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----------

----------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 vaccine 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 vaccine, any ingredient of Pentacel vaccine, 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 >30% 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: [XX/201X]

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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 vaccine 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 vaccine 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 vaccine constitute a primary immunization course against pertussis. Three doses of Pentacel vaccine 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 Vaccine 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 vaccine contains twice the amount of detoxified pertussis toxin (PT) and four times the amount of filamentous hemagglutinin (FHA) as DAPTACEL vaccine. Pentacel vaccine 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 vaccine and are also scheduled to receive the other antigens of Pentacel vaccine. However, data are not available on the safety and immunogenicity of such mixed sequences of Pentacel vaccine and DAPTACEL vaccine for successive doses of the primary DTaP series. Children who have completed a 4-dose series with Pentacel vaccine 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 vaccine and DTaP vaccine from different manufacturers.

Mixed Sequences of Pentacel Vaccine and IPV Vaccine

Pentacel vaccine 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 vaccine. However, data are not available on the safety and immunogenicity of Pentacel vaccine 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 vaccine is administered at ages 2, 4, 6, and 15-18 months, an additional booster dose of IPV vaccine should be administered at age 4-6 years, resulting in a 5-dose IPV series. (2)

Mixed Sequences of Pentacel Vaccine and Haemophilus b Conjugate Vaccine

Pentacel vaccine 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 vaccine. However, data are not available on the safety and immunogenicity of Pentacel vaccine 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” caps, cleanse the DTaP-IPV and ActHIB vial stoppers with a suitable germicide. 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 into the vial of the lyophilized ActHIB vaccine component. Gently swirl the vial now containing Pentacel vaccine 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 vaccine should not be administered.

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

Pentacel Vaccine: Instructions for Reconstitution of ActHIB Vaccine Component with DTaP-IPV Component

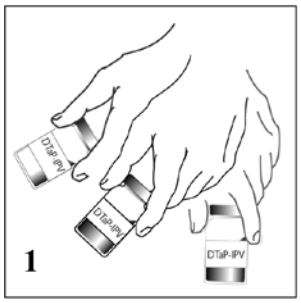

Figure 1
Gently shake the vial of DTaP-IPV component.

Figure 2
Withdraw the entire liquid content.

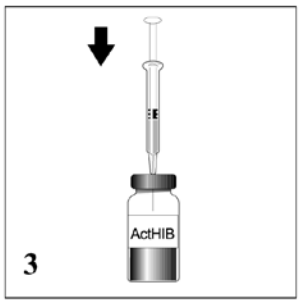

Figure 3
Insert the syringe needle through the stopper of the vial of lyophilized ActHIB vaccine component and inject the liquid into the vial.

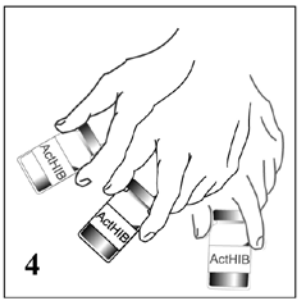

Figure 4
Swirl vial gently.

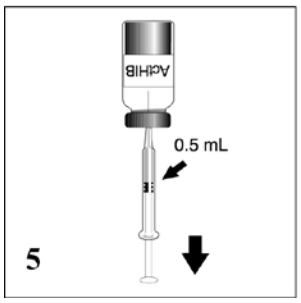

Figure 5
After reconstitution, immediately withdraw 0.5 mL of Pentacel vaccine and administer intramuscularly.
Pentacel vaccine should be used immediately after reconstitution.

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

3 DOSAGE FORMS AND STRENGTHS

Pentacel vaccine 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 (2.2)* and *How Supplied/Storage and Handling (16)*.]

4 CONTRAINDICATIONS

4.1 Hypersensitivity

A severe allergic reaction (eg, anaphylaxis) after a previous dose of Pentacel vaccine or any other diphtheria 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 Pentacel vaccine. [See *Description (11)*.]

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 vaccine.

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 vaccine. 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 pertussis vaccine, the decision to administer Pentacel vaccine 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-Barré 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 vaccine.

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 acellular pertussis antigens (including Pentacel vaccine) and for the following 24 hours, to reduce the possibility of post-vaccination fever.

5.5 Limitations of Vaccine Effectiveness

Vaccination with Pentacel vaccine may not protect all individuals.

5.6 Altered Immunocompetence

If Pentacel vaccine 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 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 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 vaccine was evaluated in four clinical studies in which a total of 5,980 participants received at least one dose of Pentacel vaccine. In three of the studies, conducted in the US, a total of 4,198 participants were enrolled to receive four consecutive doses of Pentacel vaccine. In the fourth study, conducted in Canada, 1,782 participants previously vaccinated with three doses of Pentacel vaccine received a fourth dose. The vaccination schedules of Pentacel vaccine, 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 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.

