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

PREVENAR 13® (Multidose Vial)

1. GENERIC NAME

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Individual conjugates are compounded, and then polysorbate 80 and aluminum phosphate and 2 phenoxyethanol are added to formulate the vaccine. The potency of the vaccine is determined by the quantity of the saccharide antigens and the saccharide-to-protein ratios in the individual glycoconjugates.

Name of Ingredients	Each 0.5 ml dose	Function
Polysaccharide Serotype 1	2.2 µg	Antigen
Polysaccharide Serotype 3	2.2 µg	Antigen
Polysaccharide Serotype 4	2.2 µg	Antigen
Polysaccharide Serotype 5	2.2 µg	Antigen
Polysaccharide Serotype 6A	2.2 µg	Antigen
Polysaccharide Serotype 6B	4.4 µg	Antigen
Polysaccharide Serotype 7F	2.2 µg	Antigen
Polysaccharide Serotype 9V	2.2 µg	Antigen
Polysaccharide Serotype 14	2.2 µg	Antigen
Polysaccharide Serotype 18C	2.2 µg	Antigen
Polysaccharide Serotype 19A	2.2 µg	Antigen
Polysaccharide Serotype 19F	2.2 µg	Antigen
Polysaccharide Serotype 23F	2.2 µg	Antigen
CRM_{197}	~32 µg[a]	Carrier Protein
Aluminum Phosphate	0.125 mg Al	Adjuvant

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2-phenoxyethanol[b]	4 mg	Preservative
Sodium Chloride	4.25 mg	Excipient
Succinic Acid	0.295 mg	Excipient
Polysorbate 80	0.1 mg	Excipient
Water for Injection	qs to 0.5 mL	Excipient

[a] – Vaccine is formulated on the basis of the saccharide content, and the amount of protein is dependent on polysaccharide/protein ratio of the conjugate
[b]- Multidose vial only

List of Excipients

Aluminum Phosphate, Sodium chloride USP, Ph Eur, JP, Succinic acid NF, Polysorbate 80 NF, 2-phenoxyethanol, Ph Eur, JP, Water for injection USP/NF, Ph Eur.

This is a multidose presentation. Refer to section 8.3 for the number of doses per container.

3. DOSAGE FORM AND STRENGTH

Suspension for injection in multidose container (4 x 0.5mL per doses).
The vaccine is a homogeneous white suspension.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

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

Also approved in adults more than 50 years of age.

The use of Prevenar 13 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

For intramuscular use only

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

Do not administer Prevenar 13 intravascularly.

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

ADMINISTRATION:

Shake well before use to homogenize the suspension, and only use if the vaccine is a homogenous, white suspension. Use a new sterile syringe and sterile needle for each injection.

Parenteral products should be inspected visually for particulate matter or discoloration prior to use (see section 8.4 Instructions for Use and Handling).

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

Vaccination Schedule

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

Primary Immunization Series

Infants aged 6 weeks – 6 months

Three-dose primary series with booster (3+1)

For infants, the recommended immunization series of Prevenar 13 consists of three doses of 0.5 mL each at 6 weeks, 10 weeks and 14 weeks, followed by a fourth (booster) dose of 0.5 mL at 12-15 months of age.

Three-dose primary series without booster (3+0)

When Prevenar 13 is given as part of routine infant immunization program, a series consisting of three doses, each of 0.5 mL may be given. The first dose may be administered at 8 weeks, with a second dose at 12 weeks and the third at 16 weeks.

Two-dose primary series with booster (2+1)

Alternatively, when used as a part of routine infant immunization programs in various countries, Prevenar 13 may also be recommended in a series consisting of three doses, each of 0.5 ml. The doses recommendations may be as follows:

First Dose	Second Dose	Booster Dose
2 months	4 months	11-15 months
6 weeks	14 weeks	9 months

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

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

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

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

Children who are considered incompletely vaccinated with Prevenar 13 are children who have received 3 or fewer doses of Prevenar 13 before 12 months of age and no Prevenar 13 dose after 12 months of age or children who did not complete the recommended age appropriate vaccine schedule for previously unvaccinated children (see the Vaccine Schedule for Previously Unvaccinated Children ≥7 Months of Age).

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

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

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

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

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

4.3 Contraindications

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

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

4.4 Special Warnings and Precautions for Use

Special Warnings

As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in case of a rare anaphylactic event following the administration of the vaccine (see section 4.8 Undesirable Effects).

