SCHEDULING STATUS: **S2**

PROPRIETARY NAME (and dosage form):

PREVENAR 13® (Ready-to-use Suspension for Injection)

COMPOSITION:

PREVENAR 13 is a sterile solution of saccharides of the capsular antigen of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated to non-toxic diphtheria CRM_{197} protein and adsorbed on aluminium phosphate.

Each 0,5 ml dose is formulated to contain 2,2 μg of each saccharide for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F and 23F, and 4,4 μg of saccharide for serotype 6B, approximately 28 μg.

PHARMACOLOGICAL CLASSIFICATION:

Category A. 30.1 – Biological antigens

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

PREVENAR 13 contains the 7 pneumococcal capsular polysaccharides that are in pneumococcal 7-valent conjugate vaccine (4, 6B, 9V, 14, 18C, 19F, 23F) plus 6 additional polysaccharides (1, 3, 5, 6A, 7F, 19A) all conjugated to CRM_{197} carrier protein. B-cells produce antibodies in response to antigenic stimulation via T-dependent and T-independent mechanisms. The immune response to protein antigens is T-dependent and involves the collaboration of CD4 + T-cells and B-cells, recognizing the antigen in a co-ordinated 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 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 of 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.

Pharmacokinetic properties:

Evaluation of pharmacokinetic properties is not available for vaccines.

INDICATIONS:

PREVENAR 13 is indicated for the prevention of invasive disease, pneumonia, and otitis media caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in infants, children and adolescents.

For adults aged 18 years and older, PREVENAR 13 is indicated for the prevention of pneumooccal disease (including pneumonia and invasive disease) caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

CONTRA-INDICATIONS:

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

WARNINGS AND SPECIAL PRECAUTIONS:

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 Side-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 aetiology. The administration of PREVENAR 13 should be postponed in subjects suffering from acute severe febrile illness.

As with any intramuscular injection, PREVENAR 13 should be given with caution to infants, children or adults with thrombocytopaenia 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 micro-organisms 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.

Safety and immunogenicity data on PREVENAR 13 are not available for individuals in immunocompromised groups (e.g., individuals with malignancy or nephrotic syndrome) and vaccination should be considered on an individual basis.

Infants and children aged 6 weeks through 5 years:

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.

The use of pneumococcal conjugate vaccine does not replace the use of 23-valent pneumococcal polysaccharide vaccine (PPV23) in children ≥ 24 months of age with sickle cell disease, asplenia, HIV infection, chronic illness, or who are otherwise immunocompromised. Data on sequential vaccination with PREVENAR 13

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

As with all injectable paediatric vaccines, the potential risk of apnoea should be considered when administering the primary immunisation 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 hospitalised at the time of the recommended administration.

As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

When PREVENAR 13 is administered concomitantly with DTaP-HBV-IPV/Hib, the rates of febrile reactions are similar to those seen with concomitant administration of pneumococcal 7-valent conjugate vaccine and DTaP-HBV-IPV/Hib.

INTERACTIONS:

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 A, hepatitis B, meningococcal serogroup C, measles, mumps, rubella, varicella and rotavirus. Clinical studies demonstrated that the immune responses and the safety profiles of the administered vaccines were unaffected.

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

Children and adolescents 6 to 17 years of age:

In children and adolescents, there are no data on the concomitant administration of PREVENAR 13 with human papillomavirus vaccine (HPV), meningococcal protein conjugate vaccine (MCV4) or tetanus, diphtheria and acellular pertussis vaccine (Tdap).

Adults 18 to 49 years of age:

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

Adults aged 50 years and older:

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

PREGNANCY AND LACTATION:

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

DOSAGE AND DIRECTIONS FOR USE:

PREVENAR 13 is 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 antero-lateral aspect of the thigh in infants or the deltoid muscle of the upper arm in older children and adults. The vaccine should not be injected in the gluteal area.

Do not administer PREVENAR 13 intravascularly.

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

Immunisation Schedules:

Data on the interchangeability of Prevenar or PREVENAR 13 with other pneumococcal conjugate vaccines containing a protein carrier different from CRM_{197} are not available.

