SCHEDULING STATUS: **S2**

1. NAME OF THE MEDICINE

PREVENAR 13 MULTIDOSE VIAL (suspension for injection in multidose container)

pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0,5 mL) contains:

Pneumococcal polysaccharide serotype 1[1]	2,2 µg
Pneumococcal polysaccharide serotype 3[1]	2,2 µg
Pneumococcal polysaccharide serotype 4[1]	2,2 µg
Pneumococcal polysaccharide serotype 5[1]	2,2 µg
Pneumococcal polysaccharide serotype 6A[1]	2,2 µg
Pneumococcal polysaccharide serotype 6B[1]	4,4 µg
Pneumococcal polysaccharide serotype 7F[1]	2,2 µg
Pneumococcal polysaccharide serotype 9V[1]	2,2 µg
Pneumococcal polysaccharide serotype 14[1]	2,2 µg
Pneumococcal polysaccharide serotype 18C[1]	2,2 µg
Pneumococcal polysaccharide serotype 19A[1]	2,2 µg
Pneumococcal polysaccharide serotype 19F[1]	2,2 µg
Pneumococcal polysaccharide serotype 23F[1]	2,2 µg

[1]Conjugated to CRM_{197} carrier protein, adsorbed on aluminium phosphate.

1 dose (0,5 mL) contains approximately 32 µg CRM197 carrier protein and 0,125 mg aluminium.

Excipient with known effects

PREVENAR 13 MULTIDOSE VIAL contains 0,1 mg of polysorbate 80 in each 0,5 mL dose, which is equivalent to 0,2 mg/mL of polysorbate 80.

For the full list of excipients, see section 6.1.

This is a multidose presentation. See section 6.5 for the number of doses per container.

3. PHARMACEUTICAL FORM

Suspension for injection in multidose container (4 doses).

The vaccine is a homogeneous white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Active immunisation for the prevention of invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* in infants, children and adolescents from 6 weeks to 17 years of age.

Active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in adults ≥ 18 years of age and the elderly.

See sections 4.4 and 5.1 for information on protection against specific pneumococcal serotypes.

The use of PREVENAR 13 MULTIDOSE VIAL should be determined on the basis of official recommendations taking into consideration the risk of invasive disease and pneumonia in different age groups, underlying comorbidities as well as the variability of serotype epidemiology in different geographical areas.

4.2 Posology and method of administration

The immunisation schedules for PREVENAR 13 MULTIDOSE VIALshould be based on official recommendations.

Posology

Infants and children aged 6 weeks to 5 years

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

Infants aged 6 weeks - 6 months

Three-dose primary series

The recommended immunisation series consists of four doses, each of 0,5 mL. The primary infant series consists of three doses, with the first dose usually given at 2 months of age and with an interval of at least 1 month between doses. The first dose may be given as early as six weeks of age. The fourth (booster) dose is recommended between 11 and 15 months of age.

Two-dose primary series

Alternatively, when PREVENAR 13 is given as part of a routine infant immunisation programme, a series consisting of three doses, each of 0,5 mL, may be given. The first dose may be administered from the age of 2 months, with a second dose 2 months later. The third (booster) dose is recommended between 11 and 15 months of age (see section 5.1).

Preterm infants (< 37 weeks gestation)

In preterm infants, the recommended immunisation series consists of four doses, each of 0,5 mL. The primary infant series consists of three doses, with the first dose given at 2 months of age and with an interval of at least 1 month between doses. The first dose may be given as early as six weeks of age. The fourth (booster) dose is recommended between 11 and 15 months of age (see sections 4.4 and 5.1).

Unvaccinated infants and children ≥ 7 months of age

Infants aged 7 - 11 months

Two doses, each of 0,5 mL, with an interval of at least 1 month between doses. A third dose is recommended in the second year of life.

Children aged 12 - 23 months

Two doses, each of 0,5 mL, with an interval of at least 2 months between doses (see section 5.1).

Children and adolescents aged 2 - 17 years

One single dose of 0,5 mL.

PREVENAR 13 vaccine schedule for infants and children previously vaccinated with Prevenar (7 valent) (Streptococcus pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F)

PREVENAR 13 MULTIDOSE VIAL contains the same 7 serotypes included in Prevenar, using the same carrier protein CRM_{197}.

Infants and children who have begun immunisation with Prevenar may switch to PREVENAR 13 at any point in the schedule.

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

Young children who are considered completely immunised with Prevenar (7 valent) should receive one dose of 0,5 mL of PREVENAR 13 to elicit immune responses to the 6 additional serotypes. This dose of PREVENAR 13 should be administered at least 8 weeks after the final dose of PREVENAR (7 valent) (see section 5.1).

Children and adolescents 5 – 17 years

Children 5 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. This dose of PREVENAR 13 should be administered at least 8 weeks after the final dose of Prevenar (7-valent) (see section 5.1).

Adults ≥ 18 years of age, and the elderly

One single dose.

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

Regardless of prior pneumococcal vaccination status, if the use of 23 valent pneumococcal polysaccharide vaccine is considered appropriate, PREVENAR 13 should be given first (see sections 4.5 and 5.1).

Special populations

Individuals who have underlying conditions predisposing them to invasive pneumococcal disease (such as sickle cell disease or HIV infection) including those previously vaccinated with one or more doses of 23 valent pneumococcal polysaccharide vaccine may receive at least one dose of PREVENAR 13 (see section 5.1).

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 (see section 5.1).

Method of administration

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

4.3 Contraindications

Hypersensitivity to the active substances, to any of the excipients listed in section 6.1, or to diphtheria toxoid.

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

4.4 Special warnings and precautions for use

PREVENAR 13 MULTIDOSE VIAL must not be administered intravascularly.

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 PREVENAR 13 MULTIDOSE VIAL.

PREVENAR 13 MULTIDOSE VIAL should not be given as an intramuscular injection to individuals with thrombocytopaenia or any coagulation disorder that would contraindicate intramuscular injection but may be given subcutaneously if the potential benefit clearly outweighs the risks (see section 5.1).