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

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

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

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

Precautions

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

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

Infants and children aged 6 weeks through 5 years

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

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

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

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

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

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

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

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

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

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

Infants and children aged 6 weeks to 5 years

Prevenar 13 can be given with any of the following vaccine antigens, either as monovalent or combination vaccines: diphtheria, tetanus, acellular or whole-cell pertussis, *Haemophilus influenzae* type b, inactivated poliomyelitis, hepatitis B, meningococcal serogroup C, measles, mumps, rubella and varicella. Clinical studies demonstrated that the immune responses and the safety profiles of the administered vaccines were unaffected.

Previously, studies with pneumococcal 7-valent conjugate vaccine and rotavirus vaccines have demonstrated that the immune responses of the seven pneumococcal serotypes in pneumococcal 7-valent conjugate vaccine and the rotavirus vaccine were unaffected. It is not expected that any differences in immune response for the six additional serotypes or the rotavirus vaccine will be observed in Prevenar 13.

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

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

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

Pregnancy

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

Lactation

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

Fertility

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

4.7 Effects on Ability to Drive and Use Machine

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

4.8 Undesirable Effects

Infants and children aged 6 weeks to 5 years

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

In a catch-up study, 354 children (7 months to 5 years of age) receiving at least one dose of

Prevenar 13 were also assessed for safety.

Adverse Reactions from Clinical Trials with Prevenar 13

Infants and children aged 6 weeks to 5 years

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

System Organ Class	Adverse Reaction
Metabolism and nutrition disorders	
Very common	Decreased appetite
Psychiatric disorders	
Very common	Irritability
Uncommon	Crying
Nervous system disorders	
Very common	Drowsiness/increased sleep; restless sleep/decreased sleep
Uncommon	Seizures (including febrile seizures)
Rare	Hypotonic–Hyporesponsive episode
Gastrointestinal disorders	
Very common	Decreased appetite
Common	Diarrhea; vomiting
Immune system disorders	
Rare	Hypersensitivity reaction including face edema, dyspnea, bronchospasm
Skin and subcutaneous tissue disorders	
Common	Rash
Uncommon	Urticaria or urticaria-like rash

General disorders and administration site conditions

Very common	Fever; any injection-site erythema, induration/swelling or pain/tenderness; injection-site erythema or duration/swelling 2.5 cm - 7.0 cm (after toddler dose and in older children [age 2 to 5 years]).
Common	Fever greater than 39°C; injection-site erythema or Induration/swelling 2.5 cm - 7.0 cm (after infant series); Injection-site pain/tenderness interfering with movement
Uncommon	Injection-site induration/swelling or erythema greater than 7.0 cm; crying

Adverse reactions from Prevenar 13 Post-marketing experience

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

System Organ Class	Adverse Reaction
Blood and lymphatic system disorders	
Lymphadenopathy localized to the region of the vaccination-site	
Immune system disorders	
Anaphylactic/anaphylactoid reaction including shock	
Skin and subcutaneous tissue disorders	
Angioneurotic edema; erythema multiforme	
General disorders and administration site conditions	
Vaccination-site dermatitis; vaccination-site urticaria; vaccination-site pruritus; flushing	

Reporting of suspected adverse reactions

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

4.9 Overdose

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, and more than the recommended dose of Prevenar 13 from the multidose vial (amount >0.5 mL). In general, adverse events reported with overdose are consistent with those that have been reported with doses given in the recommended pediatric schedules of Prevenar 13. There are no cases of overdose reported with the use of Prevenar 13 from a multidose container.

1. PHARMACOLOGICAL PROPERTIES

Pharmacological class, therapeutic class

Vaccines

5.1 Pharmacodynamic Properties

Mode of Action

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

Bacterial capsular polysaccharides (PSs), while varied in chemical structure, share the common immunological property of being largely T-independent antigens. In the absence of T-cell help, PS-stimulated B-cells predominantly produce IgM antibodies; there is generally no affinity maturation of the antibodies, and no memory B-cells are generated. As vaccines, PSs are associated with poor or absent immunogenicity in infants less than 24 months of age and failure to induce immunological memory at any age. Conjugation of PSs to a protein carrier overcomes

the T-cell-independent nature of PS antigens. Protein carrier-specific T-cells provide the signals needed for maturation of the B-cell response and generation of B-cell memory. Conversion of *Streptococcus pneumoniae* PSs to a T-cell-dependent antigen by covalent coupling to the immunogenic protein carrier CRM_{197} enhances the antibody response, induces immune memory, and elicits booster responses on re-exposure in infants and young children to pneumococcal polysaccharides.

PHARMACODYNAMICS, CLINICAL EFFICACY

Burden of disease

Infants and children aged 6 weeks to 5 years

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

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

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

Prevenar 13 immunogenicity clinical studies in infants and children

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

Study of Prevenar 13 containing the preservative 2-phenoxyethanol (2-PE):

Safety and immunogenicity of Prevenar 13 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 Prevenar 13 without added preservative (250 infants per group).