Infants and children aged 6 weeks to 17 years (prior to the 18th birthday):

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

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

Primary Immunisation:

For infants, the recommended immunisation series of PREVENAR 13 consists of 3 doses of 0,5 ml each, at approximately 2-month intervals, followed by a fourth dose of 0,5 ml at 12-15 months of age. The customary age for the first dose is 2 months of age, but it can be given as early as 6 weeks of age. The recommended dosing interval is 4 to 8 weeks. The fourth (booster) dose should be administered at approximately 12-15 months of age, and at least 2 months after the third dose.

PREVENAR 13 Routine Vaccine Schedule for Infants and Toddlers

Dose	Dose 1*†	Dose 2†	Dose 3†	Dose 4‡
Age at Dose	2 months	4 months	6 months	12-15 months

* Dose 1 may be given as early as 6 weeks of age.

† The recommended dosing interval is 4 to 8 weeks.

‡The fourth dose should be administered at approximately 12-15 months of age, and at least 2 months after the third dose.

Alternatively, when PREVENAR 13 is given as part of a routine infant immunisation program, a three-dose schedule may be considered. The first dose may be given from the age of 2 months, with a second dose 2 months later, and a third (booster) dose is recommended between 11-15 months of age.

Prevenar 13 Schedule for 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 with an interval of at least 1

month between doses. The first dose may be given as early as six weeks of age. The fourth (booster) dose is recommended at approximately 12 months of age.

PREVENAR 13 vaccine schedule for unvaccinated 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 apart between doses. A third dose is recommended in the second year of life (separated from the second dose by at least 2 months).

Children aged 12-23 months:

Two doses, each of 0,5 ml, with an interval of at least 2 months between doses.

Children aged 2 years to 5 years (prior to the 6th birthday):

One single dose.

PREVENAR 13 vaccine schedule for Infants and Children Previously Vaccinated with Pneumococcal 7-valent conjugate vaccine (*Streptococcus pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F):*

PREVENAR 13 contains the same 7 serotypes contained in the pneumococcal 7-valent conjugate vaccine and is manufactured based on the same conjugate technology using the same carrier protein CRM_{197}. Children who have begun immunisation with pneumococcal 7-valent conjugate vaccine may complete immunisation by switching to PREVENAR 13 at any point in the schedule. In clinical trials, immunogenicity and safety profiles are comparable. Children 15 months to 5 years of age who are considered completely immunised, or with any incomplete pneumococcal 7-valent conjugate vaccine schedule may receive one dose of PREVENAR 13 to elicit immune responses to the 6 additional serotypes. The catch-up (supplemental) dose of PREVENAR 13 should be administered with an interval of at least 8 weeks after the final dose of pneumococcal 7-valent conjugate vaccine. To ensure adequate protection against all 13 serotypes, children 15 to 23 months of age that received only a single dose of pneumococcal 7 valent conjugate vaccine before the age of 12 months, should receive 2 doses of PREVENAR 13 at least 2 months apart and separated from the first dose by at least 2 months.

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

PREVENAR 13 Schedule for Children 24 Months to 17 Years of Age

Children 24 months to 5 years of age and children 6 years to 17 years of age may receive a single dose of PREVENAR 13 whether or not they have been previously vaccinated with 1 or more doses of pneumococcal 7-valent conjugate vaccine. If pneumococcal 7-valent conjugate vaccine was previously administered, then at least 8 weeks should elapse before receiving PREVENAR 13.

In children 5 to <10 years of age who received a single dose of PREVENAR 13, there were no differences in the antibody concentrations compared to antibody concentrations following the fourth dose of either pneumococcal 7-valent conjugate vaccine or PREVENAR 13. In children 10 to 17 years of age, functional antibody responses were comparable to those in the 5 to <10 year age group after each group received a single dose of PREVENAR 13.

Adults aged 18 years and older:

PREVENAR 13 is to be administered as a single dose to adults 18 years and older including those previously vaccinated with a pneumococcal polysaccharide vaccine.

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

PREVENAR 13 is a suspension containing an adjuvant. The vaccine should be shaken well to obtain a homogenous 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.