PREVENAR 13 MULTIDOSE VIAL will only protect against *Streptococcus pneumoniae* serotypes included in the vaccine and will not protect against other microorganisms that cause invasive disease, pneumonia, or otitis media. As with any vaccine, PREVENAR 13 MULTIDOSE VIAL may not protect all individuals receiving the vaccine from pneumococcal disease. For the most recent epidemiological information in your country, you should consult with the relevant national organisation.

Individuals with impaired immune responsiveness, whether due to the use of immuno-suppressive therapy, a genetic defect, human immunodeficiency virus (HIV) infection, or other causes, may have reduced antibody response to active immunisation.

Safety and immunogenicity data are available for a limited number of individuals with sickle cell disease, HIV infection, or with a haematopoietic stem cell transplant (see section 5.1). Safety and immunogenicity data for PREVENAR 13 are not available for individuals in other specific immuno-compromised groups (e.g., malignancy or nephrotic syndrome) and vaccination should be considered on an individual basis.

Excipients

PREVENAR 13 MULTIDOSE VIAL contains polysorbate 80 (see section 2). Polysorbate 80 may cause hypersensitivity reactions.

PREVENAR 13 MULTIDOSE VIAL contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

Infants and children aged 6 weeks to 5 years

In clinical studies, PREVENAR 13 elicited an immune response to all thirteen serotypes included in the vaccine. The immune response for serotype 3 following the booster dose was not increased above the levels seen after the infant vaccination series; the clinical relevance of this observation regarding the induction of serotype 3 immune memory is unknown (see section 5.1).

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

Limited data have demonstrated that PREVENAR 7-valent (three-dose primary series) induces an acceptable immune response in infants with sickle cell disease with a safety profile similar to that observed in non-high-risk groups (see section 5.1).

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

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

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

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

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

4.5 Interaction with other medicines and other forms of interaction

Infants and children aged 6 weeks to 5 years

PREVENAR 13 can be given concomitantly 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 (see section 4.4 for guidance on Infanrix hexa), meningococcal serogroup C, measles, mumps, rubella, varicella and rotavirus vaccine.

PREVENAR 13 can also be given concomitantly between 12 - 23 months with the tetanus toxoid conjugated meningococcal polysaccharide serogroups A, C, W and Y vaccine to children who have been adequately primed with PREVENAR 13 (as per local recommendations).

Data from a post-marketing clinical study evaluating the impact of prophylactic use of antipyretics (ibuprofen and paracetamol) on the immune response to PREVENAR 13 suggest that administration of paracetamol concomitantly or within the same day of vaccination may reduce the immune response to PREVENAR 13 after the infant series. Responses to the booster dose administered at 12 months were unaffected. The clinical significance of this observation is unknown.

Children and adolescents 6 to 17 years of age

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

Adults 18 to 49 years of age

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 inactivated influenza vaccine (TIV).

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

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

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

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

Concomitant use with other vaccines has not been investigated.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

It is unknown whether pneumococcal 13-valent conjugate vaccine is excreted in human milk.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

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 effects mentioned under section 4.8 “Undesirable effects” may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

Adverse reactions are reported in clinical studies or from the post-marketing experience for all age groups listed below by MedDRA body system organ class and the following frequency convention: Very common (≥ 1 / 10); common (≥ 1 / 100 to < 1 / 10); uncommon (≥ 1 / 1 000 to < 1 / 100; rare (≥ 1 / 10 000 to < 1 / 1 000); very rare (< 1 / 10 000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Infants and children aged 6 weeks to 5 years

The safety of the vaccine was assessed in controlled clinical studies where 14 267 doses were given to 4 429 healthy infants from 6 weeks of age at first vaccination and 11 - 16 months of age at booster dose. In all infant studies, PREVENAR 13 was co-administered with routine paediatric vaccines (see section 4.5).

Safety in 354 previously unvaccinated children (7 months to 5 years of age) was also assessed.

The most commonly reported adverse reactions in children 6 weeks to 5 years of age were vaccination-site reactions, fever, irritability, decreased appetite, and increased and/or decreased sleep.

In a clinical study 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, fever ≥ 38°C was reported in 50,0 % of infants who received PREVENAR (7-valent) and Infanrix hexa at the same time as compared to 33,6 % of infants receiving Infanrix hexa alone. These reactions were mostly moderate (less than or equal to 39 °C) and transient.

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

Adverse reactions from clinical studies

In clinical studies, the safety profile of PREVENAR 13 was similar to Prevenar. The following frequencies are based on adverse reactions assessed in PREVENAR 13 clinical studies:

MedDRA system organ class	**Frequency**	**Adverse reaction**
Immune system disorders	Rare	Hypersensitivity reaction including face oedema, dyspnoea, bronchospasm
Nervous system disorders	Uncommon	Convulsions (including febrile convulsions)
	Rare	Hypotonic-hyporesponsive episode
Gastrointestinal disorders	Very common	Decreased appetite
	Uncommon	Vomiting, diarrhoea
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Urticaria or urticaria-like rash
General disorders and administration site conditions	Very common	Pyrexia, irritability, any vaccination-site erythema, induration/swelling or pain/tenderness; somnolence; poor quality sleep,

		vaccination-site erythema or induration/swelling 2,5 cm – 7,0 cm (after the booster dose and in older children [age 2 to 5 years])
	Common	Pyrexia > 39 °C, vaccination-site movement impairment (due to pain); vaccination site erythema or induration/swelling 2,5 cm – 7,0 cm (after infant series)
	Uncommon	Vaccination-site erythema, induration/swelling > 7,0 cm; crying

Additional information in special populations:

Apnoea in very premature infants (≤ 28 weeks of gestation) (see section 4.4).

