# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

PREVENAR 13®: Pneumococcal polysaccharide conjugate vaccine, 13-valent adsorbed

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Prevenar 13 consists of a combination of 13 capsular polysaccharide antigens of *Streptococcus pneumoniae* serotypes. Each serotype is a purified polysaccharide from a fermentation process, individually conjugated to non-toxic plasmid-derived *diphtheria* $CRM_{197}$ protein and adsorbed on aluminium phosphate (0.565 mg).

The vaccine is a ready to use homogeneous white suspension for intramuscular injection, supplied as a pre-filled syringe.

**Active ingredients**

Each 0.5 mL dose contains:

2.2 µg of pneumococcal purified capsular polysaccharides for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F and 23F

4.4 µg of pneumococcal purified capsular polysaccharides for serotype 6B.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Prevenar 13 is presented as a suspension in 0.5 mL.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Active immunisation for the prevention of pneumococcal disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in adults and children aged more than 6 weeks of age.

The use of Prevenar 13 should be guided by official recommendations.

### 4.2 Dose and Method of Administration

The dose of Prevenar 13 is 0.5 mL given intramuscularly only, with care to avoid injection into or near nerves and blood vessels. The preferred sites are anterolateral aspect of the thigh (vastus lateralis muscle) in infants or the deltoid muscle of the upper arm in children and adults.

Do not administer Prevenar 13 intravascularly or into the gluteal area. Do not administer Prevenar 13 intravenously, subcutaneously or intradermally, since the safety and immunogenicity of these routes have not been evaluated.

Upon storage, a white deposit and clear supernatant can be observed. The vaccine should be well shaken to obtain a homogeneous white suspension and be inspected visually for any particulate matter and/or variation of physical aspect prior to administration. Do not use if the content appears otherwise. Prevenar 13 is a suspension containing an adjuvant. The vaccine must not be used if it cannot be uniformly suspended.

Prevenar 13 is not to be mixed with other vaccines or products in the same syringe. Prevenar 13 is for single-use in one patient only. The suspension contains no antimicrobial agent. Discard any residue.

***Immunisation schedules***

Data on the interchangeability of Prevenar (7-valent) or Prevenar 13 with other pneumococcal conjugate vaccines containing a protein carrier different from $CRM_{197}$ are not available.

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

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

*Infants aged 6 weeks - 6 months*

The primary infant series consists of three doses, each of 0.5 mL, 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 six weeks of age. A fourth (booster) dose is recommended after 12 months of age, and at least 2 months after the third dose.

**Table 1: Routine vaccination schedule for infants (6 weeks – 6 months of age)**

| **Dose:** | Dose 1 | Dose 2 | Dose 3 | Dose 4 |
|---|---|---|---|---|
| **Age at Dose:** | 2 months | 4 months | 6 months | 12-15 months |

Alternatively, when Prevenar 13 is given as part of a routine immunisation program, a series consisting of 3 doses, each of 0.5 ml, may be given. The first dose may be given from the age of 2 months, with a second dose 2 months later, and a third (booster) dose is recommended between 11-15 months of age (see Section 5.1 Pharmacodynamic Properties – Clinical Trials *Immune responses following a two-dose primary infant series*).

*Preterm infants (< 37 weeks gestation)*

In preterm infants, the primary infant series consists of three doses, each of 0.5 mL, with the first dose given at 2 months of age and with an interval of at least 1 month between doses. The first may be given as early as six weeks of age. A fourth (booster) dose is recommended between 11 and 15 months of age (see section 5 Pharmacological properties and 5.1 Pharmacodynamic Properties – Clinical Trials).

*Unvaccinated infants and children 7 months – 17 years of age*

**Table 2: Vaccination schedule for previously unvaccinated children ≥7 months of age**

| **Age at first dose** | **Total number of 0.5 mL doses** | **Duration between doses** |
|---|---|---|
| 7-11 months of age | 3 | Between dose 1 and 2: At least 1 month<br>Between dose 2 and 3: At least 2 months<br>(3rd dose after 12 months of age) |
| 12-23 months of age | 2 | At least 2 months |
| 24 months to 17 yrs of | 1 | N/A |

| | | |
|---|---|---|
| age | | |

*Infants and children previously vaccinated with Prevenar (7-valent)*

Prevenar 13 contains the same 7 serotypes contained in Prevenar (7-valent) and is manufactured based on the same conjugate technology using the same carrier protein $CRM_{197}$.

Infants and children who have begun immunisation with Prevenar (7-valent) may complete immunisation by switching to Prevenar 13 at any point in the schedule. In clinical trials, immunogenicity and safety profiles were comparable.

*Young children (12 – 59 months) completely immunised with Prevenar (7-valent)*

Children aged 12 months to 5 years of age who have completed primary infant immunisation with Prevenar (7-valent) may receive one dose of Prevenar 13 to elicit immune responses to the six additional serotypes. This catch-up (supplemental) dose of Prevenar 13 should be administered with an interval of at least 8 weeks after the final dose of Prevenar (7-valent).

*Children 6 –17 years (prior to 18th birthday) previously immunised with Prevenar (7-valent)*

Children 6 to 17 years of age may receive a single dose of Prevenar 13 if they have been previously vaccinated with one or more doses of Prevenar (7-valent). This dose of Prevenar 13 should be administered at least 8 weeks after the final dose of Prevenar (7-valent).

*Adults*

One single dose in adults including those previously vaccinated with pneumococcal polysaccharide vaccine.

The need for revaccination with a subsequent dose of Prevenar 13 has not been established. Refer to local recommendations.

If sequential administration of Prevenar 13 and 23vPPV is considered, Prevenar 13 should be given first for maximal efficacy and to avoid blunting of the immune response by 23vPPV.

*Special populations*

Individuals who may be at higher risk of pneumococcal infection (such as sickle cell disease or HIV infection) including those previously vaccinated with one or more doses of 23vPPV may receive at least one dose of Prevenar 13. Subsequent doses of Prevenar 13 produce immune responses that are comparable or higher than those after the first dose and therefore may be of benefit in certain individuals.

In individuals with a haematopoietic stem cell transplant (HSCT), the recommended immunisation series consists of four doses of Prevenar 13, each of 0.5 mL. The primary series consists of three doses, with the first dose given at 3 to 6 months after HSCT and with an interval of at least 1 month between doses. A fourth (booster) dose is recommended 6 months after the third dose.

The dosing schedule of Prevenar 13 in special populations should be guided by official recommendations (see also 5.1 Pharmacodynamic Properties – Clinical Trials– Immune responses in special populations).

## 4.3 Contraindications

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

Allergic reaction or anaphylactic reaction following prior administration of Prevenar (7-valent).

## 4.4 Special Warnings and Precautions For Use

Do not administer Prevenar 13 intravenously. Do not administer Prevenar 13 intravascularly. Take care to avoid injecting into or near nerves and blood vessels. The vaccine should not be injected in the gluteal area (see 4.2 Dose and Method of Administration).

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.

As with other vaccines, the administration of Prevenar 13 should be postponed in individuals suffering from acute moderate or severe febrile illness.

***Use in the elderly***

Prevenar 13 has been shown to be safe and immunogenic in the population ≥ 65 years. Of the 48,806 adults in the 7 studies of the clinical development program who received Prevenar 13, 30,793 (63.1%) were 65 to 74 years of age, and 14,498 (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.

***Disease coverage***

Prevenar 13 will not protect against *Streptococcus pneumoniae* serotypes other than those included in the vaccine nor other micro-organisms 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.

***Blood disorders***

As with other vaccines administered intramuscularly, this vaccine should not be given to individuals with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration.

***Impaired immune response***

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 immunisation.

***Vaccination in high-risk groups***

Safety and immunogenicity data for Prevenar 13 are available for certain high-risk groups such as children and adolescents with sickle cell disease and children and adults with HIV infection or with a haematopoietic stem cell transplant (see 4.2 Dose and Method of Administration - Special Populations). Data are not currently available for individuals in other immunocompromised groups (e.g. malignancy or nephrotic syndrome) and vaccination should be considered on an individual basis.

Children below 2 years old should receive the appropriate-for-age Prevenar 13 vaccination series. Where recommended, individuals at risk who are ≥ 24 months of age and already primed with Prevenar 13 should receive 23-valent pneumococcal polysaccharide vaccine. There are no data available to indicate whether the administration of 23-valent pneumococcal polysaccharide vaccine to unprimed individuals or to individuals primed with Prevenar 13 might result in hyporesponsiveness to further doses of Prevenar 13.

***Risk of apnoea***

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 ≤ 30 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.

***Prophylactic antipyretics***

Antipyretic treatment should be initiated according to local treatment guidelines.

Prophylactic antipyretic medication is recommended:

- for all children receiving Prevenar 13 simultaneously with vaccines containing whole cell pertussis because of higher rate of febrile reactions
- for children with seizure disorders or with a prior history of febrile seizures.

## 4.5 Interactions With Other Medicines 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. Prevenar 13 can also be given concomitantly between 12-23 months with the tetanus toxoid conjugated meningococcal polysaccharide serogroup A, C, W and Y vaccine. Clinical trials demonstrated that the immune responses and the safety profiles of the administered vaccines were unaffected.

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. Responses to the booster dose administered at 12 months were unaffected. The clinical significance of this observation is unknown.

Previously, trials with Prevenar (7-valent) and rotavirus vaccines have demonstrated that the immune responses of the seven pneumococcal serotypes in Prevenar (7-valent) 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 if Prevenar 13 is used. 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.

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 Prevenar (7-valent) and Infanrix hexa (see 4.8 Undesirable Effects - Infants and children aged 6 weeks to 5 years).

***Children 6 to 17 years of age***

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

***Adults aged 18 to 49 years***

No data are available regarding concomitant use with other vaccines.

***Adults aged 50 years and older***

Prevenar 13 may be administered concomitantly with the seasonal trivalent or quadrivalent inactivated influenza vaccine (TIV or QIV) with no interference with the immune responses to TIV or QIV. Concomitant use with other vaccines has not been investigated.