Pneumococcal immune responses were compared using non-inferiority criteria, including the percentage of subjects with serum anti-polysaccharide serotype-specific IgG concentration

≥0.35 µg/ml and the comparison of IgG GMCs one month after the infant series. In addition, OPA GMTs between subjects receiving Prevenar 13 with or without 2-PE were compared.

Non-inferiority for the proportion of subjects achieving an IgG concentration >0.35 µg/ml was demonstrated for all 13 serotypes (lower bound of the 97.5% confidence interval (CI) for the difference in percentage of responders at 0.35 µg/ml between groups was >-10%). Additionally, all 13 serotypes met the pre-defined non-inferiority criterion for IgG GMCs (lower 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 Prevenar 13 with 2-PE.

Prevenar 13 containing the preservative 2-PE had an acceptable safety and tolerability profile that was comparable to Prevenar 13. The local reactions, systemic events, and the use of antipyretic medication were generally mild and comparable in both groups. Adverse events were generally mild and reported in similar proportion in both groups, 49.2% and 50.8% for Prevenar 13 containing the preservative 2-PE and Prevenar 13 without added preservative respectively. No safety concerns were identified for local and systemic reactions following vaccinations. One serious adverse event of sudden infant death syndrome assessed as unrelated to study vaccine occurred 20 days after the third vaccine occurred 20 days after the third vaccination with Prevenar 13 containing the preservative 2-PE

Studies of Prevenar 13 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 randomized non-inferiority studies (Germany using a 2, 3, 4 month primary series [006] and US using a 2, 4, 6 month primary series [004]). In these two studies pneumococcal immune responses were compared using a set of non-inferiority criteria including the percentage of subjects with serum anti-polysaccharide serotype-specific IgG ≥0.35 µg/mL one month after the primary series and the comparison of IgG geometric mean concentrations (ELISA GMCs); in addition, functional antibody titres (OPA) between subjects receiving Prevenar 13 and Prevenar were compared. For the six additional serotypes, these values were compared with the lowest response among all of the seven common serotypes in the Prevenar recipients.

The non-inferiority immune response comparisons for study 006, based on the proportion of infants achieving anti-polysaccharide IgG concentrations ≥0.35 µg/ml, are shown in Table 1. Results for study 004 were similar. Prevenar 13 non-inferiority (lower bound of the 95% CI for the difference in percentage of responders at 0.35 µg/mL between groups was ≥10%) was demonstrated for all 7 common serotypes, except for serotype 6B in study 006 and serotypes 6B and 9V in study 004, which missed by a small margin. All seven common serotypes met pre-

defined non-inferiority criteria for IgG ELISA GMCs. Prevenar 13 elicited comparable, although slightly lower, antibody levels than Prevenar for the 7 common serotypes. The clinical relevance of these differences is not known.

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

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

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

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

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

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

Immune Responses Following a Two-dose Primary Series

The immunogenicity after two doses in infants has been documented in four studies. The proportion of infants achieving a pneumococcal anti-capsular polysaccharide IgG concentration ≥0.35 µg/ml one month after the second dose ranged from 79.6% to 98.5% across 11 of the 13 vaccine serotypes. Smaller proportions of infants achieved this antibody concentration threshold for serotype 6B (27.9% to 58.4%) 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 Prevenar 13 arms after the primary series at 2 and 4 months of age and after the booster dose at 12 months of age. For Prevenar 13 recipients, the proportion of responders with an OPA titer ≥1:8 was at least 87% following the infant series, and at least 93% following the booster dose. The OPA geometric mean titres for serotypes 1, 3 and 5 were lower than the titres for each of the other additional serotypes; the clinical relevance of this observation is unknown.

Booster Responses Following Two-dose and Three-dose Primary Schedules

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

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

For children aged from 7 months to 5 years, age appropriate catch-up immunization schedules (as described in section Dosage and Administration) result in levels of anti-capsular polysaccharide IgG antibody responses to each of the 13 serotypes that are at least comparable to those of a three-dose primary series in infants.

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

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

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

Preterm Infants

Safety and immunogenicity of Prevenar 13 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 subjects 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 Prevenar 13 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 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). 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.

