PT. PFIZER INDONESIA
Local Product Document

Generic Name: Pneumococcal 13-valent Conjugate Vaccine
Trade Name: Prevenar 13™
CDS Effective Date: July 01, 2019
Supersedes: July 13, 2017

1. NAME OF THE MEDICINAL PRODUCT

Prevenar 13 suspension for injection
Pneumococcal polysaccharide conjugated vaccine, (13-valent, adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 mL) contains:

Pneumococcal polysaccharide serotype 1*	2.2 µg
Pneumococcal polysaccharide serotype 3*	2.2 µg
Pneumococcal polysaccharide serotype 4*	2.2 µg
Pneumococcal polysaccharide serotype 5*	2.2 µg
Pneumococcal polysaccharide serotype 6A*	2.2 µg
Pneumococcal polysaccharide serotype 6B*	4.4 µg
Pneumococcal polysaccharide serotype 7F*	2.2 µg
Pneumococcal polysaccharide serotype 9V*	2.2 µg
Pneumococcal polysaccharide serotype 14*	2.2 µg
Pneumococcal polysaccharide serotype 18C*	2.2 µg
Pneumococcal polysaccharide serotype 19A*	2.2 µg
Pneumococcal polysaccharide serotype 19F*	2.2 µg
Pneumococcal polysaccharide serotype 23F*	2.2 µg

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

3. PHARMACEUTICAL FORM

Suspension for injection.

The vaccine is a homogeneous white suspension.

Supplied as a pre-filled syringe, single dose vials and multidose vials (4 doses per vial).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Children 6 weeks to 5 years of age

Active immunization for the prevention of invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* in infants and children from 6 weeks to 5 years of age (see sections **4.4 Special Warnings and Precautions for Use** and **5.1**

Pharmacodynamic Properties for information on protection against specific pneumococcal serotypes).

Adults 50 years of age and older

Prevenar 13 is indicated for active immunization for prevention of pneumococcal disease (including pneumonia and invasive disease) in adults 50 years of age and older caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

This indication is based on immune responses elicited by Prevenar 13, and there have been no controlled trials in adults demonstrating a decrease in invasive pneumococcal disease or pneumococcal pneumonia after vaccination with Prevenar 13.

The use of Prevenar 13 should be determined on the basis of official recommendations taking into consideration the impact of invasive disease in different age groups as well as the variability of serotype epidemiology in different geographical areas.

4.2 Posology and Method of Administration

Posology

For intramuscular use only.

The dose is 0.5 mL given intramuscularly, with care to avoid injection into near nerves and blood vessel. The vaccine should not be injected in the gluteal area. Do not administer Prevenar 13 intravascularly.

Children 6 weeks to 5 years of age

The immunization schedules for Prevenar 13 should be based on official recommendations.

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

Infants Aged 6 weeks-6 months

3-dose primary series

The recommended immunization series consists of 4 doses, each of 0.5 mL. The primary infant series consists of 3 doses, with the first dose usually given at 2 months of age and with an interval of at least 1 month between doses. The first dose may be given as early as 6 weeks of age. The fourth (booster) dose is recommended between 11 and 15 months of age.

2-dose primary series

Alternatively, when Prevenar 13 is given as part of a routine infant immunization program, a series consisting of 3 doses, each of 0.5 mL, may be given. The first dose may be administered from the age of 2 months, with a second dose 2 months later. The third (booster) dose is recommended between 11 and 15 months of age (see section **5.1 Pharmacodynamic Properties**).

Prevenar 13 Schedule for Preterm Infants (<37 weeks gestation)
In preterm infants, the recommended immunization series consists of 4 doses, each of 0.5 mL. The primary infant series consists of 3 doses, with the first dose given at 2 months of age and with an interval of at least 1 month between doses. The first dose may be given as early as six weeks of age. The fourth (booster) dose is recommended at approximately 12 months of age.

Unvaccinated Infants and Children ≥7 Months of Age
Infants aged 7-11 months
2 doses, each of 0.5 mL, with an interval of at least 1 month between doses. A third dose is recommended in the second year of life.

Children aged 12-23 months
2 doses, each of 0.5 mL, with an interval of at least 2 months between doses.

Children aged 2-5 years
One single dose of 0.5 mL.

Prevenar 13 Vaccine Schedule for Infants and Children Previously Vaccinated with pneumococcal 7-valent conjugate vaccine (Streptococcus pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F)
Prevenar 13 contains the same 7 serotypes included in pneumococcal 7-valent conjugate vaccine, using the same carrier protein CRM_{197}. Infants and children who have begun immunization with pneumococcal 7-valent conjugate vaccine may switch to Prevenar 13 at any point in the schedule.

Switch Vaccination Table

3-dose primary series			Booster Doses (12-24 months)	
7V	7V	7V	13V	13V
7V	7V	13V	13V	-
7V	13V	13V	13V	-

2-dose primary series		Booster Doses (12-24 months)	
7V	7V	13V	13V
7V	13V	13V	-

Children aged 12 - 23 months
Children who have not received 2 doses of Prevenar 13 during the infant series should receive 2 doses of the vaccine (with an interval of at least 2 months between doses) to complete the immunization series for the six additional serotypes.

Children aged 2 - 5 years
One single dose.

Adults 50 Years of Age and Older

Prevenar 13 is to be administered as a single dose to adults 50 years and older including those previously vaccinated with a pneumococcal polysaccharide vaccine.

The need for re-vaccination with a subsequent dose of Prevenar 13 has not been established. For specific guidelines, please refer to local recommendation.

Special Populations

Individuals who may be at higher risk of pneumococcal infection (i.e. individuals with HIV infection). Individuals who are previously vaccinated with 23-valent pneumococcal polysaccharide vaccine (PPSV23) may receive 2 doses of Prevenar 13 with interval of 6 months between doses. Individuals who are naïve may receive 2 doses of Prevenar 13 with interval of 1 month between dose. Prevenar 13 is not recommended for children below 2 years.

Method of Administration

The vaccine should be given by intramuscular injection. The preferred sites are the anterolateral aspect of the thigh (vastus lateralis muscle) in infants or the deltoid muscle of the upper arm in young children.

4.3 Contraindications

Hypersensitivity to the active substances, to any of the excipients, or to diphtheria toxoid.

As with other vaccines, the administration of Prevenar 13 should be postponed in subjects suffering from acute, severe febrile illness. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

4.4 Special Warnings and Precautions for Use

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

This vaccine should not be given to individuals with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection or to those receiving anticoagulant therapy, unless the potential benefit clearly outweighs the risk of administration.

Prevenar 13 will only protect against *Streptococcus pneumoniae* serotypes included in the vaccine, and will not protect against other microorganisms that cause invasive disease, pneumonia, or otitis media. As with any vaccine, Prevenar 13 may not protect all individuals receiving the vaccine from pneumococcal disease.

