Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) I.P., 13-valent

PREVENAR 13®

1. GENERIC NAME

Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) I.P., 13-valent

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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, 0.02% polysorbate 80 and 0.125 mg of aluminum as aluminum phosphate adjuvant.

List of Excipients:

Aluminum Phosphate, Sodium chloride USP, Ph Eur, JP, Succinic acid NF, Polysorbate 80 NF, Ph Eur, JP, Water for injection USP/NF, Ph Eur.

3. DOSAGE AND STRENGTH

Sterile suspension for injection in single dose vial.
The vaccine is a homogeneous white suspension.

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4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

For active immunization for the prevention of disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (including sepsis, meningitis, bacteraemia, pneumonia) and acute otitis media in infants and children from 6 weeks to 5 years of age.

For active immunization for the prevention of Pneumonia and invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in children of 6 years to 17 years of age.

For active immunization for the prevention of Pneumonia and invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in adults of 50 years and older age group.

4.2 Posology and Method of 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 Prevenar 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 (see section 8.4. Storage and handling instruction).

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

Vaccination Schedule

Primary Immunization

For infants, the recommended infant immunization series of Prevenar 13 consists of three doses of 0.5 mL each, at 6 weeks, 10 weeks and 14 weeks of age. 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 to 8 weeks. The fourth (booster) dose should be administered at approximately 12-15 months of age, and at least 2 months after the third dose.

For children who are beyond the age of routine infant schedule, the following Prevenar 13 schedule applies:

Prevenar 13 Vaccine Schedule for Previously Unvaccinated Children ≥7 Months of Age	
Age at First Dose	**Total Number of 0.5 mL Doses**
7-11 months of age	3*
12-23 months of age	2†
≥24 months through 5 years of age (prior to the 6th birthday)	1
Adolescents 6 years to 17 years of age	1
*2 doses at least 4 weeks apart; third dose after the one-year birthday, separated from the second dose by at least 2 months. †2 doses at least 2 months apart.	

Prevenar 13 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 contained in pneumococcal 7-valent conjugate vaccine and is manufactured based on the same conjugate technology using the same carrier protein CRM_{197}. Children who have begun immunization with pneumococcal 7-valent conjugate vaccine may complete immunization by switching to Prevenar 13 at any point in the schedule. In clinical trials, immunogenicity and safety profiles were comparable. Children 15 months through 5 years of age who are considered completely immunized, or with any incomplete pneumococcal 7-valent conjugate vaccine schedule may receive one dose of Prevenar 13 to elicit immune responses to the six additional serotypes. The catch-up (supplemental) dose of Prevenar 13 should be administered with an interval of at least 8 weeks after the final dose of pneumococcal 7-valent conjugate vaccine. To ensure adequate protection against all 13 serotypes, children 15 to 23 months of age that received only a single dose of pneumococcal 7-valent conjugate vaccine before the age of 12 months, should receive 2 doses of Prevenar 13 at least 2 months apart and separated from the first dose by at least 2 months.

Prevenar 13 Schedule for Children 12 Months through 5 Years of Age Incompletely Vaccinated with Prevenar 13:

For children 7 months through 5 years of age that have not received any prior doses of Prevenar 13, see the Vaccine Schedule for Previously Unvaccinated Children ≥7 Months of Age.

Children who are considered incompletely vaccinated with Prevenar 13 are children who have received 3 or fewer doses of Prevenar 13 before 12 months of age and no Prevenar 13 dose after 12 months of age or children who did not complete the recommended age appropriate vaccine

schedule for previously unvaccinated children (see the Vaccine Schedule for Previously Unvaccinated Children ≥7 Months of Age).

For children 12 months through 5 years of age with any incomplete Prevenar 13 schedule, the following schedule applies to complete the Prevenar 13 immunization schedule:

Vaccine Schedule for Children 12 months through 5 years of Age Incompletely Vaccinated with Prevenar 13		
Current age	Previous Prevenar 13 vaccination history	Total number of 0.5 mL Doses
12-23 months	1 dose <12 months	2*
	2 or 3 doses <12 months	1†
24-71 months	Any incomplete schedule	1†
*Two doses at least 2 months apart and separated from the first dose by at least 2 months. †Separated from the previous dose by at least 2 months.		