Immune responses after subcutaneous administration

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

Prevenar 13 Effectiveness

Invasive Pneumococcal Disease

Data published by Public Health England showed that, four years after the introduction of Prevenar as a two dose primary infant series with booster dose in the second year of life and with a 94% vaccine uptake, there was a 98% (95% CI 95; 99) reduction in disease caused by the

7 vaccine serotypes in England and Wales. Subsequently, four years following the switch to Prevenar 13, the additional reduction in incidence of IPD due to the 7 serotypes in Prevenar was 76% in children less than 2 years of age. The serotype specific reductions for each of the 5 additional serotypes in Prevenar 13 (no cases of serotype 5 IPD were observed) by age group are shown in Table 2 and ranged from 68% (serotype 3) to 100% (serotype 6A) for children less than 5 years of age. Significant incidence reductions were also observed in older age groups who had not been vaccinated with Prevenar 13 (indirect effect).

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

	<5 years of age			**≥65 years of age**		
	2008-10[§]	2013/14 [§]	%Incidence reduction (95% CI[*])	2008-10[§]	2013/14 [§]	%Incidence reduction (95% CI[*])
Additional serotypes covered by Prevenar 13						
1	59 (54)	5 (5)	91% (98%; 68%)[**]	102 (89)	13 (13)	87% (94%; 72%)[**]
3	26 (24)	8 (8)	68% (89%; 6%)	256 (224)	143 (146)	44% (57%; 27%)[**]
6A	10 (9)	0 (0)	100% (100%; 62%)[**]	94 (82)	5 (5)	95% (99%; 81%)[**]
7F	90 (82)	8 (8)	91% (97%; 74%)[**]	173 (152)	75 (77)	56% (70%; 37%)[**]
19A	85 (77)	7 (7)	91% (97%; 75%)[**]	279 (246)	97 (99)	65% (75%; 53%)[**]

[§]Corrected for proportion of samples serotyped, missing age, denominator compared with 2009/10, and for the trend in total invasive pneumococcal disease up to 2009/10 (after which no trend correction was applied).
[*]95% CI inflated from a Poisson interval based on over-dispersion of 2.1 seen from modelling of 2000-06 pre-Prevenar all IPD data.
[**]$p<0.005$ to cover 6A where $p=0.002$

Otitis media

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

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

Pneumonia

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

Effect on nasopharyngeal carriage

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

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

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 randomized, double-blind, active-control studies in which infants were randomized 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

5.2 Pharmacokinetic Properties

Not applicable.

6. Non clinical Properties

6.1. Animal Toxicology and Pharmacology

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

In single-dose subcutaneous (SC) safety pharmacology studies of pneumococcal 13-valent conjugate vaccine in rats or monkeys, there were no effects on central nervous, respiratory, or cardiovascular systems. In repeated dose (7 SC doses) toxicity studies in rats and monkeys, no

significant adverse effects were observed. In addition, in a repeated dose (5 SC doses) toxicity study in juvenile rats, no significant adverse effects were observed.

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

7. DESCRIPTION

13-Valent Pneumococcal Conjugate (13vPnC) vaccine Multidose Vial (MDV) is a sterile liquid suspension of capsular polysaccharide antigens of Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, with each saccharide individually conjugated to plasmid derived Diphtheria CRM_{197} protein. The vaccine contains 2.2 µg/dose of each of the serotypes, except for serotype 6B at 4.4 µg/dose. The vaccine is formulated in 5 mM succinate buffer containing 0.85% NaCl and 0.02% polysorbate 80, at pH 5.8, contains aluminum phosphate at 0.125 mg/dose aluminum, as an adjuvant and 8mg/mL of 2-Phenoxyethanol (2-PE) as an antimicrobial preservative. Each 2 mL vial contains four 0.5 mL doses of vaccine for parenteral administration.

The container closure system for the 13vPnC vaccine is a 2 mL glass vial with a latex-free rubber stopper. The vial presentation includes the following non-product contact components: aluminum flip-off seal and polypropylene flip-off cap.

8. PHARMACEUTICAL PARTICULARS

8.1. Incompatibilities

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

8.2. Shelf-life

36 months

8.3. Packaging information

2 ml (4 x 0.5 ml doses) suspension for injection in a container (Type I glass) with a latex-free grey chlorobutyl rubber stopper and sealed with an aluminum flip-off seal and a polypropylene flip-off cap.

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

Not all pack sizes may be marketed.

8.4. Storage and handling instructions

Store refrigerated at 2°C to 8°C.

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

Once opened, multi-dose vials should be kept between +2°C and +8°C. Multi-dose vials of Prevenar 13 from which one or more doses of vaccine have been removed during an immunization session may be used in subsequent immunization sessions for up to a maximum of 28 days provided that all of the following conditions are met:

- The expiry date has not passed.
- The vaccines are stored under appropriate cold chain conditions.
- The vaccine vial septum has not been submerged in water.
- Aseptic technique has been used to withdraw all doses.
- The vaccine vial monitor (VVM), if attached, has not reached the discard point (see Figure 1).