Children and adolescents aged 6 to 17 years of age

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

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

MedDRA system organ class	**Frequency**	**Adverse reaction**
Nervous system disorders	Common	Headaches

Gastrointestinal disorders	Very common	Decreased appetite
	Common	Vomiting; diarrhoea
Skin and subcutaneous tissue disorders	Common	Rash; urticaria or urticaria-like rash
General disorders and administration site conditions	Very common	Irritability; any vaccination-site erythema; induration/swelling or pain/tenderness; somnolence; poor quality sleep, vaccination-site tenderness (including impaired movement)
	Common	Pyrexia

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

Additional information in special populations

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

Adults ≥ 18 years and elderly

Safety was assessed in 7 clinical studies including 91 593 adults ranging in age 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 %) aged 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 23 valent pneumococcal polysaccharide vaccine. 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, and pyrexia was very common in adults aged 18 to 29 years and common in all other age groups. Severe vaccination-site pain/tenderness and severe limitation of arm movement was very common in adults 18 to 39 years and common 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 are based on adverse reactions assessed in PREVENAR 13 clinical studies in adults:

MedDRA system organ class	**Frequency**	**Adverse reaction**
Metabolism and nutrition disorders	Very common	Decreased appetite

Nervous system disorders	Very common	Headaches
Gastrointestinal disorders	Very common	Diarrhoea; vomiting (in adults aged 18 to 49 years)
	Common	Vomiting (in adults aged 50 years and over)
	Uncommon	Nausea
Immune system disorders	Uncommon	Hypersensitivity reaction including face oedema, dyspnoea, bronchospasm
Skin and subcutaneous tissue disorders	Very common	Rash
General disorders and administration site conditions	Very common	Chills; fatigue; vaccination-site erythema; vaccination-site induration/swelling; vaccination-site pain/tenderness (severe vaccination-site pain/tenderness very common in adults aged 18 to 39 years); limitation of arm movement (severe limitation of arm

		movements very common in adults aged 18 to 39 years)
	Common	Pyrexia (very common in adults aged 18 to 29 years)
	Uncommon	Lymphadenopathy localized to the region of the vaccination-site
Musculoskeletal and connective tissue disorders	Very common	Arthralgia; myalgia

Overall, no significant differences in frequencies of adverse reactions were seen when PREVENAR 13 was given to adults previously vaccinated with the pneumococcal polysaccharide vaccine.

Additional information in special populations

Adults with HIV infection have similar frequencies of adverse reactions, except that pyrexia and vomiting were very common and nausea common.

Adults with an haematopoietic stem cell transplant have similar frequencies of adverse reactions, except that pyrexia and vomiting were very common.

Higher frequency in some solicited systemic reactions was observed when PREVENAR 13 was administered concomitantly with trivalent inactivated influenza vaccine (TIV) compared to TIV given alone (headache, chills, rash, decreased appetite, arthralgia, and myalgia) or PREVENAR 13 given alone (headache, fatigue, chills, decreased appetite, and arthralgia).

Adverse reactions from PREVENAR 13 postmarketing experience

The following are considered adverse drug reactions for PREVENAR 13; because these reactions were derived from spontaneous reports, the frequencies could not be determined and are thus considered as not known.

MedDRA system organ class	**Adverse reaction**
Blood and lymphatic system disorders	Lymphadenopathy (localised to the region of the vaccination-site)
Immune system disorders	Anaphylactic/anaphylactoid reaction including shock; angioedema
Skin and subcutaneous tissue disorders	Erythema multiforme
General disorders and administration site conditions	Vaccination-site urticaria; vaccination-site dermatitis; vaccination-site pruritus; flushing

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Report any suspected adverse drug reactions associated with the use of the medicine directly to Pfizer via ZAF.AEReporting@pfizer.com.

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, pneumococcal vaccines; ATC code: J07AL02

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

Burden of disease

Infants and children aged 6 weeks to 5 years

Based on serotype surveillance in Europe performed before the introduction of Prevenar, 13-valent pneumococcal polysaccharide vaccine is estimated to cover 73 – 100 % (depending on the country) of serotypes causing invasive pneumococcal disease (IPD) in children less than 5 years of age. In this age group, serotypes 1, 3, 5, 6A, 7F, and 19A account for 15,6 % to 59,7 % of invasive disease, depending on the country, the time period studied, and the use of PREVENAR.

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

13-valent pneumococcal polysaccharide vaccine is estimated to cover over 90 % of serotypes causing antimicrobial-resistant IPD.

Children and adolescents aged 6 to 17 years

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

Adults ≥ 18 years and the elderly

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

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

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

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

13-Valent pneumococcal polysaccharide vaccine immunogenicity clinical studies in infants, children and adolescents

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

Study of 13-valent pneumococcal polysaccharide vaccine containing the preservative 2-phenoxyethanol (2-PE):

Safety and immunogenicity of 13-valent pneumococcal polysaccharide vaccine containing the preservative 2-PE (presented in a multidose container) given to healthy infants at 8, 12 and 16 weeks of age were compared to those of 13-valent pneumococcal polysaccharide vaccine without added preservative (250 infants per group).

Pneumococcal immune responses were compared using non-inferiority criteria, including the percentage of individuals with serum anti-polysaccharide serotype-specific IgG concentration ≥ 0,35 µg/mL and the comparison of IgG GMCs one month after the infant series. In addition, OPA GMTs between individuals receiving 13-valent pneumococcal polysaccharide vaccine with or without 2-PE were compared.

Non-inferiority for the proportion of individuals achieving an IgG concentration ≥ 0,35 µg/mL was demonstrated for all 13 serotypes (lower bound of the 97,5 % confidence interval (CI) for the difference in percentage of responders at 0,35 µg/mL between groups was > -10 %). Additionally, all 13 serotypes met the pre-defined non-inferiority criterion for IgG GMCs (lower bound of the 97,5 % CI of GMC ratio [GMR] was greater than 0,5).

Correspondingly, OPA GMTs were similar in both groups, except for serotype 3, which was lower, and serotype 18C, which was higher, in the group that received 13-valent pneumococcal polysaccharide vaccine with 2-PE.

Studies of 13-valent pneumococcal polysaccharide vaccine not containing the preservative 2-PE

Immune responses following a three-dose primary infant series

Clinical studies have been conducted in a number of European countries and the US using a range of vaccination schedules, including two randomised non-inferiority studies (Germany using a 2, 3, 4-month primary series [006] and US using a 2, 4, 6-month primary series [004]). In these two studies pneumococcal immune responses were compared using a set of non-inferiority criteria including the percentage of individuals with serum anti-polysaccharide serotype-specific IgG ≥ 0,35 µg/mL one month after the primary series and the comparison of IgG geometric mean concentrations (ELISA GMCs); in addition, functional antibody titres (OPA) between individuals receiving 13-valent pneumococcal polysaccharide vaccine and Prevenar were compared. For the six additional serotypes, these values were compared with the lowest response among all of the seven common serotypes in the Prevenar recipients.