In clinical studies, Prevenar 13 elicited an immune response to all 13 serotypes included in the vaccine. The immune response for serotype 3 following the booster dose was not increased above the levels seen after the infant vaccination series; the clinical relevance

of this observation regarding the induction of serotype 3 immune memory is unknown (see section **5.1 Pharmacodynamic Properties**).

The proportions of functional antibody responders (Opsonophagocytic Activity (OPA) titres ≥1:8) to serotypes 1, 3 and 5 were high. However, the OPA geometric mean titres were lower than those against each of the remaining additional vaccine serotypes; the clinical relevance of this observation for protective efficacy is unknown (see section **5.1 Pharmacodynamic Properties**).

Individuals with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunization.

Limited data have demonstrated that pneumococcal 7-valent conjugate vaccine (3-dose primary series) induces an acceptable immune response in infants with sickle cell disease with a safety profile similar to that observed in non-high-risk groups (see section **5.1 Pharmacodynamic Properties**). Safety and immunogenicity data are not yet available for individuals in other specific high-risk groups for invasive pneumococcal disease (e.g., individuals with malignancy, hematopoietic stem, nephrotic syndrome). Vaccination in high-risk groups should be considered on an individual basis. Specific data are not yet available for Prevenar 13.

Children younger than 2 years old should receive the appropriate-for-age Prevenar 13 vaccination series (see section **4.2 Posology and Method of Administration**). The use of pneumococcal conjugate vaccine does not replace the use of 23-valent pneumococcal polysaccharide vaccines (PPSV23) in children ≥24 months of age with conditions (such as asthma, diabetes mellitus, sickle cell disease, asplenia, HIV infection, chronic illness, or those who are immunocompromised) placing them at higher risk for invasive disease due to *Streptococcus pneumoniae*. Whenever recommended, children at risk who are ≥24 months of age and already primed with Prevenar 13 should receive 23-valent pneumococcal polysaccharide vaccine. The interval between the 13-valent pneumococcal conjugate vaccine (Prevenar 13) and the 23-valent pneumococcal polysaccharide vaccine should not be less than 8 weeks. There are no data available to indicate whether the administration of 23-valent pneumococcal polysaccharide vaccine to unprimed children or to children primed with Prevenar 13 might result in hyporesponsiveness to further doses of Prevenar 13.

The potential risk of apnoea and the need for respiratory monitoring for 48 h – 72 h should be considered when administering the primary immunization series to very premature infants (born ≤28 weeks of gestation), and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

For vaccine serotypes, protection against otitis media is expected to be lower than protection against invasive disease. As otitis media is caused by many organisms other than pneumococcal serotypes represented in the vaccine, protection against all otitis media is expected to be low (see section **5.1 Pharmacodynamic Properties**).

Antipyretic treatment should be initiated according to local treatment guidelines for children with seizure disorders or with a prior history of febrile seizures and for all children receiving Prevenar 13 simultaneously with vaccines containing whole cell pertussis.

When Prevenar 13 is administered concomitantly with Infanrix hexa (DTaP HBV-IPV/Hib), the rates of febrile reactions are similar to those seen with concomitant administration of pneumococcal 7-valent conjugate vaccine and Infanrix hexa (see section **4.7 Undesirable Effects**).

Use in Specific Population
Pediatric Use
Safety and effectiveness of Prevenar 13 in children below the age of 6 weeks or on or after the 6th birthday have not been established. Prevenar 13 is not approved for use in children in these age groups.

Immune responses elicited by Prevenar 13 among infants born prematurely have not been specifically studied.

Geriatric Use
Prevenar 13 has been shown to be safe and immunogenic in the geriatric population.

Of the 48,806 adults enrolled 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 Prevenar 13 alone, 63.1% were 65 to 74 years of age, while 29.7% were 75 years of age and over. No clinically significant differences in safety or immunogenicity were observed between 65 to 74 year old individuals and greater than 75 year old individuals.

Additional Information in Special Populations
Individuals who may be at higher risk of pneumococcal infection (i.e., individuals with HIV infection) who are previously vaccinated with 23-valent pneumococcal polysaccharide vaccine (PPSV23) may receive 2 doses of Prevenar 13 with interval of 6 months between doses. Individuals who are naïve may receive 2 doses of Prevenar 13 with interval of 1 month between doses.

Adults with HIV infection had similar frequencies of adverse reactions as adults 50 years of age and older, except that fever and vomiting were very common and nausea was common.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction
Children 6 weeks to 5 years of age
Prevenar 13 can be given with any of the following vaccine antigens, either as monovalent or combination vaccines: diphtheria, tetanus, acellular or whole cell pertussis, *Haemophilus influenzae* type b, inactivated poliomyelitis, hepatitis B, meningococcal serogroup C, measles, mumps, rubella and varicella. Clinical studies

demonstrated that the immune responses and the safety profiles of the administered vaccines were unaffected.

Prevenar 13 can also be given concomitantly between 12-23 months of age with the tetanus toxoid conjugated meningococcal polysaccharide serogroups A, C, W and Y vaccine.

Data from a post marketing clinical study evaluating the impact of prophylactic use of antipyretics on the immune response to Prevenar 13 suggest that concomitant administration of paracetamol may reduce the immune response to Prevenar 13 after the infant series. The clinical significance of this observation is unknown.

In clinical trials, where there was concomitant administration of Prevenar 13 and rotavirus vaccine, no change in the safety profiles of these vaccines was observed.

Different injectable vaccines should always be given at different injection sites.

Adults aged 50 years and older
In adults, Prevenar 13 was administered concomitantly with *Trivalent influenza vaccine* (TIV).

When Prevenar 13 is administered at the same time as another injectable vaccine(s), the vaccines should always be administered with different syringes and given at different injection sites.

Do not mix Prevenar 13 with other vaccines/products in the same syringe.

4.6 Effects on Ability to Drive and Use Machines
Prevenar 13 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section **4.7 Undesirable Effects** may temporarily affect the ability to drive or use machines.

4.7 Undesirable Effects
Children 6 weeks to 5 years of age
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 to 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.

The most commonly reported adverse reactions were injection-site reactions, fever, irritability, decreased appetite, and increased and/or decreased sleep.

An increase in injection site reactions was reported in children older than 12 months compared to rates observed in infants during the primary series with Prevenar 13.

Adverse reactions reported in clinical studies or from the post-marketing experience are listed in the following table per body system and per frequency, and this is for all age groups.

Adults 50 years of age and older

The safety of Prevenar 13 was assessed in 6 clinical studies including 6,198 adults ranging in age from 50 to 95 years. Prevenar 13 was administered to 5,667 adults; 2,616 adults were aged 50 to 64 years and 3,051 adults were 65 years and older. Of the Prevenar 13 recipients 1,916 adults were previously vaccinated with PPSV23 at least 3 years prior, and 3,751 adults were PPSV23 unvaccinated. Frequencies shown below are for adults aged 50 to 64 years of age, and 65 and older. Subjects older than 65 years of age reported fewer events than younger adults, regardless of prior immunization status. Overall, the frequency categories were similar for both age groups.

