PRODUCT MONOGRAPH

Prevnar* 13

Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein)

Suspension for Intramuscular Injection

Active Immunizing Agent

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Date of Initial Approval: December 21, 2009

Control No. 219617

Date of Revision: August 8, 2019

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Prevnar® 13

Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular injection	Suspension for injection 1 dose (0.5 mL pre-filled syringe) contains: Pneumococcal polysaccharide serotype 1 2.2 µg[a] Pneumococcal polysaccharide serotype 3 2.2 µg[a] Pneumococcal polysaccharide serotype 4 2.2 µg[a] Pneumococcal polysaccharide serotype 5 2.2 µg[a] Pneumococcal polysaccharide serotype 6A 2.2 µg[a] Pneumococcal polysaccharide serotype 6B 4.4 µg[a] Pneumococcal polysaccharide serotype 7F 2.2 µg[a] Pneumococcal polysaccharide serotype 9V 2.2 µg[a] Pneumococcal polysaccharide serotype 14 2.2 µg[a] Pneumococcal polysaccharide serotype 18C 2.2 µg[a] Pneumococcal polysaccharide serotype 19A 2.2 µg[a] Pneumococcal polysaccharide serotype 19F 2.2 µg[a] Pneumococcal polysaccharide serotype 23F 2.2 µg[a]	Sodium Chloride, Succinic Acid, Polysorbate 80, Water for Injection

[a] conjugated to CRM_{197} carrier protein and adsorbed on aluminum phosphate (0.125 mg aluminum)

INDICATIONS AND CLINICAL USE

Children 6 Weeks to 5 Years of Age

Prevnar 13 is indicated for active immunization of infants and children from 6 weeks to 5 years of age (prior to the 6th birthday) for the prevention of invasive pneumococcal disease (including sepsis, meningitis, bacteraemic pneumonia, pleural empyema and bacteraemia) and acute otitis media caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

Children 6 Years to 17 Years of Age

Prevnar 13 is indicated for active immunization of children from 6 years to 17 years of age (prior to the 18th birthday) for the prevention of invasive pneumococcal disease (including sepsis, meningitis, bacteraemic pneumonia, pleural empyema and bacteraemia) caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

Adults 18 Years of Age and Older

Prevnar 13 is indicated for active immunization of adults 18 years of age and older for the prevention of pneumonia and invasive pneumococcal disease (including sepsis, meningitis, bacteraemic pneumonia, pleural empyema and bacteraemia) caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including diphtheria toxoid.

(For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section)

WARNINGS AND PRECAUTIONS

General

- Immunocompromised individuals may have a reduced antibody response to the vaccine.

- Safety and immunogenicity data on Prevnar 13 are not available for individuals in certain immunocompromised groups (e.g., individuals with malignancy or nephrotic syndrome) and vaccination should be considered on an individual basis. Some safety and immunogenicity data are available in individuals with sickle cell disease (SCD), with human immunodeficiency virus (HIV) infection, or with hematopoietic stem cell transplant (see PART II, CLINICAL TRIALS).

- As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

- Minor illnesses, such as mild respiratory infection, with or without low-grade fever, are not generally contraindications to vaccination. The decision to administer or delay vaccination because of a current or recent febrile illness depends largely on the severity of the symptoms and their etiology. The administration of Prevnar 13 should be postponed in subjects suffering from acute severe febrile illness.

- As with any intramuscular injection, Prevnar 13 should be given with caution to infants, children or adults with thrombocytopenia or any coagulation disorder, or to those receiving anticoagulant therapy.

- Prevnar 13 will not protect against Streptococcus pneumoniae serotypes not included in the vaccine. Prevnar 13 will not protect against other microorganisms that cause invasive disease, pneumonia or otitis media. This vaccine is not intended to be used for treatment of active infection.

- As with any vaccine, Prevnar 13 may not protect all individuals receiving the vaccine from pneumococcal disease.

Infants and Children Aged 6 Weeks to 5 Years

- The use of pneumococcal conjugate vaccine does not replace the use of 23-valent pneumococcal polysaccharide vaccine (PPSV23) in children ≥ 24 months of age with sickle cell disease, asplenia, HIV infection, chronic illness, or who are otherwise immunocompromised. Data on sequential vaccination with Prevnar 13 followed by PPSV23 are not available; data on sequential vaccination with Prevnar (7-valent) vaccine followed by PPSV23 are limited.

- As with all injectable pediatric vaccines, the potential risk of apnea should be considered when administering the primary immunization series to premature infants. The need for monitoring for at least 48 hours after vaccination should be considered for very premature infants (born ≤ 30 weeks of gestation) who remain hospitalized at the time of the recommended administration. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

- Immunization with Prevnar 13 does not substitute for routine diphtheria immunization.

- When Prevnar 13 is administered concomitantly with Infanrix hexa (DTaP-HBV-IPV/Hib), there are no data that would suggest that the rates of febrile reactions would be different to those seen with concomitant administration of pneumococcal 7-valent conjugate vaccine and Infanrix hexa. A higher incidence of fever (≥ 38.0°C to ≤ 39.0°C) was reported in infants receiving Infanrix hexa and pneumococcal 7-valent conjugate vaccine compared to infants receiving the hexavalent vaccine alone. Increased reporting rates of convulsions (with or without fever) and hypotonic-hyporesponsive episode (HHE) were observed with concomitant administration of Prevnar 13 and Infanrix hexa (see ADVERSE REACTIONS section).

Special Populations

Pregnant Women:
A reproduction study has been performed in female rabbits at doses equal to the human dose and has revealed no evidence of impaired fertility or harm to the fetus due to Prevnar 13. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this vaccine should be used during pregnancy only if clearly needed.

Nursing Women:
Safety during lactation has not been established.
It is not known whether vaccine antigens or antibodies are excreted in human milk.

Pediatrics:
The safety and immunogenicity of Prevnar 13 in children below the age of 6 weeks have not been established.

Geriatrics:
Prevnar 13 has been studied in the geriatric population (see PART II, CLINICAL TRIALS section).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

1. Infants and Children Aged 6 Weeks to 5 Years

The safety of the vaccine was assessed in 13 controlled clinical trials where approximately 15,000 doses were given to 4,729 healthy infants in ages ranging from 6 weeks to 16 months of age. In all trials, Prevnar 13 was co-administered with routine pediatric vaccines.

In a catch-up study, 354 children (7 months to 5 years of age) receiving at least 1 dose of Prevnar 13 were also assessed for safety.

In a clinical study (0887X-100811) with pneumococcal 7-valent conjugate vaccine in infants vaccinated at 2, 3 and 4 months of age, fever ≥38°C was reported at higher rates among infants who received pneumococcal 7-valent conjugate vaccine concomitantly with Infanrix hexa (28.3% to 42.3%) than in infants receiving Infanrix hexa alone (15.6% to 23.1%). After a booster dose at 12-15 months of age, the rate of fever ≥38°C was 50.0% in infants who received pneumococcal 7-valent conjugate vaccine and Infanrix hexa at the same time as compared to 33.6% in infants receiving Infanrix hexa alone. These reactions were mostly moderate (less than or equal to 39°C) and transient.

Analysis of postmarketing reporting rates suggests a potential increased risk of convulsions, with or without fever, and hypotonic-hyporesponsive episode when comparing groups which reported use of Prevnar 13 with Infanrix hexa to those which reported use of Prevnar 13 alone.

2. Children and Adolescents 5 to 17 Years of Age

Safety was evaluated in 592 healthy children and adolescents, including 17.4% of subjects with a history of asthma. Two hundred and ninety-four (294) children aged 5 to <10 years had previously been immunized with at least 1 dose of Prevnar (7-valent) vaccine and 298 children aged 10-17 years had not previously been vaccinated with a pneumococcal vaccine.

3. Adults 18 Years and Older

Safety was assessed in 7 clinical studies including 91,593 adults ranging in ages from 18 to 101 years. Prevnar 13 was administered to 48,806 adults; 2,616 adults were aged 50-64 years and 45,291 adults were 65 years and older. Of the Prevnar 13 recipients, 1,916 adults were previously vaccinated with PPSV23 at least 3 years prior, and 46,890 adults were PPSV23 unvaccinated. One of the 7 studies included a group of adults (n=899) ranging from 18-49 years who received Prevnar 13 and who were not previously vaccinated with PPSV23.

Immunogenicity Studies

Two of the 6 clinical studies supporting safety were randomized trials comparing the safety and immunogenicity of Prevnar 13 with PPSV23 as a single dose in PPSV23 unvaccinated adults aged 50-64 years (study 6115A1-004) and in adults ≥70 years PPSV23 previously vaccinated (≥5 years prior to enrollment) (study 6115A1-3005). Study 6115A1-004 also included a cohort of PPSV23 unvaccinated adults aged 18-49 years. One study was randomized comparing the safety and immunogenicity of a single dose of Prevnar 13 compared to a single dose of PPSV23 in PPSV23 unvaccinated adults aged 60-64 years (study 6115A1-3010). One clinical safety study (study 6115A1-3000) of Prevnar 13, conducted in PPSV23 previously vaccinated (≥ 3 years prior to enrollment) adults aged ≥ 68 years was a single arm study. Two studies, 1 in the US (study 6115A1-3001) in adults aged 50-59 years and the other in Europe (study 6115A1-3008) in adults aged ≥65 years, evaluated the concomitant administration of Prevnar 13 with trivalent inactivated influenza vaccine (TIV) in these 2 age groups in PPSV23 unvaccinated adults.

A trend to lower frequency of adverse reactions was associated with increasing age; adults >65 years of age (regardless of pneumococcal vaccination status) reported fewer adverse reactions than younger adults, with adverse reactions generally more common in adults 18-29 years of age.

Overall, the frequency categories were similar in adults 18-49 years of age compared to adults >50 years of age, with the exception of vomiting which was very common (≥ 1/10) in adults aged 18-49 years and common (≥ 1/100 to < 1/10) in adults >50 years of age.

Efficacy Study

Study 6115A1-3006, conducted in the Netherlands in adults aged 65 years and older, was a randomized, double-blind, placebo-controlled study. A single dose of Prevnar 13 was compared to placebo for efficacy in prevention of the first episodes of vaccine-type (VT) pneumococcal community-acquired pneumonia (CAP) and VT-IPD. 84,496 subjects received either Prevnar 13 (42,240) or placebo (42,256) in a 1:1 randomization.

For 1,006 Prevnar 13 vaccinated subjects, solicited adverse events were monitored by recording local and systemic events using electronic diaries for 7 days after vaccination; adverse events were collected for 28 days after vaccination, and serious adverse events were collected for 6 months after vaccination. For the remaining 41,234 Prevnar 13 vaccinated subjects, serious adverse events were collected for 28 days after vaccination.

Subjects with pre-existing medical conditions (heart disease, lung disease or asthma, diabetes mellitus with or without insulin use, liver disease and splenectomy) as well as subjects with a history of smoking were enrolled, except those with immunocompromising conditions.

Clinical Trial Adverse Drug Reactions

1. Infants and Children Aged 6 Weeks to 5 Years

These data are from clinical trials in which Prevnar 13 was administered simultaneously with other routine childhood vaccines. Expected frequency of adverse reactions is presented in CIOMS frequency categories:

Table 1: Adverse Reactions in Infants and Children Aged 6 Weeks to 5 Years

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000
Immune System Disorders				Hypersensitivity reaction including face edema, dyspnea, bronchospasm
Metabolism and Nutrition Disorders	Decreased appetite			
Psychiatric Disorders	Irritability		Crying	
Nervous System Disorders	Drowsiness/increased sleep; restless sleep/decreased sleep		Seizures (including febrile seizures)	Hypotonic-hyporesponsive episode
Gastrointestinal Disorders		Diarrhea; vomiting		
Skin and Subcutaneous Tissue Disorders		Rash	Urticaria or urticaria-like rash	
General Disorders and Administration Site Conditions	Fever; any vaccination-site erythema, induration/swelling or pain/tenderness; vaccination-site erythema or induration/swelling 2.5 cm – 7.0 cm (after toddler dose and in older children [age 2-5 years])	Fever greater than 39°C; vaccination-site erythema or induration/swelling 2.5 cm – 7.0 cm (after infant series); vaccination-site pain/tenderness interfering with movement	Vaccination-site induration/swelling or erythema greater than 7.0 cm	

Serious Adverse Events (SAEs)

During the 13 controlled clinical trials, SAEs that the investigator considered related to study vaccine were reported for 11 out of 7,489 total subjects (0.1%); 6 out of 4,729 subjects (0.1%) in the Prevnar 13 group and 5 out of 2,760 (0.2%) in the Prevnar (7-valent) group. Of these 11

cases, there were 3 cases of febrile convulsions and 4 cases of fever. Out of the 4 cases with fever, 1 subject had diffuse body rash, 1 subject had respiratory distress, and 1 subject had tense fontanelle. The remaining related SAE cases were crying (1), bronchitis (1), infantile spasms (1) and nephroblastoma (1).

Deaths

During the 13 controlled clinical trials, death occurred in 4 (out of 7,489) infants. All 4 cases were attributable to Sudden Infant Death Syndrome (SIDS). Three (out of 4,729 cases receiving 15,739 doses) cases were among Prevnar 13 recipients, and 1 (out of 2,760 cases receiving 9,030 doses) was in the Prevnar (7-valent) group. None of these cases were assessed by the investigator as causally related to vaccination.

2. Children and Adolescents 5 to 17 Years of Age

The incidence and severity of solicited adverse events that occurred within 7 days following 1 dose of Prevnar 13 administered to children and adolescents 5-17 years of age are shown in Tables 2 and 3.

Table 2: Percentage of Subjects 5-17 Years of Age Reporting Solicited Local Reactions[a] Within 7 Days After Prevnar 13 Vaccination

	Study 6096A1-3011 Vaccine Group (as Administered)					
	Prevnar 13 (5 to <10 years)			Prevnar 13 (10-17 years)		
Local Reaction	N[b]	n[c]	%	N[b]	n[c]	%
Tenderness						
Any	265	230	86.8	283	252	89.0
Significant[d]	221	43	19.5	242	106	43.8
Swelling						
Any	226	85	37.6	233	86	36.9
Mild[e]	220	48	21.8	221	50	22.6
Moderate[e]	219	48	21.9	226	48	21.2
Severe[e]	211	7	3.3	214	4	1.9
Redness						
Any	233	100	42.9	232	70	30.2
Mild[e]	226	63	27.9	226	48	21.2
Moderate[e]	218	48	22.0	221	31	14.0
Severe[e]	212	7	3.3	213	4	1.9
Any of the above	270	242	89.6	285	258	90.5

[a] All reported local reactions, regardless of causality.
[b] N = Number of subjects reporting yes for at least 1 day or no for all days.
[c] n = Number of subjects reporting the specific characteristic.
[d] Significant = present and interfered with limb movement.
[e] Mild, 0.5 – 2.0 cm; moderate, 2.5 – 7.0 cm; severe, >7.0 cm.

Table 3: Percentage of Subjects 5 to 17 Years of Age Reporting Solicited Systemic Adverse Events[a] and Anti-Pyretic Medication Use Within 7 Days After Prevnar 13 Vaccination

Systemic Event	Study 6096A1-3011 Vaccine Group (as Administered)					
	Prevnar 13 (5 to <10 years)			Prevnar 13 (10-17 years)		
	N[b]	n[c]	%	N[b]	n[c]	%
Fever ≥38°C but ≤39°C	212	9	4.2	214	11	5.1
Fever >39°C but ≤40°C	212	5	2.4	212	1	0.5
Fever >40°C	210	1	0.5	212	1	0.5
Decreased appetite	227	52	22.9	223	51	22.9
Irritability	234	73	31.2	234	59	25.2
Increased sleep	226	48	21.2	229	61	26.6
Decreased sleep	212	12	5.7	224	42	18.8
Hives (urticaria)	213	4	1.9	214	3	1.4
Use of medication to treat symptoms	232	88	37.9	232	66	28.4
Use of medication to prevent symptoms	225	58	25.8	225	47	20.9
Use of medication to treat or to prevent symptoms	237	107	45.1	236	78	33.1
Use of medication to treat and to prevent symptoms	220	35	15.9	221	29	13.1
Any systemic event[d]	250	118	47.2	253	130	51.4

[a] All reported systemic adverse events, regardless of causality.
[b] N = Number of subjects reporting yes for at least 1 day or no for all days.
[c] n = Number of subjects reporting the event.
[d] Includes any fever ≥38°C, decreased appetite, irritability, increased sleep, decreased sleep, and hives (urticaria).

Other adverse reactions observed in other age groups may also be applicable in this age group but due to the small sample size in this study (6096A1-3011) were not seen.

Additional Information in Special Populations

In a single-arm study (6096A1-3014) conducted in 158 children and adolescents 6-17 years of age with sickle cell disease (see Part II, CLINICAL TRIALS), the frequencies of solicited local reactions after the first or second doses of Prevnar 13 were comparable to those reported after a single Prevnar 13 dose in healthy children and adolescents 5-17 years of age from study 6096A1-3011 (see Table 2). All solicited systemic events were reported by ≥10% of subjects in study 6096A1-3014. Frequencies after the first and second doses of Prevnar 13, respectively, were muscle pain (74.8% and 75.5%), fatigue (66.1% and 62.5%), headache (53.6% and 59.3%), joint pain (39.8% and 44.9%), vomiting (15.4% and 13.4%) fever ≥38°C but ≤38.4°C (13.6% and 9.5%) and diarrhea (13.3% and 25.0%).

In a single-arm study (6115A1-3002) which included 150 HIV-infected children and adolescents 6-17 years of age not previously vaccinated with a pneumococcal vaccine (see Part II, CLINICAL TRIALS), the frequencies of solicited local reactions reported within 14 days after the first, second or third dose of Prevnar 13(range across the 3 doses) were: redness (8.3-20.7%), swelling (18.0-29.9%), and pain at the injection site (52.9-68.4%). Frequencies of solicited systemic events reported within 14 days of each dose (range across the 3 doses) were: fever ≥38ºC (10.6-19.1%), fatigue (25.0-47.7%), headache (18.2-39.3%), vomiting (8.2-18.0%), diarrhea (4.9-25.5%), muscle pain (37.4-48.1%), and joint pain (24.2-34.0%).

In children and adolescents 2-17 years of age with a hematopoietic stem cell transplant (N=59) vaccinated with up to 4 doses of Prevnar 13 in single-arm study 6115A1-3003 (see Part II, CLINICAL TRIALS), the frequencies of solicited local reactions reported within 14 days after each study vaccination (range across the 4 doses) were: redness (21.1-71.4%), swelling (25.0-66.7%), and pain (70.3-86.7%). Frequencies of solicited systemic events (range across the 4 doses) were: fever ≥38ºC (12.8-27.8%), fatigue (48.6-67.9%), headache (32.3-52.4%), vomiting (6.3-21.4%), diarrhea (15.4-31.8%), muscle pain (44.4-58.3%), and joint pain (25.0-32.3%).

3. Adults 18 Years and Older

Solicited Adverse Events in Adult Clinical Studies

The incidence and severity of solicited adverse events that occurred within 14 days following each dose of Prevnar 13 or PPSV23 administered to adults in 4 immunogenicity studies (safety data presented from 2 studies in PPSV23 unvaccinated adults and 2 studies in PPSV23 pre-vaccinated adults), and within 7 days following the dose of Prevnar 13 or placebo administered to PPSV23 unvaccinated adults in the efficacy study, are shown in Tables 4 and 5.