The non-inferiority immune response comparisons for study 006, based on the proportion of infants achieving anti-polysaccharide IgG concentrations ≥ 0,35 µg/mL, are shown in Table 1. Results for study 004 were similar. 13-Valent pneumococcal polysaccharide vaccine non-inferiority (lower bound of the 95 % CI for the difference in percentage of responders at 0,35 µg/mL between groups was > -10 %) was demonstrated for all 7 common serotypes, except for serotype 6B in study 006 and serotypes 6B and 9V in study 004, which missed by a small margin. All seven common serotypes met pre-defined non-inferiority criteria for IgG ELISA GMCs. 13-Valent pneumococcal polysaccharide vaccine elicited comparable, although slightly lower, antibody levels than Prevenar for the 7 common serotypes. The clinical relevance of these differences is not known.

Non-inferiority was met for the 6 additional serotypes based on the proportion of infants achieving antibody concentrations ≥ 0,35 µg/mL and comparison of IgG ELISA GMCs in study 006 and was met for 5 out of the 6 serotypes, with the exception of serotype 3 for study 004. For serotype 3, the percentages of 13-valent pneumococcal polysaccharide vaccine recipients with serum IgG ≥ 0,35 µg/mL were 98,2 % (study 006) and 63,5 % (study 004).

Table 1: Comparison of the proportion of individuals achieving a pneumococcal anti-polysaccharide IgG antibody concentration ≥ 0,35 µg/mL after dose 3 of the infant series – study 006

Serotypes	13-Valent pneumococcal polysaccharide vaccine % (N=282-285)	7-valent Prevenar % (N=277-279)	Difference (95 % CI)
7-valent Prevenar serotypes			
4	98,2	98,2	0,0 (-2,5; 2,6)
6B	77,5	87,1	-9,6 (-16,0; -3,3)
9V	98,6	96,4	2,2 (-0,4; 5,2)
14	98,9	97,5	1,5 (-0,9; 4,1)
18C	97,2	98,6	-1,4 (-4,2; 1,2)
19F	95,8	96,0	-0,3 (-3,8; 3,3)
23F	88,7	89,5	-0,8 (-6,0; 4,5)
Additional serotypes in 13 Valent pneumococcal polysaccharide vaccine			
1	96,1	87,1*	9,1 (4,5; 13,9)
3	98,2	87,1	11,2 (7,0; 15,8)
5	93,0	87,1	5,9 (0,8; 11,1)
6A	91,9	87,1	4,8 (-0,3; 10,1)
7F	98,6	87,1	11,5 (7,4; 16,1)
19A	99,3	87,1	12,2 (8,3; 16,8)

* The serotype in Prevenar with the lowest percent response rate was 6B in study 006 (87,1 %),

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

For each of the 6 additional serotypes; 13-valent pneumococcal polysaccharide vaccine elicited OPA titres ≥ 1:8 in 91,4 % to 100 % of vaccinees one month after the primary series in studies 004/006. The functional antibody (OPA) geometric mean titres for serotypes 1; 3 and 5 were lower than the titres for each of the other additional serotypes; the clinical relevance of this observation for protective efficacy is unknown.

Immune responses following a 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 57,3 %) and 23F (55,8 % to 68,1 %) for all studies using a 2, 4-month regimen; compared to 58,4 % for serotype 6B and 68,6 % for 23F for a study using a 3; 5-month regimen. After the booster dose, all vaccine serotypes including 6B and 23F had immune responses consistent with adequate priming with a two-dose primary series. In a UK study, the functional antibody (OPA) responses were comparable for all serotypes including 6B and 23F in the Prevenar and 13-valent pneumococcal polysaccharide vaccine arms after the primary series at two and four months of age and after the booster dose at 12 months of age.

For 13-valent pneumococcal polysaccharide vaccine recipients, the proportion of responders with an OPA titre ≥ 1:8 was at least 87 % following the infant series, and at least 93 % following the booster dose. The OPA geometric mean titres for serotypes 1, 3 and 5 were lower than the titres for each of the other additional serotypes; the clinical relevance of this observation is unknown.

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

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

Antibody responses to booster doses following 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 (as described in section 4.2) result in levels of anti-capsular polysaccharide IgG antibody responses to each of the 13 serotypes that are at least comparable to those of a three-dose primary series in infants.

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

The single dose of 13-valent pneumococcal polysaccharide vaccine, in children approximately 3,4 years of age regardless of previous vaccination history with Prevenar or 13-valent pneumococcal polysaccharide vaccine, induced a robust antibody response for both the 7 common serotypes and the 6 additional serotypes in 13-valent pneumococcal polysaccharide vaccine.

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

Preterm infants

Safety and immunogenicity of 13-valent pneumococcal polysaccharide vaccine given at 2, 3, 4 and 12 months was assessed in approximately 100 prematurely born infants (mean Estimated Gestational Age [EGA], 31 weeks; range, 26 to 36 weeks) and compared with approximately 100 infants born at term (mean EGA, 39 weeks, range, 37 to 42 weeks).

Immune responses in preterm and term infants were compared using the proportion of individuals achieving a pneumococcal polysaccharide IgG binding antibody concentration ≥ 0,35 µg/mL 1 month after the infant series, the approach used for immunogenicity comparisons of 13-valent pneumococcal polysaccharide vaccine to Prevenar based on WHO guidelines.

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. Approximately one month after the toddler dose, the proportion of individuals in each group achieving this same antibody concentration threshold was > 97 %, except for serotype 3 (71 % in preterm infants and 79 % in term infants). It is unknown whether immunological memory to all serotypes is induced in pre-term infants. In general, serotype-specific IgG GMCs were lower for preterm infants than term infants.

After the infant series, OPA GMTs were similar in preterm infants compared to term infants except for serotype 5, which was lower in preterm infants. OPA GMTs after the toddler dose relative to those after the infant series were similar or lower for 4 serotypes (4, 14, 18C, and 19F) and were statistically significantly higher for 6 of 13 serotypes (1, 3, 5, 7F, 9V, and 19A) in preterm infants compared to 10 of 13 serotypes (1, 3, 4, 5, 6A, 7F, 9V, 18C, 19A, and 23F) in term infants.