The immune responses induced by this Prevenar 13 schedule may result in lower antibody concentrations compared to antibody concentrations following four doses of Prevenar 13 (given at 2, 4, 6 and 12 to 15 months).

Protective immunity to the six new serotypes in Prevenar 13 requires age-appropriate dosing as described above.

Vaccination Schedule for 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.

Pediatric Use

The safety and effectiveness of Prevenar 13 in children below the age of 6 weeks have not been established.

Geriatric Use

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

Of the 5,667 adults in the 6 studies of the clinical development program who received Prevenar 13; 1,785 (31.5%) were 65 to 74 years of age, and 1,266 (22.3%) 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.

4.3 Contraindications

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

4.4 Special Warnings and Special Precautions for Use

Special Warnings

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 (see section 4.8 Undesirable Effects).

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 Prevenar 13 should be postponed in subjects suffering from acute severe febrile illness.

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

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. This vaccine is not intended to be used for treatment of active infection.

As with any vaccine, Prevenar 13 may not protect all individuals receiving the vaccine from pneumococcal disease. For the most recent epidemiological information in your country, you should consult with the relevant national organisation.

Precautions

Safety and immunogenicity data on Prevenar 13 are not available for individuals in immunocompromised group (e.g., individuals with congenital or acquired splenic dysfunction, HIV infection, malignancy, nephrotic syndrome) and vaccination should be considered on an individual basis.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium free’.

Infants and children aged 6 weeks through 5 years

In clinical studies, Prevenar 13 elicited an immune response to all thirteen 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 (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).

Limited data have demonstrated that pneumococcal 7-valent conjugate vaccine (three-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.

Children younger than 2 years old should receive the appropriate-for-age Prevenar 13 vaccination series (see section 4.2). The use of pneumococcal conjugate vaccine does not replace the use of 23-valent pneumococcal polysaccharide vaccines in children ≥2 years of age with conditions (such as sickle cell disease, asplenia, HIV infection, chronic illness, or those who are immuno-compromised) 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.

Data on sequential vaccination with Prevenar 13 followed by 23-valent pneumococcal polysaccharide vaccine are not available; data on sequential vaccination with pneumococcal 7-valent conjugate vaccine followed by PPV23 are limited.

The potential risk of apnoea and the need for respiratory monitoring for 48-72 h should be considered when administering the primary immunisation 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.

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 with-held 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).

When Prevenar 13 is administered concomitantly with Infanrix hexa (DTPa-HBV-IPV/Hib), the rates of febrile reactions are similar to those seen with concomitant administration of Prevenar (7-valent) and Infanrix hexa (see section 4.8 Undesirable Effects). Increased reporting rates of convulsions (with or without fever) and hypotonic hyporesponsive episode (HHE) were observed with concomitant administration of Prevenar 13 and Infanrix hexa (see section 4.8 Undesirable Effects).

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.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

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

Infants and children aged 6 weeks to 5 years

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 with the tetanus toxoid conjugated meningococcal polysaccharide serogroups A, C, W and Y vaccine to children who have been adequately primed with Prevenar 13. Previously, studies with pneumococcal 7-valent conjugate vaccine and rotavirus vaccines have demonstrated that the immune responses of the seven pneumococcal serotypes in pneumococcal 7-valent conjugate vaccine and the rotavirus vaccine were unaffected. It is not expected that any differences in immune response for the six additional serotypes or the rotavirus vaccine will be observed in Prevenar 13.

In clinical trials, when Prevenar 13 was given concomitantly, but at a different site/route, with rotavirus vaccine or hepatitis A vaccine, no change in the safety profiles for these infants was observed.

Data from a post-marketing clinical study evaluating the impact of prophylactic use of antipyretics (ibuprofen and paracetamol) on the immune response to Prevenar 13 suggest that administration of paracetamol concomitantly or within the same day of vaccination may reduce the immune response to Prevenar 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

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

Adults aged 50 years and older

Prevenar 13 can be administered concomitantly with trivalent inactivated influenza vaccine (TIV).

In two studies conducted in adults aged 50-59 and 65 years and older, it was demonstrated that Prevenar 13 may be given concomitantly with trivalent inactivated influenza vaccine (TIV). The responses to all three TIV antigens were comparable when TIV was given alone or concomitantly with Prevenar 13.