154 **Table 1: Clinical Safety Studies of Pentacel Vaccine: Vaccination Schedules**

Study	Pentacel	Control Vaccines	Concomitantly Administered Vaccines
494-01	2, 4, 6 and 15 months	HCPDT + POLIOVAX + ActHIB at 2, 4, 6, and 15 months	7-valent pneumococcal conjugate vaccine* (PCV7) at 2, 4, and 6 months in a subset of participants† Hepatitis B vaccine at 2 and 6 months‡
P3T06	2, 4, 6, and 15-16 months	DAPTACEL + IPOL + ActHIB at 2, 4, and 6 months; and DAPTACEL + ActHIB at 15-16 months	PCV7* at 2, 4, and 6 months Hepatitis B vaccine at 2 and 6 months‡
494-03	2, 4, 6, and 15-16 months	None	PCV7* at 2, 4, and 6 months in all participants; and at 15 months in a random subset of participants 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) Measles, mumps, rubella vaccine§ (MMR) and varicella§ vaccine at 12 or 15 months in random subsets of participants
5A9908	15-18 months**	None	None

HCPDT: non-US licensed DTaP vaccine that is identical to the DTaP component of Pentacel vaccine.
POLIOVAX: US licensed Poliovirus Vaccine Inactivated, Sanofi Pasteur Limited.
IPOL: US licensed Poliovirus Vaccine Inactivated, Sanofi Pasteur SA.

* PCV7 manufactured by Wyeth Laboratories.

† PCV7 was introduced after the study was initiated, and thus, administered concomitantly with Pentacel vaccine in a subset of participants.

‡ 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.

§ MMR and varicella vaccines were both manufactured by Merck and Co.

** Study participants previously had received three doses of Pentacel vaccine by 8 months of age.

155

Solicited Adverse Reactions

The incidence and severity of selected solicited injection site and systemic adverse reactions that occurred within 3 days following each dose of Pentacel or Control vaccines in Study P3T06 is shown in Table 2. Information on these reactions was recorded daily by parents or guardians on diary cards. In Table 2, injection site reactions are reported for the Pentacel vaccine and DAPTACEL vaccine injection sites.

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

Injection Site Reactions	Pentacel Vaccine				DAPTACEL Vaccine			
	Dose 1 N = 465-467 %	**Dose 2** N = 451 %	**Dose 3** N = 438-440 %	**Dose 4** N = 387-396 %	**Dose 1** N = 1,400-1,404 %	**Dose 2** N = 1,358-1,359 %	**Dose 3** N = 1,311-1,312 %	**Dose 4** N = 376-380 %
Redness								
>5 mm	7.1	8.4	8.7	17.3	6.2	7.1	9.6	16.4
>25 mm	2.8	1.8	1.8	9.2	1.0	0.6	1.9	7.9
>50 mm	0.6	0.2	0.0	2.3	0.4	0.1	0.0	2.4
Swelling								
>5 mm	7.5	7.3	5.0	9.7	4.0	4.0	6.5	10.3
>25 mm	3.0	2.0	1.6	3.8	1.6	0.7	1.1	4.0
>50 mm	0.9	0.0	0.0	0.8	0.4	0.1	0.1	1.3
Tenderness*								
Any	47.5	39.2	42.7	56.1	48.8	38.2	40.9	51.1
Moderate or Severe	19.6	10.6	11.6	16.7	20.7	12.2	12.3	15.8
Severe	5.4	1.6	1.4	3.3	4.1	2.3	1.7	2.4
Increase in Arm Circumference								
>5 mm	–	–	–	33.6	–	–	–	30.6
>20 mm				4.7				6.9
>40 mm				0.5				0.8
Systemic Reactions	**Pentacel Vaccine**				**DAPTACEL + IPOL + ActHIB Vaccines**			**DAPTACEL + ActHIB Vaccines**
	Dose 1 N = 466-467 %	**Dose 2** N = 451-452 %	**Dose 3** N = 435-440 %	**Dose 4** N = 389-398 %	**Dose 1** N = 1,390-1,406 %	**Dose 2** N = 1,346-1,360 %	**Dose 3** N = 1,301-1,312 %	**Dose 4** N = 379-381 %
Fever†‡								
≥38.0°C	5.8	10.9	16.3	13.4	9.3	16.1	15.8	8.7
>38.5°C	1.3	2.4	4.4	5.1	1.6	4.3	5.1	3.2
>39.5°C	0.4	0.0	0.7	0.3	0.1	0.4	0.3	0.8