Prevenar 13 is not contraindicated in people who have previously been vaccinated with 23vPPV. Clinical studies have demonstrated Prevenar 13 can be safely given one year after 23vPPV. However, when Prevenar 13 was given 1 year after 23vPPV the immune responses were lower for all serotypes compared to when Prevenar 13 was given to subjects not previously immunised with 23vPPV. The clinical significance of this is unknown (see also 4.2 Dose and Method of Administration in adults).

Studies in which Prevenar 13 was given to subjects who had 23vPPV at least one year prior have not found an increased incidence of local or systemic side effects.

## 4.6 Fertility, Pregnancy and Lactation

***Pregnancy***

Category B2

Prevenar 13 is not indicated or recommended for use in pregnant women and has not been evaluated for potential harmful effects during pregnancy in humans.

Prevenar 13 showed no treatment-related effects on mating, fertility, pregnancy, parturition, fetal gross, external, soft tissue and skeletal alternations, and pup survival and growth in a combined fertility and embryofetal development study in which female rabbits were administered the human dose of the vaccine intramuscularly 17 and 3 days prior to mating, and on gestation days 10 and 24. Serotype-specific antibodies against each of the 13 vaccine serotypes were detected in does, fetuses, and pups.

***Breastfeeding***

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

In a female rabbit fertility and embryofetal development study, serotype–specific antibodies against each of the 13 vaccine serotypes were detected in the pups of does administered the vaccine prior to mating and during gestation. There were no adverse findings in these pups.

***Fertility***

Prevenar 13 showed no adverse effects on mating or fertility in a combined fertility and embryofetal development study in which female rabbits were administered the human dose of the vaccine intramuscularly 17 and 3 days prior to mating, and on gestation days 10 and 24 (see also Pregnancy).

## 4.7 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 reported adverse reactions may temporarily affect the ability to drive or use machines (see 4.8 Undesirable Effects).

## 4.8 Undesirable Effects

Adverse reaction frequencies are listed below 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%

***Children***

These data in Tables 3, 4 and 5 are from clinical trials in which Prevenar 13 was administered to children simultaneously with other routine childhood vaccines.

**Table 3: Adverse reactions in children administered Prevenar 13 with other routine childhood vaccines**

| | |
|---|---|
| **General disorders and administration site conditions** | |
| Very common: | Fever; any vaccination-site erythema, induration/swelling or pain/tenderness; vaccination-site erythema or induration/swelling 2.5 cm –7.0 cm (after toddler dose and in older children [age 2 to 5 years]). |
| Common: | Fever greater than 39ºC; vaccination-site erythema or induration/swelling 2.5 cm - 7.0 cm (after infant series); vaccination-site pain/tenderness interfering with movement |
| Uncommon: | Vaccination-site induration/swelling or erythema greater than 7.0 cm |
| **Gastrointestinal disorders** | |
| Common: | Diarrhoea; vomiting |
| **Immune system disorders** | |
| Rare: | Hypersensitivity reaction including face oedema, dyspnoea, bronchospasm |
| **Metabolism and nutrition disorders** | |
| Very common: | Decreased appetite |
| **Nervous system disorders** | |
| Very common: | Drowsiness/increased sleep; restless sleep/decreased sleep |
| Uncommon: | Seizures (including febrile seizures) |
| Rare: | Hypotonic-hyporesponsive episode |
| **Skin and subcutaneous tissue disorders** | |
| Common: | Rash |
| Uncommon: | Urticaria or urticaria-like rash |
| **Psychiatric disorders** | |
| Very common: | Irritability |
| Uncommon: | Crying |

**Table 4: Percentage of infant and toddler subjects reporting solicited local reactions at the Prevenar 13 or Prevenar (7-valent) injection sites**

| | Dose 1[a] | | Dose 2[a] | | Dose 3[a] | | Dose 4[b] | |
|---|---|---|---|---|---|---|---|---|
| Graded Local Reaction | Prevenar 13 (N[c]=3601-3878) | Prevenar 7 (N[c]=2025-2148) | Prevenar 13 (N[c]=3087-3388) | Prevenar 7 (N[c]=1699-1824) | Prevenar 13 (Nc=2603-2809) | Prevenar 7 (N[c]=1245-1364 | Prevenar 13 (N[c]=1049-1198) | Prevenar 7 (N[c]=654-791) |
| **Tenderness** | | | | | | | | |
| Any | 46.8 | 44.9 | 44.7 | 43.9 | 41.0 | 39.5 | 52.1 | 56.0 |
| Significant[d] | 8.3 | 9.3 | 6.3 | 8.6* | 6.0 | 5.9 | 6.2 | 8.1 |
| **Induration** | | | | | | | | |
| Any | 23.0 | 21.9 | 28.0 | 28.9 | 30.1 | 30.3 | 32.6 | 33.5 |
| Mild[e] | 19.8 | 20.0 | 25.6 | 26.5 | 27.6 | 27.9 | 29.8 | 29.4 |
| Moderate[e] | 6.9* | 4.7 | 7.0 | 6.1 | 8.0 | 7.2 | 12.0 | 10.5 |
| Severe[e] | 0 | 0 | 0.1 | 0 | 0 | 0 | 0 | 0 |
| **Erythema** | | | | | | | | |
| Any | 26.3 | 27.8 | 35.3 | 35.1 | 38.3 | 37.0 | 43.6 | 43.7 |
| Mild[e] | 24.7 | 26.8 | 33.9 | 33.9 | 36.5 | 35.3 | 39. 4 | 40.0 |
| Moderate[e] | 2.7* | 1.8 | 3.0 | 3.1 | 5.0 | 5.3 | 11.8 | 11.7 |
| Severe[e] | 0 | 0 | 0.1 | 0 | 0 | 0 | 0.1 | 0.2 |

* Statistically significant difference $p < 0.05$
Follow-up time = 4 days following each dose for most studies. Two studies had a follow-up time of 7 days and one study had a follow-up time of 15 days for stage 1 and 8 days for stage 2.

a. Infant dose data are included for 12 infant studies.
b. Toddler dose data are included for the 6 infant studies with toddler dose data.
c. Number of subjects reporting Yes for at least 1 day or No for all days.
d. Significant = present and interfered with limb movement.
e. Intensity of induration and erythema are rated by the diameter of the affected area: 0.5-2.0 cm = mild; 2.5-7.0 cm = moderate; >7.0 cm = severe.

**Table 5: Percentage of infant and toddler subjects reporting solicited systemic adverse reactions, fever and antipyretic medications after each vaccination**

| | Dose 1[a] | | Dose 2[a] | | Dose 3[a] | | Dose 4[b] | |
|---|---|---|---|---|---|---|---|---|
| Graded Systemic Events | Prevenar 13 (N[c]=3594-4022) | Prevenar 7 (N[c]=1998-2215) | Prevenar 13 (N[c]=3110-3606) | Prevenar 7 (N[c]=1718-1969) | Prevenar 13 (N[c]=2580-3024) | Prevenar 7 (N[c]=1253-1480) | Prevenar 13 (N[c]=1073-1283) | Prevenar 7 (N[c]=666-873) |
| **Decreased Appetite** | 38.4 | 37.2 | 37.8 | 41.0 | 36.6 | 38.1 | 42.2 | 50.2 |
| **Irritability** | 69.2 | 63.9 | 68.8 | 68.1 | 61.9 | 60.6 | 63.4 | 69.6 |
| **Increased Sleep** | 59.0 | 57.4 | 50.9 | 51.1 | 41.2 | 40.7 | 42.7 | 52.3 |
| **Decreased Sleep** | 36.4* | 33.5 | 35.3 | 34.9 | 34.0 | 32.8 | 30.1 | 33.2 |
| **Fever[d]** | | | | | | | | |
| Any | 25.0* | 24.4 | 32.2 | 38.4 | 27.8 | 32.4 | 43.0 | 49.8 |
| Mild | 24.1* | 23.5 | 30.7 | 37.3 | 26.8 | 31.3 | 41.1 | 48.2 |
| Moderate | 1.5 | 1.2 | 3.0 | 2.9 | 2.9 | 2.6 | 6.6 | 8.3 |
| Severe | 0.0 | 0.2* | 0.1 | 0.1 | 0.2 | 0.2 | 0.3 | 0.2 |
| **Antipyretic Medications** | | | | | | | | |
| Treat | 45.9 | 45.9 | 49.8 | 55.3 | 46.1 | 51.9 | 43.0 | 50.4 |
| Prevent | 46.5 | 46.0 | 48.9 | 50.9 | 47.1 | 51.1 | 36.1 | 46.5 |

* Statistically significant difference $p < 0.05$
Follow-up time = 4 days following each dose for most studies. Two studies had a follow-up time of 7 days and one study had a follow-up time of 15 days for stage 1 and 8 days for stage 2.

a. Infant dose data are included for 12 infant studies.
b. Toddler dose data are included for the 6 infant studies with toddler dose data.
c. Number of subjects reporting Yes for at least 1 day or No for all days.
d. "Any" fever = subjects with any temperature ≥38°C; for subcategories of fever by grading, subjects may be included in more than 1 row. Fever grading: mild ≥38°C but ≤39°C, moderate >39°C but ≤40°C, severe >40°C.

*Infants and children aged 6 weeks to 5 years*

In a clinical study (0887X-100811) with Prevenar (7-valent) in infants vaccinated at 2, 3, and 4 months of age, fever ≥ 38°C was reported at higher rates among infants who received Prevenar

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

In clinical studies with Prevenar 13, reports of mild fever (≥38.0°C but ≤39.0°C) ranged from 20.9% to 55.5% (across the 3 infant doses) and 31.4% to 63.7% (after toddler dose) when co-administered with Infanrix hexa. Moderate fever (39.0°C but ≤40.0°C) ranged from 0.8% to 8.8% in infants and 4.5% to 12.6% after the toddler dose, when co-administered with Infanrix hexa. The incidence of severe fever (>40.0°C) across all studies was ≤1.1%. When fever was present, it was most commonly observed in the first 2 days after vaccination.