When Prevenar 13 was given concomitantly with TIV, the immune responses to Prevenar 13 were lower compared to when Prevenar 13 was given alone; however, there was no long-term impact on circulating antibody levels.

In a third study in adults aged 50-93 years, it was demonstrated that Prevenar 13 may be given concomitantly with the seasonal quadrivalent inactivated influenza vaccine (QIV). The immune responses to all four QIV strains were noninferior when Prevenar 13 was given concomitantly with QIV compared to when QIV was given alone.

The immune responses to Prevenar 13 were noninferior when Prevenar 13 was given alone. As with concomitant administration with trivalent vaccines, immune responses to some pneumococcal serotypes were lower when both vaccines were given concomitantly.

Concomitant use with other vaccines has not been investigated.

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

Concomitant administration of Prevenar 13 and 23-valent pneumococcal polysaccharide vaccine has not been studied. In clinical studies when Prevenar 13 was given 1 year after 23-valent pneumococcal polysaccharide vaccine the immune responses were lower for all serotypes compared to when Prevenar 13 was given to subjects not previously immunised with 23-valent pneumococcal polysaccharide vaccine. The clinical significance of this is unknown.

4.6 Use in special populations (Fertility, Pregnancy and Lactation)

Pregnancy

There are no data from the use of pneumococcal 13-valent conjugate vaccine in pregnant women. Therefore, the use of Prevenar 13 should be avoided during pregnancy.

Lactation

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

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 6.1. Animal Toxicology and Pharmacology).

4.7 Effects on Ability to Drive and Use Machine

Prevenar 13 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 “Undesirable Effects” may temporarily affect the ability to drive or use machines.

4.8 Undesirable Effects

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, Prevenar 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 one dose of Prevenar 13 were also assessed for safety.

Adults aged 50 years and older

Safety was assessed in 6 clinical studies including 6,198 adults ranging in ages 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 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.

Expected frequency of adverse reactions is presented in CIOMS frequency categories.

Very common: ≥10%

Common:	≥1% and <10%
Uncommon:	≥0.1% and <1%
Rare:	≥0.01% and <0.1%
Very rare:	<0.01%

Adverse Reactions from Clinical Trials with Prevenar 13

Infants and children aged 6 weeks to 5 years

These data are from clinical trials in which Prevenar 13 was administered simultaneously with other routine childhood vaccines.

System Organ Class	Adverse Reaction
Metabolism and nutrition disorders	
Very common	Decreased appetite
Psychiatric disorders	
Very common	Irritability
Uncommon	Crying
Nervous system disorders	
Very common	Drowsiness/increased sleep; restless sleep/decreased sleep
Uncommon	Seizures (including febrile seizures)
Rare	Hypotonic–Hyporesponsive episode
Gastrointestinal disorders	
Common	Diarrhea; vomiting
Immune system disorders	
Rare	Hypersensitivity reaction including face edema, dyspnea, bronchospasm
Skin and subcutaneous tissue disorders	
Common	Rash
Uncommon	Urticaria or urticaria-like rash
General disorders and administration site conditions	
Very common	Fever; any injection-site erythema, induration/swelling or pain/tenderness; injection-site erythema or duration/swelling 2.5 cm - 7.0 cm (after toddler dose and in older children [age 2 to 5 years]).
Common	Fever greater than 39°C; injection-site erythema or Induration/swelling 2.5 cm - 7.0 cm (after infant series); Injection-site pain/tenderness interfering with movement
Uncommon	Injection-site induration/swelling or erythema greater than 7.0 cm

Children and adolescents aged 6 to 17 years of age

Safety was evaluated in 592 children (294 children aged 5 to 10 years previously immunised with at least one dose of Prevenar and 298 children aged 10 to 17 years who had not received a pneumococcal vaccine).

The most often reported adverse events in children and adolescents 6 to 17 years of age were:

Nervous system disorders:
Common: Headaches

Gastrointestinal disorders:
Very common: Decreased appetite
Common: Vomiting; diarrhea

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

General disorders and administration site conditions:
Very common: Irritability; any vaccination-site erythema; induration/swelling or pain/tenderness; somnolence; poor quality sleep; vaccination-site tenderness (including impaired movement)
Common: Pyrexia

Other adverse events previously observed in infants and children 6 weeks to 5 years of age may also be applicable to this age group but were not seen in this study possibly due to the small sample size.