Decreased Activity/Lethargy§								
Any	45.8	32.7	32.5	24.1	51.1	37.4	33.2	24.1
Moderate or Severe	22.9	12.4	12.7	9.8	24.3	15.8	12.7	9.2
Severe	2.1	0.7	0.2	2.5	1.2	1.4	0.6	0.3
Inconsolable Crying								
Any	59.3	49.8	47.3	35.9	58.5	51.4	47.9	36.2
≥1 hour	19.7	10.6	13.6	11.8	16.4	16.0	12.2	10.5
>3 hours	1.9	0.9	1.1	2.3	2.2	3.4	1.4	1.8
Fussiness/Irritability								
Any	76.9	71.2	68.0	53.5	75.8	70.7	67.1	53.8
≥1 hour	34.5	27.0	26.4	23.6	33.3	30.5	26.2	19.4
>3 hours	4.3	4.0	5.0	5.3	5.6	5.5	4.3	4.5

* 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.

‡ Following Doses 1-3 combined, the proportion of temperature measurements that were taken by axillary, rectal or other routes, or not recorded were 46.0%, 53.0%, 1.0%, and 0% respectively, for Pentacel vaccine and 44.8%, 54.0%, 1.0%, and 0.1%, respectively, for DAPTACEL + IPOL + ActHIB vaccines. Following Dose 4, the proportion of temperature measurements that were taken by axillary, rectal or other routes, or not recorded were 62.7%, 34.4%, 2.4% and 0.5%, respectively, for Pentacel vaccine, and 61.1%, 36.6%, 1.7% and 0.5%, respectively, for DAPTACEL + ActHIB vaccines.

§ Moderate: interferes with or limits usual daily activity; Severe: disabling, not interested in usual daily activity.

Hypotonic Hyporesponsive Episodes

In Study P3T06, the diary cards included questions pertaining to HHEs. In Studies 494-01, 494-03, and 5A9908, a question about the occurrence of fainting or change in mental status was asked during post-vaccination phone calls. Across these 4 studies, no HHEs, as defined in a report of a US Public Health Service workshop (4) were reported among participants who received Pentacel vaccine (N = 5,979), separately administered HCPDT + POLIOVAX + ActHIB vaccines (N = 1,032) or separately administered DAPTACEL + IPOL + ActHIB vaccines (N = 1,455). Hypotonia not fulfilling HHE criteria within 7 days following vaccination was reported in 4 participants after the administration of Pentacel vaccine (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 vaccines (4 days following the 1st dose).

Seizures

Across Studies 494-01, 494-03, 5A9908 and P3T06, a total of 8 participants experienced a seizure within 7 days following either Pentacel vaccine (4 participants; N = 4,197 for at least one of Doses 1-3; N = 5,033 for Dose 4), separately administered HCPDT + POLIOVAX + ActHIB vaccines (3 participants; N = 1,032 for at least one of Doses 1-3, N = 739 for Dose 4), separately administered DAPTACEL + IPOL + ActHIB vaccines (1 participant; N = 1,455 for at least one of Doses 1-3), or separately administered DAPTACEL + ActHIB vaccines (0 participants; N = 418 for Dose 4). Among the four participants who experienced a seizure within 7 days following Pentacel vaccine, 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 the same day as the third dose, and two participants in Study 5A9908 had a febrile 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 the same day as the first dose of DAPTACEL + IPOL + ActHIB vaccines, one participant had an afebrile seizure the same day as the second dose of HCPDT + POLIOVAX + ActHIB vaccines, and two participants had a febrile seizure 6 and 7 days, respectively, after the fourth dose of HCPDT + POLIOVAX + ActHIB vaccines.

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 vaccine and 50 of 1,455 (3.4%) participants who received DAPTACEL + IPOL + ActHIB vaccines experienced a serious adverse event. Within 30 days following Dose 4 of Pentacel or Control vaccines, 5 of 431 (1.2%) participants who received Pentacel vaccine and 4 of 418 (1.0%) participants who received DAPTACEL + ActHIB vaccines experienced a serious adverse event. In Study 494-01, within 30 days following any of Doses 1-3 of Pentacel or Control vaccines, 23 of 2,506 (0.9%) participants who received Pentacel vaccine and 11 of 1,032 (1.1%) participants who received HCPDT + POLIOVAX + ActHIB vaccines experienced a serious adverse event. Within 30 days following Dose 4 of Pentacel or Control vaccines, 6 of 1,862 (0.3%) participants who received Pentacel vaccine and 2 of 739 (0.3%) participants who received HCPDT + POLIOVAX + ActHIB vaccines experienced a serious adverse event.

