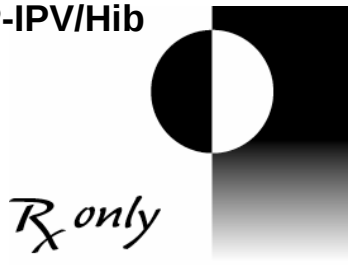
AHFS Category: 80:12

DTaP-IPV/Hib



Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine

Pentacel®

DESCRIPTION

Pentacel, [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine] (DTaP-IPV/Hib) is a vaccine for intramuscular injection. It consists of a Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus (DTaP-IPV) component and an ActHIB® vaccine component. ActHIB vaccine (Haemophilus b Conjugate Vaccine [Tetanus Toxoid Conjugate]), consists of *Haemophilus 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 of Pentacel vaccine contains the following active ingredients:

diphtheria toxoid	15 Lf
tetanus toxoid	5 Lf
acellular pertussis antigens:	
pertussis toxin (PT) detoxified	20 µg
filamentous hemagglutinin (FHA)	20 µg
pertactin (PRN)	3 µg
fimbriae types 2 and 3 (FIM)	5 µg
inactivated polioviruses:	
Type 1 (Mahoney)	40 D-antigen units
Type 2 (MEF-1)	8 D-antigen units
Type 3 (Saukett)	32 D-antigen units
PRP of *Haemophilus influenzae* type b covalently bound to	
24 µg of tetanus toxoid (PRP-T)	10 µg

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), ≤5 µg 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) and <4 pg of neomycin and <4 pg polymyxin B sulfate.

Corynebacterium diphtheriae is grown in modified Mueller's growth medium. (1) 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. (2) 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 (3) 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. (4) (5) 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 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 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. (6) 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. (7) 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.

CLINICAL PHARMACOLOGY

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. 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.

The vaccination schedules of Pentacel vaccine, Control vaccines, and concomitantly administered vaccines used in clinical studies of Pentacel vaccine that are referred to in this package insert are provided in Table 1. With the exception of Study 5A9908, which was conducted in Canada, all other studies listed in Table 1 were conducted in the US.

Table 1: Clinical 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
M5A10	2, 4, and 6 months	DAPTACEL + IPOL + ActHIB at 2, 4, and 6 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 [Studies 494-01, 494-03 (subset of participants), and P3T06] or from birth to 30 days prior to Dose 1 of study vaccines (Study M5A10). Subsequent doses were with hepatitis B vaccine manufactured by Merck and Co. (Studies 494-01, 494-03, and P3T06) or manufactured either by Merck and Co. or GlaxoSmithKline Biologicals (Study M5A10).

§ 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.

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. (8) Levels of 1.0 IU/mL have been associated with long term protection. (9)

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 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 toxin. A serum tetanus antitoxin level of at least 0.01 IU/mL, measured by neutralization assay is considered the minimum protective level. (8) (10) A tetanus antitoxoid level of ≥0.1 IU/mL as measured by the ELISA used in clinical studies of Pentacel vaccine is considered protective.

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 2.

Table 2: Study P3T06 Diphtheria Antitoxin and Tetanus Antitoxoid Responses One Month Following Dose 3 and Dose 4 of Pentacel Vaccine or DAPTACEL + IPOL + ActHIB 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.

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.

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. (11) 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%). (12) (13) 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. (11)

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 3). 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 3. 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 3: 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 4). 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.

Table 4: Pertussis Antibody Responses One Month Following Doses 3 and 4 of Pentacel Vaccine or DAPTACEL + IPOL + ActHIB Vaccines in US Infants Vaccinated at 2, 4, 6, and 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].

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. (14)

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.

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 (15) and an efficacy study with *H influenzae* type b polysaccharide vaccine in Finland, (16) a post-vaccination anti-PRP level of 0.15 µg/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 µg/mL 3 weeks after vaccination predicts protection through a subsequent one-year period. (17) (18) These levels have been used to evaluate the effectiveness of Haemophilus b Conjugate Vaccines, including the ActHIB vaccine component of Pentacel vaccine.