Additional information in special populations

Adults with HIV previously vaccinated with the pneumococcal polysaccharide vaccine, have similar frequencies of adverse reactions as adults 50 years of age and older, except that vomiting was very common.

The frequency is defined as follows: very common: ≥1/10, common: ≥1/100 and <1/10, uncommon: ≥1/1,000 and <1/100, rare: ≥1/10,000 and <1/1,000, very rare: ≤1/10,000.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse Reactions from Clinical Trials

Children 6 weeks to 5 years of age

In clinical studies, the safety profile of Prevenar 13 was similar to pneumococcal 7-valent conjugate vaccine. The following frequencies are based on adverse reactions assessed as related to vaccination in Prevenar 13 clinical studies:

Immune system disorders

Rare : Hypersensitivity reaction including face oedema, dyspnoea, bronchospasm

Nervous system disorders

Very common : Drowsiness/increased sleep; restless sleep/decreased sleep
Uncommon : Seizure (including febrile convulsions)
Rare : Hypotonic-hyporesponsive episode

Gastrointestinal disorders

Very common: Decreased appetite
Common : Vomiting; diarrhoea

Skin and subcutaneous tissue disorders
Common : Rash
Uncommon : Urticaria or urticaria-like rash

General disorders and administration site conditions
Very common: Pyrexia; irritability; any injection-site erythema, induration/swelling or pain/tenderness; somnolence; poor quality sleep
injection-site erythema or induration/swelling 2.5 cm – 7.0 cm (after the booster dose and in older children [age 2 to 5 years])
Common : Pyrexia >39°C; injection-site pain/tenderness interfering with movement; injection-site erythema or induration/swelling 2.5 cm – 7.0 cm (after infant series)
Uncommon : Injection-site erythema, or induration/swelling >7.0 cm; Crying

Adults 50 years of age and older
Metabolism and nutrition disorders
Very common: Decreased appetite

Nervous system disorders
Very common: Headaches

Gastrointestinal disorders
Very common: Diarrhea
Common : Vomiting
Uncommon : Nausea

Immune system disorders
Uncommon : Hypersensitivity reaction including face edema, dyspnea, bronchospasm

Skin and subcutaneous tissue disorders
Very common : Rash

Musculoskeletal and connective tissue disorders
Very common : Generalized new/aggravated joint pain; generalized new/aggravated muscle pain

General disorders and administration site conditions
Very common : Chills; fatigue; injection-site erythema; injection-site induration/swelling; injection-site pain/tenderness; limitation of arm movement
Common : Fever
Uncommon : Lymphadenopathy localized to the region of injection site

Overall, no significant differences in frequencies of adverse reactions were noted if Prevenar 13 was given to adults pre-vaccinated with PPSV23 adults or PPSV23 unvaccinated. Frequency categories for all adverse reactions of adults aged 50 to 64 years and adults ≥65 years of age were similar.

Solicited Adverse Reactions in Adult Clinical Studies of Concomitant Administration of Prevenar 13 and TIV
Frequencies of local reactions in adults aged 50-59 years and in adults aged ≥65 years were similar after Prevenar 13 was administered with TIV compared to Prevenar 13 administered alone.

Higher frequency in some solicited systemic reactions was observed when Prevenar 13 administered concomitantly with TIV compared to TIV given alone (headache, chills, rash, decreased appetite, muscle and joint pain) or Prevenar 13 given alone (headache, fatigue, chills, decreased appetite, and joint pain).

Adverse Reactions from Pneumococcal 7-valent conjugate vaccine Post-marketing Experience
Children 6 weeks to 5 years of age
Although the following adverse drug reactions were not observed in the Prevenar 13 clinical studies, the following are considered adverse drug reactions for pneumococcal 7-valent conjugate vaccine and are considered adverse drug reactions for Prevenar 13 as well. These frequencies are based on spontaneous reporting rates for pneumococcal 7-valent conjugate vaccine.

Blood and lymphatic system disorders
Very rare : Lymphadenopathy (localised to the region of the injection site)

Immune system disorders
Rare : Anaphylactic/anaphylactoid reaction including shock;
Angioedema

Skin and subcutaneous tissue disorders
Very rare : Erythema multiforme

General disorders and administration site conditions
Rare : Injection-site urticaria; injection-site dermatitis;
injection-site pruritus; flushing

Additional information in special populations:
Apnoea in very premature infants (≤28 weeks of gestation) (see section **4.4 Special Warnings and Precautions for Use**).

4.8 Overdose
Overdose with Prevenar 13 is unlikely due to its presentation as a pre-filled syringe. However, there have been reports of overdose with Prevenar 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 schedules of Prevenar 13.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: pneumococcal vaccines; ATC code: J07AL02

Prevenar 13 contains the 7 pneumococcal capsular polysaccharides that are in pneumococcal 7-valent conjugate vaccine (4, 6B, 9V, 14, 18C, 19F, 23F) plus 6 additional polysaccharides (1, 3, 5, 6A, 7F, 19A) all conjugated to CRM197 carrier protein.

Children 6 weeks to 5 years of age

Based on serotype surveillance in Europe performed before the introduction of pneumococcal 7-valent conjugate vaccine, Prevenar 13 is estimated to cover 73%-100% (depending on the country) of serotypes causing invasive pneumococcal disease (IPD) in children less than 5 years of age. In this age group, serotypes 1, 3, 5, 6A, 7F, and 19A account for 15.6% to 59.7% of invasive disease, depending on the country, the time period studied, and the use of pneumococcal 7-valent conjugate vaccine.

Acute otitis media (AOM) is a common childhood disease with different aetiologies. Bacteria can be responsible for 60%-70% of clinical episodes of AOM. *Streptococcus pneumoniae* is one of the most common causes of bacterial AOM worldwide.

Prevenar 13 is estimated to cover over 90% of serotypes causing antibiotic-resistant IPD.

Prevenar 13 Immunogenicity Clinical Studies

The protective efficacy of Prevenar 13 against IPD has not been studied. As recommended by the World Health Organization (WHO) the assessment of potential efficacy against IPD has been based on a comparison of immune responses to the seven common serotypes shared between Prevenar 13 and pneumococcal 7-valent conjugate vaccine, for which protective efficacy has been proven. Immune responses to the additional 6 serotypes were also measured.