Across Studies 494-01, 494-03 and P3T06, within 30 days following any of Doses 1-3 of Pentacel or Control vaccines, overall, the most frequently reported serious adverse events were bronchiolitis, dehydration, pneumonia and gastroenteritis. Across Studies 494-01, 494-03, 5A9908 and P3T06, within 30 days following Dose 4 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, 5A9908 and P3T06, two cases of encephalopathy were reported, both in participants who had received Pentacel vaccine (N = 5,979). One case occurred 30 days post-vaccination and was secondary to cardiac arrest following cardiac surgery. One infant who had onset of neurologic symptoms 8 days post-vaccination was subsequently found to have structural cerebral abnormalities and was diagnosed with congenital encephalopathy.

A total of 5 deaths occurred during Studies 494-01, 494-03, 5A9908 and P3T06: 4 in children who had received Pentacel vaccine (N = 5,979) and one in a participant who had received DAPTACEL + IPOL + ActHIB vaccines (N = 1,455). There were no deaths reported in children who received HCPDT + POLIOVAX + ActHIB vaccines (N = 1,032). Causes of death among children who received Pentacel vaccine 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 222 days following DAPTACEL + IPOL + ActHIB vaccines.

6.2 Data from Post-Marketing Experience

The following additional adverse events have been spontaneously reported during the post-marketing use of Pentacel vaccine worldwide, since 1997. Between 1997 and 2007, Pentacel vaccine 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 vaccine.

- ***Cardiac disorders***
  Cyanosis
- ***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, 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***

  Pallor

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

In clinical trials, Pentacel vaccine 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 vaccine 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 vaccine. [See *Warnings and Precautions (5.6).*]

7.3 Drug/Laboratory Test Interactions

Antigenuria has been detected in some instances following receipt of ActHIB vaccine. Urine antigen detection may not have definite diagnostic value in suspected *H influenzae* type b disease within one week following receipt of Pentacel vaccine. (5)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with Pentacel vaccine. It is also not known whether Pentacel vaccine 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 vaccine 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 vaccine in the age group 19 months through 4 years is supported by evidence in children 6 weeks through 18 months. The safety and effectiveness of Pentacel vaccine in infants less than 6 weeks of age and in children 5 to 16 years of age have not been established.

11 DESCRIPTION

Pentacel vaccine consists of a Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus (DTaP-IPV) component and an ActHIB® vaccine component combined through reconstitution for intramuscular injection. ActHIB vaccine (Haemophilus b Conjugate Vaccine [Tetanus Toxoid Conjugate]), consists of *H influenzae* type b capsular polysaccharide (polyribosyl-ribitol-phosphate [PRP]) covalently bound to tetanus toxoid (PRP-T). The DTaP-IPV component is supplied as a sterile liquid used to reconstitute the lyophilized ActHIB vaccine component to form Pentacel vaccine. Pentacel vaccine is a uniform, cloudy, white to off-white (yellow tinge) suspension.

Each 0.5 mL dose contains 15 Lf diphtheria toxoid, 5 Lf tetanus toxoid, acellular pertussis antigens [20 mcg detoxified pertussis toxin (PT), 20 mcg filamentous hemagglutinin (FHA), 3 mcg pertactin (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 (Saukett)] 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 mcg residual formaldehyde, <50 ng residual glutaraldehyde, ≤50 ng residual bovine serum albumin, 3.3 mg (0.6% v/v) 2-phenoxyethanol (not as a preservative), <4 pg of neomycin and <4 pg 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 diafiltered.

Clostridium tetani is grown in modified Mueller-Miller casamino acid medium without beef heart infusion. (7) Tetanus toxin is detoxified 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-Scholte 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.

Poliovirus Type 1, Type 2 and Type 3 are each grown in separate cultures of MRC-5 cells, a line of normal human diploid cells, by the microcarrier method. (9) (10) The cells are grown in CMRL (Connaught Medical Research Laboratories) 1969 medium, supplemented with calf serum. For viral growth, the culture medium is replaced by Medium 199, without calf serum. After clarification and filtration, the viral suspensions are concentrated by ultrafiltration, and purified by liquid chromatography steps. The monovalent viral suspensions are inactivated with formaldehyde. Monovalent concentrates of each inactivated poliovirus are combined to produce a trivalent poliovirus concentrate.

The adsorbed diphtheria, tetanus and acellular pertussis antigens are combined with aluminum phosphate (as adjuvant), 2-phenoxyethanol (not as a preservative) and water for injection, into an intermediate concentrate. The trivalent poliovirus concentrate is added and the DTaP-IPV component is diluted to its final concentration. The DTaP-IPV component does not contain a preservative.