Additional information in special populations
Children and adolescents with sickle cell disease, HIV infection, or a haematopoietic stem cell transplant have similar frequencies of adverse reactions, except that headaches, vomiting, diarrhoea, pyrexia, fatigue, arthralgia, and myalgia were very common.

Adults aged 50 years and older

System Organ Class	**Adverse Reaction**
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; vaccination-site erythema, vaccination site Induration/swelling; vaccination-site pain/tenderness; limitation of arm movement
Common	Fever
Uncommon	Lymphadenopathy localized to the region of the vaccination site

Overall, no significant differences in frequencies of adverse reactions were noted if Prevenar 13 was given to adults pre-vaccinated with PPSV23 or adults 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 studies with Prevenar 13 and trivalent inactivated influenza vaccine

The safety of concomitant administration of Prevenar 13 with trivalent inactivated influenza vaccine was assessed in 2 studies in PPSV23 unvaccinated adults.

Frequencies of local reactions in adults aged 50-59 years and in adults aged ≥65 years were similar after Prevenar 13 was administered with trivalent inactivated influenza vaccine compared to Prevenar 13 administered alone.

Higher frequency in some solicited systemic reactions was observed when Prevenar 13 was administered concomitantly with trivalent inactivated influenza vaccine compared to trivalent inactivated influenza vaccine 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 Prevenar 13 Post-marketing experience

Although the following adverse reactions were not observed in clinical trials, they are considered adverse drug reactions for Prevenar 13 as they were reported in the post-marketing experience.

System Organ Class	Adverse Reaction

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
Angioneurotic edema; erythema multiforme

General disorders and administration site conditions
Vaccination-site dermatitis; vaccination-site urticaria; vaccination-site pruritus; flushing

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

Overdose with Prevenar 13 is unlikely due to its presentation as a pre-filled syringe and as a single dose vial. 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 events reported with overdose are consistent with those that have been reported with doses given in the recommended schedules of Prevenar 13.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological class, therapeutic class

Vaccines

5.1 Mechanism of Action

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 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, induces immune memory, and elicits booster responses on re-exposure in infants and young children to pneumococcal polysaccharides.

5.2 Pharmacodynamic Properties

Burden of disease

Infants and children aged 6 weeks to 5 years

Based on serotype surveillance in Europe performed before the introduction of Prevenar, 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 Prevenar.

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

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

Children and adolescents aged 6 to 17 years

In children and adolescents aged 6 to 17 years, the incidence of pneumococcal disease is low, however, there is an increased risk of morbidity and mortality in those with underlying comorbidities.

Adults ≥50 years and the elderly

Pneumonia is the most common clinical presentation of pneumococcal disease in adults.

The reported incidence of community-acquired pneumonia (CAP) and IPD in Europe varies by country, increases with age from 50 years and is highest in individuals aged ≥65 years. *S. pneumoniae* is the most frequent cause of CAP, and is estimated to be responsible for approximately 30% of all CAP cases requiring hospitalisation in adults in developed countries.

Bacteraemic pneumonia (approximately 80% of IPD in adults), bacteraemia without a focus, and meningitis are the most common manifestations of IPD in adults. Based on surveillance data following the introduction of Prevenar but before the introduction of Prevenar 13 in childhood vaccination programmes, the pneumococcal serotypes in Prevenar 13 may be responsible for at least 50 – 76% (depending on country) of IPD in adults.

The risk for CAP and IPD in adults also increases with chronic underlying medical conditions, specifically, anatomical or functional asplenia, diabetes mellitus, asthma, chronic cardiovascular, pulmonary, kidney or liver disease, and it is highest in those who are immune-suppressed such as those with malignant haematological diseases or HIV infection.

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

Prevenar 13 immunogenicity clinical studies in infants and children and adolescents

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 in infants and young children has been based on a comparison of immune responses to the seven common serotypes shared between Prevenar 13 and Prevenar, for which protective efficacy has been proven. Immune responses to the additional 6 serotypes were also measured for comparability to the seven common serotypes.