Immune Responses Following a 3-Dose Primary Infant Series

Clinical studies have been conducted in a number of European countries and the US using a range of vaccination schedules, including two randomized non-inferiority studies (Germany using a 2, 3, 4 month primary series [006] and US using a 2, 4, 6 month primary series [004]). In these two studies pneumococcal immune responses were compared using a set of non-inferiority criteria including the percentage of subjects with serum anti-polysaccharide serotype specific IgG ≥0.35 µg/mL one month after the primary series and the comparison of IgG geometric mean concentrations (ELISA GMCs); in addition, functional antibody titres (OPA) between subjects receiving Prevenar 13 and pneumococcal 7-valent conjugate vaccine were compared. For the six additional serotypes, these values were compared with the lowest response

among all of the seven common serotypes in the pneumococcal 7-valent conjugate vaccine recipients.

The non-inferiority immune response comparisons for study 006, based on the proportion of infants achieving anti-polysaccharide IgG concentrations ≥0.35 µg/mL, are shown in Table 1. Results for study 004 were similar. Prevenar 13 non-inferiority (lower bound of the 95% CI for the difference in percentage of responders at 0.35 µg/mL between groups was >-10%) was demonstrated for all 7 common serotypes, except for serotype 6B in study 006 and serotypes 6B and 9V in study 004, which missed by a small margin. All seven common serotypes met pre-defined non-inferiority criteria for IgG ELISA GMCs. Prevenar 13 elicited comparable, although slightly lower, antibody levels than pneumococcal 7-valent conjugate vaccine for the 7 common serotypes. The clinical relevance of these differences is not known.

Non-inferiority was met for the 6 additional serotypes based on the proportion of infants achieving antibody concentrations ≥0.35 µg/mL and comparison of IgG ELISA GMCs in study 006 and was met for 5 out of the 6 serotypes, with the exception of serotype 3 for study 004. For serotype 3, the percentage of Prevenar 13 recipients with serum IgG ≥0.35 µg/mL were 98.2% (study 006) and 63.5% (study 004).

Table 1: Comparison of the proportion of subjects achieving a pneumococcal anti-polysaccharide IgG antibody concentration ≥0.35 µg/mL after dose 3 of the infant series – study 006

Serotypes	Prevenar 13 % (N=282-285)	Pneumococcal 7-valent conjugate vaccine % (N=277-279)	Difference (95% CI)
Pneumococcal 7-valent conjugate vaccine serotypes			
4	98.2	98.2	0.0 (-2.5, 2.6)
6B	77.5	87.1	-9.6 (-16.0, -3.3)
9V	98.6	96.4	2.2 (-0.4, 5.2)
14	98.9	97.5	1.5 (-0.9, 4.1)
18C	97.2	98.6	-1.4 (-4.2, 1.2)
19F	95.8	96.0	-0.3 (-3.8, 3.3)
23F	88.7	89.5	-0.8 (-6.0, 4.5)
Additional serotypes in Prevenar 13			
1	96.1	87.1*	9.1 (4.5, 13.9)
3	98.2	87.1	11.2 (7.0, 15.8)
5	93.0	87.1	5.9 (0.8, 11.1)
6A	91.9	87.1	4.8 (-0.3, 10.1)
7F	98.6	87.1	11.5 (7.4, 16.1)
19A	99.3	87.1	12.2 (8.3, 16.8)

* The serotype in Prevenar with the lowest percent response rate was 6B in study 006 (87.1%).

Prevenar 13 elicited functional antibodies to all 13 vaccine serotypes in studies 004 and 006. For the 7 common serotypes there were no differences between groups in the proportion of subjects with OPA titres ≥1:8. For each of the seven common serotypes, >96% and >90% of the Prevenar 13 recipients reached an OPA titre ≥1:8 one month after the primary series in studies 006 and 004, respectively.

For each of the 6 additional serotypes, Prevenar 13 elicited OPA titres ≥1:8 in 91.4% to 100% of vaccinees one month after the primary series in studies 004/006. The functional antibody (OPA) geometric mean titres for serotypes 1, 3 and 5 were lower than the titres for each of the other additional serotypes; the clinical relevance of this observation for protective efficacy is unknown.

Immune Responses Following a 2-Dose Primary Series
The immunogenicity after 2 doses in infants has been documented in four studies. The proportion of infants achieving a pneumococcal anti-capsular polysaccharide IgG concentration ≥0.35 μg/mL one month after the second dose 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 study using a 3, 5 month regimen. After the booster dose, all vaccine serotypes including 6B and 23F had immune responses consistent with adequate priming with a 2-dose primary series. In a UK study, the functional antibody (OPA) responses were comparable for all serotypes including 6B and 23F in the pneumococcal 7-valent conjugate vaccine and Prevenar 13 arms after the primary series at 2 and 4 months of age and after the booster dose at 12 months of age. For Prevenar 13 recipients, the proportion of responders with an OPA titre ≥1:8 was at least 87% following the infant series, and at least 93% following the booster dose. The OPA geometric mean titres for serotypes 1, 3 and 5 were lower than the titres for each of the other additional serotypes; the clinical relevance of this observation is unknown.

Booster Responses Following 2-Dose and 3-Dose Primary Series
Following the booster dose, antibody concentrations increased from the pre-booster level for all 13 serotypes. Post-booster antibody concentrations were higher for 12 serotypes than those achieved after the infant primary series. These observations are consistent with adequate priming (the induction of immunologic memory). The immune response for serotype 3 following the booster dose was not increased above the levels seen after the infant vaccination series; the clinical relevance of this observation regarding the induction of serotype 3 immune memory is unknown.

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

For children aged from 7 months to 5 years, age appropriate catch-up immunization schedules (as described in section **4.2 Posology and Method of Administration**) 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.

Long-term persistence of antibodies has not been investigated after administration of Prevenar 13 as either a primary series in infants plus booster or after administration of a single priming dose in older children. Since the introduction of pneumococcal 7-valent conjugate vaccine in 2000, pneumococcal disease surveillance data have not shown that

the immunity elicited by pneumococcal 7-valent conjugate vaccine in infancy have waned over time.

Preterm Infants

Safety and immunogenicity of Prevenar 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, evidence of priming was observed as 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.

Pneumococcal 7-valent conjugate vaccine Protective Efficacy

The efficacy of pneumococcal 7-valent conjugate vaccine was evaluated in two major studies – the Northern California Kaiser Permanente (NCKP) study and the Finnish Otitis Media (FinOM) study. Both studies were randomised, double-blind, active-control studies in which infants were randomised to receive either pneumococcal 7-valent conjugate vaccine or control vaccine (NCKP, meningococcal serogroup C CRM-conjugate [MnCC] vaccine; FinOM, hepatitis B vaccine) in a 4-dose series at 2, 4, 6, and 12 - 15 months of age. The efficacy results from these studies (for invasive pneumococcal disease, pneumonia, and acute otitis media) are presented below (Table 2).