Both diphtheria and tetanus toxoids induce at least 2 neutralizing units per mL in the guinea pig potency test. The potency of the acellular pertussis antigens is evaluated by the antibody response of immunized mice to detoxified PT, FHA, PRN and FIM as measured by enzyme-linked immunosorbent assay (ELISA). The immunogenicity of the inactivated polioviruses is evaluated by the antibody response in monkeys measured by virus neutralization.

PRP, a high molecular weight polymer, is prepared from the *Haemophilus influenzae* type b strain 1482 grown in a semi-synthetic medium. (11) The tetanus toxoid for conjugation to PRP is prepared by ammonium sulfate purification, and formalin inactivation of the toxin from cultures of *Clostridium tetani* (Harvard strain) grown in a modified Mueller and Miller medium. (12) The toxoid is filter sterilized prior to the conjugation process. The ActHIB vaccine component does not contain a preservative. Potency of the ActHIB vaccine component is specified on each lot by limits on the content of PRP polysaccharide and protein per dose and the proportion of polysaccharide and protein that is characterized as high molecular weight conjugate.

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

12 CLINICAL PHARMACOLOGY

12.1 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)

Tetanus

Tetanus is an acute disease caused by an extremely potent neurotoxin produced by *C tetani*. Protection against disease is due to the development of neutralizing antibodies to tetanus toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assay is considered the minimum protective level. (13) (15) A tetanus antitoxoid level ≥0.1 IU/mL as measured by the ELISA used in clinical studies of Pentacel vaccine is considered protective.

Pertussis

Pertussis (whooping cough) is a respiratory disease caused by *B pertussis*. This Gram-negative coccobacillus 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. (16)

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 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 vaccine component of Pentacel vaccine.

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Pentacel vaccine has not been evaluated for carcinogenic or mutagenic potential or impairment of fertility.

14 CLINICAL STUDIES

The efficacy of Pentacel vaccine is based on the immunogenicity of the individual antigens compared to separately administered vaccines. Serological correlates of protection exist for diphtheria, tetanus, poliomyelitis, and invasive disease due to *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 vaccine in US children to responses following DAPTACEL vaccine (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 vaccines contain the same pertussis antigens, manufactured by the same process, Pentacel vaccine contains twice as much detoxified PT and four times as much FHA as DAPTACEL vaccine.

Immune responses to Pentacel vaccine were evaluated in four US studies: Studies 494-01, P3T06, 494-03, and M5A10. The vaccination schedules of Pentacel vaccine, Control vaccines, and concomitantly administered vaccines used in Studies 494-01, P3T06, and 494-03 are provided in Table 1. [See *Adverse Reactions (6.1)*.] In Study M5A10, participants were randomized to receive Pentacel vaccine or separately administered DAPTACEL, IPOL, and ActHIB vaccines at 2, 4, and 6 months of age. 7-valent pneumococcal conjugate vaccine (PCV7, Wyeth Pharmaceuticals Inc.) at 2, 4, and 6 months of age, and Hepatitis B vaccine (Merck and Co. or GlaxoSmithKline Biologicals) at 2 and 6 months of age, were administered concomitantly with Pentacel vaccine or Control vaccines.

14.1 Diphtheria

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

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

	Pentacel Vaccine	**DAPTACEL + IPOL + ActHIB Vaccines**
Post-Dose 3	**N = 331-345**	**N = 1,037-1,099**
Diphtheria Antitoxin		
% ≥0.01 IU/mL*	100.0%	100.0%
% ≥0.10 IU/mL†	98.8%	98.5%
Tetanus Antitoxoid		
% ≥0.10 IU/mL†	99.7%	100.0%
Post-Dose 4	**N = 341-352**	**N = 328-334**
Diphtheria Antitoxin		
% ≥0.10 IU/mL*	100.0%	100.0%
% ≥1.0 IU/mL†	96.5%	95.7%
Tetanus Antitoxoid		
% ≥0.10 IU/mL*	100.0%	100.0%
% ≥1.0 IU/mL†‡	92.9%	99.4%

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 is <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.

413

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 vaccine 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 vaccine 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% confidence interval [CI] 80.1%, 88.6%). The protective efficacy of DAPTACEL vaccine against mild pertussis (≥1 day of cough with laboratory confirmation) was 77.9% (95% CI 72.6%, 82.2%). Protection against pertussis by DAPTACEL vaccine was sustained for the 2-year follow-up period.