For Prevenar (7-valent) efficacy in infants and children, see below

Immune responses following a three-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 randomised 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 Prevenar were compared. For the six additional serotypes, these values were compared with the lowest response among all of the seven common serotypes in the Prevenar 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 Prevenar 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 percentages 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)	7-valent Prevenar % (N=277-279)	Difference (95 % CI)
7-valent Prevenar 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 vaccines 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 Two-dose Primary Series

The immunogenicity after two 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 68.1% 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 two-dose primary series. In a UK study, the functional antibody (OPA) responses were comparable for all serotypes including 6B and 23F in the Prevenar and Prevenar 13 arms after the primary series at two and four 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 Two-dose and Three-dose Primary Schedules

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, which is 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 two-dose or three-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 Dosage and 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 three-dose primary series in infants.

Antibody persistence and immunological memory were evaluated in a study in healthy children who received a single dose of Prevenar 13 at least 2 years after they had been previously immunised with either 4 doses of Prevenar, a 3-dose infant series of Prevenar followed by Prevenar 13 at 12 months of age, or 4 doses of Prevenar 13.

The single dose of Prevenar 13, in children approximately 3.4 years of age regardless of previous vaccination history with Prevenar or Prevenar 13, induced a robust antibody response for both the 7 common serotypes and the 6 additional serotypes in Prevenar 13.

Since the introduction of 7-valent Prevenar in 2000, pneumococcal disease surveillance data have not shown that the immunity elicited by Prevenar in infancy has waned over time.

Children (12-59 months) completely immunised with Prevenar (7-valent)

Following administration of a single dose of Prevenar 13 to children (12-59 months) who are considered completely immunised with Prevenar (7-valent) (either 2 or 3 dose primary series plus booster), the proportion achieving serum IgG levels ≥0.35 µg/mL and OPA titres ≥1:8 was at least 90%. However, 3 (serotypes 1, 5 and 6A) of the 6 additional serotypes showed lower IgG GMC and OPA GMT when compared with children who had received at least one previous vaccination with Prevenar 13. The clinical relevance of the lower GMCs and GMTs is currently unknown.

Unvaccinated Children (12-23 months)

Studies in unvaccinated children (12-23 months) with Prevenar (7-valent) demonstrated that 2 doses were required to achieve serum IgG concentrations for 6B and 23F similar to those induced by a 3-dose infant series.

Children and Adolescents 5 to 17 years of age

In an open-label study in 592 healthy children and adolescents including those with asthma (17.4%) who may be predisposed to pneumococcal infection, Prevenar 13 elicited immune responses to all 13 serotypes. A single dose of Prevenar 13 was given to children 5 to 10 years of age previously vaccinated with at least 1 dose of Prevenar, and children and adolescents 10 to 17 years of age who had never received a pneumococcal vaccine.

In both the children 5 to 10 years of age and children and adolescents aged 10 to 17 years, the immune response to Prevenar 13 was non inferior to Prevenar for the 7 common serotypes and to Prevenar 13 for the 6 additional serotypes compared to the immune response after the fourth dose in infants vaccinated at 2, 4, 6 and 12-15 months of age as measured by serum IgG.

In children and adolescents aged 10 to 17 years of age OPA GMTs 1 month after vaccination were noninferior to OPA GMTs in the 5 to 10 year old age group for 12 of the 13 serotypes (except serotype 3).

Immune responses after subcutaneous administration

Subcutaneous administration of Prevenar 13 was evaluated in a non-comparative study in 185 healthy Japanese infants and children who received 4 doses at 2, 4, 6 and 12-15 months of age. The study demonstrated that safety and immunogenicity were generally comparable with observations made in studies of intramuscular administration.