Table 4: Percentage of Subjects With Solicited Local Reactions[a] Within 7[†] or 14 Days After Vaccination

	Study 6115A1-004 (PPSV23Unvaccinated Adults)				Study 6115A1-3010 (PPSV23 Unvaccinated Adults)		Study 6115A1-3006 (PPSV23 Unvaccinated Adults)		Study 6115A1-3005 (PPSV23 Pre-Vaccinated Adults)		Study 6115A1-3000[b] (PPSV23 Pre-Vaccinated Adults)
Age in Years	**18-49**	**50-59**	**60-64**		**60-64**		**≥ 65**		**≥70**		**≥ 68**
Local Reaction	**Prevnar 13[b]** N[c]= 266-787 %	**Prevnar 13[b]** N[c]= 152-322 %	**Prevnar 13** N[c]= 193-331 %	**PPSV23** N[c]= 190-301 %	**Prevnar 13** N[c]= 270-370 %	**PPSV23** N[c]= 134-175 %	**Prevnar 13** N[c]= 886-914 %	**Placebo** N[c]= 859-865 %	**Prevnar 13** N[c]= 306-362 %	**PPSV23** N[c]= 324-383 %	**Prevnar 13** N[c]= 664-777 %
Redness[d]											
Any	30.5	15.8	20.2	14.2	12.2	11.2	4.9*	1.2	10.8	22.2*	14.3
Mild	26.4	15.2	15.9	11.2	8.3	9.7	3.7*	0.8	9.5	13.5	12.6
Moderate	11.9	5.0	8.6	4.9	6.4	3.9	1.7*	0.3	4.7	11.5*	6.5
Severe	2.8	0.7	1.7	0.0	1.2	0.8	0.5	0.1	1.7	4.8*	1.1
Swelling[d]											
Any	39.4	21.7	19.3	13.1	10.0	10.4	6.8*	1.2	10.4	23.1*	12.8
Mild	37.2	20.6	15.6	10.1	8.2	6.1	5.5*	0.7	8.9	14.0*	10.9
Moderate	15.1	4.3	8.2	4.4	3.8	7.6	2.6*	0.6	4.0	13.6*	5.5
Severe	1.4	0.0	0.6	1.1	0.0	0.0	0.1	0.1	0.0	4.8*	0.6
Pain[e]											
Any	96.7	88.8	80.1	73.4	69.2*	58.3	36.1*	6.1	51.7	58.5	51.0
Mild	93.2	85.9	78.6*	68.6	66.1*	52.9	32.9*	5.6	50.1	54.1	49.4
Moderate	77.1	39.5	23.3	30.0	20.1	21.7	7.7*	0.6	7.5	23.6*	9.0
Severe	16.0	3.6	1.7	8.6*	2.3	0.8	0.3	0.1	1.3	2.3	0.2
Limitation of arm movement[f]											
Any	75.2	40.7	28.5	30.8	23.5	28.2	14.1*	3.2	10.5	27.6*	16.2
Mild	71.5	38.6	26.9	29.3	22.7	26.1	12.4*	2.5	10.3	25.2*	14.8
Moderate	18.5	2.9	2.2	3.8	1.2	3.1	1.7*	0.5	0.3	2.6*	1.6
Severe	15.6	2.9	1.7	4.3	1.1	2.3	1.2	0.7	0.7	3.0*	1.6

[†] All studies in this table reported local reactions within 14 days after vaccination, except Study 6115A1-3006, which reported local reactions within 7 days.
***** Statistically significant difference $p < 0.05$.
[a] All reported local reactions, regardless of causality assessment.
[b] Open label administration of Prevnar 13.
[c] Number of subjects with known values for any local reaction.
[d] Mild = 2.5 to 5.0 cm, moderate = 5.1 to 10.0 cm, and severe is >10.0 cm.
[e] Mild = awareness of symptom but easily tolerated, moderate = discomfort enough to cause interference with usual activity, severe = incapacitating with inability to do usual activity.
[f] Mild = some limitation of arm movement, moderate = unable to move arm above head but able to move arm above shoulder, severe = unable to move arm above shoulder.

Table 5: Percentage of Subjects With Solicited Systemic Events[a] Within 7[†] or 14 Days After Vaccination

	Study 6115A1-004 (PPSV23 Unvaccinated Adults)				Study 6115A1-3010 (PPSV23 Unvaccinated Adults)		Study 6115A1-3006 (PPSV23 Unvaccinated Adults)		Study 6115A1-3005 (PPSV23 Pre-Vaccinated Adults)		Study 6115A1-3000[b] (PPSV23 Pre-Vaccinated Adults)
Age in Years	**18-49**	**50-59**	**60-64**		**60-64**		**≥ 65**		**≥70**		**≥68**
Systemic Event	**Prevnar 13[b]** N[c]= 221-561 %	**Prevnar 13[b]** N[c]= 137-248 %	**Prevnar 13** N[c]= 180-277 %	**PPSV23** N[c]= 185-273 %	**Prevnar 13** N[c]= 263-324 %	**PPSV23** N[c]= 127-173 %	**Prevnar 13** N[c]= 881-896 %	**Placebo** N[c]= 859-878 %	**Prevnar 13** N[c]= 299-350 %	**PPSV23** N[c]= 304-367 %	**Prevnar 13** N[c]= 638-733 %
Fever											
Any (≥38°C)	7.2	1.5	4.0	1.1	4.2	1.6	2.9*	1.3	1.0	2.3	1.1
≥38°C but <38.5°C	4.2	1.5	4.0	1.1	3.8	0.8	1.1	0.6	1.0	2.0	0.8
≥38.5°C but <39°C	1.9	0.0	0.6	0.0	0.8	0.0	0.6	0.2	0.0	0.0	0.0
≥39°C but ≤40°C	1.4	0.0	0.0	0.0	0.4	0.8	0.7	0.2	0.0	0.3	0.3
>40°C	0.5	0.0	0.0	0.0	0.0	0.0	0.8	0.3	0.0	0.0	0.0
Fatigue	80.5	63.3	63.2	61.5	50.5	49.1	18.8*	14.8	34.0	43.3*	34.4
Headache	81.4	65.9	54.0	54.4	49.7	46.1	15.9	14.8	23.7	26.0	26.1
Chills	38.1	19.6	23.5	24.1	19.9	26.9	9.4	8.4	7.9	11.2	7.5
Rash	21.3	14.2	16.5	13.0	8.6	13.4	3.3*	0.8	7.3	16.4*	8.4
Vomiting	15.0	6.9	3.9	5.4	3.1	3.1	0.3	0.9	1.7	1.3	0.9
Diarrhea	NA	NA	NA	NA	NA	NA	5.7	8.7	NA	NA	14.5
Decreased appetite	55.6	25.3	21.3	21.7	14.7	23.0*	5.3	3.7	10.4	11.5	11.2
Generalized new muscle pain	82.0	61.8	56.2	57.8	46.9	51.5	18.4*	8.4	36.8	44.7*	25.3
Generalized aggravated muscle pain	55.9	39.9	32.6	37.3	22.0	32.5*	9.1*	4.4	20.6	27.5*	12.3
Generalized new joint pain	41.7	31.5	24.4	30.1	15.5	23.8*	7.4	5.4	12.6	14.9	12.8
Generalized aggravated joint pain	28.6	25.6	24.9	21.4	14.0	21.1	5.2	4.2	11.6	16.5	9.7

[†] All studies in this table reported systemic events within 14 days after vaccination, except Study 6115A1-3006, which reported systemic events within 7 days.
* Statistically significant difference $p < 0.05$.
[a] All reported systemic events, regardless of causality assessment.
[b] Open label administration of Prevnar 13.
[c] Number of subjects with known values for any systemic event.
NA = not applicable

Solicited Adverse Events in Adult Studies with Prevnar 13 and TIV

The safety of concomitant administration of Prevnar 13 with seasonal trivalent influenza vaccine (TIV) was assessed in 2 studies in PPSV23 unvaccinated adults. The incidence of solicited local and systemic adverse events that occurred within 14 days following Prevnar 13 administered concomitantly with TIV compared to Prevnar 13 or TIV administered alone are shown in Tables 6 and 7, respectively.

Table 6: Percentage of Subjects* With Local Reactions[a] Within 14 Days After Vaccination With Prevnar 13 Administered Concomitantly With TIV Compared to Prevnar 13 Alone

	Adults Aged 50-59 Years (Study 6115A1-3001)		Adults Aged ≥65 Years (Study 6115A1-3008)	
Local Reaction	**Prevnar 13 +TIV** N[c]=262-469 %	**Prevnar 13**[b] N[c]=241-453 %	**Prevnar 13 +TIV** N[c]=428-480 %	**Prevnar 13**[b] N[c]=420-470 %
Redness[d]				
Any	16.3	12.1	16.6	12.3
Mild	15.7	10.2	14.4*	9.7
Moderate	4.2	5.6	6.0	6.1
Severe	0.4	1.2	0.7	1.0
Swelling[d]				
Any	18.4	14.7	13.8	10.2
Mild	17.0	12.3	11.8	8.1
Moderate	5.7	6.4	4.2	5.0
Severe	0.4	0.4	0.2	0.0
Pain[e]				
Any	86.8	84.5	40.0	43.4
Mild	82.8	82.1	34.3	37.9
Moderate	39.2	41.1	14.8	19.7
Severe	4.1	4.8	1.4	2.6
Limitation of Arm Movement[f]				
Any	35.6	42.5	13.9	14.8
Mild	32.6*	41.1	13.1	13.4
Moderate	5.2	5.2	1.4	1.0
Severe	3.4	2.9	1.9	1.4

* Statistically significant difference $p < 0.05$ – Prevnar 13 + TIV versus Prevnar 13.

[a] All reported local reactions, regardless of causality assessment.

[b] TIV and placebo were administered 1 month prior to Prevnar 13.

[c] Number of subjects with known values for any local reaction.

[d] Mild is 2.5-5.0 cm. moderate is 5.1-10.0 cm and severe is > 10.0 cm.

[e] Mild = awareness of symptom but easily tolerated, moderate = discomfort enough to cause interference with usual activity, and severe = incapacitating with inability to do usual activity.

[f] Mild = some limitation of arm movement, moderate = unable to move arm above head but able to move arm above shoulder, and severe = unable to move arm above shoulder.

Table 7: Percentage of Subjects* With Systemic Events[a] Within 14 Days After Vaccination With Prevnar 13 Administered Concomitantly With TIV Compared to Prevnar 13 and TIV Alone

	Adults Aged 50-59 Years (Study 6115A1-3001)			Adults Aged ≥65 Years (Study 6115A1-3008)		
Systemic Event	**Prevnar 13 +TIV** N[d]=261-399 %	**Prevnar 13[c]** N[d]=240-350 %	**TIV[b]** N[d]=257-382 %	**Prevnar 13 +TIV** N[d]=428-476 %	**Prevnar 13[c]** N[d]=420-456 %	**TIV[b]** N[d]=431-483 %
Fever						
Any (≥38°C)	3.4	2.5	1.2	4.2	3.6	3.2
≥38°C but <38.5°C	1.5	1.2	1.2	3.0	3.1	1.9
≥38.5°C but <39°C	1.5†	0.8	0.0	1.4	1.0	1.2
≥39°C but <40°C	0.4	0.4	0.0	0.0	0.0	0.2
>40°C	0.0	0.0	0.0	0.0	0.0	0.0
Fatigue	58.1	51.8	52.4	37.4*	28.5	31.9
Headache	65.9*,†	50.9	56.5	32.6*	24.7	29.7
Chills	31.4†	24.6	21.0	13.8*,†	9.1	9.1
Rash	12.6†	9.5	4.9	6.9†	6.8	3.4
Vomiting	5.3	6.1	3.4	3.0	1.7	3.4
Decreased appetite	30.2†	25.8	22.6	16.9*	11.3	14.6
Generalized new muscle pain	65.5†	59.1	37.7	26.9†	23.4	16.7
Generalized aggravated muscle pain	34.7†	36.7	24.1	18.7	15.0	14.0
Generalized new joint pain	33.0†	27.4	24.7	16.2*	11.5	13.1
Generalized aggravated joint pain	21.2	23.8	18.0	15.7*	8.6	13.0

* Statistically significant difference $p < 0.05$ – Prevnar 13 + TIV versus Prevnar 13.
† Statistically significant difference $p < 0.05$ – Prevnar 13 + TIV versus TIV
[a] All reported systemic events, regardless of causality assessment.
[b] TIV was administered with placebo.
[c] TIV and placebo were administered 1 month prior to Prevnar 13.
[d] Number of subjects with known values for any systemic event.

Additional Information in Special Populations

In a single-arm study (6115A1-3017) conducted in 329 HIV-infected adults ≥ 18 years of age previously vaccinated with PPSV23, and in a single-arm study (6115A1-3002) conducted in 151 HIV-infected adults ≥18 years of age not previously vaccinated with PPSV23 (see Part II, CLINICAL TRIALS), the frequencies of solicited local reactions and systemic adverse events after the first, second or third doses of Prevnar 13 were comparable to those reported after a single Prevnar 13 dose in healthy adults ≥18 years of age from study 6115A1-004 (see Tables 4 and 5), except that fever was very common (11.0-17.9% across the 3 doses) in study 6115A1-3002.

In adults ≥18 years of age with a hematopoietic stem cell transplant (N=188) vaccinated with up to 4 doses of Prevnar 13 in single-arm study 6115A1-3003 (see Part II, CLINICAL TRIALS), the frequencies of solicited local reactions and systemic events after the first, second, third, or fourth doses of Prevnar 13 were comparable to those reported after a single Prevnar 13 dose in healthy adults ≥18 years of age from study 6115A1-004 (see Tables 4 and 5), except that fever was very common (4.3-15.4% across the 4 doses) in study 6115A1-3003.

Serious Adverse Events (SAEs)

Immunogenicity Studies: Adults 50 Years and Older
Across the 6 studies, serious adverse events within 1 month of vaccination were reported in 0.2% to 1.7% of 5,667 persons vaccinated at any time during the study with Prevnar 13 and in 0.4% to 1.7% of 1,391 persons vaccinated at any time during the study with PPSV23. From 1 month to 6 months postvaccination, serious adverse events were reported in 1.2% to 5.8% of persons vaccinated at any time during the study with Prevnar 13 and in 2.4% to 5.5% of persons vaccinated at any time during the study with PPSV23.

Twelve of 5,667 (0.21%) Prevnar 13 recipients and 4 of 1,391 (0.29%) PPSV23 recipients died; none of the deaths were considered related to vaccination. Deaths occurred between day 3 and day 309 after study vaccination with Prevnar 13 or PPSV23. Two of 12 deaths occurred within 30 days of vaccination and both deaths were in subjects >65 years of age. One death due to cardiac failure occurred 3 days after receiving placebo. This subject had received Prevnar 13 and TIV 1 month earlier. The other death was due to peritonitis 20 days after receiving Prevnar 13. The reported causes of the 10 remaining deaths occurring greater than 30 days after receiving Prevnar 13 were cardiac disorders (4), neoplasms (4), *Mycobacterium avium* complex pulmonary infection (1) and septic shock (1).

Immunogenicity Study: Adults 18-49 Years of Age
Serious adverse events occurring within 1 month of vaccination and considered possibly related to vaccination were reported in 0.1% of 899 subjects vaccinated. There were no deaths or adverse events that led to withdrawal from the study.

Efficacy Study: Adults 65 Years and Older
Serious adverse events within 1 month of vaccination were reported in 0.8% of 42,237 Prevnar 13 recipients and in 0.7% of 42,225 placebo recipients in the safety population. In the subset of subjects where serious adverse events were monitored for 6 months, 7% of 1,006 Prevnar 13 vaccinated subjects and 6% of 1,005 placebo vaccinated subjects reported serious adverse events.

Adverse Reactions from Prevnar 13 Postmarketing Experience

Although the following adverse drug reactions were not observed in the clinical trials, they are considered adverse drug reactions for Prevnar 13 as they were reported in the postmarketing experience. Because these reactions were derived from spontaneous reports, the frequencies could not be determined and are thus considered as not known.

Table 8: Adverse Reactions from Prevnar 13 Postmarketing Experience

System Organ Class	Frequency Not Known (cannot be estimated from available data)*
Blood and lymphatic system disorders	Lymphadenopathy localized to the region of the vaccination-site
Immune system disorders	Anaphylactic/anaphylactoid reaction including shock
Skin and subcutaneous tissue disorders	Angioedema; erythema multiforme
General disorders and administration site conditions	Vaccination-site dermatitis; vaccination-site urticaria; vaccination-site pruritus

*Adverse drug reaction identified post-marketing

DRUG INTERACTIONS

Drug-Drug Interactions

Different injectable vaccines should always be given at different vaccination-sites.

Infants and Children Aged 6 Weeks to 5 Years

Prevnar 13 can be given, at a different vaccination-site, with any of the following vaccine antigens, either as monovalent or combination vaccines: diphtheria, tetanus, acellular pertussis, Haemophilus influenzae type b, inactivated poliomyelitis, hepatitis B, meningococcal serogroup C, measles, mumps, rubella and varicella.

In the clinical trials, some infants and children were given rotavirus vaccine (oral administration) or hepatitis A vaccine (at a different site) with Prevnar 13. The safety profiles were comparable for these children but immunogenicity data were not available.

Prevnar 13 can also be given concomitantly with the tetanus toxoid conjugated meningococcal polysaccharide serogroups A, C, W and Y vaccine, administered between 12-23 months of age in children who have previously received the infant series of Prevnar 13 (see PART II, CLINICAL TRIALS section).

Data from a postmarketing clinical study evaluating the impact of prophylactic use of antipyretics (ibuprofen and acetaminophen) on the immune response to Prevnar 13 suggest that prophylactic administration of acetaminophen may reduce the immune response to Prevnar 13 after the infant series. Responses to the booster dose administered at 12 months were unaffected. The clinical significance of this observation is unknown.

Children and Adolescents 6 to 17 Years of Age

In children and adolescents, data are insufficient to assess the concomitant administration of Prevnar 13 with other routinely administered vaccines in this age group, including human papillomavirus vaccine (HPV), meningococcal protein conjugate vaccine (MCV4), influenza vaccine and tetanus, diphtheria and pertussis vaccine (Tdap).

Adults 18 to 49 Years of Age

No data are currently available regarding concomitant use with other vaccines.

Adults 50 Years and Older

Concomitant administration of Prevnar 13 and a trivalent inactivated influenza vaccine (TIV) has been studied in adults 50 years and older. Concomitant administration of Prevnar 13 and quadrivalent inactivated influenza vaccine (QIV) has been studied in adults 50 years of age and older who had previously received the 23-valent pneumococcal polysaccharide vaccine (PPSV23) at least one year prior (see PART II, CLINICAL TRIALS section).

Drug-Lifestyle Interactions

Some of the effects mentioned under the ADVERSE REACTIONS section may temporarily affect the ability to drive or use machines.

DOSAGE AND ADMINISTRATION

For intramuscular use only.