Based on comparisons of the immune responses to DAPTACEL vaccine 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 vaccine 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 vaccine 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 vaccine (Table 4). Available stored sera from infants who received DAPTACEL vaccine in the Sweden I Efficacy Trial and sera from children who received PCV7 concomitantly with the first three doses of Pentacel vaccine 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 vaccine in the subset of infants from the Sweden I Efficacy Trial and one month following Dose 3 and Dose 4 of Pentacel vaccine 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 vaccine relative to Dose 3 of DAPTACEL vaccine. The non-inferiority criterion for anti-PRN seroconversion following Dose 4 of Pentacel vaccine relative to Dose 3 of DAPTACEL vaccine 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 vaccine in US children relative to Dose 3 of DAPTACEL vaccine in Swedish infants correlates with diminished efficacy of Pentacel vaccine against pertussis is unknown.

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

	Post-Dose 3 DAPTACEL Vaccine Sweden I Efficacy Trial N = 80	**Post-Dose 3 Pentacel Vaccine* US Study 494-01 N = 730-995**	**Post-Dose 4 Pentacel Vaccine† US Study 494-01 N = 507-554**
Anti-FHA			
% achieving 4-fold rise‡	68.8	79.8	91.7§
GMC (EU/mL)	40.70	71.46	129.85§
Anti-PRN			
% achieving 4-fold rise‡	98.8	74.4	89.2**
GMC (EU/mL)	111.26	38.11	90.82§
Anti-FIM			
% achieving 4-fold rise‡	86.3	86.5	91.5§
GMC (EU/mL)	339.31	265.02	506.57§

Analyzed sera were from subsets of the Per Protocol Immunogenicity populations in each study.
Data on anti-PT levels using an adequately specific assay were not available.

* Non-inferiority criteria were not pre-specified for the comparisons of immune responses to Pentacel vaccine Post-Dose 3 vs. DAPTACEL vaccine Post-Dose 3.

† Pre-specified non-inferiority analyses compared immune responses to Pentacel vaccine Post-Dose 4 vs. DAPTACEL vaccine Post-Dose 3.

‡ Fold rise was calculated as Post-Dose 3/Pre-Dose 1 antibody level or Post-Dose 4/Pre-Dose 1 antibody level.

§ Percent achieving 4-fold rise or GMC Post-Dose 4 Pentacel vaccine is not inferior to Post-Dose 3 DAPTACEL vaccine [upper limit of 95% CI for difference in rates (DAPTACEL minus Pentacel) <10% and upper limit of 90% CI for GMC ratio (DAPTACEL/Pentacel) <1.5].

** Non-inferiority criterion is not met for percent achieving 4-fold rise in anti-PRN Post-Dose 4 Pentacel vaccine relative to Post-Dose 3 DAPTACEL vaccine [upper limit of 95% CI for difference in rates (DAPTACEL minus Pentacel) = 13.24%, exceeds the non-inferiority criterion of <10%].

In a separate study, Study P3T06, US infants were randomized to receive either Pentacel vaccine or DAPTACEL + IPOL + ActHIB vaccines 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 vaccine 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 vaccine relative to Dose 3 of DAPTACEL vaccine. Following Dose 4 of Pentacel vaccine relative to Dose 4 of DAPTACEL vaccine, 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 vaccine relative to Dose 4 of DAPTACEL vaccine in US children correlates with diminished efficacy of Pentacel vaccine against pertussis is unknown.

469 **Table 5: Pertussis Antibody Responses One Month Following Doses 3 and 4 of Pentacel**
470 **Vaccine or DAPTACEL + IPOL + ActHIB Vaccines in US Infants Vaccinated at 2, 4, 6, and**
471 **15-16 Months of Age in Study P3T06**

	Post-Dose 3 Pentacel Vaccine	**Post-Dose 3 DAPTACEL + IPOL + ActHIB Vaccines**	**Post-Dose 4 Pentacel Vaccine**	**Post-Dose 4 DAPTACEL + ActHIB Vaccines**
	N = 143	**N = 481-485**	**N = 113**	**N = 127-128**
Anti-PT **% achieving 4-fold rise*** **GMC (EU/mL)**	95.8† 102.62†	87.3 61.88	93.8‡ 107.89‡	91.3 100.29
	N = 218-318	**N = 714-1,016**	**N = 230-367**	**N = 237-347**
Anti-FHA **% achieving 4-fold rise*** **GMC (EU/mL)**	81.9§ 73.68§	60.9 29.22	88.4** 107.94**	79.3 64.02
Anti-PRN **% achieving 4-fold rise*** **GMC (EU/mL)**	74.2§ 36.05§	75.4 43.25	92.7** 93.59††	98.3 186.07
Anti-FIM **% achieving 4-fold rise*** **GMC (EU/mL)**	91.7§ 268.15§	86.3 267.18	93.5** 553.39**	91.6 513.54

Per Protocol Immunogenicity population for anti-FHA, anti-PRN, and anti-FIM.
Non-random subset of per Protocol Immunogenicity population for anti-PT. See text for further information on the subset evaluated.