*Children and adolescents aged 5 to 17 years of age*

Safety was evaluated in 592 children aged 5 to 17 years of age, 294 children aged 5 to 10 years previously immunised with at least one dose of Prevenar (7-valent) and 298 children aged 10 to 17 years who had not received a pneumococcal vaccine (see Table 6).

**Table 6: Most common adverse events in children and adolescents 5 to 17 years of age**

| | |
|---|---|
| **General disorders and administration site conditions** | |
| Very common: | Any vaccination-site erythema; induration/swelling or pain/tenderness; vaccination-site tenderness (including impaired movement) |
| Common: | Fever |
| **Gastrointestinal disorders** | |
| Common: | Vomiting; diarrhoea |
| **Metabolism and nutrition disorders** | |
| Very common: | Decreased appetite |
| **Nervous system disorders** | |
| Very common: | Drowsiness/increased sleep; restless sleep/decreased sleep |
| Common: | Headache |
| **Skin and subcutaneous tissue disorders** | |
| Common: | Rash; urticaria or urticaria-like rash |
| **Psychiatric disorders** | |
| Very common: | Irritability |

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.

***Adults ≥18 years and the elderly***

Safety was assessed in 7 clinical studies including 91,953 adults ranging in ages from 18 to 101 years. Prevenar 13 was administered to 48,806 adults; 2,616 (5.4%) aged 50 to 64 years and 45,291 (92.8%) adults 65 years and older. One of the 7 studies included a group of adults (n=899) ranging from 18 to 49 years who received Prevenar 13 and who were not previously vaccinated with 23vPPV. Of the Prevenar 13 recipients, 1,916 adults were previously vaccinated with the 23-valent pneumococcal polysaccharide vaccine at least 3 years prior to study vaccination, and 46,890 were 23-valent pneumococcal polysaccharide vaccine unvaccinated.

A trend to lower frequency of adverse reactions was associated with greater age; adults >65 years of age (regardless of prior pneumococcal vaccination status) reported fewer adverse reactions than younger adults, with adverse reactions generally most common in the youngest adults, 18 to 29 years of age. Overall, the frequency categories were similar for all age groups, with the

exception of vomiting which was very common (≥ 1/10) in adults aged 18 to 49 years and common (≥ 1/100 to < 1/10) in all other age groups..

***Adverse reactions from clinical studies***

Local reactions and systemic events were solicited daily after each vaccination for 14 days in 6 studies and 7 days in the remaining study. The following frequencies in Table 7 are based on adverse reactions assessed in Prevenar 13 clinical studies in adults:

**Table 7: Local and systemic reactions in adults**

| | |
|---|---|
| **Gastrointestinal disorders:** | |
| Very common:<br>Common:<br>Uncommon: | Diarrhoea; vomiting (in adults aged 18 to 49 years)<br>Vomiting (in adults aged 50 years and over)<br>Nausea |
| **General disorders and administration site conditions** | |
| Very common**:**<br><br>Common:<br>Uncommon: | Chills; fatigue; vaccination-site erythema; vaccination-site induration /swelling; vaccination-site pain/tenderness; limitation of arm movement<br>Fever<br>Lymphadenopathy localised to the region of the vaccination-site |
| **Immune system disorders** | |
| Uncommon: | Hypersensitivity reaction including face oedema, dyspnoea, bronchospasm |
| **Musculoskeletal and connective tissue disorders** | |
| Very common | Generalised new joint pain/aggravated joint pain; generalised new muscle pain/aggravated muscle pain |
| **Metabolism and nutrition disorders** | |
| Very common: | Decreased appetite |
| **Nervous system disorders** | |
| Very common: | Headache |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Rash |

Overall, no significant differences in frequencies of adverse reactions were seen when Prevenar 13 was given to adults previously vaccinated with the 23-valent pneumococcal polysaccharide vaccine or adults not vaccinated with 23-valent pneumococcal polysaccharide vaccine.

***Solicited adverse reactions in adult studies with Prevenar 13***

The proportion of adults reporting local and systemic adverse reactions within 14 days of vaccination with Prevenar 13 are listed below in tables 8 and 9, respectively.

**Table 8: Percentage of adults reporting solicited local reactions at Prevenar 13 injection site within 14 days after vaccination**

| | - Naïve to 23vPPV - | | | | Pre-immunised with 23vPPV |
|---|---|---|---|---|---|
| | Age (years) Number of Subjects | | | | |
| **Local Reaction** | **18-49** 209-787 | **50-59** 136 - 322 | **60-64** 178 - 331 | **≥65** 848 - 950 | **≥70** 297 - 362 |
| Redness[a] | | | | | |
| Any | 30.5 | 15.8 | 20.2 | 14.4 | 10.8 |
| Mild | 26.4 | 15.2 | 15.9 | 12.1 | 9.5 |
| Moderate | 11.9 | 5 | 8.6 | 6.1 | 4.7 |
| Severe | 2.8 | 0.7 | 1.7 | 0.8 | 1.7 |
| | | | | | |
| Swelling[a] | | | | | |
| Any | 39.4 | 21.7 | 19.3 | 12 | 10.4 |
| Mild | 37.2 | 20.6 | 15.6 | 10 | 8.9 |
| Moderate | 15.1 | 4.3 | 8.2 | 4.6 | 4 |
| Severe | 1.4 | 0 | 0.6 | 0.1 | 0 |
| | | | | | |
| Pain[b] | | | | | |
| Any | 96.7 | 88.8 | 80.1 | 41.7 | 51.7 |
| Mild | 93.2 | 85.9 | 78.6 | 36.1 | 50.1 |
| Moderate | 77.1 | 39.5 | 23.3 | 17.2 | 7.5 |
| Severe | 16.0 | 3.6 | 1.7 | 2 | 1.3 |
| | | | | | |
| Limitation of arm movement[c] | | | | | |
| Any | 75.2 | 40.7 | 28.5 | 14.4 | 10.5 |
| Mild | 71.5 | 38.6 | 26.9 | 13.2 | 10.3 |
| Moderate | 18.5 | 2.9 | 2.2 | 1.2 | 0.3 |
| Severe | 15.6 | 2.9 | 1.7 | 1.6 | 0.7 |

a. Mild is 2.5 to 5.0 cm, moderate is 5.1 to 10.0 cm, and severe is >10.0 cm.
b. Mild = awareness of symptom but easily tolerated, moderate = discomfort enough to cause interference with usual activity, and severe = incapacitating with inability to do usual activity.
c. Mild = some limitation of arm movement, moderate = unable to move arm above head but able to move arm above shoulder, and severe = unable to move arm above shoulder.

**Table 9: Percentage of adults reporting solicited systemic adverse reactions, use of medication to treat pain and fever within 14 days after vaccination with Prevenar 13**

| | - Naïve to 23vPPV - | | | | Pre-immunised with 23vPPV |
|---|---|---|---|---|---|
| | Age (years) Number of Subjects | | | | |
| **Systemic Event** | **18-49** 208-561 | **50-59** 136 - 248 | **60-64** 177 - 277 | **≥65** 420 - 456 | **≥70** 297 - 350 |
| Fever | | | | | |
| -Any (≥38°C) | 7.2 | 1.5 | 7.7 | 4.2 | 1.0 |
| -Mild (≥38°C but <38.5°C) | 4.2 | 1.5 | 3.9 | 3.1 | 1.0 |
| -Moderate (≥38.5°C but <39°C) | 1.9 | 0.0 | 0.6 | 1.0 | 0.0 |
| -Severe (≥39°C but ≤40°C) | 1.4 | 0.0 | 0.0 | 0.0 | 0.0 |
| -Potentially life threatening (>40°C) | 0.5 | 0.0 | 0.0 | 0.0 | 0.0 |
| Fatigue | 80.5 | 63.3 | 63.2 | 28.5 | 34.0 |
| Headache | 81.4 | 65.9 | 54.0 | 24.7 | 23.7 |
| Chills | 38.1 | 19.6 | 23.5 | 9.1 | 7.9 |
| Rash | 21.3 | 14.2 | 16.5 | 6.8 | 7.3 |
| Vomiting | 15.0 | 6.9 | 3.9 | 1.7 | 1.7 |
| Diarrhoea | N/A | N/A | N/A | N/A | N/A |
| Decreased appetite | 55.6 | 25.3 | 21.3 | 11.3 | 10.4 |
| New muscle pain | 82.0 | 61.8 | 56.2 | 23.4 | 36.8 |
| Aggravated muscle pain | 55.9 | 39.9 | 32.6 | 15.0 | 20.6 |
| New joint pain | 41.7 | 31.5 | 24.4 | 11.5 | 12.6 |
| Aggravated joint pain | 28.6 | 25.6 | 24.9 | 8.6 | 11.6 |
| Use of medication to treat pain | N/A | N/A | N/A | 9.9 | 22.0 |
| Use of medication to treat fever | N/A | N/A | N/A | 5.4 | 3.0 |
| Abbreviation: N/A = not applicable | | | | | |

***Solicited adverse reactions in adult studies with Prevenar 13 and TIV***

The safety of concomitant administration of Prevenar 13 with Trivalent Inactivated Influenza Vaccine (TIV) was assessed in two studies in 23vPPV 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 TIV compared to Prevenar 13 administered alone.

Higher frequency of some solicited systemic reactions was observed when Prevenar 13 was 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).

***Additional information in special populations***

*Children and adolescents*

Children and adolescents with sickle cell disease, HIV infection or a haematopoietic stem cell transplant had similar frequencies of adverse reactions as children and adolescents 2-17 years of age, except that headaches, vomiting, diarrhoea, fever, fatigue, arthralgia and myalgia were very common.

*Adults*

Adults with HIV previously vaccinated with the pneumococcal polysaccharide vaccine, have similar frequencies of adverse reactions, except that fever and vomiting were very common and nausea was common.

Adults with a haematopoietic stem cell transplant have similar frequencies of adverse reactions as adults 18 years and older, except that fever and vomiting were very common.

***Adverse reactions from Prevenar 13 post-marketing experience***

Although the following adverse drug reactions were not observed in the clinical trials, they are considered adverse drug reactions for Prevenar 13 as they were reported in the post-marketing experience (Table 10). Because these reactions were derived from spontaneous reports, the frequencies could not be determined and are thus considered as not known.