Prevenar 13 Effectiveness

Invasive Pneumococcal Disease

Data published by Public Health England showed that, four years after the introduction of Prevenar as a two dose primary infant series with booster dose in the second year of life and with a 94% vaccine uptake, there was a 98% (95% CI 95; 99) reduction in disease caused by the 7 vaccine serotypes 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 Prevenar was 76% in children less than 2 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 2 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 2: 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			≥65 years of age		
	2008-10[§]	2013/14[§]	% Incidence reduction (95% CI*)	2008-10[§]	2013/14[§]	% Incidence reduction (95% CI[*])
Additional serotypes covered by Prevenar 13						
1	59 (54)	5 (5)	91% (98%; 68%)[**]	102 (89)	13 (13)	87% (94%; 72%)[**]
3	26 (24)	8 (8)	68% (89%; 6%)	256 (224)	143 (146)	44% (57%; 27%)[**]
6A	10 (9)	0 (0)	100% (100%; 62%)[**]	94 (82)	5 (5)	95% (99%; 81%)[**]
7F	90 (82)	8 (8)	91% (97%; 74%)[**]	173 (152)	75 (77)	56% (70%; 37%)[**]
19A	85 (77)	7 (7)	91% (97%; 75%)[**]	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-Prevenar all IPD data.

[**] $p<0.005$ to cover 6A where $p=0.002$

Otitis media (OM)

In a published study performed in Israel, using a 2-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 with tympanocentesis culturing of middle ear fluid in Israeli children less than 2 years of age with OM.

Following the introduction of Prevenar and subsequently Prevenar 13 there was a decline in incidence from 2.1 to 0.1 cases per 1000 children (95%) for the Prevenar serotypes plus serotype 6A and a decline in incidence from 0.9 to 0.1 cases per 1000 children (89%) for the additional serotypes 1, 3, 5, 7F, and 19A in Prevenar 13. The annual overall pneumococcal incidence of OM declined from 9.6 to 2.1 cases per 1000 children (78%) between July 2004 (prior to the introduction of Prevenar) and June 2013 (post Prevenar 13 introduction).

Pneumonia

In an ongoing surveillance system (2004 to 2013) to document the impact of Prevenar 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 Prevenar.

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 Prevenar (7-valent) 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 Prevenar. 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 Prevenar (7-valent) 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 Prevenar. 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.

In this study, reductions of *S. pneumoniae* serotypes 19A, 19F, and 6A not susceptible to a number of antibiotics were documented. The reductions ranged between 34% and 62% depending on serotype and antibiotic.

Prevenar (7-valent vaccine) protective efficacy in infants and children

The efficacy of 7-valent Prevenar 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 Prevenar or control vaccine (NCKP, meningococcal serogroup C CRM-conjugate [MnCC] vaccine; FinOM, hepatitis B vaccine) in a four-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 3).

Table 3: Summary of efficacy of 7-valent Prevenar[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

Prevenar (7-valent) effectiveness

The effectiveness (both direct and indirect effect) of 7-valent Prevenar against pneumococcal disease has been evaluated in both three-dose and two-dose primary infant series immunisation programmes, each with booster doses (Table 4). Following the widespread use of Prevenar, the incidence of IPD has been consistently and substantially reduced.

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 4: Summary of effectiveness of 7-valent Prevenar 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: Two 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.			

Acute Otitis Media

Effectiveness of Prevenar in a 3+1 schedule has also been observed against acute otitis media and pneumonia since its introduction in a national immunisation 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). While direct cause-and-effect cannot be inferred from observational analyses of this type, these findings suggest that Prevenar plays an important role in reducing the burden of mucosal disease (AOM and pneumonia) in the target population.

Efficacy study in adults 65 years and older

Efficacy against vaccine-type (VT) pneumococcal CAP and IPD was assessed in a large-scale randomised 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.

The CAPiTA study enrolled volunteers ≥65 years of age whose demographic and health characteristics may differ from those seeking vaccination.

A first episode of hospitalised, chest X-ray confirmed pneumonia was identified in about 2% of this population (n=1,814 subjects) of which 329 cases were confirmed pneumococcal CAP and 182 cases were VT pneumococcal CAP in the per protocol and modified intent to treat (mITT)

populations. For the primary endpoint (per protocol population), there were 139 (49 Prevenar 13: 90 Placebo) first episodes of VT-CAP resulting in an efficacy of 45.56% (95.2% CI, 21.82-62.49; p=0.0006).

Efficacy was also demonstrated for the two secondary endpoints in the per protocol population. For the non-bacteraemic/non-invasive (NB/NI) pneumococcal CAP secondary endpoint, there were 93 (33 Prevenar 13: 60 Placebo) first episodes of NB/NI VT pneumococcal CAP resulting in an efficacy of 45.00% (95.2% CI, 14.21-65.31; p=0.0067). For the IPD secondary endpoint, there were 35 (7 Prevenar 13: 28 Placebo) first episodes of VT-IPD, resulting in an efficacy of 75.00% (95.2% CI, 41.06-90.87; p=0.0005).