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

Following administration of a single dose of 13 valent pneumococcal polysaccharide vaccine to children (12 - 59 months) who are considered completely immunised with Prevenar (7-valent) (either 2 or 3 dose primary series plus booster); the proportion achieving serum IgG levels ≥ 0,35 µg/mL and OPA titres ≥ 1:8 was at least 90 %. However, 3 (serotypes 1, 5 and 6A) of the 6 additional serotypes showed lower IgG GMC and OPA GMT when compared with children who had received at least one previous vaccination with 13 valent pneumococcal polysaccharide vaccine. The clinical relevance of the lower GMCs and GMTs is currently unknown.

Unvaccinated children (12 - 23 months)

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

Children and adolescents 5 to 17 years of age

In an open-label study in 592 healthy children and adolescents including those with asthma (17,4 %) who may be predisposed to pneumococcal infection, 13-valent pneumococcal polysaccharide vaccine elicited immune responses to all 13 serotypes. A single dose of 13-valent pneumococcal polysaccharide vaccine 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 13-valent pneumococcal polysaccharide vaccine was non inferior to Prevenar for the 7 common serotypes and to 13-valent pneumococcal polysaccharide vaccine for the 6 additional serotypes compared to the immune response after the fourth dose in infants vaccinated at 2, 4, 6 and 12 - 15 months of age as measured by serum IgG.

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

Immune responses after subcutaneous administration

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

13-Valent pneumococcal polysaccharide vaccine effectiveness

Invasive pneumococcal disease

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

Table 2: Serotype specific number of cases and incidence reductions of IPD in 2013/14 compared to 2008/09-2009/10 (2008/10) by age in England and Wales

	< 5 years of age			**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 13 valent pneumococcal polysaccharide vaccine									
1	59 (54)	5 (5)	91 % (98 %;	458 (382)	77 (71)	83 % (88 %;	102 (89)	13 (13)	87 % (94 %;

			68 %)**			74 %)**			72 %)**
3	26 (24)	8 (8)	68 % (89 %; 6 %)	178 (148)	73 (68)	59 % (72 %; 38 %)**	256 (224)	143 (146)	44 % (57 %; 27 %)**
6A	10 (9)	0 (0)	100 % (100 %; 62 %)**	53 (44)	5 (5)	90 % (97 %; 56 %)**	94 (82)	5 (5)	95 % (99 %; 81 %)**
7F	90 (82)	8 (8)	91 % (97 %; 74 %)**	430 (361)	160 (148)	63 % (71 %; 50 %)**	173 (152)	75 (77)	56 % (70 %; 37 %)**
19A	85 (77)	7 (7)	91 % (97 %; 75 %)**	225 (191)	104 (97)	54 % (65 %; 32 %)**	279 (246)	97 (99)	65 % (75 %; 53 %)**

§ Corrected for proportion of samples serotyped, missing age, denominator compared with 2009/10; and for the trend in total invasive pneumococcal disease up to 2009/10 (after which no trend correction was applied).

* 95 % CI inflated from a Poisson interval based on over-dispersion of 2,1 seen from modelling of 2000-06 pre-Prevenar all IPD data.

** p < 0,005 to cover 6A where p=0,002

Otitis media (OM)

In a published study performed in Israel, using a 2-dose primary series plus booster dose in the second year of life; the impact of 13-valent pneumococcal polysaccharide vaccine on OM was documented in a population-based active-surveillance system with tympanocentesis culturing of middle ear fluid in Israeli children less than 2 years of age with OM.

Following the introduction of Prevenar and subsequently 13-valent pneumococcal polysaccharide vaccine there was a decline in incidence from 2,1 to 0,1 cases per 1 000 children (95 %) for the Prevenar serotypes plus serotype 6A and a decline in incidence from 0,9 to 0,1 cases per 1 000 children (89 %) for the additional serotypes 1, 3, 5, 7F, and 19A in 13-valent pneumococcal polysaccharide vaccine. The annual overall pneumococcal incidence of OM declined from 9,6 to 2,1 cases per 1 000 children (78 %) between July 2004 (prior to the introduction of Prevenar) and June 2013 (post 13-valent pneumococcal polysaccharide vaccine introduction).

Pneumonia

In a multicentre observational study in France comparing the periods before and after the switch from Prevenar to 13-valent pneumococcal polysaccharide vaccine, there was 16 % (2 060 to 1 725 cases) reduction in all community acquired pneumonia (CAP) cases in emergency departments in children 1 month to 15 years of age. Reductions were 53 % (167 to 79 cases) ($p < 0,001$) for CAP cases with pleural effusion and 63 % (64 to 24 cases) ($p < 0,001$) for microbiologically confirmed pneumococcal CAP cases. In the second year after the introduction of 13-valent pneumococcal polysaccharide vaccine the total number of CAP cases due to the 6 additional vaccine serotypes in 13 valent pneumococcal polysaccharide vaccine was reduced from 27 to 7 isolates (74 %).

The decrease in all cause pneumonia cases was most pronounced in the younger vaccinated age groups with a decrease of 31,8 % (757 to 516 cases) and 16,6 % (833 to 695 cases) in the age groups < 2 years and 2 to 5 years, respectively. The incidence in older, predominantly non-vaccinated children (> 5 years) did not change over the duration of the study.

In an ongoing surveillance system (2004 to 2013) to document the impact of Prevenar and subsequently 13-valent pneumococcal polysaccharide vaccine on CAP in children less than 5 years in Southern Israel using a 2 dose primary series with a booster dose in the second year of life, there was a reduction of 68 % (95 % CI 73; 61) in outpatient visits and 32 % (95 % CI 39; 22) in hospitalizations for alveolar CAP following the introduction of 13-valent pneumococcal polysaccharide vaccine when compared to the period before the introduction of Prevenar.

Effect on nasopharyngeal carriage

In a surveillance study in France in children presenting with acute otitis media, changes in nasopharyngeal (NP) carriage of pneumococcal serotypes were evaluated following the introduction of Prevenar (7-valent) and subsequently 13-valent pneumococcal polysaccharide vaccine. 13-Valent pneumococcal polysaccharide vaccine significantly reduced NP carriage of the 6 additional serotypes (and serotype 6C) combined and individual serotypes 6C, 7F, 19A when compared with Prevenar. A reduction in carriage was also seen for serotype 3 (2,5 % vs 1,1 %; p=0.1). There was no carriage of serotypes 1 and 5 observed.