The dose is 0.5 mL given intramuscularly, with care to avoid injection into or near nerves and blood vessels. The preferred sites are the anterolateral aspect of the thigh in infants or the deltoid muscle of the upper arm in older children and adults. The vaccine should not be injected in the gluteal area. **Do not administer Prevnar 13 intravascularly.**

The vaccine should not be injected intradermally, subcutaneously or intravenously, since the safety and immunogenicity of these routes have not been evaluated.

Parenteral products should be inspected visually for particulate matter or discoloration prior to use.

The vaccine is not to be mixed with other vaccines/products in the same syringe.
Data on the interchangeability of Prevnar 13 with other pneumococcal conjugate vaccines containing a protein carrier different from CRM_{197} are not available.

1. Infants and Children Aged 6 Weeks to 5 Years (Prior to the 6th Birthday)

It is recommended that infants who receive a first dose of Prevnar 13 complete the vaccination course with Prevnar 13.

Vaccination Schedule

Primary Immunization:
For infants, the recommended immunization series of Prevnar 13 consists of 3 doses of 0.5 mL each, at approximately 2-month intervals, followed by a fourth dose (booster) of 0.5 mL at 12-15

months of age (3+1 schedule). The customary age for the first dose is 2 months of age, but it can be given as young as 6 weeks of age. The recommended dosing interval is 4-8 weeks. The fourth dose should be administered at approximately 12-15 months of age, and at least 2 months after the third dose.

Table 9: Prevnar 13 Routine Vaccine Schedule for Infants and Toddlers

Dose	Dose 1 [a]	Dose 2 [b]	Dose 3 [b]	Dose 4 [c]
Age at Dose	2 months	4 months	6 months	12-15 months

a. Dose 1 may be given as early as 6 weeks of age.
b. The recommended dosing interval is 4-8 weeks.
c. The fourth dose should be administered at approximately 12-15 months of age, and at least 2 months after the third dose.

Prevnar 13 Schedule for Preterm Infants (< 37 Weeks Gestation):
Preterm infants in stable condition should be immunized with Prevnar 13 at the same chronological age and according to the same schedule as full-term infants (see Table 9, WARNINGS AND PRECAUTIONS – Infants and Children Aged 6 Weeks to 5 Years, and PART II, CLINICAL TRIALS – Preterm Infants).

Previously Unvaccinated Infants and Children 7 Months to 5 Years of Age:
For children who are beyond the age of the routine infant schedule, the following Prevnar 13 schedule applies:

Table 10: Prevnar 13 Schedule for Previously Unvaccinated Children ≥7 Months to 5 Years of Age (Prior to the 6th Birthday)

Age at First Dose	**Total Number of 0.5 mL Doses**
7-11 months of age	3[a]
12-23 months of age	2[b]
≥24 months to 5 years of age	1

a. 2 doses at least 4 weeks apart; third dose after the 1-year birthday, separated from the second dose by at least 2 months.
b. 2 doses at least 2 months apart.

If Prevnar 13 is given as part of a routine infant immunization program, a 3-dose (2+1) schedule may be considered. The first dose may be given from the age of 2 months, with a second dose 2 months later, and a third (booster) dose is recommended between 11-12 months of age. Lower immunogenicity responses for serotypes 6B and 23F were observed when Prevnar 13 is given as a 2-dose (e.g., at 2 and 4 months of age, or at 3 and 5 months of age) schedule in infants up to 6 months of age. After the booster dose, all vaccine serotypes had immune responses consistent with adequate priming with a 2-dose primary series (See PART II, CLINICAL TRIALS section).

Infants and Children Previously Vaccinated with Prevnar (7-valent) (Streptococcus pneumoniae Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F):
Prevnar 13 contains the same 7 serotypes contained in Prevnar (7-valent) and is manufactured based on the same conjugate technology using the CRM_{197} carrier protein. A booster dose of Prevnar 13 in children (n = 100) previously vaccinated with 3 doses of Prevnar (7-valent) elicited anti-capsular antibody levels (GMCs) to each of the seven common serotypes that were comparable to those elicited by 4 doses of Prevnar (7-valent) (see Table 15 of PART II, CLINICAL TRIALS section).

Children who have completed the infant series with Prevnar (7-valent) can receive a single dose of Prevnar 13 in the second year of life. A single dose of Prevnar 13 in children >1 year of age elicits immune responses to the 6 additional serotypes that are comparable to those elicited by a 3-dose infant series of Prevnar 13, but are generally lower than those elicited by a 3 infant doses + 1 toddler dose schedule of Prevnar 13.

2. Children and Adolescents 6 to 17 Years of Age (Prior to the 18th Birthday)

Children 6 years to 17 years of age may receive a single dose of Prevnar 13. If Prevnar (7-valent) was previously administered, then at least 8 weeks should elapse before receiving Prevnar 13.

3. Adults 18 Years and Older

Prevnar 13 is to be administered as a single dose of 0.5 mL to adults 18 years and older including those previously vaccinated with a pneumococcal polysaccharide vaccine.

Regardless of prior pneumococcal vaccination status, if sequential administration of Prevnar 13 and pneumococcal polysaccharide vaccine is considered, Prevnar 13 should be given first.

The need for re-vaccination with a subsequent dose of Prevnar 13 has not been established.

4. Special Populations

(Also see WARNINGS AND PRECAUTIONS – General, and PART II, CLINICAL TRIALS – Immune Responses in Special Populations)

Individuals who may be at higher risk of pneumococcal infection (e.g., individuals with sickle cell disease or HIV infection), including those previously vaccinated with 1 or more doses of 23-valent pneumococcal polysaccharide vaccine (PPSV23), may receive 1 dose of Prevnar 13.

In individuals aged ≥ 2 years with a hematopoietic stem cell transplant (HSCT), the recommended immunization series consists of 4 doses of Prevnar 13, each of 0.5 mL. The primary series consists of 3 doses, with the first dose given 3 to 6 months after HSCT and with an interval of at least 1 month between doses. A booster dose is recommended 6 months after the third dose.

Based on the National Advisory Committee on Immunization (NACI) recommendations, if sequential administration of Prevnar 13 and pneumococcal polysaccharide vaccine is considered, it is recommended that Prevnar 13 be given first.[11]

OVERDOSAGE

Overdose with Prevnar 13 is unlikely due to its presentation as a pre-filled syringe. However, in infants and children there have been reports of overdose with Prevnar 13 defined as subsequent doses administered closer than recommended to the previous dose. In general, adverse reactions reported with overdose are consistent with those that have been reported with doses given in the recommended pediatric schedules of Prevnar 13.

For management of a suspected overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Prevnar 13 contains the 7 pneumococcal capsular polysaccharides that are in Prevnar (7-valent) (4, 6B, 9V, 14, 18C, 19F, 23F) plus 6 additional polysaccharides (1, 3, 5, 6A, 7F, 19A) all conjugated to CRM_{197} carrier protein. B-cells produce antibodies in response to antigenic stimulation via T-dependent and T-independent mechanisms. The immune response to most antigens is T-dependent and involves the collaboration of CD4+ T-cells and B-cells, recognizing the antigen in a linked fashion. CD4+ T-cells (T-helper cells) provide signals to B-cells directly through cell surface protein interactions, and indirectly through the release of cytokines. These signals result in proliferation and differentiation of the B-cells, and production of high-affinity antibodies. CD4+ T-cell signaling is a requisite for the generation of long-lived B-cells called plasma cells, which continuously produce antibodies of several isotypes (with an IgG component) and memory B-cells that rapidly mobilize and secrete antibodies upon re-exposure to the same antigen.

Bacterial capsular polysaccharides (PSs), while varied in chemical structure, share the common immunological property of being largely T-independent antigens. In the absence of T-cell help, PS stimulated B-cells predominantly produce IgM antibodies; there is generally no affinity maturation of the antibodies, and no memory B-cells are generated. As vaccines, PSs are associated with poor or absent immunogenicity in infants less than 24 months of age and failure to induce immunological memory at any age. Conjugation of PSs to a protein carrier overcomes the T-cell–independent nature of PS antigens. Protein carrier-specific T-cells provide the signals needed for maturation of the B-cell response and generation of B-cell memory. Conversion of Streptococcus pneumoniae PSs to a T-cell-dependent antigen by covalent coupling to the immunogenic protein carrier CRM_{197} enhances the antibody response and induces immune memory. This has been demonstrated to elicit booster responses on re-exposure in infants and young children to pneumococcal polysaccharides.

Disease Burden

Infants and Children

Prior to the licensure of 7-valent pneumococcal conjugate vaccine (Prevnar) in Canada in 2001, the observed incidence rates of invasive pneumococcal disease (IPD) among children <2 years of age and <5 years of age were 58.8-112.2 per 100,000 and 35.0-63.8 per 100,000 per year, respectively. The overall fatality rate was 2.0%. The incidence rate of pneumococcal meningitis among children <2 years of age was 9.0 per 100,000 per year, with a case fatality rate of 5.9%. Since the introduction of Prevnar (7-valent) in Canada in 2001, it has been shown that the incidence of IPD caused by Prevnar (7-valent) serotypes decreased by 92% in Vancouver, 94% in Calgary and by 72% in Quebec.

While the effect of routine use of Prevnar (7-valent) in infants and young children has been dramatic, with a near-total elimination of the serotypes contained in this vaccine, an increase in other serotypes causing IPD has been observed (as an increasing percentage of residual disease). Data from Canadian surveillance systems (National Centre for Streptococcus [NCS]; Immunization Monitoring Program, Active [IMPACT]; and Institut National de Santé Publique du Québec [INSPQ]) showed that serotypes 19A, 6A and 3 have emerged as the predominant pneumococcal serotypes causing IPD in Canadian children, accounting for approximately one-third of the residual IPD in 2007 in children <5 years of age. Compounding the issue of the predominance of emerging serotype 19A is that it is increasingly likely to be nonsusceptible to commonly used first-line antimicrobial agents.

Serotype surveillance of invasive S. pneumoniae performed by the National Microbiology Laboratory in 2010 to establish a baseline serotype distribution in Canada during introduction of Prevnar 13 revealed that serotypes 19A, 7F and 3 were the most common serotypes in children, accounting for 57% of all invasive isolates in <2 year olds, 62% in 2-4 year olds and 45% in 5-14 year olds. Prevnar 13 serotypes represented 65%, 71% and 61% of pneumococci isolated from <2 year olds, 2-4 year olds, and 5-14 year olds, respectively.

Following Prevnar 13 introduction in the Calgary area in mid 2010, the overall pneumococcal nasopharyngeal colonization rate in healthy children declined from 19% in 2003-2006 to 13% in 2010-2012 ($p<0.001$), and colonization with serotype 19A decreased from 18% of all serotypes in 2010 to 4% in 2012. Children who received 2 or more doses of either Prevnar (7-valent) or Prevnar 13 had reduced odds of colonization with any pneumococcus in adjusted logistic regression (Odds ratio: 0.75; 95% CI: 0.63-0.9).

Adults

Prior to the introduction of Prevnar (7-valent) into the National Immunization Program (NIP), the IPD incidence for Canadian adults aged 65 years and older ranged from 16 to 31 per 100,000. A ten-year population-based surveillance of all cases of invasive pneumococcal infection occurring in the Calgary Health Region reported a decrease of 92% in 2007 vs. 1998-2001 in Prevnar (7-valent) serotypes among adults 65 years and older suggesting a herd immunity, a phenomenon that occurs via interruption of transmission of disease to otherwise susceptible populations. However, the incidence of IPD in adults, especially the elderly, has remained high, ranging from 23 per 100,000 to 29.4 per 100,000. Although the incidence estimates among adults

younger than 65 are lower than those among adults older than 65, IPD represents a major public health burden among younger adults as well.

Canadian serotype surveillance performed by the National Microbiology Laboratory in 2010 revealed that serotypes 19A, 7F and 3 were the most common serotypes in adults, accounting for 44% of invasive S. pneumoniae isolates in 15-49 year olds, 41% in 50-64 year olds and 36% in ≥65 year olds. Prevnar 13 serotypes represented 60%, 53% and 49% of pneumococci isolated from 15-49 year olds, 50-64 year olds, and ≥65 year olds, respectively.

STORAGE AND STABILITY

Store refrigerated at +2 °C to +8 °C. Do not freeze. Discard if the vaccine has been frozen.

Store in original package.

Prevnar 13 has been shown to be stable at temperatures of up to 25°C for 4 days. Cumulative multiple temperature excursions between 8°C and 25°C are permitted, as long as the total time does not exceed 4 days (96 hours). These data are not recommendations for shipping or storage, but may guide decisions for use in case of temporary temperature excursions.

Do not use after the expiry date shown on the label.

SPECIAL HANDLING INSTRUCTIONS

Prevnar 13 is a suspension containing an adjuvant. The vaccine should be shaken well to obtain a homogeneous white suspension prior to expelling air from the syringe, and should be inspected visually for any particulate matter and/or variation of physical aspect prior to administration. Do not use if the content appears otherwise.

The vaccine is not to be mixed with other vaccines/products in the same syringe.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each 0.5 mL dose of the vaccine is formulated to contain approximately 2.2 µg of each saccharide for Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F and 23F, 4.4 µg of saccharide for serotype 6B, 34 µg CRM_{197} carrier protein, 4.25 mg sodium chloride, 100 µg polysorbate 80, 295 µg succinic acid and 125 µg aluminum as aluminum phosphate adjuvant.

The vaccine is a white suspension for injection and provided in a single-dose, pre-filled syringe (0.5 mL). Pack sizes of 1 and 10, without needles. The tip cap and rubber plunger of the pre-filled syringe do not contain latex.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein)

Product Characteristics

Pneumococcal 13-valent conjugate vaccine is a sterile solution of saccharides of the capsular antigens of Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated by reductive amination to non-toxic diphtheria CRM_{197} protein. The polysaccharides are chemically activated, and then covalently linked to the protein carrier CRM_{197} to form the glycoconjugate.

Individual conjugates are compounded, and then polysorbate 80 and aluminum phosphate are added to formulate the vaccine. The potency of the vaccine is determined by the quantity of the saccharide antigens and the saccharide-to-protein ratios in the individual glycoconjugates. Each 0.5 mL dose is formulated to contain 2.2 µg of each saccharide for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F and 4.4 µg of saccharide for serotype 6B, conjugated to CRM_{197} carrier protein, and 0.125 mg of aluminum as aluminum phosphate adjuvant.

CLINICAL TRIALS

1. Clinical Trials in Infants and Children 6 Weeks to 5 Years of Age

Table 11: Overview of 13vPnC Clinical Studies in Infants and Children 6 Weeks to 5 Years of Age

Study	Study Design	Primary Objectives	Study Vaccine Schedule (Months)	Concomitant Vaccine Schedule (Months)	N Vaccinated per Group (as Randomized)
Pivotal Studies					
6096A1-004[16]	Multi-centre, randomized, double-blind, controlled	Demonstrate that the PnC serotype-specific IgG responses (proportion of responders at ≥0.35 µg/mL) induced by 13vPnC are non-inferior to those induced by 7vPnC or 7vPnC reference[a] measured 1 month after the infant series. Demonstrate that the serotype-specific geometric mean IgG concentrations induced by 13vPnC are non-inferior to those induced by 7vPnC or 7vPnC reference[a] measured 1 month after the toddler dose. Assess the non-inferiority of antigen-specific response (Dip, PT, FHA, PRN, Hib) 1 month after dose 3 of PnC and concomitant vaccine in the 13vPnC group relative to the 7vPnC group.	13vPnC or 7vPnC (2, 4, 6, 12-15)	Pediarix (2, 4, 6) ActHIB (2, 4, 6) PedvaxHIB (12-15) ProQuad (12-15) VAQTA (12-15)	13vPnC: 332 7vPnC: 331
6096A1-006[10]	Multi-centre, randomized, double-blind, controlled	Demonstrate that the PnC serotype-specific IgG responses induced by 13vPnC are non-inferior to those induced by 7vPnC or 7vPnC reference[a] measured 1 month after the infant series. Assess the non-inferiority of antigen-specific response (Dip, HBV, Hib) 1 month after dose 3 of PnC and concomitant vaccine in the 13vPnC group relative to the 7vPnC group.	13vPnC or 7vPnC (2, 3, 4, 11 12)	Infanrix hexa (2, 3, 4, 11-12)	13vPnC: 300 7vPnC: 303

Table 11: Overview of 13vPnC Clinical Studies in Infants and Children 6 Weeks to 5 Years of Age (Cont'd)

Study	Study Design	Primary Objectives	Study Vaccine Schedule (Months)	Concomitant Vaccine Schedule (Months)	N Vaccinated per Group (as Randomized)
Additional Vaccine Schedules and Concomitant Vaccine Immunogenicity Trials					
6096A1-007	Multi-centre, randomized, double-blind, controlled	Evaluate the immune response after NeisVac-C (MnC using SBA) and 13vPnC relative to NeisVac-C and 7vPnC measured 1 month after the infant series. Evaluate the immune response after Pediacel (antigens assessed: PT, FHA, PRN, FIM, Hib) and 13vPnC relative to Pediacel and 7vPnC measured 1 month after the infant series. Assess the immune response (IgG) to 13vPnC measured 1 month after the infant series and before and 1 month after the toddler dose.	13vPnC or 7vPnC (2, 4, 12)	NeisVac C (2, 4) Pediacel (2, 3, 4) Menitorix (12)	13vPnC: 139 7vPnC: 139
6096A1-008[5]	Multi-centre, randomized, double-blind, controlled	Demonstrate that the immune responses after Pentavac (antigens assessed: PT, FHA, Hib, Dip, Tet, polio types 1, 2, 3) and 13vPnC are non-inferior to the response after Pentavac and 7vPnC measured 1 month after the infant series. Assess the immune responses to 13vPnC measured 1 month after the infant series. Assess immune responses, 1 month after the toddler dose, to the following (infant series/toddler dose) sequences: 13vPnC/13vPnC and 7vPnC/13vPnC relative to 7vPnC/7vPnC. Post toddler dose pneumococcal responses induced by 13vPnC/13vPnC relative to 7vPnC/13vPnC were also assessed.	13vPnC or 7vPnC (2, 3, 4, 12)	Pentavac (2, 3, 4, 12)	13vPnC: 302 7vPnC: 309
6096A1-011	Multi-centre, randomized, double-blind, controlled	Assess the PnC immune response after 13vPnC relative to 7vPnC measured 1 month after the infant series. Assess the immune response after Easyfive, ie, DTP-Hib-HBV vaccine (antigens assessed: PT, FHA, PRN) and 13vPnC relative to DTP-Hib-HBV and 7vPnC measured 1 month after the infant series.	13vPnC or 7vPnC (6, 10, 14 weeks, 12 months)	Easyfive (6, 10, 14 weeks) Biopolio (6, 10, 14 weeks)	13vPnC: 178 7vPnC:175

Table 11: Overview of 13vPnC Clinical Studies in Infants and Children 6 Weeks to 5 Years of Age (Cont'd)