The duration of protective efficacy against a first episode of VT pneumococcal CAP, NB/NI VT pneumococcal CAP, and VT-IPD extended throughout the 4-year study.

The study was not designed to demonstrate efficacy in subgroups, and the number of subjects ≥85 years of age was not sufficient to demonstrate efficacy in this age group.

Prevenar 13 Immunogenicity Clinical Trials in Adults

An antipolysaccharide binding antibody IgG level to predict protection against invasive pneumococcal disease or non-bacteremic pneumonia has not been defined for adults. However, non-clinical and clinical data support functional antibody, measured by opsonophagocytic activity (OPA) antibody assay, as a contributor to protection against pneumococcal disease. The OPA antibody assay 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 antibody 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 pneumococcal polysaccharide vaccine (PPSV23).

Serotype-specific OPA antibody 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) greater than 0.5 (2-fold criterion); statistically significantly greater responses were defined as the lower bound of the 2-sided 95% CI for the GMR greater than 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 antibody 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 antibody titer greater than zero. For comparison of OPA antibody GMTs, a statistically greater response for serotype 6A was defined as the lower bound of the 2-sided 95% CI for the GMR greater than 2.

Five phase 3 clinical trials 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 one 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 community-acquired pneumonia and invasive pneumococcal disease.

Two (2) pivotal non-inferiority trials were conducted in which Prevenar 13 response was compared to PPSV23 immune response, one in PPSV23 unvaccinated adults aged 50-64 years (6115A1-004), and one 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 Prevenar 13 with seasonal trivalent inactivated influenza vaccine (TIV).

Clinical trials conducted in adults not previously vaccinated with PPSV23

In a head-to-head, comparative trial conducted in adults aged 60-64 years, subjects received a single dose of either Prevenar 13 or 23-valent pneumococcal polysaccharide vaccine. In the same study another group of adults aged 50-59 years and another group of adults aged 18-49 years received a single dose of Prevenar 13.

Table 5 compares the OPA GMTs, 1-month post-dose, in 60-64 year olds given either a single dose of Prevenar 13 or 23-valent pneumococcal polysaccharide vaccine, and in 50-59 year olds given a single dose of Prevenar 13.

Table 5: OPA Antibody 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	**Prevenar 13**	**PPSV 23**	**Prevenar 13 50-59 Relative to 60-64 Years**		**Prevenar 13 Relative to PPSV 23, 60-64 Years**	
Serotype	**50-59 Years N=350-384 GMT**	**60-64 Years N=359-404 GMT**	**60-64 Years N=367-402 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 for the 12 common serotypes in cohort 1 and for the 13 serotypes in cohort 2 as the lower limit of the 2-sided 95% CI for GMT ratio (Prevenar 13/PPSV23) greater than 0.5.
[b]For serotype 6A, which is unique to Prevenar 13, a statistically significantly greater response was defined for analysis in cohort 1 as the lower limit of the 2-sided 95% CI for the GMT ratio (Prevenar 13/PPSV23) greater than 2.

In adults aged 60-64 years, OPA GMTs to Prevenar 13 were non-inferior to the OPA GMTs elicited to the 23-valent pneumococcal polysaccharide vaccine for the twelve serotypes common to both vaccines. For 9 serotypes, the OPA titers were shown to be statistically significantly greater in Prevenar 13 recipients.

In adults aged 50-59 years, OPA GMTs to all 13 serotypes in Prevenar 13 were non-inferior to the Prevenar 13 responses in adults aged 60-64 years. For 9 serotypes, immune responses were related to age, with adults in the 50-59 years group showing statistically significantly greater responses than adults aged 60-64 years.

In all adults ≥50 years who received a single dose of Prevenar 13, the OPA titers to serotype 6A were significantly greater than in adults ≥60 years who received a single dose of 23-valent pneumococcal polysaccharide vaccine.