The effect of pneumococcal conjugate vaccination on nasopharyngeal carriage was studied in a randomised double-blind study in which infants received either 13-valent pneumococcal polysaccharide vaccine or Prevenar (7-valent) at 2, 4, 6 and 12 months of age in Israel. 13-Valent pneumococcal polysaccharide vaccine significantly reduced newly identified NP acquisition of the 6 additional serotypes (and serotype 6C) combined and of individual serotypes 1, 6A, 6C, 7F, 19A when compared with Prevenar. There was no reduction seen in serotype 3 and for serotype 5 the colonization was too infrequent to assess impact. For 6 of the remaining 7 common serotypes, similar rates of NP acquisition were observed in both vaccine groups; for serotype 19F a significant reduction was observed.

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

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

The efficacy of 7-valent Prevenar was evaluated in two major studies – the Northern California Kaiser Permanente (NCKP) study and the Finnish Otitis Media (FinOM) study. Both studies were randomised, double-blind, active-control studies in which infants were randomised to receive either Prevenar or control vaccine (NCKP, meningococcal serogroup C CRM-conjugate [MnCC] vaccine, FinOM, hepatitis B vaccine) in a four-dose series at 2, 4, 6, and 12 - 15 months of age. The efficacy results from these studies (for invasive pneumococcal disease; pneumonia; and acute otitis media) are presented below (Table 3).

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

[1]Per protocol

[2]Vaccine efficacy

[3]October 1995 to April 20, 1999

[4]October 1995 to April 30, 1998

Prevenar (7-valent) effectiveness

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

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

Table 4: Summary of effectiveness of 7-valent Prevenar for invasive pneumococcal disease			
Country (year of introduction)	**Recom-mended schedule**	**Disease reduction %**	**95 % CI**
UK (England & Wales)[1] (2006)	2, 4, + 13 months	Vaccine serotypes: Two doses under age 1: 85 %	49, 95 %
USA (2000) Children < 5[2] Persons ≥ 65[3]	2, 4, 6, + 12 - 15 months	 Vaccine serotypes: 98 % All serotypes: 77 % Vaccine serotypes: 76 % All serotypes: 38 %	 97, 99 % 73, 79 % NA NA
Canada (Quebec)[4] (2004)	2, 4, + 12 months	All serotypes: 73 % Vaccine serotypes: 2-dose infant series: 99 % Completed schedule: 100 %	NA 92, 100 % 82, 100 %
[1]Children < 2 years of age. Calculated vaccine effectiveness as of June 2008 (Broome method). [2]2005 data. [3]2004 data.			

[4]Children < 5 years of age. January 2005 to December 2007. Complete effectiveness for routine 2+1 schedule not yet available.

Acute otitis media

Effectiveness of Prevenar in a 3+1 schedule has also been observed against acute otitis media and pneumonia since its introduction in a national immunisation programme. In a retrospective evaluation of a large US insurance database, AOM visits were reduced by 42,7 % (95 % CI; 42,4 – 43,1 %), and prescriptions for AOM by 41,9 % in children younger than 2 years of age; compared with a pre-licensure baseline (2004 vs. 1997-99). In a similar analysis, hospitalisations and ambulatory visits for all-cause pneumonia were reduced by 52,4 % and 41,1 %, respectively. For those events specifically identified as pneumococcal pneumonia; the observed reductions in hospitalisations and ambulatory visits were 57,6 % and 46,9 %, respectively, in children younger than 2 years of age, compared with a pre-licensure baseline (2004 vs. 1997-99). While direct cause-and-effect cannot be inferred from observational analyses of this type; these findings suggest that Prevenar plays an important role in reducing the burden of mucosal disease (AOM and pneumonia) in the target population.

Efficacy study in adults 65 years and older

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

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

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

Efficacy was demonstrated for the primary and secondary endpoints in the per protocol population (Table 5).

Table 5: Vaccine efficacy (VE) for the primary and secondary endpoints of the CVA study (per protocol population)

Efficacy endpoint	Cases			VE (%) (95,2 % CI)	p-value
	Total	13-valent pneumo-coccal poly-saccharide vaccine group	Placebo group		
Primary endpoint					
First episode of confirmed VT pneumococcal CAP	139	49	90	45,56 (21,82; 62,49)	0,0006
Secondary endpoints					
First episode of confirmed NB/NI[1] vaccine type pneumococcal CAP	93	33	60	45,00 (14,21; 65,31)	0,0067
First episode of VT-IPD[2]	35	7	28	75,00 (41,06; 90,87)	0,0005

[1]NB/NI – non-bacteraemic/non-invasive

[2]VT-IPD – vaccine-type invasive pneumococcal disease

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

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

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 (VE), incidence rate reduction (IRR), and number needed to vaccinate (NNV) (Table 6).

IRR, also referred to as vaccine preventable disease incidence; is the number of cases of vaccine preventable disease per 100 000 person-years of observation.

In Table 6, NNV is a measure that quantifies the number of people that need to be vaccinated in order to prevent one clinical CAP case.

Table 6: Vaccine efficacy (VE) against clinical CAP*

	Episodes		**Vaccine efficacy[1] % (95 % CI) (1-sided p-value)**	**Incidence per 100 000 person-years of observation (PYO)**		**Incidence rate reduction[2] (95 % CI)**	**Number needed to vaccinate[3]**
	13-valent pneumo-coccal polysacc-	**Placebo**		**13-valent pneumo-coccal polysacc-**	**Placebo**		

	haride vaccine			**haride vaccine**			
All episodes analysis	1 375	1 495	8,1 (-0,6; 16,1) (0,034)	819,1	891,2	72,2 (-5,3; 149,6)	277
First episode analysis	1 126	1 214	7,3 (-0,4; 14,4) (0,031)	670,7	723,7	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] A Poisson regression model with random effects was used to calculate VE.

[2] Per 100 000 person-years of observation. IRR is calculated as the incidence in the placebo group minus the incidence in the vaccine group and was mathematically equivalent to VE × the incidence in the placebo group.