Table 2: Summary of Efficacy of Pneumococcal 7-valent conjugate vaccine [1]

Test	N	VE[2]	95% CI
NCKP: Vaccine-serotype IPD[3]	30,258	97%	85, 100
NCKP: Clinical pneumonia with abnormal chest X-ray	23,746	35%	4, 56
NCKP: Acute Otitis Media (AOM)[4]	23,746		
Total episodes		7%	4, 10
Recurrent AOM (3 episodes in 6 months, or 4 episodes in 1 year)		9%	3, 15
Recurrent AOM (5 episodes in 6 months, or 6 episodes in 1 year)		23%	7, 36
Tympanostomy tube placement		20%	2, 35
FinOM: AOM	1,662		
Total episodes		6%	-4, 16
All pneumococcal AOM		34%	21, 45
Vaccine-serotype AOM		57%	44, 67

[1]Per protocol
[2]Vaccine efficacy
[3]October 1995 to April 20, 1999
[4]October 1995 to April 30, 1998

Pneumococcal 7-valent conjugate vaccine Effectiveness

The effectiveness (both direct and indirect effect) of pneumococcal 7-valent conjugate vaccine against pneumococcal disease has been evaluated in both 3-dose and 2-dose primary infant series immunization programs, each with booster doses (Table 3). Following the widespread use of pneumococcal 7-valent conjugate vaccine, the incidence of IPD has been consistently and substantially reduced. An increase in the incidence of IPD cases caused by serotypes not contained in pneumococcal 7-valent conjugate vaccine, such as 1, 7F and 19A, has been reported in some countries. Surveillance will continue with Prevenar 13, and as countries update their surveillance data, information in this table may change.

Using the screening method, serotype specific effectiveness estimates for 2 doses under the age of 1 year in the UK were 66% (-29, 91%) and 100% (25, 100%) for serotype 6B and 23F, respectively.

Table 3. Summary of effectiveness of pneumococcal 7-valent conjugate vaccine for invasive pneumococcal disease

Country (year of introduction)	Recommended schedule	Disease reduction, %	95% CI
UK (England & Wales)[1] (2006)	2, 4, + 13 months	Vaccine serotypes: 2 doses under age 1: 85%	49, 95%
USA (2000) Children <5[2] Persons ≥65[3]	2, 4, 6, + 12 - 15 months	 Vaccine serotypes: 98% All serotypes: 77% Vaccine serotypes: 76% All serotypes: 38%	 97, 99% 73, 79% NA NA
Canada (Quebec)[4] (2004)	2, 4, + 12 months	All serotypes: 73% Vaccine serotypes: 2-dose infant series: 99% Completed schedule: 100%	NA 92, 100% 82, 100%

[1]Children <2 years of age. Calculated vaccine effectiveness as of June 2008 (Broome method).
[2]2005 data.
[3]2004 data.
[4]Children <5 years of age. January 2005 to December 2007. Complete effectiveness for routine 2+1 schedule not yet available.

Effectiveness of pneumococcal 7-valent conjugate vaccine in a 3+1 schedule has also been observed against acute otitis media and pneumonia since its introduction in a national immunization program. 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). While direct cause-and-effect cannot be inferred from observational analyses of this type, these findings suggest that pneumococcal 7-valent

conjugate vaccine plays an important role in reducing the burden of mucosal disease (AOM and pneumonia) in the target population.

Additional Pneumococcal 7-valent conjugate vaccine Immunogenicity Data: Children with Sickle Cell Disease

The immunogenicity of pneumococcal 7-valent conjugate vaccine has been investigated in an open-label, multicenter study in 49 infants with sickle cell disease. Children were vaccinated with pneumococcal 7-valent conjugate vaccine (3 doses one month apart from the age of 2 months), and 46 of these children also received a 23-valent pneumococcal polysaccharide vaccine at the age of 15 - 18 months. After primary immunization, 95.6% of the subjects had antibody levels of at least 0.35 µg/mL for all 7 serotypes found in pneumococcal 7-valent conjugate vaccine. A significant increase was seen in the concentrations of antibodies against the 7 serotypes after the polysaccharide vaccination, suggesting that immunological memory was well established.

Prevenar 13 Effectiveness

Invasive Pneumococcal Disease

Four years after the introduction of pneumococcal 7-valent conjugate vaccine as a two dose primary series plus booster dose in the second year of life and with a 94% vaccine uptake a 98% (95% CI 95; 99) reduction of disease caused by the 7 vaccine serotypes was reported in England and Wales. Subsequently, four years following the switch to Prevenar 13, the additional reduction in incidence of IPD due to the 7 serotypes in pneumococcal 7-valent conjugate vaccine ranged from 76% in children less than 2 years of age to 91% in children 5-14 years of age. The serotype specific reductions for each of the 5 additional serotypes in Prevenar 13 (no cases of serotype 5 IPD were observed) by age group are shown in Table 4 and ranged from 68% (serotype 3) to 100% (serotype 6A) for children less than 5 years of age. Significant incidence reductions were also observed in older age groups who had not been vaccinated with Prevenar 13 (indirect effect).

Table 4: Serotype Specific Number of Cases and Incidence Reductions of IPD in 2013/14 Compared to 2008/09-2009/10 (2008/10) by Age in England and Wales

	<5 years of age			5 to 64 years of age			≥65 years of age		
	2008-10§	2013/14§	% Incidence reduction (95% CI*)	2008-10§	2013/14§	% Incidence reduction (95% CI*)	2008-10§	2013/14§	% Incidence reduction (95% CI*)
Additional serotypes covered by pneumococcal 7-valent conjugate vaccine									
1	59 (54)	5 (5)	91% (98%; 68%)**	458 (382)	77 (71)	83% (88%; 74%)**	102 (89)	13 (13)	87% (94%; 72%)**
3	26 (24)	8 (8)	68% (89%; 6%)	178 (148)	73 (68)	59% (72%; 38%)**	256 (224)	143 (146)	44% (57%; 27%)**
6A	10 (9)	0 (0)	100% (100%; 62%)**	53 (44)	5 (5)	90% (97%; 56%)**	94 (82)	5 (5)	95% (99%; 81%)**
7F	90 (82)	8 (8)	91% (97%; 74%)**	430 (361)	160 (148)	63% (71%; 50%)**	173 (152)	75 (77)	56% (70%; 37%)**
19A	85 (77)	7 (7)	91% (97%; 75%)**	225 (191)	104 (97)	54% (65%; 32%)**	279 (246)	97 (99)	65% (75%; 53%)**

§ Corrected for proportion of samples serotyped, missing age, denominator compared with 2009/10, and for the trend in total invasive pneumococcal disease up to 2009/10 (after which no trend correction was applied).
* 95% CI inflated from a Poisson interval based on over-dispersion of 2·1 seen from modelling of 2000-06 pre-pneumococcal 7-valent conjugate vaccine all IPD data.
** $p<0.005$ to cover 6A where $p=0.002$

Otitis Media (OM)

In a two dose primary series plus booster dose in the second year of life the impact of Prevenar 13 on OM was documented in a population based active surveillance system in Israel with tympanocentesis culturing of middle ear fluid in children less than 2 years of age with OM. Following the introduction of pneumococcal 7-valent conjugate vaccine and subsequently Prevenar 13 there was a decline in incidence of 96% of OM for the pneumococcal 7-valent conjugate vaccine serotypes plus serotype 6A and a decline in incidence of 85% for the additional serotypes 1, 3, 5, 7F, and 19A in Prevenar 13.