Other in-use storage times and conditions are the responsibility of the user.

Prevenar 13 is a suspension containing an adjuvant. During storage, a white deposit and clear supernatant can be observed. This does not constitute a sign of deterioration. The vaccine should be shaken well to obtain a homogeneous white suspension prior to expelling air from the syringe, and should be inspected visually for any particulate matter and/or variation of physical aspect prior to administration. Do not use if the content appears otherwise. No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Keep out of reach of children

Manufactured by:
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10. Imported and marketed in India by
Pfizer Limited,
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Mumbai 400 051,
India

11. Permission or license number with date:
IMP-278/2014 dated 27 June 2016

[i] CSR-76155, Version 1.0, Interim Report: A phase 3, open-label trial evaluating the safety, tolerability, and immunogenicity of 13-valent pneumococcal conjugate vaccine in healthy children aged 15 months to 17 years in the United States, 11-Dec-2009.

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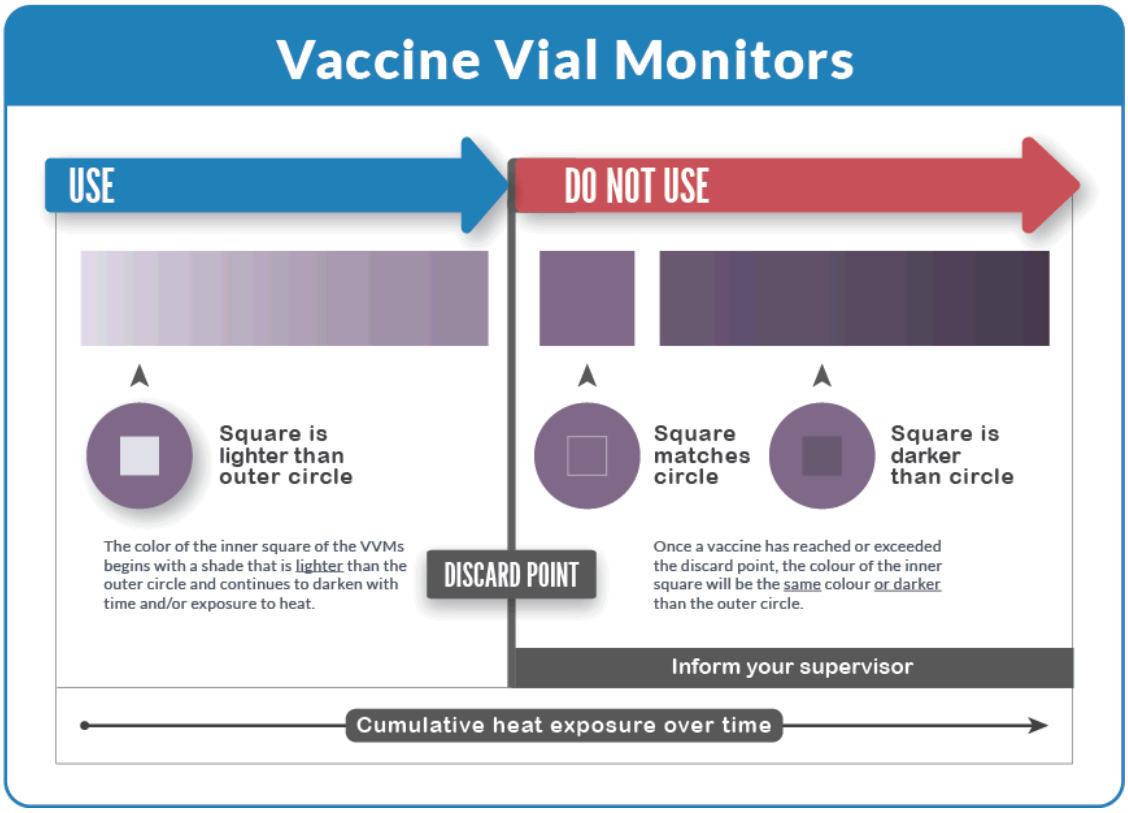
Figure 1: How to read a vaccine vial monitor



Vaccine Vial Monitors (VVMs) have been applied to the vial label on all PREVENAR 13 Multidose Vials manufactured by Pfizer Limited. The color dot which appears on the vial label is the VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its color will change progressively. As long as the color of this square is lighter than the color of the ring, then the vaccine can be used. As soon as the color of the central square is the same color as the ring or of a darker color than the ring, then the vial should be discarded.