[3] Based on a 5-year duration of protection. NNV is not a rate but instead indicates the number of cases prevented for a given number of persons vaccinated. NNV also incorporates the length of the trial or duration of protection and is calculated as 1 divided by the product of the IRR and duration of protection (or length of trial) (=1/(IRR × duration).

Immunogenicity studies in adults ≥ 18 years and the elderly

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 titers (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 13-valent pneumococcal polysaccharide vaccine 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 [1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F] one month after vaccine administration. The response to serotype 6A; which is unique to 13-valent pneumococcal polysaccharide vaccine; was assessed by demonstration of a 4-fold increase in the specific OPA titer above pre-immunised levels.

Five clinical studies were conducted in Europe and the USA evaluating the immunogenicity of 13-valent pneumococcal polysaccharide vaccine in different age groups ranging from 18 - 95 years of age. Clinical studies with 13-valent pneumococcal polysaccharide vaccine 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 23-valent pneumococcal polysaccharide vaccine, 5 years prior to enrolment. Each study included healthy adults and immuno-competent adults with stable underlying conditions known to predispose individuals to pneumococcal infection (i.e., chronic cardiovascular disease; chronic pulmonary disease including asthma, renal disorders and diabetes mellitus, chronic liver disease including alcoholic liver disease), and adults with risk factors such as smoking and alcohol abuse.

Immunogenicity and safety of 13-valent pneumococcal polysaccharide vaccine 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, individuals received a single dose of either 13-valent pneumococcal polysaccharide vaccine or 23-valent pneumococcal polysaccharide vaccine. In the same study another group of adults aged 50 - 59 years and another group of adults aged 18 - 49 years received a single dose of 13-valent pneumococcal polysaccharide vaccine.

Table 7 compares the OPA GMTs, 1-month post-dose, in 60 – 64-year-olds given either a single dose of 13-valent pneumococcal polysaccharide vaccine or 23-valent pneumococcal polysaccharide vaccine, and in 50 – 59-year-olds given a single dose of 13-valent pneumococcal polysaccharide vaccine.

Table 7: OPA GMTs in adults aged 60-64 years given 13-valent pneumococcal polysaccharide vaccine or 23-valent pneumococcal polysaccharide vaccine (PPSV23) and in adults aged 50 - 59 years given 13-valent pneumococcal polysaccharide vaccine [a,b,c]

	13-valent pneumococcal polysaccharide vaccine	**13-valent pneumococcal polysaccharide vaccine**	**PPSV23**	**13-valent pneumococcal polysaccharide vaccine 50 - 59 Relative to 60 - 64 Years**		**13-valent pneumococcal polysaccharide vaccine Relative to PPSV23. 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	GMR	(95 % CI)	GMR	(95 % CI)
1	200	146	104	1,4	(1,08; 1,73)	1,4	(1,10; 1,78)
3	91	93	85	1,0	(0,81; 1,19)	1,1	(0,90; 1,32)
4	2 833	2 062	1 295	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†	4 328	2 593	213	1,7	(1,30; 2,15)	12,1	(8,63; 17,08)
6B	3 212	1 984	788	1,6	(1,24; 2,12)	2,5	(1,82; 3,48)
7F	1 520	1 120	405	1,4	(1,03; 1,79)	2,8	(1,98; 3,87)
9V	1 726	1 164	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	1 939	1 726	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 13-valent pneumococcal polysaccharide vaccine were non-inferior to the OPA GMTs elicited to the 23-valent pneumococcal polysaccharide vaccine for the twelve serotypes common to both vaccines. For 9 serotypes; the OPA titers were shown to be statistically significantly greater in 13-valent pneumococcal polysaccharide vaccine recipients.

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

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

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

	OPA GMT levels at baseline	**OPA GMT levels one year after 13-valent pneumococcal polysaccharide vaccine**
Adults 50 - 59 years not previously vaccinated with 23-valent pneumococcal polysaccharide vaccine	5 to 45	20 to 1 234
Adults 60 - 64 years not previously vaccinated with 23-valent pneumococcal polysaccharide vaccine	5 to 37	19 to 733

Table 8 shows OPA GMTs 1-month after a single dose of Prevenar 13 in 18 – 49-year-olds compared to 60 - 64-year-olds.

Table 8: OPA GMTs in adults aged 18 - 49 years and 60-64 years given 13-valent pneumococcal polysaccharide vaccine 13[a,b]

	18-49 Years N=836-866	**60-64 Years N=359-404**	**18-49 Years Relative to 60-64 Years**	
Serotype	GMT[b]	GMT[b]	GMR	(95 % CI[c])
1	353	146	2,4	(2,03; 2,87)
3	91	93	1,0	(0,84; 1,13)
4	4 747	2 062	2,3	(1,92; 2,76)
5	386	199	1,9	(1,55; 2,42)
6A	5 746	2 593	2,2	(1,84; 2,67)
6B	9 813	1 984	4,9	(4,13; 5,93)
7F	3 249	1 120	2,9	(2,41; 3,49)
9V	3 339	1 164	2,9	(2,34; 3,52)
14	2 983	612	4,9	(4,01; 5,93)
18C	3 989	1 726	2,3	(1,91; 2,79)
19A	1 580	682	2,3	(2,02; 2,66)
19F	1 533	517	3,0	(2,44; 3,60)
23F	1 570	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 (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures.

In adults aged 18 - 49 years, OPA GMTs to all 13 serotypes in 13-valent pneumococcal polysaccharide vaccine were non-inferior to the PREVENAR 13 responses in adults aged 60 - 64 years.

One year after vaccination with 13-valent pneumococcal polysaccharide vaccine OPA titers had declined compared to one month after vaccination, however OPA titers for all serotypes remained higher than levels at baseline.

	OPA GMT levels at baseline	**OPA GMT levels one year after 13-valent pneumococcal polysaccharide vaccine**
Adults 18 - 49 years not previously vaccinated with 23-valent pneumococcal polysaccharide vaccine	5 to 186	23 to 2 948

Adults previously vaccinated with 23-valent pneumococcal polysaccharide vaccine

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

Table 9 compares the OPA GMTs; 1-month post-dose; in pneumococcal polysaccharide vaccinated adults aged ≥ 70 years given a single dose of either 13-valent pneumococcal polysaccharide vaccine or 23-valent pneumococcal polysaccharide vaccine.