**Table 10: Adverse events reported in post-market experience**

| | |
|---|---|
| **General disorders and administration site conditions** | Vaccination-site dermatitis; vaccination-site urticaria; vaccination-site pruritus; flushing |
| **Blood and lymphatic system disorders** | Lymphadenopathy localised to the region of the vaccination-site |
| **Immune system disorders** | Anaphylactic/anaphylactoid reaction including shock |
| **Skin and subcutaneous tissue disorders** | Angioedema; erythema multiforme |

Analysis of postmarketing reporting rates suggests a potential increased risk of convulsions, with or without fever, and HHE (hypotonic-hyporesponsive episode) when comparing groups which reported use of Prevenar 13 with Infanrix hexa to those which reported use of Prevenar 13 alone. These events were reported in infants less than 2 years of age.

**Reporting of Suspected Adverse Reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

### 4.9 Overdose

Overdose with Prevenar 13 is unlikely due to its presentation as a pre-filled syringe. However, in infants and children, 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 paediatric schedules of Prevenar 13.

Contact the NZ Poisons Information on 0800 764 766 for advice on the management of an overdose.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic Properties

***Burden of Disease***

*Streptococcus pneumoniae* is an important cause of morbidity and mortality in persons of all ages worldwide. It is a leading cause of death and illness in infants, among the elderly, and in persons who have certain underlying medical conditions. The organism causes invasive infections, including bacteraemia and meningitis, pneumonia and other lower respiratory tract infections, and upper respiratory tract infections including otitis media and sinusitis.

*Infants and children less than 5 years of age*

Based on serotype surveillance performed before the introduction of Prevenar (7-valent), Prevenar 13 is estimated to cover 93.3% of serotypes causing Invasive Pneumococcal Disease (IPD) among children less than 5 years of age in Australia (Watson M. *et al*., *Communicable Disease Intelligence* 2004; 28(4): 455-464) and 92.8 % in New Zealand (Heffernan H.M., *et al*,. *Epidemiology of Infections* 2007; 1-8.)

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

*Adults*

Pneumonia is one of the most common infectious diseases and the most common clinical presentation of pneumococcal disease in adults. The reported incidence of community-acquired pneumonia (CAP) and IPD 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.

The incidence of IPD in adults increases with age, risk factors (smoking status or alcohol use), and underlying co-morbidities (see Special populations below). Bacteraemic pneumonia, bacteraemia without a focus, and meningitis are the most common manifestations of IPD in adults.

Based on serotype surveillance performed before the introduction of Prevenar (7-valent), Prevenar 13 is estimated to cover 81.9% of serotypes causing IPD among adults aged 65 years and older in Australia (Watson M. *et al*., *Communicable Disease Intelligence* 2004; 28(4): 455-464) and 77.4 % in New Zealand (Heffernan H.M., *et al*., *Epidemiology of Infections* 2007; 1-8.).

Following the introduction of Prevenar (7-valent) on to the National Immunisation Program (NIP) for children, Prevenar 13 is estimated to cover 62.2% of serotypes causing IPD among adults aged 65 years and older in Australia, based on National Notifiable Diseases Surveillance System data from 2008.

*Special populations*

The risk for IPD is increased in individuals with 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.

***Pharmacodynamics***

Pharmacotherapeutic group: pneumococcal vaccines.

Prevenar 13 contains the 7 pneumococcal capsular polysaccharides that are in Prevenar (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.

***Mode of action***

The protection afforded by Prevenar 13 vaccination is mediated by the induction of antibodies against the pneumococcal capsular serotypes in the vaccine.

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, recognising 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 signalling 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 mobilise 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, unconjugated PSs are associated with poor or absent immunogenicity in infants less than 24 months of age and failure to induce immunological memory at any age. Conjugation of PSs to a protein carrier overcomes the T-cell–independent nature of PS antigens. Protein carrier-specific T-cells provide the signals needed for maturation of the B-cell response and generation of B-cell memory. Conversion of *Streptococcus pneumoniae* PSs to a T-cell-dependent antigen by covalent coupling to the immunogenic protein carrier $CRM_{197}$ enhances the antibody response and induces immune memory. This has been demonstrated to elicit booster responses on re-exposure in infants and young children to pneumococcal polysaccharides.

### *Clinical Trials*

*Prevenar (7-valent) protective efficacy*

The efficacy of Prevenar (7-valent) was evaluated in two major trials – the Northern California Kaiser Permanente (NCKP) trial and the Finnish Otitis Media trial (FinOM). Both trials were randomised, double-blind, active-control trials in which infants were randomised to receive either Prevenar (7-valent) 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 various efficacy results from these trials (for invasive pneumococcal disease, pneumonia, and acute otitis media) are presented below (Table 11).

**Table 11: Summary of efficacy of Prevenar (7-valent)**

| Test | Study | N | VE* | 95% CI |
|---|---|---|---|---|
| **Invasive Pneumococcal Disease (IPD)** | | | | |
| Per-protocol | NCKP | 30,258 | 97% | 85, 100 |
| Intent-to-treat | | 37,866 | 94% | 81, 99 |
| **Pneumonia (Per-protocol)** | | | | |
| *With vaccine serotype bacteraemia* | | | 87.5% | 7, 99 |
| *Clinical pneumonia with abnormal chest X-ray regardless of etiologic confirmation* | | | 35% | 4, 56 |
| **Acute Otitis Media (AOM)** | | | | |
| Per-protocol (reduction of) | NCKP | 37,868 | | |
| *Total episodes* | | | 7% | 4, 10 |
| *Recurrent AOM (3 episodes in 6 mo. or 4 episodes in 1 yr.)* | | | 9% | 3, 15 |
| *Recurrent AOM (5 episodes in 6 mo. or 6 episodes in 1 yr.)* | | | 23% | 7, 36 |
| *Tympanostomy tube placement* | | | 20% | 2, 35 |
| Per-protocol (reduction of) | FinOM | 1662 | | |
| *Total episodes* | | | 6% | -4, 16 |
| *All pneumococcal AOM* | | | 34% | 21, 45 |
| *Vaccine-serotype AOM* | | | 57% | 44, 67 |
| Intent-to-treat | | | | |
| *Vaccine-serotype AOM* | | | 54% | 41, 64 |

*Vaccine efficacy

*Prevenar 13 immunogenicity clinical trials in infants and children*

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

*Immune responses following a three-dose primary infant series*

Clinical trials have been conducted in a number of European countries and the US using a range of primary vaccination schedules. The percentage of infants achieving pneumococcal anti-capsular polysaccharide IgG antibody concentrations ≥ 0.35 µg/mL and opsonophagocytic activity (OPA) antibody titers ≥ 1:8, one month after a three-dose primary series (at 2, 4 and 6 months) and after booster dosing, from representative studies are presented below (Table 12):

**Table 12: Percentage of subjects with pneumococcal anti-capsular polysaccharide IgG antibody concentrations ≥ 0.35 µg/mL and OPA antibody titer ≥ 1:8 following Prevenar 13 administration in a 2, 4, 6 month primary schedule**

| Serotype | | Primary Schedule (2, 4, 6 months) | Booster |
|---|---|---|---|
| | | IgG (N=897-924)<br>OPA (N=91-94) | IgG (N=458-479)<br>OPA (N=88-92) |
| **1** | IgG ≥ 0.35 µg/mL | 95.6-99.3% | 98.7-100.0% |
| | OPA Antibody ≥ 1:8 | 98.9% | 98.9% |
| **3** | IgG ≥ 0.35 µg/mL | 63.5-90.3% | 90.5-92.2% |
| | OPA Antibody ≥ 1:8 | 96.8% | 97.8% |
| **4** | IgG ≥ 0.35 µg/mL | 94.4-98.9% | 99.1-99.2% |
| | OPA Antibody ≥ 1:8 | 97.8% | 98.9% |
| **5** | IgG ≥ 0.35 µg/mL | 89.7-97.3% | 99.1-99.6% |
| | OPA Antibody ≥ 1:8 | 92.3% | 98.9% |
| **6A** | IgG ≥ 0.35 µg/mL | 96.0-98.2% | 99.1-100.0% |
| | OPA Antibody ≥ 1:8 | 100.0% | 98.9% |
| **6B** | IgG ≥ 0.35 µg/mL | 87.3-98.5% | 99.6% |
| | OPA Antibody ≥ 1:8 | 98.9% | 98.9% |
| **7F** | IgG ≥ 0.35 µg/mL | 98.4-100.0% | 98.8-99.6% |
| | OPA Antibody ≥ 1:8 | 100.0% | 100.0% |
| **9V** | IgG ≥ 0.35 µg/mL | 90.5-99.3% | 99.1-100.0% |
| | OPA Antibody ≥ 1:8 | 100.0% | 98.9% |
| **14** | IgG ≥ 0.35 µg/mL | 97.4-98.2% | 98.7-100.0% |
| | OPA Antibody ≥ 1:8 | 100.0% | 100.0% |
| **18C** | IgG ≥ 0.35 µg/mL | 96.8-98.1% | 98.7-99.6% |
| | OPA Antibody ≥ 1:8 | 100.0% | 98.9% |
| **19A** | IgG ≥ 0.35 µg/mL | 98.4-99.6% | 100.0% |
| | OPA Antibody ≥ 1:8 | 100.0% | 97.8% |
| **19F** | IgG ≥ 0.35 µg/mL | 98.0-99.3% | 99.6-100.0% |
| | OPA Antibody ≥ 1:8 | 90.4% | 96.7% |
| **23F** | IgG ≥ 0.35 µg/mL | 87.2-94.6% | 99.1-99.6% |
| | OPA Antibody ≥ 1:8 | 98.9% | 98.9% |

In Prevenar 13 recipients, antipolysaccharide binding antibody for each of the 13 serotypes has been demonstrated to be correlated with functional antibacterial opsonophagocytic activity (biologically active antibody).