Anti-PRP seroprotection rates and GMCs one month following Dose 3 of Pentacel vaccine or separately administered ActHIB vaccine in studies P3T06 and M5A10 are presented in Table 5. In Study 494-01, non-inferiority criteria were not met for the proportion of participants who achieved an anti-PRP level ≥1.0 μg/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 μg/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 5: 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 µg/mL	95.4*	98.3
% achieving anti-PRP ≥1.0 µg/mL	79.1†	88.8
Anti-PRP GMC (µg/mL)	3.19‡	6.23
	Study P3T06	
	Pentacel Vaccine N = 365	**DAPTACEL + IPOL + ActHIB Vaccines N = 1,128**
% achieving anti-PRP ≥0.15 µg/mL	92.3*	93.3
% achieving anti-PRP ≥1.0 µg/mL	72.1*	70.8
Anti-PRP GMC (µg/mL)	2.31§	2.29
	Study M5A10	
	Pentacel Vaccine N = 826	**DAPTACEL + IPOL + ActHIB Vaccines N = 421**
% achieving anti-PRP ≥0.15 µg/mL	93.8**	90.3
% achieving anti-PRP ≥1.0 µg/mL	75.1**	74.8
Anti-PRP GMC (µg/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 µg/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 µg/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 µg/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 µg/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 µg/mL.

Concomitantly Administered Vaccines

Vaccines administered concomitantly with Pentacel vaccine in clinical trials are listed in Table 1.

In Study P3T06, there was no evidence for reduced antibody responses to hepatitis B vaccine (percent of participants with anti-HBsAg ≥10 mIU/mL and GMCs) or PCV7 (percent of participants with antibody levels ≥0.15 µg/mL and ≥0.5 µg/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, there was no evidence for interference in the immune response to the fourth dose of PCV7 (percent of participants with antibody levels ≥0.15 µg/mL and ≥0.5 µg/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.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

A severe allergic reaction (e.g., anaphylaxis) after a previous dose of Pentacel vaccine, any ingredient of this vaccine, or any other tetanus toxoid, diphtheria toxoid, pertussis-containing vaccine, inactivated poliovirus vaccine or *H influenzae* type b vaccine is a contraindication to administration of Pentacel vaccine. (See DESCRIPTION). Because of uncertainty as to which ingredient of the vaccine may be responsible, none of the ingredients should be administered. Alternatively, such individuals may be referred to an allergist for evaluation if further immunizations are considered.

The following events are contraindications to administration of any pertussis-containing vaccine, (19) including Pentacel vaccine.

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

- Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, progressive encephalopathy. Pertussis vaccine should not be administered to individuals with such conditions until the neurologic status is clarified and stabilized.

WARNINGS

If any of the following events occur within the specified period after administration of a whole-cell pertussis or acellular pertussis-containing vaccine, the decision to administer Pentacel vaccine or any pertussis-containing vaccine should be based on careful consideration of potential benefits and possible risks. (19) (See DOSAGE AND ADMINISTRATION.)

- 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.
- Seizure with or without fever within 3 days.

A review by the Institute of Medicine (IOM) found evidence for a causal relation between tetanus toxoid and brachial neuritis, Guillain-Barré syndrome and anaphylaxis. (20) If Guillain-Barré syndrome occurred within 6 weeks of receipt of a prior vaccine containing tetanus toxoid, the decision to give Pentacel vaccine or any vaccine containing tetanus toxoid should be based on careful consideration of the potential benefits and possible risks. (19)

Vaccination with Pentacel vaccine may not protect all individuals.

PRECAUTIONS

General

Before administration of Pentacel vaccine, the patient's current health status and medical history should be reviewed in order to determine whether any contraindications exist and to assess the benefits and risks of vaccination. (See CONTRAINDICATIONS and WARNINGS).

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.

For infants or children at higher risk for seizures than the general population, an appropriate antipyretic may be administered (in the dosage recommended in its prescribing information) at the time of vaccination with an acellular pertussis-containing vaccine (including Pentacel vaccine) and for the following 24 hours, to reduce the possibility of post-vaccination fever. (19)

If Pentacel vaccine is administered to immunocompromised persons, including persons receiving immunosuppressive therapy, the expected immune response may not be obtained.

Information for Vaccine Recipients and Parents/Guardians

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.