One year after vaccination with Prevenar 13 OPA titers had declined compared to one month after vaccination, however, OPA titers for all serotypes remained higher than levels at baseline:

	OPA GMT levels at baseline	OPA GMT levels one year after Prevenar 13
Adults 50-59 years not previously vaccinated with 23-valent pneumococcal polysaccharide vaccine	5 to 45	20 to 1234
Adults 60-64 years not previously vaccinated with 23-valent pneumococcal polysaccharide vaccine	5 to 37	19 to 733

Clinical Trials Conducted in Adults Previously Vaccinated with PPSV23 (pre-vaccinated)

Immune responses to Prevenar 13 and 23-valent pneumococcal polysaccharide vaccine were compared in a head to head trial in adults aged ≥70 years, who had received a single dose of pneumococcal polysaccharide vaccine at least 5 years before study vaccination.

Table 6 compares the OPA GMTs, 1-month post-dose, in pneumococcal polysaccharide vaccinated adults aged ≥70 years given a single dose of either Prevenar 13 or 23-valent pneumococcal polysaccharide vaccine.

Table 6: OPA Antibody GMTs in PPSV23-Previously Vaccinated Adults Aged ≥70 Years Given Prevenar 13 or PPSV23[a,b]

Serotype	**Prevenar 13** N=400-426	**PPSV23** N=395-445	**Prevenar 13 Relative to PPSV23**	
	GMT	GMT	GMT 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]For the 12 common serotypes, non-inferiority was defined as the lower limit of the 2-sided 95% CI for GMT ratio (Prevenar 13/PPSV23) greater than 0.5.
[b]For serotype 6A, which is unique to Prevenar 13, a statistically significantly greater response was defined as the lower limit of the 2-sided 95% CI for the GMT ratio (Prevenar 13/PPSV23) greater than 2.

In adults vaccinated with pneumococcal polysaccharide vaccine at least 5 years prior to the clinical study, OPA GMTs to Prevenar 13 were non-inferior to the 23-valent pneumococcal polysaccharide vaccine responses for the 12 serotypes in common. Furthermore, in this study statistically significantly greater OPA GMTs were demonstrated for 10 of the 12 serotypes in common. Immune responses to serotype 6A were statistically significantly greater following vaccination with Prevenar 13 than after 23-valent pneumococcal polysaccharide vaccine.

One year after vaccination with Prevenar 13 in adults aged 70 years and over who were vaccinated with 23-valent pneumococcal polysaccharide vaccine, at least 5 years prior to study entry, OPA titers had declined compared to one month after vaccination, however, OPA titers for all serotypes remained higher than levels at baseline:

	OPA GMT levels at baseline	OPA GMT levels one year after Prevenar 13
Adults ≥70 years vaccinated with 23-valent pneumococcal polysaccharide vaccine at least 5 years prior	9 to 122	18 to 381

5.3 Pharmacokinetic Properties

Not applicable.

6. Non clinical Properties

6.1 Animal Toxicology and Pharmacology

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity, local tolerance, and reproduction and developmental toxicity.

7. DESCRIPTION

Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) I.P., 13 valent is a sterile liquid suspension for intramuscular administration of capsular polysaccharide antigens of Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, with each saccharide individually conjugated to plasmid-derived Diphtheria CRM197 protein. The container closure system for the Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) I.P., 13 valent vaccine is a 2 mL glass vial with a latex-free rubber stopper. The vial presentation includes the following non-product contact components: aluminium flip-off seal and polypropylene flip-off cap.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

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

8.2 Shelf-life

36 months

8.3. Packaging Information

0.5 ml suspension for injection in a vial (Type I glass) with a latex-free grey chlorobutyl rubber stopper and sealed with an aluminum flip-off seal and a polypropylene flip-off cap

8.4 Storage and handling instruction

Store refrigerated at 2°C to 8°C.

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

Store in original package.

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 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.

No special requirements for disposal.

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

Keep out of reach of children

9. Manufactured by:

Pfizer Manufacturing Belgium N.V.,
Rijksweg 12, 2870 Puurs,
Belgium

10. Imported and Marketed in India by:

Pfizer Limited
The Capital- A Wing,
1802, 18th Floor,
Plot No. C-70, G Block,
Bandra Kurla Complex,
Bandra (East),
Mumbai 400 051,
India.

11. Permission or license number with date:

This should be replaced as IMP-278/2014 dated 18 December 2014, subsequent approval dated 13 April 2016