*Immune responses following a two-dose primary infant 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 58.4%) and 23F (55.8% to 68.6%). Compared to a three-dose infant series, pneumococcal anti-capsular polysaccharide IgG GMCs were lower after a two-dose infant series for most serotypes.

*Booster responses following two-dose and three-dose primary infant series*

Post-booster antibody concentrations were higher for 12 serotypes than those achieved after the infant primary series, which is consistent with adequate priming (the induction of immunologic memory). For serotype 3, antibody concentrations following the infant primary series and booster dose were similar. 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 immunisation schedules result in levels of anti-capsular polysaccharide IgG antibody responses to each of the 13 serotypes that are at least comparable to those of a three-dose primary series in infants.

*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% achieved a pneumococcal polysaccharide IgG binding antibody concentration ≥0.35 μg/mL 1 month after the infant series, except for 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 achieving this same antibody concentration threshold was >97%, except for serotype 3 (71% in preterm infants and 79% in term infants). In general, serotype-specific IgG GMCs were lower for preterm infants than term infants.

*Effect on nasopharyngeal carriage of S. pneumoniae serotypes*

Prevenar 13 is associated with the prevention of nasopharyngeal colonisation of vaccine type serotypes and this may contribute to protection against pneumococcal disease.

In a randomised double-blind study, 930 infants received Prevenar 13 and 933 received Prevenar (7-valent) at 2, 4, 6 and 12 months of age in Israel. The proportion of subjects with a newly identified nasopharyngeal (NP) acquisition in each vaccine group was assessed at 7, 12, 13, 18 and 24 months. 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. Among the common serotypes, a significant reduction in the proportion of subjects with newly identified NP acquisition of serotype 19F was observed in the Prevenar13 group compared with the Prevenar group. For the remaining 6 common serotypes, similar rates of NP acquisition were observed in both vaccines groups.

*Children and Adolescents 5 to 17 years of age*

In an open-label study in 592 healthy children and adolescents including those with asthma 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 (i.e. the lower limit of the 2-sided 95%Cl for the GMR >0.5) to Prevenar (7-valent) 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.

**Table 13: Comparison of Pneumococcal IgG GMC (µg/mL) post vaccination – *Evaluable Immunogenicity Population***

| Serotype | 13vPnC Group 3c (Study 3011) | | | 7vPnC (Study 3005) | | | Ratio |
|---|---|---|---|---|---|---|---|
| | n | GMC | 95% CI | n | GMC | 95% CI | |
| 7vPnC | | | | | | | |
| 4 | 169 | 8.45 | 7.24, 9.87 | 173 | 2.79 | 2.45, 3.18 | 3.03 (2.48, 3.71) |
| 6B | 171 | 53.56 | 45.48, 63.07 | 173 | 9.47 | 8.26, 10.86 | 5.66 (4.57, 6.99) |
| 9V | 171 | 9.51 | 8.38, 10.78 | 173 | 1.97 | 1.77, 2.19 | 4.83 (4.10, 5.70) |
| 14 | 169 | 29.36 | 24.78, 34.78 | 173 | 8.19 | 7.31, 9.18 | 3.58 (2.93, 4.39) |
| 18C | 171 | 8.23 | 7.13, 9.51 | 173 | 2.33 | 2.05, 2.65 | 3.53 (2.91, 4.29) |
| 19F | 171 | 17.58 | 14.95, 20.67 | 173 | 3.31 | 2.87, 3.81 | 5.31 (4.29, 6.58) |
| 23F | 169 | 11.26 | 9.79, 12.95 | 173 | 4.49 | 3.86, 5.23 | 2.51 (2.04, 3.08) |

**Table 14: Comparison of Pneumococcal IgG GMC (µg/mL) post-vaccination – *Evaluable Immunogenicity Population***

| Serotype | 13vPnC Group 3c (Study 3011) | | | 13vPnC (Study 3005) | | | Ratio |
|---|---|---|---|---|---|---|---|
| | n | GMC | 95% CI | n | GMC | 95% CI | |
| Additional | | | | | | | |
| 1 | 171 | 3.57 | 3.05, 4.18 | 1068 | 2.90 | 2.75, 3.05 | 1.23 (1.07, 1.42) |
| 3 | 171 | 2.38 | 2.07, 2.74 | 1065 | 0.75 | 0.72, 0.79 | 3.17 (2.78, 3.62) |
| 5 | 171 | 5.52 | 4.82, 6.32 | 1068 | 2.85 | 2.72, 2.98 | 1.94 (1.71, 2.20) |
| 6A | 169 | 21.51 | 18.15, 25.51 | 1063 | 7.11 | 6.78, 7.46 | 3.03 (2.64, 3.47) |
| 7F | 170 | 6.24 | 5.49, 7.08 | 1067 | 4.39 | 4.18, 4.61 | 1.42 (1.24, 1.62) |
| 19A | 170 | 17.18 | 15.01, 19.67 | 1056 | 8.44 | 8.05, 8.86 | 2.03 (1.78, 2.32) |

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

**Table 15: Comparison of Pneumococcal OPA GMTs post-vaccination – *Evaluable Immunogenicity Population***

| Serotype | Prevenar 13 (10 through 17 years of age) n | GMT | 95% CI | Prevenar 13 (5 through 9 years of age) n | GMT | 95% CI | Ratio |
|---|---|---|---|---|---|---|---|
| 7vPnC | | | | | | | |
| 4 | 188 | 6912 | 6101, 7831 | 181 | 4629 | 4017, 5334 | 1.5 (1.24, 1.80) |
| 6B | 183 | 14224 | 12316, 16427 | 178 | 14496 | 13164, 17083 | 0.9 (0.78, 1.15) |
| 9V | 186 | 4485 | 4001, 5027 | 180 | 4733 | 4203, 5328 | 0.9 (0.80, 1.12) |
| 14 | 187 | 6894 | 6028, 7884 | 176 | 4759 | 4120, 5497 | 1.4 (1.19, 1.76) |
| 18C | 182 | 6263 | 5436, 7215 | 175 | 8815 | 7738, 10041 | 0.7 (0.59, 0.86) |
| 19F | 184 | 2280 | 1949, 2668 | 178 | 1559 | 1293, 1879 | 1.5 (1.15, 1.86) |
| 23F | 187 | 3808 | 2255, 4323 | 176 | 3245 | 2819, 3736 | 1.2 (0.97, 1.42) |
| Additional | | | | | | | |
| 1 | 189 | 319 | 271, 376 | 179 | 187 | 160, 219 | 1.7 (1.35, 2.13) |
| 3 | 181 | 114 | 100, 129 | 178 | 202 | 181, 226 | 0.6 (**0.48**, 0.67) |
| 5 | 183 | 336 | 270, 418 | 178 | 491 | 426, 565 | 0.7 (0.53, 0.89) |
| 6A | 182 | 9928 | 8457, 11655 | 178 | 7514 | 6351, 8891 | 1.3 (1.05, 1.67) |
| 7F | 185 | 6584 | 5829, 7436 | 178 | 10334 | 9099, 11737 | 0.6 (0.53, 0.76) |
| 19A | 187 | 1276 | 1132, 1439 | 180 | 1180 | 1048, 1329 | 1.1 (0.91, 1.28) |

*Prevenar 13 Effectiveness*

*Invasive Pneumococcal Disease*

The information captured in this section comes from published literature.

The impact of Prevenar 13 on the rates of IPD in the United States was measured using an active population-based and laboratory-based surveillance system: the Active Bacterial Core surveillance (ABCs). In 2000, Prevenar (7-valent) was introduced into the routine infant immunisation programme in the USA, with a 3 dose primary series and a booster dose in the second year of life. In 2010, Prevenar 13 replaced Prevenar.

For the 2012-2013 period, there were statistically significant declines in the incidence of IPD for the Prevenar-13 unique serotypes (i.e."Prevenar 13 minus Prevenar" serotypes. The disease reductions were calculated using a model of observed versus expected (if Prevenar 13 had not replaced Prevenar) IPD cases with 95% Interval Estimates (IEs) and are shown in Table 16.

**Table 16: United States: Prevenar 13 minus Prevenar-type IPD (Observed vs Expected)**

| Age Group, Years | Percent Change in Rate (95% IE) 2010-2011 | Percent Change in Rate (95% IE) 2011-2012 | Percent Change in Rate (95% IE) 2012-2013 |
|---|---|---|---|
| <5 | -66 (-61, -70) | -88 (-86, -89) | -93 (-91, -94) |
| 5-17 | -33 (-21, -45) | -59 (-48, -66) | -75 (-67, -80) |
| 18-49 | -33 (-26, -38) | -64 (-60, -68) | -72 (-69, -75) |
| 50-64 | -23 (-18, -28) | -54 (-50, -57) | -62 (-59, -65) |
| ≥65 | -23 (-13,-31) | -46 (-39, -52) | -58 (-52, -64) |

In all age groups, these reductions were driven principally by declines in IPD caused by serotypes 19A and 7F. There was no significant increase in disease caused by non-Prevenar 13 serotypes among children younger than 5 years and most adult age groups, except for adults 50–64 years old where a 26% increase (95% IE 13–44) was detected in non-Prevenar 13 type IPD during 2012–13 compared to expected incidence, although no non-Prevenar 13 serotype predominated. However, serotype replacement may not be expected within 2 years after introduction of Prevenar 13.

The prevalence of at least one risk factor increased among children and adults with IPD after the introduction of Prevenar 13. The proportions of cases resulting in hospital admission were also higher in the period after the introduction of Prevenar 13 in both children and adults, but case-fatality rates did not change.

After the introduction of Prevenar 13, a reduction in the incidence of antibiotic-resistant IPD (vaccine serotype or non-vaccine serotype IPD) was also identified. Penicillin-non-susceptible IPD, erythromycin-non-susceptible IPD and multiply-non-susceptible IPD decreased by 78-96% among children younger than 5 years. Among adults, reductions in the incidence of penicillin-non-susceptible IPD and multiply-non-susceptible IPD were also seen. The reductions in antibiotic non-susceptible IPD were largely attributable to reductions in IPD caused by serotype 19A, the serotype associated with increased antibiotic non-susceptibility before the introduction of Prevenar 13.Overall, it is estimated that in the first 3 years after the introduction of Prevenar 13, around 10,000 IPD cases among children and 20,000 cases among adults were probably prevented in the USA, with around 3,000 fewer deaths, mostly among adults.