Study	Study Design	Primary Objectives	Study Vaccine Schedule (Months)	Concomitant Vaccine Schedule (Months)	N Vaccinated per Group (as Randomized)
6096A1-500	Multi-centre, randomized, double-blind, controlled	Demonstrate that the immune response after Infanrix hexa (antigen assessed: HBV) and 13vPnC is non-inferior to the response after Infanrix hexa and 7vPnC measured 1 month after the toddler dose. Assess the immune response to 13vPnC measured 1 month after the infant series and just before the toddler dose. Assess the immune responses induced by 13vPnC relative to 7vPnC measured 1 month after the toddler dose.	13vPnC or 7vPnC (3, 5, 11)	Infanrix hexa (3, 5, 11)	13vPnC: 302 7vPnC: 302
6096A1-501	Multi-centre, randomized, double-blind, controlled	Demonstrate that the immune response after Meningitec (antigen assessed: MnC by SBA) and 13vPnC is non-inferior to response after Meningitec and 7vPnC measured 1 month after a 2-dose Meningitec infant series. Assess the non-inferiority of antigen specific response to PT, FHA, PRN, Dip, Tet, and polio types 1, 2, 3 after Infanrix hexa and 13vPnC relative to Infanrix hexa and 7vPnC. Assess the immune responses to 13vPnC measured 1 month after dose 2 and 1 month after dose 3 of the infant series and 1 month after the toddler dose.	13vPnC or 7vPnC (2, 4, 6, 15)	Infanrix hexa (2, 4, 6) Meningitec (2, 4, 15) Infanrix-IPV+Hib (15) MMR II (12)	13vPnC: 314 7vPnC: 302
6096A1-3007	Multi-centre, randomized, double-blind, controlled	Demonstrate the non-inferiority of immune response after NeisVac-C and 13vPnC relative to NeisVac-C (antigen assessed: MnC using SBA) and 7vPnC measured 1 month after a 2-dose NeisVac-C infant series. Demonstrate the non-inferiority of immune response after Infanrix hexa (antigens assessed: Dip, Tet) and 13vPnC relative to Infanrix hexa and 7vPnC measured 1 month after a 3-dose infant series. Assess the immune responses to 13vPnC measured 1 month after dose 2 and 1 month after dose 3 of the infant series.	13vPnC or 7vPnC (2, 4, 6, 15)	Infanrix hexa (2, 4, 6) NeisVac-C (2, 4, 15) Priorix (12) Infanrix-IPV+Hib (15)	13vPnC: 218 7vPnC: 226

Table 11: Overview of 13vPnC Clinical Studies in Infants and Children 6 Weeks to 5 Years of Age (Cont'd)

Study	Study Design	Primary Objectives	Study Vaccine Schedule (Months)	Concomitant Vaccine Schedule (Months)	N Vaccinated per Group (as Randomized)
Other Clinical Studies					
6096A1-3005	Multi-centre, randomized, double-blind, controlled	Demonstrate that the immune responses induced by 3 lots of 13vPnC are equivalent at 1 month after the infant series. Demonstrate the non-inferiority of immune response induced by Pediarix given with 13vPnC relative to Pediarix given with 7vPnC 1 month after the infant series (antigens assessed: Tet; polio types 1, 2, 3; HBV).	13vPnC pilot lot 1, 13vPnC pilot lot 2, or 13vPnC man lot or 7vPnC (2, 4, 6, 12)	Pediarix (2, 4, 6) Act-HIB (2, 4, 6) MMR II and Varivax (12) Havrix (12)	13vPnC pilot 1: 486 13vPnC pilot 2: 484 13vPnC man: 485 7vPnC: 244
Trial in Older Infants and Young Children					
6096A1-3002	Multi-centre, non-randomized, open-label, uncontrolled	Assess the PnC response induced by 13vPnC when measured 1 month after the last scheduled dose in each age group.	13vPnC: Group 1: (3 doses) 7 to <12 months, 1 month later, and 12-16 months Group 2: (2 doses) 12 to <24 months and 56 to 70 days later Group 3: (1 dose) 24 to <72 months	N/A	Group 1: 90 Group 2: 112 Group 3: 152

a. In studies 004 and 006, values for the additional serotypes in the 13vPnC group are compared with the 7vPnC reference value, defined as the lowest value among the 7 common serotypes in the 7vPnC group.

Abbreviations: Dip = diphtheria; FHA = filamentous hemagglutinin; FIM = fimbrial agglutinogens; HBV = hepatitis B virus vaccine; Hib = Haemophilus influenzae type b; man = manufacturing; MnC = meningococcal C; NA = not applicable; PnC = pneumococcal conjugate vaccine; polio types 1, 2, 3 = poliovirus vaccine type 1, type 2, and type 3; PRN = pertactin; PT = pertussis toxoid; SBA = serum bactericidal assay; Tet = tetanus.

Components of vaccines by trade name: ActHIB = Hib; Biopolio = OPV; Easyfive = DTP (whole cell pertussis), Hib, and HBV; Havrix = HAV; Infanrix hexa = DTaP, Hib, HBV, and IPV; Infanrix-IPV+Hib = DTaP, IPV, and Hib; Meningitec = meningococcal C vaccine; Menitorix = Hib and meningococcal C vaccine; MMR II = measles, mumps, and rubella vaccine; NeisVac-C = meningococcal C vaccine; Pediacel = DTaP, Hib, and IPV; Pediarix = DTaP, HBV, and IPV; PedvaxHIB = Hib; Pentavac = DTaP, Hib, and IPV; Priorix = MMR; ProQuad = MMR and varicella vaccine; Varivax = varicella vaccine; VAQTA = HAV.

The World Health Organization (WHO) has recommended a serum anti-capsular polysaccharide antibody concentration of 0.35 µg/mL measured 1 month after the primary infant series as a single antibody reference concentration to estimate the efficacy of new pneumococcal conjugate vaccines against Invasive Pneumococcal Disease (IPD). This recommendation is based upon the observed correlation between immunogenicity and IPD efficacy from 3 placebo-controlled trials with either Prevnar (7-valent) or the investigational 9-valent CRM_{197} conjugate polysaccharide vaccine. This reference concentration is only applicable on a population basis and cannot be used to predict protection against IPD on an individual basis.

The WHO also requires demonstration of functionality of the elicited antibodies. Opsonophagocytosis (antibody mediated killing of the bacteria) is recognized as the main mechanism of protection against pneumococcal disease, which can be measured by an opsonophagocytosis activity assay (OPA). The percentage of subjects with an OPA titer ≥ 1:8 is used for comparison between vaccines, although the data to support the OPA titer ≥ 1:8 as a marker of protection are currently insufficient.

Finally, the ability to induce immune memory is also required.

In line with WHO recommendations, post-marketing studies will be undertaken to confirm the effectiveness of Prevnar 13.

Immune Responses Following a 3-Dose Primary Infant Series

The immunological comparison between Prevnar 13 and Prevnar (7-valent) was conducted in 2 pivotal studies (USA study 6096A1-004[16] and Germany study 6096A1-006[10]) and was performed post-hoc in USA study 6096A1-3005. The percentage of infants achieving pneumococcal anti-capsular polysaccharide IgG antibody concentrations ≥ 0.35 µg/mL 1 month after a 3-dose primary infant series for the 7 common serotypes are presented in Table 12. The immunological non-inferiority was met when the lower bound of the 95% CI for the difference between groups (Prevnar 13 minus Prevnar (7-valent)) in terms of subjects with antibody concentration ≥ 0.35 µg/mL was greater than -10%.

As shown in Table 12, Prevnar 13 non-inferiority was demonstrated by ELISA for all serotypes in study 6096A1-3005, all except 6B in study 6096A1-006 and all except for 6B and 9V in study 6096A1-004, each of which missed non-inferiority by a small margin at the lower bound of the 95% CI for the difference between groups. The clinical relevance of these differences is not known.

Table 12: Percentage of Subjects with Pneumococcal Anti-capsular Polysaccharide IgG Antibody Concentrations ≥ 0.35 µg/mL 1 Month after the Infant Series for the 7 Common Serotypes

Antibody	Prevnar 13		Prevnar (7-valent)		Difference in % of ≥ 0.35 µg/mL (Prevnar 13 minus Prevnar (7-valent))	
	N	%	N	%	%	95% CI
USA study 6096A1-004 (1 month after 3-dose primary infant series at 2, 4, and 6 months of age)						
Anti-4	252	94.4	251	98.0	-3.6	-7.3, -0.1
Anti-6B	252	87.3	250	92.8	-5.5	-10.9, -0.1
Anti-9V	252	90.5	252	98.4	-7.9	-12.4, -4.0
Anti-14	251	97.6	252	97.2	0.4	-2.7, 3.5
Anti-18C	252	96.8	252	98.4	-1.6	-4.7, 1.2
Anti-19F	252	98.0	251	97.6	0.4	-2.4, 3.4
Anti-23F	252	90.5	252	94.0	-3.6	-8.5, 1.2
Germany study 6096A1-006 (1 month after 3-dose primary infant series at 2, 3, and 4 months of age)						
Anti-4	285	98.2	279	98.2	0.0	-2.5, 2.6
Anti-6B	284	77.5	278	87.1	-9.6	-16.0, -3.3
Anti-9V	285	98.6	279	96.4	2.2	-0.4, 5.2
Anti-14	284	98.9	279	97.5	1.5	-0.9, 4.1
Anti-18C	285	97.2	277	98.6	-1.4	-4.2, 1.2
Anti-19F	284	95.8	277	96.0	-0.3	-3.8, 3.3
Anti-23F	284	88.7	277	89.5	-0.8	-6.0, 4.5
USA study 6096A1-3005 (1 month after 3-dose primary infant series at 2, 4, and 6 months of age) – post-hoc analysis						
Anti-4	1216	97.2	165	98.8	-1.6	(-3.2, 1.4)
Anti-6B	1209	93.0	165	97.0	-4.0	(-6.6, -0.1)
Anti-9V	1212	95.8	158	98.7	-2.9	(-4.7, 0.2)
Anti-14	1175	98.8	163	99.4	-0.6	(-1.7, 2.1)
Anti-18C	1214	97.2	165	98.8	-1.6	(-3.2, 1.4)
Anti-19F	1208	98.2	165	97.6	0.6	(-1.3, 4.0)
Anti-23F	1214	88.9	165	95.2	-6.3	(-9.5, -1.8)

The percentage of subjects, who received Prevnar 13 and reached the threshold of ≥0.35 µg/mL for serotypes 1, 5, 6A, 7F and 19A, was at 89.7% to 99.5%; and the non-inferiority criterion was met when compared to the lowest response of the 7 common serotypes in Prevnar (7-valent) recipients. For serotype 3, the percentage of subjects, who received Prevnar 13 and reached the threshold, was 63.5% and 73.3% in the USA studies and the non-inferiority criterion was not met when compared to Prevnar (7-valent) response against serotype 6B (92.8% study 6096A1-004) or serotype 23F (95.2% study 6096A1-3005) respectively. In the Germany study the 98.2% of subjects responded to serotype 3 and the non-inferiority was met against serotype 6B (87.1% study 6096A1-006).

The geometric mean concentrations (GMCs) of anti-capsular polysaccharide IgG antibody pneumococcal antibodies for the 7 common serotypes following the primary infant series are presented in Table 13. Geometric mean ratios were calculated (Prevnar 13/ Prevnar (7-valent)) and non-inferiority criteria were met if the lower 95% CI was greater than 0.5, a 2-fold criterion. The non-inferiority criteria were met for all serotypes in the 3 studies; although the post-primary GMCs elicited by Prevnar 13 against the 7 common serotypes were generally lower than those elicited by Prevnar (7-valent).

Table 13: Pneumococcal Anti-capsular Polysaccharide IgG Antibody GMC (µg/mL) 1 Month after the Infant Series

Antibody	Prevnar 13		Prevnar (7-valent)		Geometric Mean Ratio (Prevnar 13/ Prevnar (7-valent))	
	N	GMC (95% CI)	N	GMC (95% CI)	Ratio	95% CI
USA study 6096A1-004 (2, 4, 6 months of age)						
Anti-4	252	1.31 (1.19, 1.45)	251	1.93 (1.75, 2.13)	0.68	(0.59, 0.78)
Anti-6B	252	2.10 (1.77, 2.49)	250	3.14 (2.64, 3.74)	0.67	(0.52, 0.85)
Anti-9V	252	0.98 (0.89, 1.08)	252	1.40 (1.27, 1.55)	0.70	(0.61, 0.80)
Anti-14	251	4.74 (4.18, 5.39)	252	5.67 (5.02, 6.40)	0.84	(0.70, 1.00)
Anti-18C	252	1.37 (1.24, 1.52)	252	1.79 (1.63, 1.96)	0.77	(0.67, 0.88)
Anti-19F	252	1.85 (1.69, 2.04)	251	2.24 (2.01, 2.50)	0.83	(0.72, 0.96)
Anti-23F	252	1.33 (1.17, 1.51)	252	1.90 (1.68, 2.15)	0.70	(0.59, 0.84)
Germany study 6096A1-006 (2, 3, 4 months of age)						
Anti-4	285	2.18 (1.98, 2.40)	279	2.99 (2.68, 3.33)	0.73	(0.63, 0.84)
Anti-6B	284	0.98 (0.84, 1.14)	278	1.49 (1.27, 1.75)	0.65	(0.52, 0.82)
Anti-9V	285	1.65 (1.51, 1.80)	279	1.96 (1.77, 2.17)	0.84	(0.74, 0.96)
Anti-14	284	4.14 (3.68, 4.66)	279	4.61 (4.07, 5.23)	0.90	(0.76, 1.07)
Anti-18C	285	1.94 (1.76, 2.14)	277	2.25 (2.04, 2.49)	0.86	(0.75, 0.99)
Anti-19F	284	1.73 (1.56, 1.92)	277	2.86 (2.53, 3.24)	0.60	(0.51, 0.71)
Anti-23F	284	1.26 (1.11, 1.43)	277	1.44 (1.25, 1.65)	0.88	(0.73, 1.06)
USA study 6096A1-3005 (2, 4, 6 months of age) – post-hoc analysis						
Anti-4	1216	1.46 (1.40, 1.52)	165	1.95 (1.73, 2.19)	0.75	(0.66, 0.85)
Anti-6B	1209	2.52 (2.36, 2.69)	165	2.93 (2.47, 3.48)	0.86	(0.71, 1.04)
Anti-9V	1212	1.09 (1.05, 1.14)	158	1.35 (1.23, 1.49)	0.81	(0.72, 0.90)
Anti-14	1175	5.10 (4.85, 5.36)	163	6.21 (5.40, 7.14)	0.82	(0.71, 0.95)
Anti-18C	1214	1.37 (1.32, 1.43)	165	1.61 (1.44, 1.80)	0.85	(0.76, 0.95)
Anti-19F	1208	2.15 (2.06, 2.25)	165	2.30 (2.02, 2.61)	0.94	(0.83,1.07)
Anti-23F	1214	1.18 (1.11, 1.25)	165	1.71 (1.48, 1.97)	0.69	(0.59, 0.81)

Opsonophagocytic activity assay (OPA) was measured in 2 studies (004 and 006) in a randomly selected subset of about 100 subjects per group in each study. Prevnar 13 elicited functional antibodies to all vaccine serotypes. For each of the 7 common serotypes, 90.4% to 100% of Prevnar 13 vaccinees and 92.6% to 100% of Prevnar (7-valent) vaccinees achieved an OPA titer ≥1:8 one month after the 3-dose primary infant series. For the 6 additional serotypes, at least 91.4% of Prevnar 13 vaccinees achieved an OPA titer ≥1:8 one month after the 3-dose primary infant series.

The OPA GMT was generally lower in the Prevnar 13 vaccinees compared with the Prevnar (7-valent) vaccinees (i.e., the OPA GMT ratios of Prevnar 13 vaccinees versus Prevnar (7-valent) vaccinees was less than 1) for the 7 common serotypes, but most were within 2-fold.

Immune Responses Following a 2-Dose Primary Series

The immunogenicity after 2 doses in infants has been documented in 4 studies. The proportion of infants achieving a pneumococcal anti-capsular polysaccharide IgG concentration ≥ 0.35 µg/mL 1 month after the second dose of Prevnar 13 ranged from 79.6% to 98.5% across 11 of the 13

vaccine serotypes. Smaller proportions of infants achieved this antibody concentration threshold for serotype 6B (27.9% to 57.3%) and 23F (55.8% to 68.1%) for all studies using a 2,4 month regimen, compared to 58.4% for serotype 6B and 68.6% for 23F for a trial (Italy study 6096A1-500) using a 3,5 month regimen. After the booster dose, the proportion of infants who achieved this antibody concentration threshold was increased for all vaccine serotypes including 6B and 23F and ranged from 88.2%-100% in study 6096A1-007 and 93.9%-100% in study 6096A1-500. In UK study 6096A1-007, the post-hoc analysis showed that the functional antibody (OPA) responses were comparable for the 7 common serotypes including 6B and 23F in the Prevnar (7-valent) (n= 45-60) and Prevnar 13 (n= 64-77) arms after the primary series at 2 and 4 months of age and after the booster dose at 12 months of age.

Booster Responses Following 2-Dose and 3-Dose Primary Schedules

Antibody responses to booster doses following 2-dose or 3-dose infant primary series in different studies were comparable for all 13 vaccine serotypes.

Post-booster antibody concentrations were higher for 12 serotypes than those achieved after the infant primary series, which is consistent with adequate priming (the induction of immunologic memory). For serotype 3, antibody concentrations declined after the infant series; after the booster dose antibody concentrations were lower than those after the infant primary series in some clinical trials, and higher in others (See the following table. In all studies where OPA was assessed, including both pivotal non-inferiority studies, the anti-type 3 opsonophagocytic activity of 13vPnC-induced antibody was clearly demonstrated. The proportion of subjects with OPA titers ≥1:8 ranged from 96.8% to 100% after the infant series and from 97.8% to 100% after the toddler dose. Functional antibody (OPA) GMTs were higher after the toddler dose than after the infant series in 3 of 4 studies).

The serotype 3 serum IgG GMC induced by only 1 toddler dose of Prevnar 13 was slightly greater than that induced by 3-infant doses plus 1 toddler dose of Prevnar 13. However, the point estimate of the proportion of responders in both groups exceeded 93% at ≥ 0.35 μg/mL and was slightly higher in the 13vPnC/13vPnC group (94.8%) than the 7vPnC/13vPnC group (93.8%). The proportion of OPA responders at ≥ 1:8 was high in both groups (97.8 and 100%) , but OPA GMT was greater in the subjects who received only 1 toddler dose of Prevnar 13 (428.88; 95% CI: 346.69, 530.56) compared to those who received 3-infant doses plus 1 toddler dose of Prevnar 13 (345.33; 95% CI: 296.06, 402.80). The OPA GMT (504.66; 95% CI: 435.71, 584.53) from study 6096A1-500 was even greater in the subjects who received 2-infant doses plus 1 toddler dose of Prevnar 13 (2+1) compared to those who received only 1 toddler dose of Prevnar 13 (7vPnC/13vPnC group) in study 6096A1-008[5] (See Table 14). The clinical significance of these observations is unknown.