* Fold rise was calculated as Post-Dose 3/Pre-Dose 1 antibody level or Post-Dose 4/Pre-Dose 1 antibody level.

† Percent achieving 4-fold rise or GMC Post-Dose 3 Pentacel vaccine not inferior to Post-Dose 3 DAPTACEL vaccine [upper limit of 95% CI for GMC ratio (DAPTACEL/Pentacel) <1.5 and upper limit of 95% CI for differences in rates (DAPTACEL minus Pentacel) <10%].

‡ Percent achieving 4-fold rise or GMC Post-Dose 4 Pentacel vaccine not inferior to Post-Dose 4 DAPTACEL vaccine [upper limit of 95% CI for GMC ratio (DAPTACEL/Pentacel) <1.5 and upper limit of 95% CI for differences in rates (DAPTACEL minus Pentacel) <10%].

§ Percent achieving 4-fold rise or GMC Post-Dose 3 Pentacel vaccine not inferior to Post-Dose 3 DAPTACEL vaccine [upper limit of 90% CI for GMC ratio (DAPTACEL/Pentacel) <1.5 and upper limit of 90% CI for differences in rates (DAPTACEL minus Pentacel) <10%].

** Percent achieving 4-fold rise or GMC Post-Dose 4 Pentacel vaccine not inferior to Post-Dose 4 DAPTACEL vaccine [upper limit of 90% CI for GMC ratio (DAPTACEL/Pentacel) <1.5 and upper limit of 90% CI for differences in rates (DAPTACEL minus Pentacel) <10%].

†† Non-inferiority criterion is not met for GMC Post-Dose 4 Pentacel vaccine relative to Post-Dose 4 DAPTACEL vaccine [upper limit of 90% CI for GMC ratio (DAPTACEL/Pentacel) = 2.25, which exceeds the non-inferiority criterion of <1.5].

472

14.4 Poliomyelitis

In Study P3T06 (Table 1), in which infants were randomized to receive the first three doses of Pentacel vaccine or DAPTACEL + IPOL + ActHIB vaccines 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 vaccine or HCPDT + POLIOVAX + ActHIB vaccines, GMTs (1/dil) of antibodies to Poliovirus types 1, 2, and 3 one month following Dose 4 of Pentacel vaccine (N = 851-857) were 2,304, 4,178, and 4,415, respectively, and one month following Dose 4 of POLIOVAX vaccine (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 vaccine or separately administered ActHIB vaccine 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 vaccine compared with separately administered ActHIB vaccine. 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 vaccine compared with separately administered ActHIB vaccine. In Study M5A10, the non-inferiority criterion was met for anti-PRP GMCs following Pentacel vaccine compared with separately administered ActHIB vaccine.

Table 6: Anti-PRP Seroprotection Rates and GMCs One Month Following Three Doses of Pentacel Vaccine or Separate DTaP + IPV + ActHIB Vaccines Administered at 2, 4, and 6 Months of Age in Studies 494-01, P3T06, and M5A10

	Study 494-01	
	Pentacel Vaccine N = 1,127	**HCPDT + POLIOVAX + ActHIB Vaccines N = 401**
% achieving anti-PRP ≥0.15 mcg/mL	95.4*	98.3
% achieving anti-PRP ≥1.0 mcg/mL	79.1†	88.8
Anti-PRP GMC (mcg/mL)	3.19‡	6.23
	Study P3T06	
	Pentacel Vaccine N = 365	**DAPTACEL + IPOL + ActHIB Vaccines N = 1,128**
% achieving anti-PRP ≥0.15 mcg/mL	92.3*	93.3
% achieving anti-PRP ≥1.0 mcg/mL	72.1*	70.8
Anti-PRP GMC (mcg/mL)	2.31§	2.29
	Study M5A10	
	Pentacel Vaccine N = 826	**DAPTACEL + IPOL + ActHIB Vaccines N = 421**
% achieving anti-PRP ≥0.15 mcg/mL	93.8**	90.3
% achieving anti-PRP ≥1.0 mcg/mL	75.1**	74.8
Anti-PRP GMC (mcg/mL)	2.52††	2.38

Per Protocol Immunogenicity population for all studies.

IPV indicates Poliovirus Vaccine Inactivated.

* Percent achieving specified level following Pentacel vaccine not inferior 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%].

‡ 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 95% CI for difference in rates (ActHIB minus Pentacel) <10%].