In a prospective, population-based, long-term surveillance study conducted in Israel between 2004 and 2015 following the introduction of pneumococcal 7-valent conjugate vaccine and subsequently Prevenar 13, reductions of non-pneumococcal bacteria isolated from children <3 years of age with OM were 75% for all NTHi cases, and 81% and 62% for cases of OM due to *M. catarrhalis* and *S. pyogenes*, respectively.

Pneumonia
In a multicenter observational study in France comparing the periods before and after the switch from pneumococcal 7-valent conjugate vaccine to Prevenar 13, there was 16% reduction in all community acquired pneumonia (CAP) cases in emergency departments in children 1 month to 15 years of age. Reductions were 53% ($p<0.001$) for CAP cases with pleural effusion and 63% ($p<0.001$) for microbiologically confirmed pneumococcal CAP cases. In the second year after the introduction of Prevenar 13 the total number of CAP cases due to the 6 additional vaccine serotypes in Prevenar 13 was reduced by 74% (27 to 7 isolates).

In an ongoing surveillance system (2002 to 2013) to document the impact of pneumococcal 7-valent conjugate vaccine and subsequently Prevenar 13 on CAP in children less than 5 years in Southern Israel using a 2 dose primary series with a booster dose in the second year of life, there was a reduction of 68% (95% CI 73; 61) in outpatient visits and 32% (95% CI 39; 22) in hospitalizations for alveolar CAP following the introduction of Prevenar 13 when compared to the period before the introduction of pneumococcal 7-valent conjugate vaccine was introduced.

Reduction of Antimicrobial Resistance (AMR)
Following the introduction of pneumococcal 7-valent conjugate vaccine and subsequently Prevenar 13, a reduction in AMR has been shown as a result of direct reduction of serotypes and clones associated with AMR from the population (including 19A), reduction of transmission (herd effects), and reduction in the use of antimicrobial agents.

In a double–blind, randomized, controlled study in Israel comparing pneumococcal 7-valent conjugate vaccine and Prevenar 13 that reported the acquisition of *S. pneumoniae,* reductions of serotypes 19A, 19F, and 6A not susceptible to either penicillin, erythromycin, clindamycin, penicillin plus erythromycin, or multiple drugs (≥3 antibiotics) ranged between 34% and 62% depending on serotype and antibiotic.

Analyses of data from the United States Centers for Disease Control and Prevention evaluated temporal trends for four antibiotic classes and showed that compared to 2009 (the last year of pneumococcal 7-valent conjugate vaccine use in the US, following which it was replaced with Prevenar 13), by 2013 the annual incidence of IPD due to pneumococci non-susceptible to macrolides, cephalosporins, penicillins, and tetracyclines had decreased by 63%, 81%, 83%, and 81% in children less than 5 years of age and 24%, 49%, 57%, and 53% in persons 65 years of age and older.

Prevenar 13 Effect on Nasopharyngeal Carriage
In a surveillance study in France in children presenting with acute otitis media, changes in nasopharyngeal (NP) carriage of pneumococcal serotypes were evaluated following the introduction of pneumococcal 7-valent conjugate vaccine and subsequently Prevenar 13. Prevenar 13 significantly reduced NP carriage of the 6 additional serotypes (and serotype 6C) combined and individual serotypes 6C, 7F, 19A when compared with pneumococcal 7-valent conjugate vaccine. A reduction in carriage was also seen for serotype 3 (2.5% vs. 1.1%; p=0.1). There was no carriage of serotypes 1 and 5 observed.

The effect of pneumococcal conjugate vaccination on nasopharyngeal carriage was studied in a randomised double-blind study in which infants received either Prevenar 13 or pneumococcal 7-valent conjugate vaccine at 2, 4, 6 and 12 months of age in Israel. Prevenar 13 significantly reduced newly identified NP acquisition of the 6 additional serotypes (and serotype 6C) combined and of individual serotypes 1, 6A, 6C, 7F, 19A when compared with pneumococcal 7-valent conjugate vaccine. There was no reduction seen in 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.

Efficacy Study in Adults 65 Years and Older
Efficacy against vaccine type (VT) pneumococcal CAP and IPD was assessed in a large-scale randomized double-blind, placebo controlled study (Community-Acquired Pneumonia Immunization Trial in Adults–CAPiTA) in the Netherlands. 84,496 subjects, 65 years and older received a single vaccination of either Prevenar 13 or placebo in a 1:1 randomization.

Efficacy of Prevenar 13 in preventing a first episode of VT pneumococcal CAP (the primary endpoint of the study) and the two secondary endpoints was demonstrated as shown in Table 5.

Table 5: Vaccine Efficacy (VE) in Primary and Secondary Endpoints of the CAPiTA Study (per protocol population)

Efficacy Endpoint	Cases			VE (%) (95.2% CI)	p-value
	Total	Prevenar 13 group	Placebo group		
Primary endpoint					
First episode of confirmed VT pneumococcal CAP	139	49	90	45.56 (21.82, 62.49)	0.0006
Secondary endpoints					
First episode of confirmed NB/NI[1] vaccine type pneumococcal CAP	93	33	60	45.00 (14.21, 65.31)	0.0067
First episode of VT-IPD[2]	35	7	28	75.00 (41.06, 90.87)	0.0005

[1]NB/NI – non-bacteraemic/non-invasive.
[2]VT-IPD – vaccine-type invasive pneumococcal disease.

The protective efficacy of Prevenar 13 against a first episode of VT pneumococcal CAP, VT NB/NI pneumococcal CAP, and VT-IPD was evident shortly after vaccination and was sustained throughout the duration of the study.

A post-hoc analysis was used to estimate the following public health outcomes against clinical CAP (as defined in the CAPiTA study, and based on clinical findings regardless of radiologic infiltrate or etiologic confirmation): vaccine efficacy, incidence rate reduction and number needed to vaccinate (see Table 6):

Table 6: Public Health Outcomes Against Clinical CAP* (modified intent-to-treat population)

	Vaccine efficacy % (95% CI)	Incidence rate reduction[1] (95% CI)	Number needed to vaccinate[2]
All episodes analysis	8.1 (-0.6, 16.1)	72.2 (-5.3, 149.6)	277
First episode analysis	7.3 (-0.4, 14.4)	53.0 (-2.7, 108.7)	378

* Patients with at least 2 of the following: Cough; purulent sputum, temperature >38°C or <36.1°C; pneumonia (auscultatory findings); leukocytosis; C-reactive protein value >3 times the upper limit of normal; hypoxemia with a partial oxygen pressure <60 mm Hg while breathing room air.
[1] per 100,000 person-years of follow-up.
[2] based on a 5-year duration of protection.