Table 14: Pneumococcal Anti-capsular Polysaccharide IgG Antibody Geometric Mean Concentrations (µg/mL), OPA Percentage of Subjects ≥1:8 and OPA Geometric Mean Titers for Serotype 3

Study	Group	GMC (95% CI) for the serotype 3			N	OPA ≥1:8	OPA GMT	N	OPA ≥1:8	OPA GMT
		After infant series	Before toddler dose	After toddler dose	After infant series			After toddler dose		
6096A1-004 [a]	13vPnC	0.49 (0.43, 0.55)	0.15 (0.13, 0.17)	0.94 (0.83, 1.05)	94	96.8	120.67	91	97.8	380.41
6096A1-006 [a]	13vPnC	1.55 (1.41, 1.72)	0.25 (0.23, 0.28)	1.02 (0.92, 1.13)	100	99.0	250.73	98	98.0	187.54
6096A1-009 [a]	13vPnC	1.50 (1.38, 1.63)	0.14 (0.13, 0.16)	1.09 (0.99, 1.20)						
	13vPnC	1.62 (1.49, 1.75)	0.18 (0.16, 0.20)	1.16 (1.05, 1.29)						
6096A1-007 [d]	13vPnC	0.63 (0.56, 0.71)	0.14 (0.10, 0.18)	0.98 (0.78, 1.22)	70	100.0	109.25	77	100.0	306.50
6096A1-008 [a]	13vPnC/ 13vPnC [c]	1.25 (1.13, 1.37)	0.2 (0.2, 0.2)	1.0 (0.9, 1.1)				88	100.0	345.33
	7vPnC/ 13vPnC [b]	-	0.1 (0.1, 0.1)	1.32 (1.1, 1.5)				90	97.8	428.88
6096A1-500 [d]	13vPnC	1.15 (1.04, 1.28)	0.25 (0.22, 0.27)	1.22 (1.09, 1.35)	100	99.0	176.07	96	100.0	504.66
6096A1-501 [a]	13vPnC	0.97 (0.88, 1.08)	-	1.07 (0.95, 1.20)						

a. Subjects received 3 infant doses plus 1 toddler dose.
b. 7vPnC/13vPnC: 3 infant doses of 7vPnC plus 1 toddler dose of 13vPnC.
c. 13vPnC/13vPnC: 3 infant doses plus 1 toddler dose of 13vPnC.
d. Subjects received 2 infant doses plus 1 toddler dose.

Booster Responses to Prevnar 13 Following a 3-Dose Primary Infant Series of Prevnar (7-valent) or Prevnar 13

In a randomized, double-blind, active control study in France (6096A1-008) infants were randomly assigned to 3 groups in a 2:1:1 ratio: (1) Prevnar 13 at 2, 3, 4 and 12 months or (2) Prevnar (7-valent) at 2, 3, and 4 months followed by Prevnar 13 at 12 months or (3) Prevnar (7-valent) at 2, 3, 4 and 12 months.[5] Geometric mean concentrations of anti-capsular polysaccharide IgG antibody responses to each of the 13 serotypes in the 3 groups are shown in Table 15.

Table 15: Pneumococcal Anti-capsular Polysaccharide IgG Antibody Geometric Mean Concentrations (µg/mL), OPA percentage of Subjects ≥1:8 and OPA Geometric Mean Titers 1 Month After Toddler Booster Dose

Serotype	13v/13v Post Toddler N=233-236	7v/13v Post Toddler N=108-113	7v/7v Post Toddler N=111-127	13v/13v Post Toddler			7v/13v Post Toddler		
				N	OPA ≥ 1:8	OPA GMT	N	OPA ≥ 1:8	OPA GMT
4	4.20	4.04	4.85	-	-	-	-	-	-
6B	8.99	10.33	9.63	-	-	-	-	-	-
9V	2.59	2.29	3.24	-	-	-	-	-	-
14	9.52	7.81	10.83	-	-	-	-	-	-
18C	2.30	2.43	2.81	-	-	-	-	-	-
19F	5.18	3.73	4.11	-	-	-	-	-	-
23F	3.01	3.12	3.69	-	-	-	-	-	-
1	4.08	1.83	0.04	88	100.0	126.00	90	98.9	61.58
3	0.99	1.32	0.10	88	100.0	345.33	90	97.8	428.88
5	3.30	1.14	0.53	88	100.0	244.18	90	97.8	130.99
6A	6.14	2.60	1.54	86	100.0	1346.83	90	98.9	891.44
7F	4.52	3.71	0.05	86	100.0	8126.24	89	100.0	17034.59
19A	9.50	5.33	3.98	86	98.8	804.06	90	97.8	1072.43

Table 15 shows that GMCs to the seven Prevnar (7-valent) serotypes did not differ in the 3 groups. Although the GMCs to the 6 additional serotypes in the Prevnar (7-valent)/ Prevnar 13 recipients were lower than those observed with the 4-dose Prevnar 13 regimen (except for serotype 3), they were at least comparable to those of a 3-dose primary series of Prevnar 13 in infants. In both groups that received Prevnar 13, ≥98.7% of subjects had OPA titers ≥1:8 and OPA GMTs were comparable in both groups.

Preterm Infants (Study 6096A1-4001 [B1851037])

Safety and immunogenicity of Prevnar 13 given at 2, 3, 4 and 12 months was assessed in 100 prematurely born infants (estimated gestational age [EGA] mean, 31 weeks; range, 26 to 36 weeks) and compared with 100 infants born at term (EGA mean, 39 weeks; range, 37 to 42 weeks). More than 85% of subjects in the preterm group in the evaluable immunogenicity population achieved a pneumococcal polysaccharide IgG binding antibody concentration ≥ 0.35 µg/mL 1 month after the infant series for all serotypes except serotypes 5 (71.7%), 6A (82.7%), and 6B (72.7%) in the preterm group. For these 3 serotypes, the proportion of responders among preterm infants was significantly lower than among term infants. One month after the toddler dose, the proportion of subjects in each group in the evaluable toddler immunogenicity population achieving this same antibody concentration threshold was >97%, except for serotype 3 (70.6% in preterm infants and 79.3% in term infants). In general, serotype-specific IgG GMCs were lower for preterm infants than term infants.

Previously Unvaccinated Older Infants and Children

In an open label study of Prevnar 13 in Poland (6096A1-3002), children 7-11 months of age, 12-23 months and ≥24 months to 5 years of age (prior to the 6th birthday) who were naïve to pneumococcal conjugate vaccine, were given 3, 2 or 1 dose of Prevnar 13 according to their age at first dose (see Table 10). Serum IgG concentrations were measured 1 month after the final dose in each age group and the data are shown in Table 16.

The age appropriate catch-up immunization schedules result in levels of anti-capsular polysaccharide IgG antibody responses to each of the 13 serotypes that are at least comparable to those of a 3-dose primary series in infants.

Table 16: Pneumococcal Anti-capsular Polysaccharide IgG Antibody Geometric Mean Concentrations (µg/mL) 1 Month After the Final Dose by Age Group in Study 6096A1-3002, Compared with 1 Month Post 3 Infant Doses in Study 6096A1-004 and Study 6096A1-3005

Serotype	7-11 months of age (N= 83-84)	12-23 months of age (N=104-110)	≥24 months to 5 years of age (N=135-152)	Post-infant (Study 6096A1-004) (N=249-252)	Post-infant (Study 6096A1-3005) (N=1172-1213)
1	2.88	2.74	1.78	2.03	1.78
3	1.94	1.86	1.42	0.49	0.56
4	3.63	4.28	3.37	1.31	1.46
5	2.85	2.16	2.33	1.33	1.24
6A	3.72	2.62	2.96	2.19	2.21
6B	4.77	3.38	3.41	2.10	2.51
7F	5.30	5.99	4.92	2.57	2.57
9V	2.56	3.08	2.67	0.98	1.09
14	8.04	6.45	2.24	4.74	5.09
18C	2.77	3.71	2.56	1.37	1.37
19A	4.77	4.94	6.03	2.07	1.91
19F	2.88	3.07	2.53	1.85	2.15
23F	2.16	1.98	1.55	1.33	1.18

Simultaneous Administration With Other Vaccines

In studies 6096A1-004, 6096A1-3005 and 6096A1-3008[15] routine pediatric vaccines were administered at the same visit as Prevnar 13. Immune responses to selected concomitant vaccine antigens were compared in infants receiving Prevnar (7-valent) and Prevnar 13. The proportion of responders at pre-specified antibody levels are shown in Table 17. Responses to all antigens in Prevnar 13 recipients were similar to those in Prevnar (7-valent) recipients and met formal criteria for non-inferiority. Varicella responses as measured by a commercial whole cell ELISA kit, designed to detect immunity after natural infection, were low in both groups, but there was no evidence of interference with the immune response by concomitantly administered Prevnar 13.

Table 17: Subjects Achieving a Pre-specified Antibody Level for Concomitant Vaccine Antigens (in Study 6096A1-004, Study 6096A1-3005, and Study 6096A1-3008)

Concomitant Vaccine Name/ Vaccine Antigen (Prespecified Antibody Level)	Administered with Prevnar 13 % Responders (n^a/N^b)	Administered with Prevnar (7-valent) % Responders (n^a/N^b)
Pediarix (DTaP-IPV-HepB) Responses After the 3-dose Infant Series		
Dip (≥0.1 IU/mL)	95.7 (223/233)	96.1 (221/230)
Tet (≥0.1 IU/mL)	98.4 (181/184)	98.5 (193/196)
PT ≥16.5 EU/mL	94.1 (225/239)	95.0 (228/240)
FHA ≥40.5 EU/mL	96.7 (231/239)	95.0 (228/240)
PRN ≥26 EU/mL	93.7 (224/239)	95.8 (230/240)
Polio Type 1 (titer ≥1:8)	100.0 (183/183)	100.0 (187/187)
Polio Type 2 (titer ≥1:8)	98.9 (181/183)	99.5 (186/187)
Polio Type 3 (titer ≥1:8)	100.0 (182/182)	99.5 (186/187)
HBV ≥10.0 mIU/mL	100.0 (153/153)	100.0 (173/173)
ActHIB (PRP) Responses After the Infant Series		
Hib (PRP) (≥0.15 µg/mL)	97.9 (232/237)	97.8 (225/230)
Hib (PRP) (≥1.0 µg/mL)	77.6 (184/237)	78.3 (180/230)
Pentacel (DTaP-IPV-Hib) Responses After the Infant Series		
Hib (PRP) (≥0.15 µg/mL)	97.8 (266/272)	99.6 (265/266)
Hib (PRP) (≥1.0 µg/mL)	81.6 (222/272)	84.6 (225/266)
PT ≥12.00 EU/mL	98.6 (278/282)	96.0 (266/277)
FHA ≥20.00 EU/mL	99.3 (281/283)	95.7 (266/278)
PRN ≥7.00 EU/mL	96.8 (274/283)	96.0 (266/277)
FIM ≥4.00 EU/mL	93.6 (264/282)	95.3 (262/275)

Table 17: Subjects Achieving a Pre-specified Antibody Level for Concomitant Vaccine Antigens (in Study 6096A1-004, Study 6096A1-3005, and Study 6096A1-3008) (Cont'd)

Concomitant Vaccine Name/ Vaccine Antigen (Prespecfied Antibody Level)	Administered with Prevnar 13 % Responders (n^a/N^b)	Administered with Prevnar (7-valent) % Responders (n^a/N^b)
PedvaxHIB (PRP-OMP) Responses at 12-15 Months Following Infant Series with ActHIB		
Hib (PRP) (≥0.15 µg/mL)	100.0 (230/230)	100.0 (214/214)
Hib (PRP) (≥1.0 µg/mL)	90.4 (208/230)	92.1 (197/214)
ProQuad (MMR-Varicella) Responses at 12-15 Months		
Measles (≥1.10 I.V.)	96.4 (213/221)	97.1 (204/210)
Mumps (≥1.10 I.V.)	76.5 (169/221)	72.9 (153/210)
Rubella (≥15 IU/mL)	91.9 (192/209)	90.7 (185/204)
Varivax (Varicella) Responses at 12-15 Months		
Varicella (≥1.25 gpELISA units/mL)	100 (163/163)	100 (173/173)
Varicella (≥5.00 gpELISA units/mL)	98.8 (161/163)	97.7 (169/173)

a. Number of subjects achieving the pre-specified antibody level
b. Number of subjects in the evaluable immunogenicity population

In Study 104, the immunogenicity of concomitantly administered Prevnar 13 with quadrivalent meningococcal polysaccharide conjugate vaccine (tetanus toxoid conjugate; MenACWY-TT) versus Prevnar 13 or MenACWY-TT given alone was evaluated in toddlers 12-14 months of age who had previously received the infant series of Prevnar 13. Immune responses were evaluated by comparison of GMCs for each of the 13 pneumococcal serotypes and by percentage of subjects with rabbit complement serum bactericidal assay (rSBA) titers ≥1:8 for each of the 4 meningococcal serogroups one month after receiving a single dose of either or both vaccines. The non-inferiority of the immune response to Prevnar 13 when co-administered with MenACWY-TT versus Prevnar 13 given alone was demonstrated for each pneumococcal serotype separately (lower limit of 2-sided 95% CI of the GMC ratio >0.5). Additionally, the non-inferiority of the immune response to MenACWY-TT when co-administered with Prevnar 13 compared with MenACWY-TT given alone was demonstrated for each meningococcal serogroup separately (lower limit of 95% CI for group difference in % subjects with rSBA titers ≥1:8 was ≥-10% for each serogroup).

Effect on Nasopharyngeal Carriage

The effect of pneumococcal conjugate vaccination on nasopharyngeal (NP) carriage was studied in a randomized, double-blind study (6096A1-3006) in which infants received either Prevnar 13 (N=930) or Prevnar (7-valent) (N=933) at 2, 4, 6 and 12 months of age in Israel. Values were statistically significantly lower in Prevnar 13 recipients if the upper bound of the 95% confidence interval (CI) for the rate ratio (new acquisition) or odds ratio (prevalence) (Prevnar 13/Prevnar 7-valent) was less than 1. Prevnar 13 significantly reduced newly identified NP acquisition of the 6

additional serotypes (and serotype 6C) combined (21.8% vs 38.4%) and of individual serotypes 1 (0.0% vs 0.9%), 6A (7.7% vs 13.2%), 6C (2.7% vs 6.0%), 7F (0.3% vs 1.3%), and 19A (12.6% vs 22.9%) when compared with Prevnar (7-valent). There was no reduction seen for serotype 3 and for serotype 5 the colonization was too infrequent to assess impact. For 6 of the remaining 7 common serotypes, similar rates of NP acquisition were observed in both vaccine groups; for serotype 19F a significant reduction was observed in the Prevnar 13 group (7.9% vs 12.2%).

In a surveillance study in France in children presenting with acute otitis media (AOM), changes in nasopharyngeal (NP) carriage of pneumococcal serotypes were evaluated following introduction of Prevnar (7-valent) and subsequently Prevnar 13.[2] Carriage of pneumococcal serotypes overall was significantly reduced in children vaccinated with at least 1 dose of Prevnar 13 compared with Prevnar (7-valent) (53.9% vs 64.6%; p=0.002). In addition, Prevnar 13 significantly reduced NP carriage of the 6 additional serotypes combined (9.5% versus 20.7%; p<0.001) and individual serotypes 19A (7.5% versus 15.4%; p<0.001), 7F (0.5% vs 2.8%; p=0.002) and 6C (3.7% vs 8.4%; p=0.003) when compared to Prevnar (7-valent). A reduction in carriage was also seen for serotype 3 (1.1% vs 2.5%; p=0.1). There was no carriage of serotypes 1 or 5 observed. This study is limited by the short observation period and the fact that it is not a randomized controlled trial. Another limitation is that only children with AOM were enrolled in this study; as the NP flora of normal children could be very different, further studies are needed to assess the impact of Prevnar 13 on this population.

Efficacy Against Acute Otitis Media and Pneumonia

There are no randomized, placebo-controlled trials of Prevnar 13 against AOM and pneumonia. However, the efficacy and effectiveness of Prevnar (7-valent) has been established for invasive disease, pneumonia and otitis media.

Effectiveness of Prevnar (7-valent) using a 4-dose schedule (3 doses in the first year of life with a booster dose in the second year) has also been observed against AOM and pneumonia since its introduction in a national immunization programme. In a retrospective evaluation of a large US insurance database, AOM visits were reduced by 42.7% (95% CI, 42.4-43.1%), and prescriptions for AOM by 41.9% in children younger than 2 years of age, compared with a pre-licensure baseline (2004 vs. 1997-99). In a similar analysis, hospitalisations and ambulatory visits for all-cause pneumonia were reduced by 52.4% and 41.1%, respectively. For those events specifically identified as pneumococcal pneumonia, the observed reductions in hospitalisations and ambulatory visits were 57.6% and 46.9%, respectively, in children younger than 2 years of age, compared with a pre-licensure baseline (2004 vs. 1997-99).

Effectiveness of Prevnar (7-valent) against AOM and pneumonia has also been observed in Quebec after the implementation of a publicly funded program in all children using a 3-dose immunization schedule (2 doses in the first year of life with a booster dose in the second year). In the 3 years following vaccine introduction, there was a 13.2% reduction in otitis media claims attributable to Prevnar (7-valent) and an estimated 100,000 otitis media visits averted in children under 5 years of age. Similarly, a 13% reduction in hospital admissions for all-cause pneumonia was observed with no increase in cases of empyema.

While direct cause-and-effect cannot be concluded from observational analyses of this type,

these findings suggest that Prevnar (7-valent) plays an important role in reducing the burden of mucosal disease (AOM and pneumonia) in the target population.

Effectiveness of Prevnar 13 against AOM due to the six additional S. pneumoniae serotypes included in Prevnar 13 (i.e., 1, 3, 5, 6A, 7F, and 19A) has been observed in a prospectively designed, single-centre, non-randomized pediatric surveillance study in the US (4-dose schedule).

Study B1851018 evaluated the effectiveness of Prevnar 13 against AOM in children who were recruited after receiving 3 doses of Prevnar 13 in the first year of life, at a single site in the US that performed tympanocentesis nearly universally for AOM. Of the 239 children who were under 30 months of age who enrolled in the study, 162 (67.8%) completed (followed until approximately 30 to 36 months of age) and 77 (32.2%) withdrew. For comparative purposes, the analysis of historical data from the same center, collected prior to the market authorization of Prevnar 13, was conducted on 348 children who had received 3 doses of Prevnar (7-valent).

Details regarding the disposition of subjects in the Prevnar 13 and Prevnar cohorts and the distribution of middle ear fluid (MEF) samples obtained during AOM visits in each cohort are shown in Table 18 and Table 19 below. Of the MEF samples positive for S. pneumoniae, the proportion identified as one of the 6 additional serotypes included in Prevnar 13 was 46/89 (51.7%) in the period of Prevnar use (2007 to 2009) and 4/53 (7.5%) in the period of Prevnar 13 use (2010 to 2015). These findings should be interpreted with caution, as this observational study is limited by a reliance on historical data to serve as a comparator and by a lack of randomization.

Table 18: Summary of Subject Disposition (Study B1851018)

	Prevnar 13	Prevnar
Total number of children enrolled	239	348
Children presenting to the clinic with an episode of AOM, n	103	169
Children who provided at least 1 MEF sample during an AOM visit, n	90	166
Total number of MEF samples collected at AOM visits	255	426
Total number of MEF samples positive for any bacterial pathogen	223	284
Abbreviations: AOM = acute otitis media; MEF = middle ear fluid.		