†† 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 vaccine recipients (N = 829) and 80.8% of separately administered ActHIB vaccine recipients (N = 276) had an anti-PRP level ≥0.15 mcg/mL. Following Dose 4 of study vaccines, 98.2% of Pentacel vaccine recipients (N = 874) and 99.0% of separately administered ActHIB vaccine recipients (N = 291) had an anti-PRP level ≥1.0 mcg/mL.

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

14.6 Concomitantly Administered Vaccines

In Study P3T06, (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 vaccine (N = 321-325) relative to these vaccines administered concomitantly with DAPTACEL + IPOL + ActHIB vaccines (N = 998-1,029). The immune responses to hepatitis B vaccine and PCV7 were evaluated one month following the third dose.

In Study 494-03, (Table 1) 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 vaccine (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 vaccine (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.

2 CDC. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding routine poliovirus vaccination. MMWR 2009;58:829-30.

3 Stratton KR, et al. editors. Adverse events associated with childhood vaccines; evidence bearing on causality. Washington D.C.: National Academy Press. 1994. p. 67-117.

4 Braun MM. Report of a US Public Health Service workshop on hypotonic-hyporesponsive episode (HHE) after pertussis immunization. Pediatrics 1998;102(5)1-5.

5 Rothstein EP, et al. Comparison of antigenuria after immunization with three Haemophilus influenzae type b conjugate vaccines. Pediatr Infect Dis J 1991;10:311-4.

6 Stainer DW. Production of diphtheria toxin. In: Manclark CR, editor. Proceedings of an informal consultation on the World Health Organization requirements for diphtheria, tetanus, pertussis and combined vaccines. United States Public Health Service, Bethesda, MD. DHHS 91-1174. 1991. p. 7-11.

7 Mueller JH, Miller PA. Variable factors influencing the production of tetanus toxin. J Bacteriol 1954;67(3):271-7.

8 Stainer DW, et al. A simple chemically defined medium for the production of phase 1 Bordetella pertussis. J Gen Microbiol 1971;63:211-20.

9 van Wezel AL, et al. Inactivated poliovirus vaccine: current production methods and new developments. Rev Infect Dis 1984;6 (Suppl 2):S335-40.

10 Montagnon BJ et al. Industrial scale production of inactivated poliovirus vaccine prepared by culture of vero cells on microcarrier. Rev Infect Dis 1984;6 (Suppl 2):S341-4.

11 Chu CY, et al. Further studies on the immunogenicity of Haemophilus influenzae type b and pneumococcal type 6A polysaccharide-protein conjugates. Infect Immun 1983;40:245-56.

12 Mueller JH, et al. Production of diphtheria toxin of high potency (100 Lf) on a reproducible medium. J Immunol 1941;40:21-32.

13 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.

14 Vitek CR, Wharton M. Diphtheria toxoid. In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. 5th ed. Philadelphia, PA: W. B. Saunders; 2008. p. 139-56.

15 Wassilak SGF, et al. Tetanus toxoid. In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. 5th ed. Philadelphia, PA: W.B. Saunders; 2008. p. 805-39.

16 Sutter RW, et al. Defining surrogate serologic tests with respect to predicting protective vaccine efficacy: Poliovirus vaccination. In: Williams JC, et al. eds. Combined vaccines and simultaneous administration. Current issues and perspectives. New York, NY: The New York Academy of Sciences. 1995:289-99.

17 Robbins JB, et al. Quantitative measurement of "natural" and immunization-induced Haemophilus influenzae type b capsular polysaccharide antibodies. Pediatr Res 1973;7:103-10.

18 Peltola H, et al. Haemophilus influenzae type b capsular polysaccharide vaccine in children: a double-blind field study of 100,000 vaccinees 3 months to 5 years of age in Finland. Pediatrics 1977;60:730-7.

19 Kayhty H, et al. The protective level of serum antibodies to the capsular polysaccharide of Haemophilus influenzae type b. J Infect Dis 1983;147:1100.

20 Anderson P. The protective level of serum antibodies to the capsular polysaccharide of Haemophilus influenzae type b. J Infect Dis 1984;149:1034.

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 vaccine 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 vaccine should be used immediately after reconstitution.

17 PATIENT COUNSELING INFORMATION

Before administration of Pentacel vaccine, 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 vaccine 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.

Manufactured by:
Sanofi Pasteur Limited
Toronto Ontario Canada

and **Sanofi Pasteur SA**
Lyon France

599 Distributed by:

600 **Sanofi Pasteur Inc.**

601 Swiftwater PA 18370 USA

602 Pentacel® is a registered trademark of Sanofi Pasteur, its affiliates and subsidiaries.

603

604 R4-0413 USA

605

606 SANOFI PASTEUR