age with pertussis immunization. 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 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; 2011.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

5 Dose Package (NDC No. 49281-510-05) containing 5 vials of DTaP-IPV component (NDC No. 49281-560-05) to be used to reconstitute 5 single dose vials of lyophilized ActHIB vaccine component (NDC No. 49281-545-15).

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.

Pentacel should be used immediately after reconstitution.

17 PATIENT COUNSELING INFORMATION

Before the 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.

Distributed by: Sanofi Pasteur Inc.
Swiftwater PA 18370 USA

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