Table 19: Summary of Results (Study B1851018)

	Prevnar 13	Prevnar
Total number of MEF samples collected at AOM visits positive for any S. pneumoniae serotype[a]	53	89
Total number (%) of MEF samples positive for:		
Serotype 3	2 (3.8%)	4 (4.5%)
Serotype 6A	0 (0.0%)	6 (6.7%)
Serotype 19A	2 (3.8%)	36 (40.4%)
Any of the 6 additional serotypes in Prevnar 13 (1, 3, 5, 6A, 7F, 19A)[b]	4 (7.5%)	46 (51.7%)

Abbreviations: AOM = acute otitis media; MEF = middle ear fluid.
[a] 41/90 (45.6%) and 70/166 (42.2%) of children provided at least 1 sample (collected at an AOM visit) positive for any S. pneumoniae serotype.
[b] No samples collected at an AOM visit were positive for serotypes 1, 5 or 7F.

2. Clinical Trials in Children and Adolescents 5 to 17 Years of Age

An open-label study in the US (study 6096A1-3011) evaluated the immunogenicity, safety and tolerability of Prevnar 13 in 592 healthy children and adolescents 5-17 years of age, including 17.4% of subjects with a history of asthma.[4] A single dose of Prevnar 13 was given to children 5 to <10 years of age previously vaccinated with at least 1 dose of Prevnar (7-valent), and to children and adolescents 10-17 years of age who had never received a pneumococcal vaccine.

In children 5 to <10 years of age previously vaccinated with at least 1 dose of Prevnar (7-valent), and in pneumococcal vaccine-naïve children and adolescents 10-17 years of age, 1 dose of Prevnar 13 elicited immune responses to all 13 serotypes.
In children 5 to <10 years of age, serum IgG concentrations for the 7 common serotypes 1 month after administration of a single dose of Prevnar 13 (study 6096A1-3011) were non-inferior (i.e., the lower limit of the 2-sided 95% CI for the Geometric Mean Ratio [GMR] of >0.5) to those elicited by the fourth dose of Prevnar (7-valent) at 12-15 months of age (study 6096A1-3005). In addition, IgG concentrations elicited by a single dose of Prevnar 13 for the 6 additional serotypes in children 5 to <10 years of age were non-inferior to those elicited by the fourth dose of Prevnar 13 at 12-15 months of age (study 6096A1-3005) as shown in Tables 20 and 21.

Table 20: Comparison of Pneumococcal IgG GMCs (µg/mL) for the 7 Common Serotypes After a Single Dose of Prevnar 13 (Study 6096A1-3011) Relative to Prevnar (7-valent) After the Fourth Dose (Study 6096A1-3005)[a]

Serotype (Common)	Vaccine Group (as Enrolled/Randomized)						Ratio[e]	(95% CI[f])
	Prevnar 13 5 to <10 years of age (Study 6096A1-3011)			Prevnar (7-valent) 12-15 months of age (Study 6096A1-3005)				
	n[b]	GMC[c]	(95% CI[d])	n[b]	GMC[c]	(95% CI[d])		
4	169	8.45	(7.24, 9.87)	173	2.79	(2.45, 3.18)	3.03	(2.48, 3.71)
6B	171	53.56	(45.48, 63.07)	173	9.47	(8.26, 10.86)	5.66	(4.57, 6.99)
9V	171	9.51	(8.38, 10.78)	172	1.97	(1.77, 2.19)	4.83	(4.10, 5.70)
14	169	29.36	(24.78, 34.78)	173	8.19	(7.31, 9.18)	3.58	(2.93, 4.39)
18C	171	8.23	(7.13, 9.51)	173	2.33	(2.05, 2.65)	3.53	(2.91, 4.29)
19F	171	17.58	(14.95, 20.67)	173	3.31	(2.87, 3.81)	5.31	(4.29, 6.58)
23F	169	11.26	(9.79, 12.95)	173	4.49	(3.86, 5.23)	2.51	(2.04, 3.08)

[a] Evaluable Immunogenicity Population: subjects who were eligible for the study, were within the specified age range on the day of vaccination, had valid and determinate assay results, had their blood drawn before and after vaccination within the required time frames, and had no major protocol violations
[b] n = Number of subjects with a determinate antibody concentration for the specified serotype.
[c] Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw. GMCs after the fourth dose for Prevnar (7-valent) (study 6096A1-3005).
[d] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.
[e] Ratio of GMCs: Prevnar 13 (study 6096A1-3011) to Prevnar (7-valent) (study 6096A1-3005).
[f] CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Prevnar 13 [study 6096A1-3011] – Prevnar (7-valent) [study 6096A1-3005]).

Table 21: Comparison of Pneumococcal IgG GMCs (µg/mL) for Additional 6 Serotypes After a Single Dose of Prevnar 13 (Study 6096A1-3011) Relative to Prevnar 13 After Fourth Dose (in Study 6096A1-3005)[a]

Serotype (Additional)	Vaccine Group (as Enrolled/Randomized)						Ratio[e]	(95% CI[f])
	Prevnar 13 (5 to <10 years) (Study 6096A1-3011)			Prevnar 13 (12-15 Months) (Study 6096A1-3005)				
	n[b]	GMC[c]	(95% CI[d])	n[b]	GMC[c]	(95% CI[d])		
1	171	3.57	(3.05, 4.18)	1068	2.90	(2.75, 3.05)	1.23	(1.07, 1.42)
3	171	2.38	(2.07, 2.74)	1065	0.75	(0.72, 0.79)	3.17	(2.78, 3.62)
5	171	5.52	(4.82, 6.32)	1068	2.85	(2.72, 2.98)	1.94	(1.71, 2.20)
6A	169	21.51	(18.15, 25.51)	1063	7.11	(6.78, 7.46)	3.03	(2.64, 3.47)
7F	170	6.24	(5.49, 7.08)	1067	4.39	(4.18, 4.61)	1.42	(1.24, 1.62)
19A	170	17.18	(15.01, 19.67)	1056	8.44	(8.05, 8.86)	2.03	(1.78, 2.32)

[a] Evaluable Immunogenicity Population: subjects who were eligible for the study, were within the specified age range on the day of vaccination, had valid and determinate assay results, had their blood drawn before and after vaccination within the required time frames, and had no major protocol violations

[b] n = Number of subjects with a determinate antibody concentration for the specified serotype.

[c] Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw. GMCs after fourth dose for Prevnar 13 (study 6096A1-3005).

[d] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.

[e] Ratio of GMCs: Prevnar 13 (study 6096A1-3011) to Prevnar 13 (study 6096A1-3005).

[f] CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (Prevnar 13 [study 6096A1-3011] – Prevnar 13 [study 6096A1-3005]).

In children and adolescents 10-17 years of age, OPA GMTs 1 month after vaccination were non-inferior (i.e., the lower limit of the 2-sided 95% CI for the GMR of >0.5) to OPA GMTs in the 5 to <10 year old group for 12 of the 13 serotypes (except for serotype 3), as shown in Table 22.

Table 22: Comparison of Pneumococcal OPA GMTs After Vaccination, Prevnar 13 (10-17 years) Relative to Prevnar 13 (5 to <10 years) in Study 6096A1-3011[a]

Serotype	Vaccine Group						Ratio[e]	(95% CI[f])
	Prevnar 13 (10-17 years)			Prevnar 13 (5 to <10 years)				
	n[b]	GMT[c]	(95% CI[d])	n[b]	GMT[c]	(95% CI[d])		
Common								
4	188	6912	(6101.2, 7831.4)	181	4629	(4017.2, 5334.3)	1.5	(1.24, 1.80)
6B	183	14224	(12316.4, 16427.3)	178	14996	(13164.1, 17083.1)	0.9	(0.78, 1.15)
9V	186	4485	(4001.1, 5027.5)	180	4733	(4203.3, 5328.4)	0.9	(0.80, 1.12)
14	187	6894	(6028.3, 7884.0)	176	4759	(4120.4, 5497.0)	1.4	(1.19, 1.76)
18C	182	6263	(5436.4, 7215.1)	175	8815	(7738.2, 10041.0)	0.7	(0.59, 0.86)
19F	184	2280	(1949.4, 2667.6)	178	1559	(1293.3, 1878.9)	1.5	(1.15, 1.86)
23F	187	3808	(3354.7, 4322.6)	176	3245	(2818.8, 3735.5)	1.2	(0.97, 1.42)
Additional								
1	189	319	(271.2, 376.0)	179	187	(160.4, 218.6)	1.7	(1.36, 2.13)
3	181	114	(100.4, 129.4)	178	202	(180.9, 226.3)	0.6	(0.48, 0.67)
5	183	336	(270.3, 417.6)	178	491	(426.3, 565.3)	0.7	(0.53, 0.89)
6A	182	9928	(8457.0, 11654.8)	178	7514	(6350.8, 8890.7)	1.3	(1.05, 1.67)

Table 22: Comparison of Pneumococcal OPA GMTs After Vaccination, Prevnar 13 (10-17 years) Relative to Prevnar 13 (5 to <10 years) in Study 6096A1-3011[a]

	Vaccine Group							
	Prevnar 13 (10-17 years)			Prevnar 13 (5 to <10 years)				
Serotype	n[b]	GMT[c]	(95% CI[d])	n[b]	GMT[c]	(95% CI[d])	Ratio[e]	(95% CI[f])
7F	185	6584	(5829.4, 7435.5)	178	10334	(9099.0, 11736.8)	0.6	(0.53, 0.76)
19A	187	1276	(1131.7, 1439.0)	180	1180	(1047.5, 1329.4)	1.1	(0.91, 1.28)

[a] Evaluable Immunogenicity Population: subjects who were eligible for the study, were within the specified age range on the day of vaccination, had valid and determinate assay results, had their blood drawn before and after vaccination within the required time frames, and had no major protocol violations

[b] n = Number of subjects with a determinate antibody titer for the specified serotype.

[c] Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.

[d] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.

[e] Ratio of GMTs: Prevnar 13 (10 to 17 years) to Prevnar 13 (5 to <10 years).

[f] CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures [Prevnar 13 (10 to 17 years) – Prevnar 13 (5 to <10 years)].

3. Clinical Trials in Adults

Of the 48,806 adults in the 7 studies (6115A1-004, 6115A1-3005, 6115A1-3010, 6115A1-3000, 6115A1-3001, 6115A1-3008, 6115A1-3006) of the clinical development program who received Prevnar 13, 899 (1.8%) were 18 to 49 years of age, 2,616 (5.4%) were 50 to 64 years of age, 30,793 (63.1%) were 65 to 74 years of age, and 14,498 (29.7%) were 75 years of age and over.

Table 23: Overview of Clinical Trials in Adults

Study #	Study Design	Study Subjects	Number Vaccinated	Dosage Regimen
6115A1-004[8,9]	Cohort 1 Randomized, active-controlled, modified double-blind[a] multicentre	Cohort 1 Male and female adults 60-64 years of age; PPSV23-unvaccinated	Cohort 1 13vPnC: 417; PPSV23: 414	Cohort 1 One IM dose of study vaccine (13vPnC or PPSV23)
	Cohort 2 Open-label, multicentre	Cohort 2 Male and female adults 50-59 years of age; PPSV23-unvaccinated	Cohort 2 404	Cohort 2 One IM dose of 13vPnC
	Cohort 3 Open-label, multicentre	Cohort 3 Male and female adults 18-49 years of age; PPSV23-unvaccinated	Cohort 3 18-49: 899 (18-29: 300 30-39: 298 40-49: 301)	Cohort 3 One IM dose of 13vPnC
6115A1-3005[7]	Randomized, active-controlled, modified double-blind, multicentre	Male and female adults ≥ 70 years of age; PPSV23-prevaccinated ≥ 5 years	13vPnC: 463; PPSV23: 473	Year 0: One IM dose of study vaccine (13vPnC or PPSV23)
6115A1-3010	Randomized, active-controlled, modified, double-blind	Male and female adults 60-64 years of age; PPSV23-unvaccinated	13vPnC: 478; PPSV23: 237	Year 0: One IM dose of study vaccine (13vPnC or PPSV23)
6115A1-3000	Single-arm, open-label, multicentre	Male and female adults ≥ 68 years of age; PPSV23-prevaccinated ≥ 3 years	1049	One IM dose of 13vPnC
6115A1-3001[3]	Randomized, double-blind, multicentre	Male or female adults 50-59 years of age; PPSV23-unvaccinated	Group 1: 551	Group 1 One IM dose each of TIV + 13vPnC, followed 1 month later by one IM dose of placebo
			Group 2: 560	Group 2 One IM dose each of TIV + placebo, followed 1 month later by one IM dose of 13vPnC
6115A1-3008[14]	Randomized, double-blind, multicentre	Male or female adults ≥ 65 years of age; PPSV23-unvaccinated	Group 1: 577	Group 1 One IM dose each of TIV + 13vPnC, followed 1 month later by one IM dose of placebo
			Group 2: 575	Group 2 One IM dose each of TIV + placebo, followed 1 month later by one IM dose of 13vPnC

Table 23: Overview of Clinical Trials in Adults

Study #	Study Design	Study Subjects	Number Vaccinated	Dosage Regimen
6115A1-3006[1]	Randomized, double-blind, placebo-controlled, single-centre with sentinel centres	Male or female adults ≥ 65 years of age; PPSV23-unvaccinated	13vPnC: 42,240 Placebo: 42,256	One IM dose of 13vPnC or placebo

Abbreviations: 13vPnC: Prevnar 13; PPSV23: 23-valent pneumococcal polysaccharide vaccine; TIV: trivalent influenza vaccine

[a] Modified double-blind means that the site staff dispensing and administering the vaccine were unblinded, but all other study personnel including the principal investigator and subject were blinded.

Prevnar 13 Efficacy Study in Adults 65 Years and Older

The efficacy of Prevnar 13 against vaccine-type (VT) pneumococcal CAP and IPD was assessed in a large-scale, randomized, double-blind, placebo-controlled study conducted over ~4 years in the Netherlands (Community-Acquired Pneumonia Immunization Trial in Adults [CAPiTA]; Study 6115A1-3006).[1] A total of 84,496 subjects 65 years and older received a single vaccination of either Prevnar 13 or placebo in a 1:1 randomization: 42,240 subjects were vaccinated with Prevnar 13 and 42,256 subjects were vaccinated with placebo. The study relied on a surveillance system for reporting cases of suspected pneumonia and IPD. Surveillance for suspected pneumonia and IPD was conducted from September 2008 through August 2013, ending after the prespecified number of first episodes of VT-CAP had been identified. The statistical approach used to analyse the data did not account for subject-specific follow-up time.

Among the 84,496 subjects, 58,072 (68.7%) were ≥65 to <75 years of age, 23,481 (27.8%) were ≥75 and <85 years of age, and 2,943 (3.5%) were ≥85 years of age, and 56.0% of subjects were male. Adults with immunocompromising conditions or those receiving immunosuppressive therapy were excluded, but those with pre-existing medical conditions were eligible for enrollment. In the safety population (n=84,492), 42.3% of subjects had pre-existing medical conditions including heart disease (25.4%), diabetes mellitus with or without insulin use (12.5%), lung disease (10.2%) and asthma (4.9%). Smoking was reported at baseline by 12.3% of subjects.

The primary endpoint was the prevention of a first episode of confirmed VT-CAP (defined as the presence of ≥2 prespecified clinical criteria, chest X-ray consistent with CAP as determined by a central committee of radiologists, and positive VT-specific Urinary Antigen Detection assay [UAD][6,12] or isolation of VT S. pneumoniae from blood or other sterile site). The secondary endpoints were the prevention of a first episode of 1) confirmed nonbacteraemic/noninvasive (NB/NI) VT-CAP (an episode of VT-CAP for which the blood culture result and any other sterile site culture results were negative for S. pneumoniae) and 2) VT-IPD (the presence of S. pneumoniae in a sterile site). The per-protocol population was the primary population for analysis of all primary and secondary efficacy objectives. The per-protocol population included subjects who were eligible for the study, received the vaccine and had no major protocol violations. In addition, the subjects who were identified as CAP or IPD cases were not immune-

deficient/suppressed at the time of hospitalisation with CAP or IPD, and the onset of symptoms was at least 14 days after vaccination.

In the per-protocol population, Prevnar 13 demonstrated statistically significant vaccine efficacy (VE) in preventing a first episode of VT pneumococcal CAP (VE 45.56%; 95.2% CI, 21.82-62.49; p=0.0006), the primary endpoint of the study, with 49 and 90 episodes in the Prevnar 13 and placebo groups, respectively.

Statistically significant efficacy was also demonstrated for the two secondary endpoints in the per-protocol population. For first episodes of NB/NI VT pneumococcal CAP, efficacy was 45.00% (95.2% CI, 14.21-65.31; p=0.0067), with 33 and 60 episodes in the Prevnar 13 and placebo groups, respectively. For first episodes of VT-IPD, efficacy was 75.00% (95.2% CI, 41.06-90.87; p=0.0005; post-hoc multiplicity adjusted CI), with 7 and 28 episodes in the Prevnar 13 and placebo groups, respectively.

Prevnar 13 Immunogenicity Clinical Trials in Adults

An antipolysaccharide binding IgG antibody level to predict protection against invasive pneumococcal disease or non-bacteraemic pneumonia has not been defined for adults. However, nonclinical and clinical data support functional antibody, measured by opsonophagocytic assay (OPA), as a contributor to protection against pneumococcal disease. OPA provides an *in vitro* measurement of the ability of serum antibodies to eliminate pneumococci by promoting complement-mediated phagocytosis and is believed to reflect relevant *in vivo* mechanisms of protection against pneumococcal disease. OPA titers are expressed as the reciprocal of the highest serum dilution that reduces survival of the pneumococci by at least 50%. Pivotal trials for Prevnar 13 were designed to show that functional OPA antibody responses for the Prevnar 13 serotypes are non-inferior and for some serotypes superior to the common serotypes in the currently licensed pneumococcal polysaccharide vaccine (PPSV23).

Serotype-specific OPA geometric mean titers (GMTs) measured 1 month after each vaccination were calculated. Non-inferiority between vaccines was defined as the lower bound of the 2-sided, 95% confidence interval (CI) for the ratio of the GMTs (GMR) >0.5 (2-fold criterion); statistically significantly greater responses were defined as the lower bound of the 2-sided 95% CI for the GMR >1.

The response to the additional serotype 6A, which is unique to Prevnar 13 but not in PPSV23, was assessed by demonstration of a 4-fold increase in the specific OPA titer above pre-immunization levels. Superiority of the response for Prevnar 13 was defined as the lower bound of the 2-sided, 95% CI for the difference in percentages of adults achieving a 4-fold increase in OPA titer greater than zero. For comparison of OPA GMTs (secondary endpoint), a statistically greater response for serotype 6A was defined as the lower bound of the 2-sided 95% CI for the GMR >2.

Five phase 3 clinical trials (6115A1-004[8,9], 6115A1-3005[7], 6115A1-3010, 6115A1-3001[3], 6115A1-3008[14]) were conducted in the U.S. and Europe evaluating the immunogenicity of Prevnar 13 in different age groups, and in individuals who were either not previously vaccinated

with PPSV23 (PPSV23 unvaccinated) or had received 1 or more doses of PPSV23 (PPSV23 pre-vaccinated). These trials are summarized in Table 23.