Although CAPiTA was not powered to demonstrate serotype specific VE, an evaluation of clinical CAP data was performed for serotypes with at least 10 outcomes in the placebo group. VE (95% CI) for the five evaluated serotypes against first clinical CAP episodes were: serotype 1, 20.0% (-83.1% to 65.8%); serotype 3, 61.5% (17.6% to 83.4%); serotype 6A, 33.3% (-58.6% to 73.2%); serotype 7F, 73.3% (40.5% to 89.4%); and serotype 19A, 45.2% (-2.2% to 71.5%).

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 Prevenar 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, Prevenar 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 Prevenar 13, immune responses were similar or higher than those after the first dose. The clinical benefit of the 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/µL and viral load <50,000 copies/mL) previously vaccinated with PPSV23 administered at least 6 months prior to enrollment. Subjects received 3 doses of Prevenar 13, at enrollment, 6 months and 12 months after the first dose of Prevenar 13. After the first vaccination, Prevenar

13 elicited antibody levels measured by both IgG GMCs and OPA GMTs that were statistically significant higher when compared to levels prior to vaccination. After the second and third dose of Prevenar 13, immune responses were comparable or higher than those after the first dose. Subjects who received 2 or more previous doses of PPSV23 showed a similar immune response compared with subjects who received a single previous dose. The clinical benefit of the second and third doses remains uncertain.

Study of Prevenar 13 containing the preservative 2-phenoxyethanol (2-PE): (note that this study applies only to Multi Dose Vials)

Safety and immunogenicity of Prevenar 13 containing the preservative 2-PE (presented in a multidose vial) given to healthy infants at 8, 12 and 16 weeks of age was compared to that of Prevenar 13 without added preservative (250 infants per group).

Pneumococcal immune responses were compared using non-inferiority criteria including the percentage of subjects with serum anti-polysaccharide serotype-specific IgG ≥0.35 µg/mL and the comparison of IgG GMCs one month after the infant series. In addition, OPA GMTs between subjects receiving Prevenar 13 with or without 2-PE were compared.

Non-inferiority for the proportion of subjects achieving an IgG concentration ≥0.35 µg/mL was demonstrated for all 13 serotypes (lower bound of the 97.5% confidence interval (CI) for the difference in percentage of responders at 0.35 µg/mL between groups was >-10%). Additionally, all 13 serotypes met the pre-defined non-inferiority criterion for IgG GMCs (lower limit of the 97.5% CI of GMR was greater than 0.5).
Correspondingly, OPA GMTs were similar in both groups, except for serotype 3, which was lower, and serotype 18C, which was higher, in the group that received Prevenar 13 with 2-PE.

Adults aged 50 years of age and older
An antipolysaccharide binding antibody IgG level to predict protection against IPD or non-bacteremic pneumonia has not been defined for adults. However, nonclinical and clinical data support functional antibody, measured by OPA assay, 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 Prevenar 13 were designed to show that functional OPA antibody responses for the Prevenar 13 serotypes are non-inferior and for some serotypes superior to the common serotypes in the currently licensed 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 Prevenar 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 Prevenar 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, 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, 6115A1-3005, 6115A1-3010, 6115A1-3001, 6115A1-3008) were conducted in a number of European countries and in the US evaluating the immunogenicity of Prevenar 13 in different age groups, and in individuals who were either not previously vaccinated (PPSV23 unvaccinated) with PPSV23 or had received 1 or more doses of PPSV23 (PPSV23 pre-vaccinated).

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 CAP and IPD.

Two (2) pivotal non-inferiority trials were conducted in which Prevenar 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 (2) studies (6115A1-3001 and 6115A1-3008) assessed the concomitant administration of Prevenar 13 with seasonal TIV.

Clinical trials conducted in adults not previously vaccinated with PPSV23
In an active-controlled modified[1] double-blind clinical trial (6115A1-004) of Prevenar 13 in the US, PPSV23-unvaccinated adults aged 60 to 64 years were randomly assigned (1:1) to receive Prevenar 13 or PPSV23. In addition, adults aged 50 to 59 years were enrolled and received 1 dose of Prevenar 13 (open-label).

The OPA antibody responses elicited by Prevenar 13 were non-inferior to those elicited by PPSV23 for the 12 serotypes in common to both vaccines. In addition, 8 of the serotypes in common exhibited a statistically significantly greater immune response after Prevenar 13 compared with after PPSV23.

For serotype 6A, which is unique to Prevenar 13, the proportions of adults with a 4-fold increase after Prevenar 13 (88.5%) were significantly greater than after PPSV23 (39.2%) in PPSV23-unvaccinated adults aged 60-64 years. OPA GMTs for serotype 6A were statistically significantly greater after Prevenar 13 compared with after PPSV23.

[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.

The OPA responses elicited by Prevenar 13 in adults aged 50-59 years were non-inferior to the Prevenar 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.

This clinical trial demonstrated that the immune responses elicited by Prevenar 13 are non-inferior and for most serotype statistically 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. In adults aged 60-64 years, antibody levels one year after vaccination were greater after Prevenar 13 compared to antibody levels after PPSV23 for 7 of 12 serotypes in common. In adults aged 50-59 years, antibody levels one year after vaccination with Prevenar 13 were greater for 12 of 13 serotypes compared to vaccination with Prevenar 13 in 60-64 year olds.

Table 7: OPA GMTs in PPSV23 Unvaccinated Adults Aged 50-59 Years Given Prevenar 13; and in Adults Aged 60-64 Years given Prevenar 13 or PPSV23[a,b]

	Prevenar 13 50-59 Years N=350-384	Prevenar 13 60-64 Years N=359-404	PPSV23 60-64 Years N=367-402	Prevenar 13, 50-59 Relative to 60-64 Years		Prevenar 13 Relative to PPSV23, 60-64 Years	
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)
6A[†]	4328	2593	213	1.7	(1.30, 2.15)	12.1	(8.63, 17.08)
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)

GMT, Geometric Mean Titer.
GMR, Geometric Mean Ratio.
[†] 6A is a serotype unique to Prevenar 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] For serotype 6A, which is unique to Prevenar 13, 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 conducted in adults previously vaccinated with PPSV23 (pre-vaccinated)

In a Phase 3 active-controlled, modified[2] double-blind clinical trial (6115A1-3005) of Prevenar 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 Prevenar 13 or PPSV23.

[2] 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.

The OPA antibody responses elicited by Prevenar 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 addition, 10 of the serotypes in common exhibited a statistically significantly greater immune response after Prevenar 13 compared with after PPSV23.

For serotype 6A, which is unique to Prevenar 13, proportions of adults with a 4-fold increase after Prevenar 13 (71.1%) was significantly greater than after PPSV23 (27.3%) in PPSV23-pre-vaccinated adults aged ≥70 years. OPA GMTs for serotype 6A were statistically significantly greater after Prevenar 13 compared with after PPSV23.