Drug Interactions

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.

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. (21)

Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed with Pentacel vaccine to evaluate carcinogenicity, mutagenic potential, or impairment of fertility.

Pregnancy Category C

Animal reproduction studies have not been conducted with Pentacel vaccine. It is not known whether Pentacel vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Pentacel vaccine is not approved for use in women of childbearing age.

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 and CLINICAL PHARMACOLOGY.) 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.

Pentacel vaccine is not approved for use in persons 5 years of age or older.

Geriatric Use

Pentacel vaccine is not approved for use in adult populations.

ADVERSE REACTIONS

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. 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.

In Studies 494-01, 494-03, 5A9908, and P3T06 (Table 1), a total of 5,980 participants received at least one dose of Pentacel vaccine, including 4,198 participants who were enrolled in one of three US studies that evaluated the safety of four consecutive doses of Pentacel vaccine administered at 2, 4, 6, and 15-16 months of age. In calculating event rates across doses and studies, one subject who received one dose of Pentacel vaccine followed by three doses of Control vaccines was included in the control group. Two of the US studies, Study 494-01 and Study P3T06, included a control group that received separately administered vaccines. In Study 5A9908 conducted in Canada, 1,782 participants previously vaccinated with three doses of Pentacel vaccine received a fourth dose at 15-18 months of age. 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.

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 6. Information on these reactions was recorded daily by parents or guardians on diary cards. In Table 6, injection site reactions are reported for the Pentacel vaccine and DAPTACEL vaccine injection sites.

Table 6: Number (Percentage) of Children with Selected Solicited Injection Site Reactions and Solicited Systemic Adverse Events 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	–	–	–	33.6	–	–	–	30.6
>5 mm				4.7				6.9
>20 mm				0.5				0.8
>40 mm								

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§	45.8	32.7	32.5	24.1	51.1	37.4	33.2	24.1
Any	22.9	12.4	12.7	9.8	24.3	15.8	12.7	9.2
Moderate or Severe	2.1	0.7	0.2	2.5	1.2	1.4	0.6	0.3
Severe								
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 (22) 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.

Data From Post-Marketing Experience

The following additional adverse events have been spontaneously reported between 1997 and 2007 during the post-marketing use of Pentacel vaccine outside of the US, primarily in Canada. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. The following adverse events were included based on severity, frequency of reporting, or the strength of causal association 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***

  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

Reporting of Adverse Events

The National Childhood Vaccine Injury Act of 1986 requires physicians and other health-care providers who administer vaccines to maintain in the recipient's permanent medical record the manufacturer, lot number, date of administration, and the name, address and title of the person administering the vaccine. The Act further requires the health-care provider to report to the US Department of Health and Human Services the occurrence of certain adverse events following immunization. For Pentacel vaccine, events required to be reported are anaphylaxis or anaphylactic shock within 7 days, brachial neuritis within 2-28 days, encephalopathy or encephalitis within 7 days following vaccination, or any acute complication or sequela (including death) of these events, or any contraindicating event listed in this Pentacel vaccine package insert. (23) (24) These events and other suspected adverse reactions should be reported to VAERS at 1-800-822-7967 or http://www.vaers.hhs.gov and to Sanofi Pasteur Inc. at 1-800-822-2463.

DOSAGE AND ADMINISTRATION

Vaccination Schedule

Pentacel vaccine is approved for administration as a 4 dose series at 2, 4 and 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 constitutes a booster vaccination against diphtheria, tetanus, *H influenzae* type b invasive disease, and poliomyelitis (See CLINICAL PHARMACOLOGY.)

If a decision is made to withhold pertussis vaccine, (see CONTRAINDICATIONS and WARNINGS), vaccination against diphtheria, tetanus, poliomyelitis and invasive disease due to *H influenzae* type b should be provided.

Children who have completed a four-dose series with Pentacel vaccine should receive a fifth dose of DTaP vaccine at 4-6 years of age. Because the pertussis antigens in DAPTACEL vaccine are the same as those in Pentacel vaccine (although with different amounts of detoxified PT and FHA), these children should receive DAPTACEL vaccine as their fifth dose of DTaP. However, data are not available to evaluate the safety of DAPTACEL vaccine following four previous doses of Pentacel vaccine.