In England and Wales, 23vPPV was in use for risk subjects >2 years of age from 1992. This vaccine was also recommended for adults ≥80 years, ≥75 years and ≥65years of age from 2003, 2004 and 2005, respectively. Prevenar (7-valent) was first recommended for risk children <2 years of age in 2002 and from 2005 for "risk children" <5 years. From 2006, Prevenar (7-valent) was introduced into the Routine Childhood Immunisation Programme with a catch-up campaign for children up to two years of age. As of April 2010 the Prevenar (7-valent) was replaced by Prevenar 13 and it simply replaced Prevenar (7-valent) at the point in the schedule that any child had reached. There was no catch up program.

Four years after the introduction of Prevenar (7-valent) 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 Prevenar (7-valent) vaccine serotypes was reported in children under 2 years, in England and Wales. However, reductions were accompanied by an increase in IPD from non-vaccine serotypes, such as 7F, 19A and 22F, thus diminishing the effect of Prevenar (7-valent) on overall IPD incidence.

Subsequently, four years following the switch to Prevenar 13, the additional reduction in incidence of IPD due to the 7 serotypes in Prevenar ranged from 76% (95% CI 7; 94) in children less than 2 years of age to 91% (95% CI 33; 99) 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 17 and ranged from 68% (95% CI 6; 89) (serotype 3) to 100% (95% CI 62; 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). Overall, the reductions observed were attenuated by the increase in non-PCV13 IPD, both in adults ≥65 years and in children younger <5 years - the two groups with the highest incidence of pneumococcal-attributable disease.

**Table 17: 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 Prevenar 13** | | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 59 | 5 | 91%<br>(68%; 98%)** | 458 | 77 | 83%<br>(74%; 88%)** | 102 | 13 | 87%<br>(72%; 94%)** |
| **3** | 26 | 8 | 68%<br>(6%; 89%) | 178 | 73 | 59%<br>(38%; 72%)** | 256 | 143 | 44%<br>(27%; 57%)** |
| **6A** | 10 | 0 | 100%<br>(62% ; 100%;)*<br>* | 53 | 5 | 90%<br>(56%; 97%)** | 94 | 5 | 95%<br>(81%; 99%)** |
| **7F** | 90 | 8 | 91%<br>(74%; 97%)** | 430 | 160 | 63%<br>(50%; 71%)** | 173 | 75 | 56%<br>(37%; 70%)** |
| **19A** | 85 | 7 | 91%<br>(75%; 97%)** | 225 | 104 | 54%<br>(32%; 65%)** | 279 | 97 | 65%<br>(53%; 75%)** |
| | | | | | | | | | |
| **NVT** | 94 | 136 | -34%<br>(-133%, 23%) | 878 | 1068 | -8%<br>(-31%, 10.1%) | 867 | 1144 | -13%<br>(-36%, 0.6%) |

§ 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
# No cases of serotype 5 IPD were identified
NVT Non-PCV13 serotypes

*Pneumonia*

Information captured in this section has been taken from published literature.

The effect of Prevenar 13 on admissions to hospital in the USA 2 years after its introduction in 2010 was assessed using data from a private inpatient discharge record database covering approximately 20% of inpatients in the USA. A multiple regression model was used to estimate change in admissions to hospital for all-cause pneumonia, invasive pneumococcal disease, non-invasive pneumococcal pneumonia, and empyema, and for negative controls, urinary tract infection and hospital admission for any reason. Direct cause and effect cannot be inferred from analyses of this type.

Reduction in hospital admission for all-cause pneumonia of 21% [95% CI 14–28] was reported for children aged less than 2 years and 17% [95% CI 7–27]. for those aged 2 – 4 years: For empyema the reduction was 50% [95% CI 22–68] for children age <2 years, 46% [95% CI 21–64] for children 2–4 years, and 37% [95% CI 13–54] for those aged 5–17 years. All-cause pneumonia was reduced in adults 18–39 years (12% (95% CI 6–17) but not for other adult age groups. Non-invasive pneumococcal or lobar pneumonia fell for all age groups except toddlers aged 2–4 years.

In a multicenter observational study in France between June 2009 and May 2012 comparing the periods before and after the switch from Prevenar (7-valent) 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<0.002) 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 Prevenar (7-valent) 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 61; 73) in outpatient visits and 32% (95% CI 22; 39) in hospitalisations for alveolar

CAP following the introduction of Prevenar 13 when compared to the period before the introduction of Prevenar (7-valent) was introduced.

*Otitis media (OM)*

Information captured in this section has been taken from published literature.

A study was conducted one year following the introduction of Prevenar 13 in the USA. It utilised an insurance claims database of a large, nationwide managed health care plan. Enrolled children aged 6 years or younger and those with OM visits were identified (5.51 million child-years). There was a significant drop in OM visit rates that coincided with the introduction of Prevenar 13 in 2010 and the observed OM visit rates in 2010 and 2011 were lower than the projected rates based on the 2005-2009 trend ($p<0.001$). In a multicenter surveillance of *Streptococcus pneumoniae* isolates from spontaneous drainage, PE tube placement, myringotomy or mastoid surgical cultures from 8 children's hospitals in the USA were obtained. In 2011, 74 of 149 (50%) isolates were Prevenar 13 plus a related serotype; in 2012 and 2013, these serotypes accounted for 47 of 116 (40.5%) and 34 of 118 (29%) of isolates, respectively. Overall, there was a reduction in the proportion of isolates included in Prevenar 13 over the 3 years following the introduction of that vaccine, including antibiotic resistant strains. Serotype 19A was the most common serotype isolated in each year. The number of serotype 19A isolates in 2013 (n = 12, 10.2% of total) decreased 76% compared with 2011 (n = 50, 33.6% of total).In a published study performed prospectively in Israel between 2004 and 2013, the impact on OM of introduction of a 2-dose primary series of Prevenar 13 plus booster dose in the second year of life was recorded in a population-based active-surveillance system including culture results of middle ear fluid obtained by tympanocentesis. The decision to perform tympanocentesis in the presence of OM was independent of the study protocol. Overall, 6,122 OM episodes with middle ear fluid cultures were recorded in children less than 2 years of age. Declines in incidence were recorded from 2.1 to 0.1 cases per 1000 children (96%) for the Prevenar serotypes plus serotype 6A and a decline in incidence from 0.9 to 0.1 cases per 1000 children (85%) 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 (77%) between July 2004 (prior to the introduction of Prevenar) and June 2013 (post Prevenar 13 introduction). However, the true reduction of overall OM incidences could not be studied, as simple OM can be subclinical, subject to over- and under diagnosis and, above all, not subjected to middle ear fluid culture.

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.

*Carriage*

The information captured in this section has been taken from published literature.

A study of nasopharyngeal carriage of *Streptococcus pneumoniae* in predominantly black children 6–59 months of age presenting to a children's hospital emergency department in Atlanta, USA between 1 July 2010 and 30 June 2013 showed a significant reduction in carriage of Prevenar 13 serotypes and antibiotic resistant strains after the introduction of Prevenar 13. The overall proportion of children with *Streptococcus pneumoniae* carriage ranged from 28% to 35.4% and did not significantly change through the study period. Carriage of Prevenar 13 serotypes decreased significantly from 29% (36/124) to 3% (3/99; $p<0.0001$), primarily due to a significant decrease in serotype 19A carriage from 25.8% (32/124) to 3% (3/99; $P < 0.0001$). The proportion of carriage isolates with nonsusceptibility to ceftriaxone declined from 22.6% to 3%

(p<0.001) and nonsusceptibility to penicillin also declined from 24% to 3% and nonsusceptibility to penicillin also declined from 24% to 3%.The proportion of pneumococcal carriage accounted for by non-PCV13 serotypes (excluding 6C) increased from 68.4% (78/114) to 96.9% (95/98; P < 0.0001). Non-PCV13 serotypes 35B, 15B/C, 11A, 21, 23B and 15A were the most commonly carried serotypes during the last 2 study periods. Carriage of serotype 35B increased during the 6 study periods from 8.9% (11/124) to 25.3% (25/99). Serotype 35B demonstrated moderate non-susceptibility to selected antibiotics.

***Reduction of Antimicrobial Resistance (AMR)***

The information captured in this section has been taken from published literature.

Following the introduction of Prevenar (7-valent) 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.

A post-hoc analysis of a double–blind, randomised, controlled study enrolling 1866 subjects in Israel conducted between February 2008 and September 2009, compared Prevenar (7-valent) and Prevenar 13. The reported reduction of new acquisitions 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.

Data from 10 surveillance sites of the United States Centers for Disease Control and Prevention covering 31 million individuals show that from 2009 to 2013, rates of antibiotic-nonsusceptible IPD caused by serotypes included in Prevenar 13 but not in Prevenar (7-valent) decreased from 6.5 to 0.5 per 100,000 in children aged <5 years and from 4.4 to 1.4 per 100,000 in adults aged ≥65 years. Antibiotic-non-susceptible IPD caused by non- Prevenar 13 serotypes increased from 41.8% (n = 1995) to 65.0% (n = 2397) (P < 0.001). Among antibiotic-non-susceptible IPD caused by non-Prevenar 13 serotypes, increases from 2009 to 2013 among children aged <5 years (from 2.5 to 3.1 per 100,000) and among adults aged ≥65 years (from 6.4 to 7.3 per 100,000) were observed. In 2013, the most frequent non-vaccine serotypes among cases with antibiotic-non-susceptible IPD were 35B (16.2%), 33F (15.5%), 22F (12.3%), and 15A (11.7%). Among multidrug-non-susceptible IPD, the most frequent non-vaccine serotypes were 35B (59.9%), 15A (17.8%), 6C (5.6%), and 15C (5.6%).***Prevenar 13 clinical trials in adults***

Of the 48,806 adults in the 7 studies of the clinical development program who received Prevenar 13, including the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) study, 3,515 (7.2%) were 18-64 years of age, 30,793 (63.1%) were 65-74 years of age, and 14,498 (29.7%) were 75 years of age and over. No clinically significant differences in safety or immunogenicity were observed between 65-74 year-old individuals and greater than 75 year-old individuals.