Each study included healthy adults and immunocompetent adults with stable underlying conditions including chronic cardiovascular disease, chronic pulmonary disease, renal disorders, diabetes mellitus, chronic liver disease including alcoholic liver disease, and alcoholism, because it is known that these are common conditions in adults that increase risk of serious pneumococcal community-acquired pneumonia and invasive pneumococcal disease.

Two pivotal non-inferiority trials were conducted in which Prevnar 13 response was compared to PPSV23 immune response, 1 in PPSV23 unvaccinated adults aged 50-64 years (6115A1-004), and 1 in PPSV23 pre-vaccinated adults aged ≥70 years (6115A1-3005). One study (6115A1-3000) in PPSV23 pre-vaccinated adults collected safety data only. Two studies (6115A1-3001 and 6115A1-3008) assessed the concomitant administration of Prevnar 13 with seasonal trivalent influenza vaccine (TIV).

Clinical Trials Conducted in Adults Not Previously Vaccinated With PPSV23

In an active-controlled modified[1] double-blind clinical trial (6115A1-004) of Prevnar 13 in the US, PPSV23-unvaccinated adults aged 60-64 years were randomly assigned (1:1) to receive Prevnar 13 or PPSV23. In addition, adults aged 18-49 years (with age sub-groups 18-29 years, 30-39 years, 40-49 years) and 50-59 years were enrolled non-randomised and received 1 dose of Prevnar 13 (open-label).[8,9]

The OPA antibody responses elicited by Prevnar 13 were non-inferior to those elicited by PPSV23 for the 12 serotypes in common to both vaccines. In the per-protocol pre-defined analysis, not adjusted for multiplicity ($p<0.05$), 8 of the serotypes in common exhibited a statistically significantly greater immune response after Prevnar 13 compared with after PPSV23. In a post-hoc, multiplicity adjusted analysis ($p<0.004$), 7 of the serotypes in common exhibited a statistically significantly greater immune response after Prevnar 13 compared with response after PPSV23.

For serotype 6A, which is unique to Prevnar 13, the proportions of adults with a 4-fold increase after Prevnar 13 (88.5%) were significantly greater than after PPSV23 (49.3%) in PPSV23-unvaccinated adults aged 60-64 years (co-primary endpoint).

The OPA responses elicited by Prevnar 13 in adults aged 50-59 years were non-inferior to the Prevnar 13 responses in adults aged 60-64 years for all 13 serotypes. In addition, 9 of the 13 serotypes exhibited a statistically significantly greater immune response in adults aged 50-59 years compared with adults aged 60-64 years (see Table 24).

This clinical trial demonstrated that the immune responses elicited by Prevnar 13 are non-inferior and for most serotypes statistically significantly greater than PPSV23. In addition, the immune responses in adults aged 50-59 years were non-inferior and for most serotypes statistically significantly greater than those observed in adults aged 60-64 years. However, the clinical

[1] Modified double-blind means that the site staff dispensing and administering the vaccine were unblinded, but all other study personnel including the principal investigator and subject were blinded.

relevance of statistically significantly higher immune response elicited by Prevnar 13 for some of the serotypes is unknown.

Table 24: OPA GMTs in PPSV23 Unvaccinated Adults Aged 50-59 Years Given Prevnar 13, and in Adults Aged 60-64 Years Given Prevnar 13 or PPSV23 (in Study 6115A1-004)[a]

	Prevnar 13	**Prevnar 13**	**PPSV23**	**Prevnar 13, 50-59 Relative to 60-64 Years**		**Prevnar 13 Relative to PPSV23, 60-64 Years**	
	50-59 Years[b] N=350-384	**60-64 Years** N=359-404	**60-64 Years** N=367-402				
Serotype	GMT	GMT	GMT	GMR	(95% CI)	GMR	(95% CI)
1	200	146	104	1.4	(1.08, 1.73)	1.4	(1.10, 1.78)
3	91	93	85	1.0	(0.81, 1.19)	1.1	(0.90, 1.32)
4	2833	2062	1295	1.4	(1.07, 1.77)	1.6	(1.19, 2.13)
5	269	199	162	1.4	(1.01, 1.80)	1.2	(0.93, 1.62)
6B	3212	1984	788	1.6	(1.24, 2.12)	2.5	(1.82, 3.48)
7F	1520	1120	405	1.4	(1.03, 1.79)	2.8	(1.98, 3.87)
9V	1726	1164	407	1.5	(1.11, 1.98)	2.9	(2.00, 4.08)
14	957	612	692	1.6	(1.16, 2.12)	0.9	(0.64, 1.21)
18C	1939	1726	925	1.1	(0.86, 1.47)	1.9	(1.39, 2.51)
19A	956	682	352	1.4	(1.16, 1.69)	1.9	(1.56, 2.41)
19F	599	517	539	1.2	(0.87, 1.54)	1.0	(0.72, 1.28)
23F	494	375	72	1.3	(0.94, 1.84)	5.2	(3.67, 7.33)
6A†	4328	2593	213	1.7[c]	(1.30, 2.15)	12.1[d]	(8.63, 17.08)

GMT, Geometric Mean Titer.
GMR, Geometric Mean Ratio.

† 6A is a serotype unique to Prevnar 13 but not contained in PPSV23.

[a] Non-inferiority was defined as the lower limit of the 2-sided 95% CI for GMR greater than 0.5. Statistically significantly greater responses were defined as the lower bound of the 2-sided 95% CI for the GMR greater than 1.

[b] This cohort was non-randomized and received open-label Prevnar 13.

[c] For serotype 6A, comparison of OPA GMTs was a primary endpoint with respect to comparing Prevnar 13 responses across age groups.

[d] For serotype 6A, which is unique to Prevnar 13, comparison of OPA GMTs to PPSV23 was a secondary endpoint. A statistically significantly greater response was defined as the lower bound of the 2 sided 95% CI for the GMR greater than 2.

Table 25 shows OPA GMTs 1 month after vaccination in subjects 18-29 years of age, 30-39 years of age, and 40-49 years of age given a single dose of Prevnar 13. It also shows a comparison of OPA GMTs in subjects 18-49 years of age and 60-64 years of age.

Table 25: OPA GMTs in Adults Aged 18-49 Years and Adults Aged 60-64 Years Given Prevnar 13 (in Study 6115A1-004)[a,b]

	18-29 Years N=276-290	30-39 Years N=276-288	40-49 Years N=279-290	18-49 Years N=836-866	60-64 Years N=359-404	18-49 Years Relative to 60-64 Years	
Serotype	**GMT[b]**	**GMT[b]**	**GMT[b]**	**GMT[b]**	**GMT[b]**	**GMR**	**(95% CI[c])**
1	409	353	305	353	146	2.4	(2.03, 2.87)
3	112	93	72	91	93	1.0	(0.84, 1.13)
4	7152	4589	3229	4747	2062	2.3	(1.92, 2.76)
5	567	375	271	386	199	1.9	(1.55, 2.42)
6A	8476	6131	3626	5746	2593	2.2	(1.84, 2.67)
6B	14134	10180	6571	9813	1984	4.9	(4.13, 5.93)
7F	3741	3276	2792	3249	1120	2.9	(2.41, 3.49)
9V	5086	3208	2292	3339	1164	2.9	(2.34, 3.52)
14	4452	2919	2049	2983	612	4.9	(4.01, 5.93)
18C	5240	3841	3171	3989	1726	2.3	(1.91, 2.79)
19A	2162	1504	1209	1580	682	2.3	(2.02, 2.66)
19F	2251	1507	1076	1533	517	3.0	(2.44, 3.60)
23F	2954	1606	814	1570	375	4.2	(3.31, 5.31)

[a] Non-inferiority was defined as the lower limit of the 2-sided 95% CI for GMR was greater than 0.5.
[b] Statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GMR greater than 1.
[c] Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures.

In adults aged 18-49 years, OPA GMTs to all 13 serotypes in Prevnar 13 were non-inferior to the Prevnar 13 responses in adults aged 60-64 years. For 12 serotypes (serotype 3 being the exception), immune responses were related to age, with adults aged 18-49 years showing statistically significantly greater responses than adults aged 60-64 years. Similarly, statistically significantly greater responses for 12 serotypes were observed for adults in age subgroups 18-29 years, 30-39 years and 40-49 years compared with adults aged 60-64 years. OPA GMTs were highest in adults aged 18-29 years and lowest in adults aged 60-64 years.

One year after vaccination with Prevnar 13, OPA titers in the 18-49 year age group had declined compared to titers measured 1 month after vaccination, ranging from 23 to 2948; however, OPA titers for all serotypes remained higher than levels measured at baseline, ranging from 5 to 186.

Clinical Trials Conducted in Adults Previously Vaccinated With PPSV23 (Pre-vaccinated)
In a phase 3 active-controlled, modified double-blind clinical trial (6115A1-3005) of Prevnar 13 in the US and Sweden, PPSV23-prevaccinated adults aged ≥70 years who had received 1 dose of PPSV23 ≥5 years prior were randomly assigned (1:1) to receive either Prevnar 13 or PPSV23.[7]

The OPA antibody responses elicited by Prevnar 13 were non-inferior for the 12 serotypes in common to those elicited by PPSV23 when the vaccines were administered at a minimum of 5 years after PPSV23. In the per-protocol pre-defined analysis, not adjusted for multiplicity ($p<0.05$), 10 of the serotypes in common exhibited a statistically significantly greater immune response after Prevnar 13 compared with after PPSV23. In a post-hoc, multiplicity adjusted analysis ($p<0.004$), 9 of the serotypes in common exhibited a statistically significantly greater immune response after Prevnar 13 compared with response after PPSV23.

For serotype 6A, which is unique to Prevnar 13, the proportion of adults with a 4-fold increase after Prevnar 13 (71.1%) was significantly greater than after PPSV23 (27.3%) in PPSV23-pre-vaccinated adults aged ≥70 years (co-primary endpoint).

This clinical trial demonstrated that in adults aged ≥70 years and pre-vaccinated with PPSV23 ≥ 5 years prior, vaccination with Prevnar 13 shows an improved immune response as compared to revaccination with PPSV23.

Table 26: OPA GMTs in PPSV23 Previously Vaccinated Adults Aged ≥70 Years (in Study 6115A1-3005) Given Prevnar 13 or PPSV23[a]

Serotype	Prevnar 13 N=400-426 GMT	PPSV23 N=395-445 GMT	Prevnar 13 Relative to PPSV23	
			Ratio	(95% CI)
1	81	55	1.5	(1.17, 1.88)
3	55	49	1.1	(0.91, 1.35)
4	545	203	2.7	(1.93, 3.74)
5	72	36	2.0	(1.55, 2.63)
6B	1261	417	3.0	(2.21, 4.13)
7F	245	160	1.5	(1.07, 2.18)
9V	181	90	2.0	(1.36, 2.97)
14	280	285	1.0	(0.73, 1.33)
18C	907	481	1.9	(1.42, 2.50)
19A	354	200	1.8	(1.43, 2.20)
19F	333	214	1.6	(1.17, 2.06)
23F	158	43	3.7	(2.69, 5.09)
6A†	903	94	9.6[b]	(7.00, 13.26)

GMT, Geometric Mean Titer.

† 6A is a serotype unique to Prevnar 13 but not contained in PPSV23.

[a] Non-inferiority was defined as the lower limit of the 2-sided 95% CI for GMR greater than 0.5. Statistically significantly greater responses defined as the lower bound of the 2-sided 95% CI for the GMR greater than 1.

[b] For serotype 6A, which is unique to Prevnar 13, comparison of OPA GMTs to PPSV23 was a secondary endpoint. A statistically significantly greater response was defined as the lower bound of the 2 sided 95% CI for the GMR greater than 2.

Clinical Trials to Assess Prevnar 13 Given With Seasonal Trivalent Inactivated Influenza Vaccine (TIV) in Adults

Two randomized, double-blind clinical trials (6115A1-3001 and 6115A1-3008) evaluated the immunogenicity of Prevnar 13 given with TIV (A/H1N1, A/H3N2, and B strains) in adults who were PPSV23 unvaccinated aged 50-59 years and in adults ≥ 65 years.

Each clinical trial compared concomitant administration of Prevnar 13 and TIV (administered in opposite arms) to either TIV given with placebo or to Prevnar 13 given alone. One group received Prevnar 13 and TIV concurrently, followed approximately 1 month later by placebo; whereas the other group received TIV and placebo concurrently, followed approximately 1 month later by Prevnar 13.

A phase 3 randomized, double-blind clinical trial (6115A1-3001) of Prevnar 13 given with TIV in adults aged 50-59 years who were PPSV23 unvaccinated in the US assessed the immune responses of TIV when TIV was given with Prevnar 13 compared with TIV given with placebo (in the following called TIV alone).[3]

A phase 3 randomized, double-blind clinical trial (6115A1-3008) of Prevnar 13 given with TIV in adults aged ≥65 years who were PPSV23 unvaccinated in Europe assessed the immune responses of TIV when TIV was given with Prevnar 13 compared with TIV given with placebo.[14]

Immune responses elicited by TIV were measured by haemagglutination inhibition (HAI) assays 1 month after TIV vaccination. The immune responses were measured as the proportion of adults achieving a ≥4-fold increase in HAI titer (responder) for each TIV strain 1 month after vaccination.

The studies also assessed the immune responses of Prevnar 13 when Prevnar 13 was given with TIV compared with Prevnar 13 given alone. The immune responses elicited by Prevnar 13 were measured by ELISA IgG GMC 1 month after Prevnar 13 vaccination.

Compatibility of concomitant TIV and Prevnar 13 administration was demonstrated only if the lower limits of the 2-sided 95% CIs for all 3 influenza virus subtype comparisons were > -0.10 and all 13 pneumococcal serotype GMC ratio comparisons were > 0.5.

TIV immune responses 50-59 years of age: Non-inferiority was met for all 3 TIV strains after Prevnar 13 given concomitantly with TIV compared to TIV alone (Table 27).

TIV immune responses in ≥65 years of age: Non-inferiority was met for A/H1N1, and B-strains but not for A/H3N2 with a lower limit of the 95% CI of -10.4% (Table 28).

Table 27: Proportion of Participants Aged 50–59 Years with a ≥ 4-fold Increase in HAI Titer After Trivalent Inactivated Influenza Vaccine (TIV) with Prevnar 13 and TIV With Placebo (in Study 6115A1-3001)

TIV HAI	TIV + Prevnar 13		TIV + Placebo		Difference
	n/N	% (95% CI)	n/N	% (95% CI)	% (95% CI)
A/H1N1	445/530	84.0 (80.6, 87.0)	431/531	81.2 (77.6, 84.4)	2.8 (-1.8, 7.4)
A/H3N2	377/530	71.1 (67.1, 75.0)	369/531	69.5 (65.4, 73.4)	1.6 (-3.9, 7.2)
B	321/530	60.6 (56.3, 64.8)	320/531	60.3 (56.0, 64.5)	0.3 (-5.6, 6.2)

HAI, haemagglutination inhibition assay

Table 28: Proportion of Participants Aged ≥ 65 Years with a ≥ 4-fold Increase in HAI Titer After Trivalent Inactivated Influenza Vaccine (TIV) with Prevnar 13 and TIV With Placebo (in Study 6115A1-3008)

TIV HAI	TIV + Prevnar 13 n/N	TIV + Prevnar 13 % (95% CI)	TIV + Placebo n/N	TIV + Placebo % (95% CI)	Difference % (95% CI)
A/H1N1	440/548	80.3 (76.7, 83.5)	429/546	78.6 (74.9, 81.9)	1.7 (-3.1, 6.5)
A/H3N2	316/545	58.0 (53.7, 62.2)	341/545	62.6 (58.4, 66.6)	-4.6 (-10.4, 1.3)
B	286/548	52.2 (47.9, 56.4)	295/546	54.0 (49.7, 58.3)	-1.8 (-7.8, 4.1)
HAI, haemagglutination inhibition assay					

Prevnar 13 immune responses in 50-59 year olds: Non-inferiority was met for all serotypes Table 29).

Prevnar 13 immune responses in ≥65 year olds: Non-inferiority was met for all serotypes except serotype 19F. The lower limit of the 95% CI of the GMR for 19F was 0.49 [criterion 0.5] (Table 30).

All point estimates of the GMC ratios were below 1. For some of the serotypes, the immune response was statistically significantly lower, compared to the response when Prevnar 13 was given alone in both of the age groups.

Table 29: Pneumococcal IgG GMC 1 Month After Prevnar 13 and Trivalent Inactivated Influenza Vaccine (TIV); and 1 Month After Prevnar 13 (Given 1 Month After Placebo and TIV) for Participants 50-59 Years (in Study 6115A1-3001) [a]

	Post-dose 1	Post-dose 2	Vaccine Comparison
	Prevnar 13 + TIV (N=247-294)	**Prevnar 13*** (N=247-289)	
Serotype	GMC, µg/mL	GMC, µg/mL	Ratio (95% CI)
1	4.05	5.45	0.74 (0.58, 0.95)
3	1.15	1.46	0.79 (0.66, 0.93)
4	2.35	3.41	0.69 (0.55, 0.87)
5	6.03	7.18	0.84 (0.67, 1.05)
6A	5.78	6.70	0.86 (0.70, 1.06)
6B	7.58	10.09	0.75 (0.60, 0.93)
7F	8.14	10.57	0.77 (0.63, 0.95)
9V	4.96	6.97	0.71 (0.59, 0.86)
14	10.77	14.05	0.77 (0.60, 0.98)
18C	9.65	13.49	0.72 (0.58, 0.88)
19A	16.80	18.84	0.89 (0.74, 1.08)
19F	6.13	7.13	0.86 (0.67, 1.10)
23F	7.17	8.54	0.84 (0.66, 1.08)

GMC, geometric mean concentration.
* Given 4 weeks after Placebo and TIV.
[a] Antibody measured by a standardized ELISA.

Table 30: Pneumococcal IgG GMC 1 Month After Prevnar 13 and Trivalent Inactivated Influenza Vaccine (TIV); and 1 Month After Prevnar 13 (Given 1 Month After Placebo and TIV) for Participants ≥ 65 Years (in Study 6115A1-3008)[a]

	Post-dose 1	Post-dose 2	Vaccine Comparison
	Prevnar 13 + TIV (N=247-294)	**Prevnar 13*** (N=247-289)	
Serotype	GMC, µg/mL	GMC, µg/mL	Ratio (95% CI)
1	2.52	3.20	0.79 (0.60, 1.04)
3	1.08	1.15	0.94 (0.78, 1.13)
4	2.15	3.24	0.66 (0.51, 0.87)
5	4.74	6.90	0.69 (0.55, 0.86)
6A	4.61	6.10	0.76 (0.61, 0.94)
6B	6.24	6.43	0.97 (0.75, 1.25)
7F	7.63	9.04	0.84 (0.67, 1.07)
9V	4.97	6.21	0.80 (0.63, 1.02)
14	8.95	12.44	0.72 (0.53, 0.97)
18C	8.88	11.07	0.80 (0.64, 1.01)
19A	11.93	17.10	0.70 (0.56, 0.87)
19F	4.78	7.39	0.65 (0.49, 0.85)
23F	5.82	6.11	0.95 (0.71, 1.27)

GMC, geometric mean concentration.
* Given 4 weeks after Placebo and TIV.
[a] Antibody measured by a standardized ELISA.