Children Previously Vaccinated With One or More Doses of DAPTACEL Vaccine:

Pentacel vaccine may be used to complete the first 4 doses of the 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, the safety and efficacy of Pentacel vaccine in such infants have not been evaluated.

Children Previously Vaccinated With One or More Doses of IPV: Pentacel vaccine may be used to complete the 4 dose IPV series in infants and children who have received 1 or more doses of another licensed IPV vaccine and are also scheduled to receive the other antigens of Pentacel vaccine. However, the safety and efficacy of Pentacel vaccine in such infants have not been evaluated.

Children Previously Vaccinated With One or More Doses of 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 a 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, the safety and efficacy of Pentacel vaccine in such infants have not been evaluated. 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.

Administration

Pentacel vaccine should be inspected visually for extraneous particulate matter and/or discoloration before administration. (See DESCRIPTION.) If these conditions exist, Pentacel vaccine should not be administered.

Reconstitution of Freeze-Dried Product and Withdrawal from Stoppered Vial

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. Shake the vial now containing Pentacel vaccine thoroughly until a cloudy, uniform suspension results. Withdraw and administer a 0.5 mL dose of Pentacel vaccine intramuscularly. 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

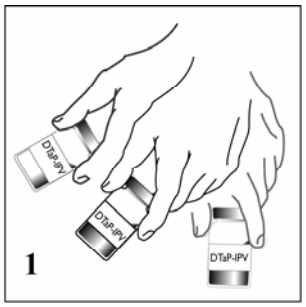


Figure 1
Gently shake the vial of DTaP-IPV component.

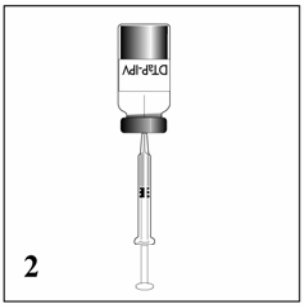


Figure 2
Withdraw the entire liquid content.

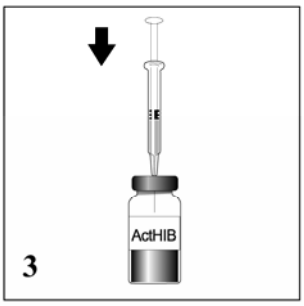


Figure 3
Insert the syringe needle through the stopper of the vial of lyophilized ActHIB vaccine component and inject the liquid into the vial.

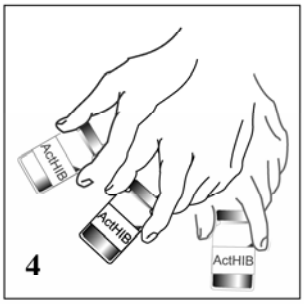


Figure 4
Shake vial thoroughly.

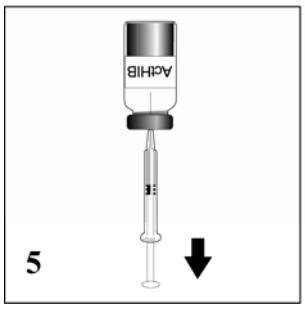


Figure 5
After reconstitution, immediately withdraw 0.5 mL of Pentacel vaccine and administer intramuscularly.
Pentacel vaccine should be used immediately after reconstitution.

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.

Concomitant Administration with Other Vaccines

In clinical trials, Pentacel vaccine was routinely administered, at separate sites, concomitantly with one or more of the following vaccines: hepatitis B vaccine, 7-valent pneumococcal conjugate vaccine, MMR and varicella vaccines. (See CLINICAL PHARMACOLOGY and ADVERSE REACTIONS.) When Pentacel vaccine is given at the same time as another injectable vaccine(s), the vaccines should be given with different syringes.

HOW SUPPLIED

5 Dose Package containing 5 vials of DTaP-IPV Component to be used to reconstitute five single dose vials of lyophilized ActHIB vaccine component - Product No. 49281-510-05.

STORAGE

Store at 2° to 8°C (35° to 46°F). Do not freeze. Discard product if exposed to freezing.

Do not use after expiration date.

Pentacel vaccine should be used immediately after reconstitution.

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