*Efficacy study in adults 65 years and older*

Efficacy of Prevenar 13 against vaccine type (VT) pneumococcal community-acquired pneumonia (CAP) and IPD was assessed in a large-scale randomised double-blind, placebo controlled study (CAPiTA) conducted over approximately 4 years in the Netherlands. A total of 84,496 subjects, 65 years and older received a single vaccination of either Prevenar 13 or placebo in a 1:1 randomisation; 42,240 subjects were vaccinated with Prevenar 13 and 42,256 subjects were vaccinated with placebo.

The primary objective was to demonstrate the efficacy of Prevenar 13 in the prevention of a first episode of confirmed VT-CAP (defined as presence of ≥2 specified clinical criteria; chest X-ray consistent with CAP as determined by a central committee of radiologists; and positive VT-specific Urinary Antigen Detection assay (UAD) or isolation of VT *S. pneumoniae* from blood or other sterile site). The secondary objectives were to demonstrate the efficacy of Prevenar 13 in the prevention of a first episode of 1) confirmed non-bacteraemic/non-invasive (NB/NI) VT-CAP (an episode of VT-CAP for which the blood culture result and any other sterile site culture results were negative for *S. pneumoniae*) and 2) VT-IPD (the presence of *S. pneumoniae* in a sterile site).

Surveillance for suspected pneumonia and IPD began immediately after vaccination and continued through identification of a pre-specified number of cases. Subjects who had a CAP or IPD episode with symptom onset less than 14 days after vaccination were excluded from all analyses.

The median duration of follow up per subject was 3.93 years (0-4.95 years). Prevenar 13 demonstrated statistically significant vaccine efficacy (VE) in preventing first episodes of VT pneumococcal CAP, non-bacteraemic/non-invasive (NB/NI) VT pneumococcal CAP, and VT-IPD (Table 18).

**Table 18: Vaccine Efficacy for the Primary and Secondary Efficacy Endpoints – Per-Protocol Population**

| | | Vaccine Group | | | | |
|---|---|---|---|---|---|---|
| | | Prevenar 13 | Placebo | | | |
| | | n=42240 | n=42256 | | | |
| **Efficacy Endpoint** | **Total Number of Episodes** | **n** | **n** | **VE (%)** | **(95.2% CI)** | **p-value** |
| **Primary endpoint:** First case of confirmed VT pneumococcal CAP | 139 | 49 | 90 | 45.6 | (21.8, 62.5) | 0.0006 |
| **Secondary endpoint:** First episode of confirmed NB/NI VT pneumococcal CAP | 93 | 33 | 60 | 45 | (14.2, 65.3) | 0.0067 |
| **Secondary endpoint:** First episode of VT-IPD | 35 | 7 | 28 | 75 | (41.1, 90.9) | 0.0005 |

Abbreviations: CAP = community-acquired pneumonia; CI = confidence interval; NB/NI = non-bacteraemic/non-invasive; IPD = invasive pneumococcal disease; VE = vaccine efficacy; VT = vaccine-type.

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 (mean follow-up time per subject was 3.97 years).

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 19).

**Table 19: 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 in a post-hoc analysis 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%).

*Immunogenicity*

In adults, an antibody threshold of serotype-specific pneumococcal polysaccharide IgG binding antibody concentration associated with protection has not been defined. For all pivotal clinical trials, a serotype-specific opsonophagocytosis assay (OPA) was used as a surrogate to assess potential efficacy against invasive pneumococcal disease and pneumonia. OPA geometric mean titres (GMTs) measured 1-month after each vaccination were calculated. OPA titres 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 13 serotypes are non-inferior, and for some serotypes superior, to the 12 serotypes in common with the licensed 23-valent pneumococcal polysaccharide vaccine (23vPPV) [1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F]. The response to serotype 6A, which is unique to Prevenar 13, was assessed by demonstration of a 4-fold increase in the specific OPA titre above pre-immunised levels.

Five clinical studies were conducted in Europe and the USA evaluating the immunogenicity of Prevenar 13 in different age groups ranging from 18-95 years of age. Clinical studies with Prevenar 13 currently provide immunogenicity data in adults aged 18 years and older, including adults aged 65 and older previously vaccinated with one or more doses of 23vPPV, 5 years prior to enrolment. Each study included healthy adults and immunocompetent adults with stable underlying conditions known to predispose individuals to pneumococcal infection (i.e., chronic cardiovascular disease, chronic pulmonary disease, renal disorders and diabetes mellitus, chronic liver disease including alcoholic liver disease, and alcoholism).

Immunogenicity and safety of Prevenar 13 has been demonstrated in adults aged 18 years and older including those previously vaccinated with a pneumococcal polysaccharide vaccine.

*Adults not previously vaccinated with 23-valent pneumococcal polysaccharide vaccine*

In a head-to-head, comparative trial conducted in adults aged 60-64 years, subjects received a single dose of either Prevenar 13 or 23vPPV. 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 20 compares the OPA GMTs, 1-month post-dose, in 60-64 year olds given either a single dose of Prevenar 13 or 23vPPV, and in 50-59 year olds given a single dose of Prevenar 13.

**Table 20: OPA GMTs in adults aged 60-64 years given Prevenar 13 or pneumococcal polysaccharide vaccine (23vPPV) and in adults aged 50-59 years given Prevenar 13**[a,b,c]

| | Prevenar 13 | Prevenar 13 | 23vPPV | Prevenar 13, 50-59 Relative to 60-64 Years | | Prevenar 13 Relative to 23vPPV, 60-64 Years | |
|---|---|---|---|---|---|---|---|
| | 50-59 Years N=350-384 | 60-64 Years N=359-404 | 60-64 Years N=367-402 | | | | |
| Serotype | GMT | GMT | GMT | GM Ratio | (95% CI) | GM Ratio | (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) |

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

In adults aged 60-64 years, OPA GMTs to Prevenar 13 were non-inferior to the OPA GMTs elicited to the 23vPPV for the twelve serotypes common to both vaccines. For 8 of the serotypes in common, the OPA titres were shown to be statistically significantly greater in Prevenar 13 recipients. In addition, OPA GMTs for serotype 6A were 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 adults aged 60-64 years, antibody levels one year after vaccination were greater after Prevenar 13 compared to antibody levels after 23vPPV 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 21 shows OPA GMTs 1-month post-dose in 18-29 years olds, 30-39 year olds, and 40-49 year olds given a single dose of Prevenar 13 and compares the OPA GMTs in 18-49 year olds and in 60-64 year olds.

**Table 21: OPA GMTs in adults aged 18-49 years and 60-64 years given Prevenar 13**[a,b]

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

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

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

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.

*Adults previously vaccinated with 23-valent pneumococcal polysaccharide vaccine*

Immune responses to Prevenar 13 and 23vPPV 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 22 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 23vPPV.

**Table 22: OPA GMTs in pneumococcal polysaccharide (23vPPV) vaccinated adults aged ≥ 70 years given either Prevenar 13 or 23vPPV**[a,b,c]

| | Prevenar 13 N=400-426 | 23vPPV N=395-445 | Prevenar 13 OPA GMT Relative to 23vPPV | |
|---|---|---|---|---|
| **Serotype** | **OPA GMT** | **OPA 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) |

[a] Non-inferiority was defined as the lower limit of the 2-sided 95% CI for GMR was greater than 0.5.
[b] Statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GMR was greater than 1.
[c] 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 GM ratio 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 23vPPV 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 23vPPV.

*Additional immunogenicity data*

In two studies conducted in adults aged 50-59 and 65 years and older, it was demonstrated that Prevenar 13 can 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. The clinical significance of this is unknown. In adults aged 50-59, non-inferiority was met for all serotypes. In adults aged 65 years and over, non-inferiority was met for all serotypes except serotype 19F.

*Immune responses in special populations*

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

*Sickle cell disease*

An open label single arm study with 2 doses of Prevenar 13 given 6 months apart was conducted in 158 children and adolescents ≥6 to <18 years of age with sickle cell disease who were previously vaccinated with one or more doses of 23vPPV at least 6 months prior to enrolment. 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 dose, immune responses were comparable to the ones after the first dose.

OPA GMTs in subjects with SCD, before and after each dose are presented in Table 23 for the evaluable immunogenicity population. In general, antibodies increased in response to dose 1, declined over the 6 months between doses 1 and 2, but remained higher than before dose 1 levels for all serotypes. OPA GMTs then increased in response to dose 2. The OPA GMTs after dose 2 were similar to or higher than those after dose 1 for subjects in the evaluable immunogenicity population for all serotypes.

**Table 23: Pneumococcal OPA GMTs at Dose 1 and Dose 2 - Evaluable Immunogenicity Population**

| Serotype | Pre-Dose 1 N[a]=95-131 | | Post-Dose 1 N[a]=89-123 | | Post-Dose 2 N[a]=89-118 | |
|---|---|---|---|---|---|---|
| | GMT[b] | (95% CI[c]) | GMT[b] | (95% CI[c]) | GMT[b] | (95% CI[c]) |
| 1 | 7 | (5.7, 8.8) | 56 | (41.0, 77.4) | 78 | (59.5, 101.2) |
| 3 | 13 | (10.1, 17.5) | 115 | (93.0, 142.1) | 105 | (87.2, 127.2) |
| 4 | 215 | (129.6, 357.2) | 2670 | (2128.1, 3351.1) | 3051 | (2536.7, 3670.3) |
| 5 | 10 | (7.8, 13.9) | 277 | (198.4, 385.8) | 273 | (213.9, 349.2) |
| 6A | 246 | (149.0, 404.8) | 7845 | (6581.6, 9349.9) | 7633 | (6439.6, 9048.6) |
| 6B | 626 | (377.5, 1037.4) | 7535 | (6320.5, 8983.5) | 7601 | (6392.6, 9038.6) |
| 7F | 344 | (220.5, 537.9) | 3348 | (2881.9, 3888.5) | 3723 | (3276.2, 4230.1) |
| 9V | 234 | (137.6, 398.7) | 2312 | (1684.0, 3172.8) | 3467 | (2784.0, 4317.6) |
| 14 | 628 | (425.8, 925.7) | 2288 | (1906.6, 2745.0) | 2081 | (1770.5, 2446.0) |
| 18C | 426 | (235.7, 771.4) | 4326 | (3250.3, 5756.8) | 5271 | (4267.8, 6510.1) |
| 19A | 137 | (100.0, 187.4) | 1449 | (1164.2, 1804.3) | 1314 | (1084.4, 1592.6) |
| 19F | 94 | (55.0, 160.7) | 1429 | (1043.5, 1957.3) | 1507 | (1139.9, 1992.2) |
| 23F | 34 | (21.5, 54.8) | 1607 | (1227.4, 2102.7) | 2330 | (1880.4, 2887.0) |

a. N = Number of subjects with a determinate OPA antibody titer to the given serotype.
b. Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.