In a post-hoc analysis without multiplicity adjustment, the non-inferiority of immune responses of OPA GMT to Prevnar 13 given with TIV was not achieved for some of the serotypes in subjects 50-59 years old and 65 years or older compared to those of Prevnar 13 alone recipients.

Clinical Trial to Assess Prevnar 13 Given With Seasonal QIV in Adults

A randomized, double-blind postmarketing study conducted in the US evaluated the immunogenicity of Prevnar 13 given with inactivated QIV (Fall 2014/Spring 2015 Fluzone, A/H1N1, A/H3N2, B/Brisbane, and B/Massachusetts strains) in adults aged ≥50 years who had been vaccinated with PPSV23 at least one year previously. Individuals with immunosuppression, immune deficiency and severe chronic disease were excluded from the study. One group received Prevnar 13 and QIV concurrently, followed approximately 1 month later by placebo. The other group received QIV and placebo concurrently, followed approximately 1 month later by Prevnar 13.

The antibody responses elicited by Prevnar 13 were measured as OPA GMTs 1 month after Prevnar 13 vaccination. Noninferiority was demonstrated if the lower limit of the 2-sided 95% CI for the OPA GMT ratios (Prevnar 13 + QIV relative to Prevnar 13 alone) was >0.5. Prevnar 13 OPA antibody responses met noninferiority for all 13 serotypes after Prevnar 13 was given concomitantly with QIV compared to Prevnar 13 given alone (Table 31).

Table 31 Pneumococcal OPA GMTs 1 Month After Prevnar 13 and QIV and 1 Month After Prevnar 13 (Given 1 Month After Placebo and QIV)

	Prevnar 13 + QIV (n[a]=412-425)	**Prevnar 13** (n[a]=405-419)	**Vaccine Comparison**
Serotype	GMT[b]	GMT[b]	Ratio[c] (95% CI[d])
1	75	83	0.9 (0.74, 1.12)
3	41	49	0.8 (0.70, 0.98)
4	587	824	0.7 (0.55, 0.91)
5	97	101	1.0 (0.78, 1.18)
6A	953	1413	0.7 (0.53, 0.85)
6B	867	1041	0.8 (0.64, 1.08)
7F	651	670	1.0 (0.83, 1.14)
9V	699	838	0.8 (0.69, 1.00)
14	574	760	0.8 (0.62, 0.92)
18C	713	865	0.8 (0.64, 1.06)
19A	337	390	0.9 (0.72, 1.04)
19F	324	360	0.9 (0.71, 1.14)
23F	278	364	0.8 (0.56, 1.03)

Abbreviations: GMT = geometric mean titer; OPA = opsonophagocytic activity.

a n = Number of subjects with a determinate OPA titer to the given serotype.

b GMTs were calculated using all subjects with available data for the specified blood draw.

c Ratio of GMTs (Prevnar 13+QIV/placebo to placebo+QIV/Prevnar 13) was calculated by back transforming the mean difference between vaccine sequences on the logarithmic scale.

d CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (Prevnar 13+QIV/placebo – placebo+QIV/Prevnar 13).

Antibody responses elicited by QIV were measured by HAI 1 month after QIV vaccination. The immune responses were measured as hemagglutination inhibition assay (HAI) GMTs for each QIV strain 1 month after vaccination. Noninferiority was demonstrated for each vaccine antigen if the lower limit of the 2-sided 95% CI for the GMT ratio of the HAI titer was >0.5.

Noninferiority was demonstrated for each of the 4 QIV strains after Prevnar 13 was given concomitantly with QIV compared with QIV given alone (Table 32).

Table 32 HAI GMTs 1 Month After Prevnar 13 With QIV and Placebo With QIV

	Prevnar 13 + QIV n[a] =427	Placebo + QIV n[a]=430	Vaccine Comparison	
Strain	**GMT[b]**	**GMT[b]**	**Ratio[c]**	**(95% CI[d])**
A/H1N1	115	113	1.0	(0.88, 1.18)
A/H3N2	226	196	1.2	(1.01, 1.32)
B/Brisbane	28	26	1.1	(0.95, 1.24)
B/Massachusetts	45	43	1.0	(0.90, 1.21)

Abbreviations: GMT = geometric mean titer; HAI = hemagglutination inhibition assay.
a n = Number of subjects with a determinate HAI titer to the given strain.
b GMTs were calculated using all subjects with available data for the specified blood draw.
c Ratio of GMTs (Prevnar 13+QIV/placebo to placebo+QIV/Prevnar 13) was calculated by back transforming the mean difference between vaccine sequences on the logarithmic scale.
d. CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (Prevnar 13+QIV/placebo – placebo+QIV/Prevnar 13).

4. Clinical Trials in Special Populations

Individuals with the conditions described below have an increased risk of pneumococcal disease.

Sickle Cell Disease

An open-label, single-arm study (6096A1-3014 [B1851013]) with 2 doses of Prevnar 13 given 6 months apart was conducted in 158 children and adolescents ≥6 to <18 years of age with sickle cell disease who were previously vaccinated with 1 or more doses of PPSV23 at least 6 months prior to enrollment. After the first vaccination, Prevnar 13 elicited antibody levels measured by both IgG GMCs and OPA GMTs that were higher when compared to levels prior to vaccination. After the second dose, IgG GMCs and OPA GMTs were generally comparable to those after the first dose. One year after the second dose, antibody levels measured by both IgG GMCs and OPA GMTs were higher than levels prior to the first dose of Prevnar 13, except the IgG GMCs for serotypes 3 and 5 that were numerically similar. The clinical benefit of the second dose remains uncertain.

HIV Infection

Children and adults not previously vaccinated with a pneumococcal vaccine

In study 6115A1-3002 (B1851021), HIV-infected children and adults (CD4 ≥200 cells/µL, viral load <50,000 copies/mL and free of active AIDS-related illness) not previously vaccinated with a pneumococcal vaccine received 3 doses of Prevnar 13. As per general recommendations, a single dose of PPSV23 was subsequently administered. Vaccines were administered at 1 month intervals. Immune responses were assessed in 259-270 evaluable subjects approximately 1 month after each dose of vaccine. After the first dose, Prevnar 13 elicited antibody levels, measured by both IgG GMCs and OPA GMTs, that were statistically significantly higher when compared to levels prior to vaccination. After the second and third dose of Prevnar 13, immune responses

were similar or higher than those after the first dose. The clinical benefit of the second and third doses remains uncertain.

Adults previously vaccinated with 23-valent pneumococcal polysaccharide vaccine
In study 6115A1-3017 (B1851028), immune responses were assessed in 329 HIV-infected adults ≥18 years of age (CD4+ T-cell count ≥200 cells/uL, viral load <50,000 copies/mL and free of active AIDS-related illness) previously vaccinated with PPSV23 administered at least 6 months prior to enrollment. Subjects received 3 doses of Prevnar 13, at enrollment, 6 months and 12 months after the first dose of Prevnar 13. After the first vaccination, Prevnar 13 elicited antibody levels measured by both IgG GMCs and OPA GMTs that were higher when compared to levels prior to vaccination. After the second and third dose of Prevnar 13, IgG GMCs and OPA GMTs were comparable to or higher than those after the first dose. Subjects who received 2 or more previous doses of PPSV23 (n=119-138) showed a similar immune response compared with subjects who received a single previous dose (n=97-117). The clinical benefit of the second and third doses remains uncertain.

Hematopoietic Stem Cell Transplant
In study 6115A1-3003 (B1851022), children and adults with an allogeneic HSCT at ≥2 years of age (complete hematologic remission of underlying disease or very good partial remission in the case of lymphoma and myeloma) received 3 doses of Prevnar 13 with an interval of at least 1 month between doses. The first dose was administered at 3 to 6 months after HSCT. A fourth (booster) dose of Prevnar 13 was administered 6 months after the third dose. As per general recommendations, a single dose of PPSV23 was administered 1 month after the fourth dose of Prevnar 13. Immune responses as measured by IgG GMCs were assessed in 168-211 evaluable subjects approximately 1 month after vaccination. Prevnar 13 elicited increased antibody levels after each dose of Prevnar 13. Immune responses after the fourth dose of Prevnar 13 were significantly increased for all serotypes compared with after the third dose for the overall age group (age ≥ 2 years).

TOXICOLOGY

A repeated dose intramuscular (5 IM doses) rabbit toxicity study of Prevnar 13 resulted in the generation of serotype-specific antibody responses and did not demonstrate any significant local or systemic adverse effects. In addition, there were no significant adverse findings in a single-dose IM local tolerance study in rabbits.

In single-dose subcutaneous (SC) safety pharmacology studies of Prevnar 13 in rats or monkeys, there were no effects on central nervous, respiratory, or cardiovascular systems. In repeated dose (7 SC doses) toxicity studies in rats and monkeys, no significant adverse effects were observed. In addition, in a repeated dose (5 SC doses) toxicity study in juvenile rats, no significant adverse effects were observed.

A reproductive toxicity study in female rabbits showed that IM administration of Prevnar 13 prior to mating and during gestation did not affect fertility, embryo/fetal development, or post-natal development.

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PART III: CONSUMER INFORMATION

Prevnar® 13

Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein)

This leaflet is part III of a three-part "Product Monograph" published when Prevnar® 13 was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Prevnar® 13. Contact your doctor, nurse or pharmacist if you have any questions about the vaccine.

ABOUT THIS VACCINE

What the vaccine is used for:
Prevnar 13 is a pneumococcal vaccine given to:

- **Children from 6 weeks to 5 years** to help protect against diseases such as: bacteraemic pneumonia (lung infection with bacteria in the blood stream), sepsis or bacteraemia (bacteria in the blood stream), meningitis (inflammation around the brain) and ear infections.
- **Children from 6 years to 17 years** to help protect against diseases such as: bacteraemic pneumonia (lung infection with bacteria in the blood stream), sepsis or bacteraemia (bacteria in the blood stream), and meningitis (inflammation around the brain).
- **Adults aged 18 years and older** to help prevent diseases such as: pneumonia (lung infection), bacteraemic pneumonia (lung infection with bacteria in the blood stream), sepsis or bacteraemia (bacteria in the blood stream), and meningitis (inflammation around the brain).

What it does:
The vaccine works by helping the body to make its own antibodies, which protects you or your child against diseases caused by thirteen types of the bacteria Streptococcus pneumoniae.

When it should not be used:
If you or your child is allergic (hypersensitive) to the active substances, to any other ingredients, or to any other vaccine that contains diphtheria toxoid.

What the medicinal ingredient is:
The active substances are:

- 2.2 µg of saccharide for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F and 23F
- 4.4 µg of saccharide for serotype 6B

Conjugated to CRM_{197} carrier protein and adsorbed on aluminum phosphate (0.125 mg aluminum).

What the important nonmedicinal ingredients are:
Sodium chloride, succinic acid, Polysorbate 80 and water for injection.

What dosage forms it comes in:
The vaccine is a white suspension for injection and provided in a single-dose, pre-filled syringe (0.5 mL). Pack size of 1 or 10, without needle.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Take special care with Prevnar 13:

- If you or your child has any present or past medical problems after any dose of Prevnar (7-valent) or Prevnar 13
- If you or your child is sick with a high fever
- If you or your child has any bleeding problems

Prevnar 13 will only protect against disease caused by the types of Streptococcus pneumoniae in the vaccine.

As with any vaccine, Prevnar 13 will not protect 100% of those who receive the vaccine.

BEFORE you use Prevnar 13 talk to your doctor or pharmacist:

Please tell your doctor, nurse or pharmacist if you or your child is taking, or has recently taken any other medicines, including medicines obtained without prescription, or has recently received any other vaccine.

Increased reporting rates of seizures (fits), with or without fever, and collapse or shock-like state were observed when Prevnar 13 was given at the same time as Infanrix hexa.

Some of the effects mentioned under the section "Side Effects and What To Do About Them" may temporarily affect the ability to drive or use machines.

INTERACTIONS WITH THIS VACCINE

The vaccine is not to be mixed with other vaccines/products in the same syringe.

Different injectable vaccines should always be given at different vaccination-sites.

PROPER USE OF THIS VACCINE

Usual dose:
The doctor or nurse will inject the recommended dose (0.5 mL) of the vaccine into you or your child's arm or leg muscle.

Infants and children
Typically, your child should receive 3 or 4 doses of the vaccine. According to official recommendations in your province, an alternative schedule may be used by your health care provider. Each dose will be given on a separate occasion. It is important to follow the instructions from the doctor/nurse so that your child completes the course of injections.

Premature infants (born < 37 weeks of gestation) should receive the vaccine according to the same schedule as full-term infants.

Prevnar 13 can be given at the same time as other childhood vaccines; in this case, different vaccination-sites should be used. Prevnar 13 should not be mixed with any other vaccines in the same syringe.

Children and adolescents 6 to 17 years of age (prior to 18th birthday)
Prevnar 13 is to be administered as a single dose to children and adolescents 6 to 17 years of age.

Adults aged 18 years and older
Prevnar 13 is to be administered as a single dose to adults 18 years and older including those previously vaccinated with pneumococcal polysaccharide vaccine.

The need for revaccination with a subsequent dose of Prevnar 13 has not been established.

Special populations
Individuals not previously vaccinated with Prevnar 13 and considered to be at a higher risk of pneumococcal infection (such as those with sickle cell disease or HIV infection) may receive 1 dose of Prevnar 13, including those previously vaccinated with pneumococcal polysaccharide vaccine.

Individuals with a stem cell transplant (blood-forming) may receive 3 injections, with the first given at 3 to 6 months after the transplant and with an interval of at least 1 month between doses. A fourth injection (booster) is recommended 6 months after the third injection.

Overdose:
Overdose with Prevnar 13 is unlikely due to it being in a pre-filled syringe.

In case of overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to go back to the doctor or nurse at the scheduled time, ask the doctor or nurse for advice.

If you have any further questions on the use of Prevnar 13, ask your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all vaccines, Prevnar 13 can cause side effects, although not everybody gets them.

The following side effects include those reported for Prevnar 13 in infants and children aged 6 weeks to 5 years.

The most common side effects reported in at least 1 in 10 children are:
- Decreased appetite
- Irritability
- Drowsiness/increased sleep, restless sleep/decreased sleep
- Fever; any pain, tenderness, redness, swelling or hardness at the vaccination-site

Common side effects reported in at least 1 in 100 children, but less than 1 in 10 children are:
- Diarrhea, vomiting
- Rash
- Fever > 39°C, pain or tenderness at the vaccination-site interfering with movement

Uncommon side effects reported in at least 1 in 1,000 children, but less than 1 in 100 children are:
- Crying
- Seizures (including febrile seizures)
- Urticaria or urticaria-like rash
- Redness, swelling, or hardness at the vaccination-site > 7.0 cm

Rare side effects reported in at least 1 in 10,000 children, but less than 1 in 1,000 children are:
- Hypotonic-hyporesponsive episode (collapse or shock-like state)
- Hypersensitivity reaction including swelling of the face and/or lips, difficulty in breathing

In babies born very prematurely (at or before 28 weeks of gestation), longer gaps than normal between breaths may occur for 2-3 days after vaccination.

The following side effects include those reported for Prevnar 13 in children and adolescents aged 5-17 years of age.

The most common side effects reported in at least 1 in 10 children and adolescents 5-17 years of age were:
- Decreased appetite
- Irritability
- Any pain, tenderness (including impaired movement), redness, swelling or hardness at the vaccination-site
- Drowsiness/increased sleep, restless sleep/decreased sleep

Common side effects reported in at least 1 in 100 but less than 1 in 10 children and adolescents 5-17 years of age were:
- Hives (urticaria)
- Fever

Children and adolescents aged 6-17 years with sickle cell disease or with HIV infection, and children and adolescents aged 2-17 years with a blood-forming stem cell transplant, generally had similar frequencies of side effects as healthy children and adolescents aged 5-17 years; however, the frequencies of muscle pain, fatigue, headache, joint pain, vomiting, fever and diarrhea were very common (>1/10).

Other side effects observed in other age groups may also be applicable in this age group but due to the small sample size in this study were not seen.

The following side effects include those reported for Prevnar 13 in adults aged 18 years and older.

The most common side effects reported in at least 1 in 10 adults are:
- Decreased appetite
- Headache
- Diarrhea; vomiting (in adults aged 18-49 years)
- Rash
- New joint pain/aggravated joint pain; new muscle pain/aggravated muscle pain
- Chills; fatigue; any pain, tenderness, redness, swelling or hardness at the injection site; limitation of arm movement

Common side effects reported in at least 1 in 100 adults, but less than 1 in 10 adults are:
- Vomiting (in adults aged 50 years and over)
- Fever

Uncommon side effects reported in at least 1 in 1,000 adults, but less than 1 in 100 adults are:
- Nausea
- Hypersensitivity reaction including swelling of the face and/or lips, difficulty breathing
- Enlarged lymph nodes (lymphadenopathy) in the region of the injection site.

Adults 18 years and older with HIV infection, or with a blood-forming stem cell transplant, had similar frequencies of side effects as healthy adults 18 years and older, however the frequencies of fever were very common (>1/10).

Other side effects have been seen with Prevnar 13 since being introduced onto the market:
- Enlarged lymph nodes (lymphadenopathy) in the region of the vaccination-site
- Anaphylactic/anaphylactoid reaction including shock (cardiovascular collapse)
- Angioneurotic edema, erythema multiforme
- Vaccination-site dermatitis, vaccination-site urticaria, vaccination-site pruritus

Please speak with your doctor or pharmacist should you have any questions or concerns. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist	
		Only if severe	**In all cases**
Common	Diarrhea; vomiting	✓	
	Rash	✓	
	Fever greater than 39°C		✓
	Vaccination-site swelling	✓	
Uncommon	Seizures		✓
Rare	Hypotonic-hyporesponsive episode (collapse or shock-like state)		✓
	Hypersensitivity reaction including facial swelling, difficulty breathing		✓

This is not a complete list of side effects. For any unexpected effects while taking Prevnar 13, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach and sight of children.

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Do not use Prevnar 13 after the expiry date stated on the carton and label. The expiry date refers to the last day of that month. Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

To monitor vaccine safety, the Public Health Agency of Canada collects case reports on adverse events following immunization.

For Health Care Professionals:
If a patient experiences an adverse event following immunization, please complete the appropriate Adverse Events Following Immunization (AEFI) Form and send it to your local Health Unit in **your province/territory**.

For the General Public:
Should you experience an adverse event following immunization, please ask your doctor, nurse, or pharmacist to complete the Adverse Events Following Immunization (AEFI) Form.

If you have any questions or have difficulties contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada.

By toll-free telephone: 866-844-0018
By toll-free fax: 866-844-5931
Email: caefi@phac-aspc.gc.ca
Web: http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php

Mail:
The Public Health Agency of Canada
Vaccine Safety Section
130 Colonnade Road, A/L 6502A
Ottawa, ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at www.pfizer.ca or can be obtained by contacting the sponsor, Pfizer Canada ULC, at: 1-800-463-6001 (Medical Information).

This leaflet was prepared by Pfizer Canada ULC

Last revised: August 8, 2019