Table 9: OPA GMTs in pneumococcal polysaccharide vaccinated adults aged ≥ 70 years given either 13-valent pneumococcal polysaccharide vaccine or 23-valent pneumococcal polysaccharide vaccine (PPSV23)[a;b;c]				
	13-valent pneumococcal polysaccharide vaccine N=400-426	**PPSV23 N=395-445**	**Prevenar OPA GMT Relative to PPSV23**	
Serotype	OPA GMT	OPA GMT	GMR	(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 13-valent pneumococcal polysaccharide vaccine, a statistically significantly greater response was defined as the lower bound of the 2-sided 95 % CI for the GMR greater than 2.

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

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

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

Immune responses in special populations

Individuals with the conditions described below have an increased risk of pneumococcal disease. The clinical relevance of the antibody levels elicited by 13-valent pneumococcal polysaccharide vaccine in these special populations is unknown.

Sickle cell disease

An open label single arm study in France, Italy, UK, US, Lebanon, Egypt and Saudi Arabia with 2 doses of 13-valent pneumococcal polysaccharide vaccine 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 23-valent pneumococcal polysaccharide vaccine at least 6 months prior to enrolment. After the first vaccination, 13-valent pneumococcal polysaccharide vaccine 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 dose immune responses were comparable to those after the first dose. One year after the second dose, antibody levels measured by both IgG GMCs and OPA GMTs were higher than levels prior to the first dose of 13-valent pneumococcal polysaccharide vaccine, except for the IgG GMCs for serotypes 3 and 5 that were numerically 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), 46 of these children also received a 23-valent pneumococcal polysaccharide vaccine at the age of 15 - 18 months. After primary immunisation, 95,6 % of the individuals had antibody levels of at least 0,35 µg/mL for all seven serotypes found in Prevenar. 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 with CD4 ≥ 200 cells/µL (mean 717,0 cells/µL), viral load < 50 000 copies/mL (mean 2 090,0 copies/mL), free of active AIDS-related illness and not previously vaccinated with a pneumococcal vaccine received 3 doses of 13-valent pneumococcal polysaccharide vaccine. 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 259 - 270 evaluable individuals approximately 1 month after each dose of vaccine. After the first dose, 13-valent pneumococcal polysaccharide vaccine 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 13-valent pneumococcal polysaccharide vaccine, immune responses were similar or higher than those after the first dose.

Adults previously vaccinated with 23-valent pneumococcal polysaccharide vaccine

HIV-infected adults ≥ 18 years of age with CD4 ≥ 200 cells/µL (mean 609,1 cells/µL) and viral load < 50 000 copies/mL (mean 330,6 copies/mL), who were free of active AIDS-related illness and were previously vaccinated with 23-valent pneumococcal polysaccharide vaccine administered at least 6 months prior to enrolment, received 3 doses of 13-valent pneumococcal polysaccharide vaccine, at enrolment, 6 months, and 12 months after the first dose of 13-valent pneumococcal polysaccharide vaccine. Immune responses were assessed in 231 - 255 evaluable individuals approximately 1 month after each dose of 13-valent pneumococcal polysaccharide vaccine. After the first dose, 13-valent pneumococcal polysaccharide vaccine 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 13-valent pneumococcal polysaccharide vaccine, immune responses were comparable or higher than those after the first dose, In the study 162 individuals had received one prior dose of 23-valent pneumococcal polysaccharide vaccine, 143 individuals 2 prior doses and 26 individuals more than 2 prior doses of 23-valent polysaccharide vaccine. Individuals who received two or more previous doses of 23-valent pneumococcal polysaccharide vaccine showed a similar immune response compared with individuals who received a single previous dose.

Haematopoietic stem cell transplant

Children and adults with an allogeneic haematopoietic stem cell transplant (HSCT) at ≥ 2 years of age with complete haematologic remission of underlying disease or with very good partial remission in the case of lymphoma and myeloma received three doses of 13-valent pneumococcal polysaccharide vaccine 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 13-valent pneumococcal polysaccharide vaccine 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 13-valent pneumococcal polysaccharide vaccine. Immune responses as measured by IgG GMCs were assessed in 168 - 211 evaluable individuals approximately 1 month after vaccination. 13-Valent pneumococcal polysaccharide vaccine elicited increased antibody levels after each dose of 13-valent pneumococcal polysaccharide vaccine. Immune responses after the fourth dose of 13-valent pneumococcal polysaccharide vaccine were significantly increased for all serotypes compared with after the third dose. Functional antibody titers (OPA titers) were not measured in this study.

Paediatric population

Refer to Section 4.2.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Succinic acid

Polysorbate 80

2-phenoxyethanol

Water for injections

For adjuvant, see section 2.

6.2 Incompatibilities

In the absence of compatibility studies, PREVENAR 13 MULTIDOSE VIALmust not be mixed with other medicines.

6.3 Shelf life

3 years.

After first use:

Once opened, the medicine may be stored for a maximum of 28 days at 2 - 8 °C. Other in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2 °C to 8 °C).

Do not freeze.

For storage conditions after first opening of the medicine, see section 6.3

6.5 Nature and contents of container

2 mL (4 x 0,5 mL doses) suspension for injection in a container (clear Type I glass) with a latex-free grey chlorobutyl rubber stopper and sealed with an aluminium flip-off seal and a light blue polypropylene flip-off cap.

Pack sizes of 1, 5, 10, 25 and 50.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

During storage, a white deposit and clear supernatant can be observed. This does not constitute a sign of deterioration.

The vaccine should be shaken well to obtain a homogeneous white suspension and should be inspected visually for any particulate matter and/or variation of physical aspect prior to administration. Do not use if the content appears otherwise.

No special requirements for disposal.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

Building 2, 1st Floor,

Maxwell Office Park, Magwa Crescent, Waterfall City,

Midrand, Gauteng, 1685

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBERS

61/30.2/0999

9. DATE OF FIRST AUTHORISATION

09 June 2026

10. DATE OF REVISION OF THE TEXT

To be advised.

Manufacturer:

Pfizer Manufcaturing Belgium NV

Rijksweg 12

2870 Puurs-Sint-Amands

Belgium