Table 8: OPA GMTs in PPSV23 previously vaccinated Adults Aged ≥70 Years Given Prevenar 13 or PPSV23[a,b]

Serotype	Prevenar 13 N=400-426 GMT	PPSV23 N=395-445 GMT	Prevenar 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)
6A†	903	94	9.6	(7.00 , 13.26)
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)

GMT, Geometric Mean Titer.
† 6A is a serotype unique to Prevenar 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 Prevenar 13, a statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GMR greater than 2.

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

Clinical Trials to Assess Prevenar 13 Given With Seasonal TIV in Adults
Two (2) randomized, double-blind clinical trials (6115A1-3001 and 6115A1-3008) evaluated the immunogenicity of Prevenar 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 Prevenar 13 and TIV (administered in opposite arms) with [1] TIV given with placebo and [2] with Prevenar 13 given alone. Group 1 received Prevenar 13 given with TIV, followed 1 month later by placebo; Group 2 received TIV given with placebo, followed one month later by Prevenar 13.

A Phase 3 randomized, double-blind clinical trial (6115A1-3001) of Prevenar 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 Prevenar 13 compared with TIV given with placebo (in the following called TIV alone).

A Phase 3 randomized, double-blind clinical trial (6115A1-3008) of Prevenar 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 Prevenar 13 compared with TIV given with placebo.

Immune responses elicited by TIV were measured by haemagglutination inhibition (HAI) assays one 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 non-inferiority criterion was achieved for each vaccine antigen if the lower limit of the 95% CI for the difference in proportions of responders was >-10%.

The studies also assessed the immune responses of Prevenar 13 when Prevenar 13 was given with TIV compared with Prevenar 13 given alone. The immune responses elicited by Prevenar 13 were measured by ELISA IgG GMC one month after Prevenar 13 vaccination. The non-inferiority criterion was achieved if the lower limit of the 2-sided, 95% CI for the IgG GMC ratios (Prevenar 13 and TIV relative to Prevenar 13 alone) was >0.5 (2-fold criterion).

TIV immune responses 50-59 years of age: The immune responses were similar after Prevenar 13 given concomitantly with TIV compared to TIV alone. Non-inferiority was met for all 3 TIV strains after Prevenar 13 given concomitantly with TIV compared to TIV alone (Table 9).

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 10).

Table 9: Proportion of Participants Aged 50–59 Years with a ≥4-fold Increase in HAI Titer after TIV with Prevenar 13 and TIV with Placebo

TIV	**TIV + Prevenar 13**		**TIV + Placebo**		**Difference**
HAI	**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)

Table 10: Proportion of Participants Aged ≥65 Years with a ≥4-fold Increase in HAI Titer after TIV with Prevenar 13 and TIV With Placebo

TIV	**TIV + Prevenar 13**		**TIV + Placebo**		**Difference**
HAI	n/N	% (95% CI)	n/N	% (95% CI)	% (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)

Prevenar 13 immune responses in 50-59 year olds: Non-inferiority was met for all serotypes (Table 11).
Prevenar 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 12).

Table 11: Pneumococcal IgG GMC 1 Month After Prevenar 13 and TIV; and 1 Month After Prevenar 13 (Given 1 Month After Placebo and TIV) for Participants 50-59 Years [a, b]

	Post-dose 1 Prevenar 13 + TIV (N=247-294)	**Post-dose 2 Prevenar 13*** (N=247-289)	**Vaccine Comparison**
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.
[b] The non-inferiority criterion was achieved if the lower limit of the 2-sided, 95% CI for the IgG GMC ratios (Prevenar 13 and TIV relative to Prevenar 13 alone) was >0.5 (2-fold criterion).

Table 12: Pneumococcal IgG GMC 1 Month After Prevenar 13 and TIV; and 1 Month After Prevenar 13 (Given 1 month After Placebo and TIV) for Participants ≥65 Years[a,b]

	Post-dose 1 Prevenar 13 + TIV (N=247-294)	**Post-dose 2 Prevenar 13*** (N=247-289)	**Vaccine Comparison**
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.
[b] The non-inferiority criterion was achieved if the lower limit of the 2-sided, 95% CI for the IgG GMC ratios (Prevenar 13 and TIV

relative to Prevenar 13 alone) was >0.5 (2-fold criterion).

Prevenar 13 may be given with TIV.
When Prevenar 13 was given concomitantly with TIV, the immune responses to Prevenar 13 were lower compared to when Prevenar 13 was given alone. The significance of this is unknown.

5.2 Pharmacokinetic Properties
Evaluation of pharmacokinetic properties is not available for vaccines.

5.3 Preclinical Safety Data
Studies with a vaccine formulation representative of Prevenar 13 revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, juvenile toxicity and local tolerance.

6 PHARMACEUTICAL PARTICULARS
6.1 List of Excipients
Sodium chloride
Succinic acid
Polysorbate 80
Water for injections
Aluminium phosphate
2-phenoxyethanol (multidose vial only)

6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

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

6.3 Shelf Life
3 years

Applies to multi-dose vials only
Once opened, the product may be stored for a maximum of 28 days at 2-8°C. Other in-use storage times and conditions are the responsibility of the user.

6.4 Special Precautions for Storage
Store in a refrigerator (2°C – 8°C).

Do not freeze. Discard if the vaccine has been frozen.

Applies to pre-filled syringe presentation only
Prevenar 13 has been shown to be stable at temperatures of up to 25°C for 4 days. These data are not recommendations for shipping or storage, but may guide decisions for use in case of temporary temperature excursions.

6.5 How Supplied
Box, 1 pre-filled syringe @ 0.5 mL (Reg No. DKI1786101643A2).
Box, 50 vial @ 0.5 mL (Reg. No.: DKI1786101643A1).
Box, 50 vial @ 2 mL (4 x 0.5 mL doses) (Reg No.DKI1786101643A1).

6.6 Special Precautions for Disposal and Other Handling
During storage, a white deposit and clear supernatant can be observed. This does not constitute a sign of deterioration.

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.

Any unused product or waste material should be disposed of in accordance with local requirements.

Applies to vial presentations only
The vaccine is to be administered immediately after being drawn up into a syringe.

HARUS DENGAN RESEP DOKTER

Pre-filled syringe:
Manufactured by:
Pfizer Ireland Pharmaceuticals, Grange Castle Business Park, Clondalkin, Dublin 22, Ireland

Packed and Released by:
Pfizer Manufacturing Belgium NV
Rijksweg 12
2870 Puurs
Belgium

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia

Vial:
Manufactured by:
Pfizer Manufacturing Belgium NV
Rijksweg 12
2870 Puurs
Belgium

Imported by:
PT. Pfizer Indonesia

Jakarta, Indonesia