One year after the second dose, antibody levels measured by both IgG GMCs and OPA GMTs were higher than levels prior to the first dose of Prevenar 13, except the IgG GMC for serotype 3 that was similar.

*Additional Prevenar (7-valent) immunogenicity data: children with sickle cell disease*

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

*HIV infection*

Children and adults not previously vaccinated with a pneumococcal vaccine

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 23-valent pneumococcal polysaccharide vaccine was subsequently administered. Vaccines were administered at 1 month intervals. Immune responses were assessed in 263-270 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.

Adults previously vaccinated with 23-valent pneumococcal polysaccharide vaccine

Immune responses were assessed in 329 HIV-infected adults ≥18 years of age (CD4 >200 cells/μL and viral load <50,000 copies/mL) previously vaccinated with 23vPPV administered at least 6 months prior to enrolment. Subjects received 3 doses of Prevenar 13, at enrolment, 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 two or more previous doses of 23vPPV showed a similar immune response compared with subjects who received a single previous dose. The immune responses to Prevenar 13 observed in HIV infected adults were lower than the immune responses reported for healthy adults.

OPA GMTs in adults with HIV, before and after each vaccine dose are presented in Table 24 for the evaluable population. In general, the OPA GMTs after vaccine dose 2 and vaccine dose 3 were similar to or higher than those after vaccine dose 1 for subjects in the evaluable population.

**Table 24: Pneumococcal OPA Antibody GMTs – Evaluable Immunogenicity Population**

| | **Pre-Dose 1[a] N[b]=230-253** | | **Post-Dose 1[a] N[b]=247-255** | | **Post-Dose 2[a] N[b]=238-246** | | **Post-Dose 3[a] N[b]=217-228** | |
|---|---|---|---|---|---|---|---|---|
| **Serotype** | **GMT[c]** | **(95% CI[d])** | **GMT[c]** | **(95% CI[d])** | **GMT[c]** | **(95% CI[d])** | **GMT[c]** | **(95% CI[d])** |
| 1 | 7 | (5.7, 7.6) | 38 | (30.9, 47.6) | 40 | (32.3, 49.2) | 48 | (38.7, 58.6) |
| 3 | 6 | (5.5, 6.9) | 28 | (23.3, 33.4) | 43 | (36.3, 50.9) | 54 | (45.9, 63.9) |
| 4 | 26 | (19.2, 36.4) | 631 | (491.4, 810.9) | 701 | (575.4, 855.1) | 743 | (605.1, 912.1) |
| 5 | 7 | (6.3, 8.7) | 63 | (49.0, 81.1) | 63 | (50.0, 80.5) | 71 | (55.9, 91.2) |
| 6A | 17 | (12.6, 22.4) | 952 | (698.8, 1296.6) | 1704 | (1339.4, 2166.8) | 2117 | (1706.8, 2624.5) |
| 6B | 83 | (58.0, 117.5) | 1050 | (783.1, 1408.4) | 1807 | (1465.4, 2228.2) | 2388 | (1975.6, 2887.4) |
| 7F | 42 | (30.1, 59.7) | 769 | (595.5, 992.1) | 939 | (777.3, 1135.4) | 1062 | (870.6, 1294.9) |
| 9V | 35 | (24.8, 49.7) | 416 | (298.7, 578.9) | 693 | (517.4, 927.7) | 880 | (663.9, 1167.1) |
| 14 | 197 | (148.3, 262.4) | 651 | (523.0, 810.3) | 700 | (580.5, 844.3) | 812 | (682.4, 965.4) |
| 18C | 33 | (23.5, 44.9) | 453 | (326.0, 630.2) | 541 | (405.3, 721.5) | 705 | (529.7, 938.3) |
| 19A | 34 | (27.1, 43.5) | 282 | (225.9, 351.0) | 387 | (330.4, 453.6) | 415 | (356.3, 484.3) |
| 19F | 13 | (10.0, 16.3) | 123 | (89.0, 170.4) | 253 | (194.1, 328.8) | 242 | (183.8, 318.9) |
| 23F | 8 | (6.4, 9.2) | 93 | (67.4, 128.3) | 281 | (211.8, 373.0) | 400 | (304.5, 526.4) |

a. Protocol-specified timing for blood sample.
b. N = Number of subjects with valid and determinate assay results for the specified serotype at the given visit.
c. Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.
d. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.

*Haematopoietic stem cell transplant*

Children and adults with an allogeneic haematopoietic stem cell transplant (HSCT) at ≥2 years of age received three doses of Prevenar 13 with an interval of at least 1 month between doses. The first dose was administered at 3 to 6 months after HSCT. A fourth (booster) dose of Prevenar 13 was administered 6 months after the third dose. As per general recommendations, a single dose of 23-valent pneumococcal polysaccharide vaccine was administered 1 month after the fourth dose of Prevenar 13. Immune responses as measured by IgG GMCs were assessed in 168-211 evaluable subjects approximately 1 month after vaccination. Prevenar 13 elicited increased antibody levels after each dose of Prevenar 13. Immune responses after the fourth dose of Prevenar 13 were significantly increased for all serotypes compared with after the third dose.

This study demonstrated that 4 doses of Prevenar 13 elicited serum IgG concentrations similar to those induced by a single dose in healthy individuals of the same age group.

*Clinical trial to assess Prevenar 13 given with seasonal QIV in adults*

A randomised, double-blind postmarketing study evaluated the immunogenicity of Prevenar 13 given with inactivated Quadrivalent Influenza Vaccine (QIV) (Fall 2014/Spring 2015 Fluzone, A/H1N1, A/H3N2, B/Brisbane, and B/Massachusetts strains) in 23vPPV previously vaccinated adults aged ≥50 years conducted in the US. One group received Prevenar 13 and QIV concurrently, followed approximately 1 month later by placebo. The other group received QIV and placebo concurrently, followed approximately 1 month later by Prevenar 13.

The antibody responses elicited by Prevenar 13 were measured as OPA GMTs 1 month after Prevenar 13 vaccination. Noninferiority was demonstrated if the lower limit of the 2-sided 95% CI for the OPA GMT ratios (Prevenar 13 + QIV relative to Prevenar 13 alone) was > 0.5. Prevenar 13 mcOPA antibody responses met noninferiority for all 13 serotypes after Prevenar 13 was given concomitantly with QIV compared to Prevenar 13 given alone (Table 25).

**Table 25. Pneumococcal OPA GMTs 1 Month after Prevenar 13 and QIV and 1 Month after Prevenar 13 (Given 1 Month after Placebo and QIV)**

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

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

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

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

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

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

Antibody responses elicited by QIV were measured by HAI 1 month after QIV vaccination. The immune responses were measured as HAI GMTs for each QIV strain 1 month after vaccination. Noninferiority was demonstrated for each vaccine antigen if the lower limit of the 2-sided 95% CI for the GMT ratio of the HAI titer was >0.5. Noninferiority was demonstrated for each of the 4 QIV strains after Prevenar 13 was given concomitantly with QIV compared with QIV given alone (Table 26).

**Table 26. HAI GMTs 1 Month after Prevenar 13 with QIV and Placebo with QIV**

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

Abbreviations: GMT = geometric mean titer; HAI = hemagglutination inhibition assay.

a. n = Number of subjects with a determinate HAI titer to the given strain.

b. GMTs were calculated using all subjects with available data for the specified blood draw.c. Ratio of GMTs (Prevenar 13+QIV/placebo to placebo+QIV/Prevenar 13) was calculated by back transforming the mean difference between vaccine sequences on the logarithmic scale.

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

### 5.2 Pharmacokinetic Properties

Evaluation of pharmacokinetic properties is not available for vaccines.

### 5.3 Preclinical Safety Data

***Genotoxicity***

Prevenar 13 has not been tested for genotoxic potential.

***Carcinogenicity***

Prevenar 13 has not been tested for carcinogenic potential.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of Excipients

Succinic acid, polysorbate 80, aluminium phosphate, sodium chloride in Water for Injections.

### 6.2 Incompatabilities

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

### 6.3 Shelf Life

3 years.

### 6.4 Special Precautions for Storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Discard if the vaccine has been frozen.

Prevenar 13 is stable at temperatures up to 25°C for four days. At the end of this period, Prevenar 13 should be used or discarded. These data are intended to guide health care professionals in case of temporary temperature excursions.

### 6.5 Nature and Contents of Container

Prevenar 13 is presented as a suspension in 0.5 mL pre-filled syringes (Type I glass) in packs of 1

and 10. All syringe components are latex-free.

### 6.6 Special Precautions for Disposal

No special requirements.

## 7. MEDICINE SCHEDULE

Prescription Only Medicine.

## 8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand, 1140

Toll Free Number: 0800 736 363 or email MedicalInformation.Australia@pfizer.com

## 9. DATE OF FIRST APPROVAL

25 March 2010

## 10. DATE OF REVISION OF THE TEXT

16 September 2021

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**SUMMARY TABLE OF CHANGES**

| Section Changed | Summary of Changes Made |
|---|---|
| Section 2 | Addition of biological origin information |