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

Special populations:

Individuals who may be at higher risk for pneumococcal infection (e.g., individuals with sickle cell disease or HIV infection) including those previously vaccinated with one or more doses of 23-valent pneumococcal polysaccharide vaccine (PPSV23) may receive at least one dose of PREVENAR 13.

In individuals with a hematopoietic stem cell transplant (HSCT), the recommended immunisation series consists of 4 doses of PREVENAR 13, each of 0.5 ml. The primary series consists of 3 doses, with the first dose given 3 to 6 months after HSCT and with an interval of at least 1 month between doses. A booster dose is recommended 6 months after the third dose.

Geriatric Use:

PREVENAR 13 has been shown to be safe and immunogenic in the geriatric population (see Pharmacological Action, Pharmacodynamics).

Of the 48 806 adults in the 7 studies of the clinical development program who received PREVENAR 13, 30 793 (63,1 %) were 65 to 74 years of age, and 14 498 (29,7 %) were 75 years of age and over. No clinically significant differences in safety or immunogenicity were observed between 65 to 74 year-old individuals and those older than 75 years of age.

Paediatric Use:

The safety and effectiveness of PREVENAR 13 in children below the age of 6 weeks has not been established (see Dosage and Directions for Use).

SIDE-EFFECTS:

Infants and children aged 6 weeks to 5 years:

In a clinical study with pneumococcal 7-valent conjugate vaccine in infants vaccinated at 2, 3, and 4 months of age, fever ≥ 38 °C was reported at higher rates among infants who received pneumococcal 7-valent conjugate vaccine concomitantly with DTaP-HBV-IPV/Hib (28,3 % to 42,3 %) than in infants receiving DTaP-HBV-IPV/Hib alone (15,6 % to 23,1 %). After a booster dose at 12 to 15 months of age, the rate of fever ≥ 38 °C was 50,0 % in infants who received pneumococcal 7-valent conjugate vaccine and DTaP-HBV-IPV/Hib at the same time as compared to 33,6 % in infants receiving DTaP-HBV-IPV/Hib alone. These reactions were mostly moderate (less than or equal to 39 °C) and transient.

Additional information in special populations

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

Adults aged 18 years and older:

A trend to lower frequency of adverse reactions was associated with increasing age; adults older than 65 years of age (regardless of prior pneumococcal vaccination status) reported fewer adverse reactions than younger adults, with adverse reactions generally most common in adults, 18 to 29 years of age.
Overall, the frequency categories were similar in adults 18 to 49 years of age compared to adults > 50 years of age, 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 adults > 50 years of age.

Additional information in special populations
Adults with HIV infection had similar frequencies of adverse reactions as adults 50 years of age and older, except that fever and vomiting were very common and nausea was common.
Adults with a haematopoietic stem cell transplant have similar frequencies of adverse reactions as adults 18 years and older, except that fever and vomiting were very common.

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

Very common:	≥ 10 %
Common:	≥ 1 % and < 10 %
Uncommon:	≥ 0,1 % and < 1 %
Rare:	≥ 0, 01 % and < 0,1 %
Very rare:	< 0, 01 %

Adverse reactions from Clinical Trials with PREVENAR 13

Infants and children aged 6 weeks to 5 years:
These data are from clinical trials in which PREVENAR 13 was administered simultaneously with other routine childhood vaccines.

Adverse Reactions Table				
System Organ Class	**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**
Immune System Disorders				Hypersensitivity reaction including face oedema, dyspnoea, bronchospasm
Metabolism and nutrition disorders	Decreased appetite			
Psychiatric disorders	Irritability		Crying	
Nervous system disorders	Drowsiness/ increased sleep; restless sleep/ decreased sleep		Seizures (including febrile seizures)	Hypotonic-hyporesponsive episode
Gastro-intestinal disorders		Diarrhoea; vomiting		
Skin and subcutaneous tissue disorders		Rash		

Adverse Reactions Table				
System Organ Class	**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**
General disorders and administration site conditions	Fever; any injection-site erythema, induration/ swelling or pain/ tenderness; Injection-site erythema or induration/ swelling 2,5 cm – 7,0 cm (after toddler dose and in older children [age 2 to 5years]).	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	Injection-site induration/ swelling or erythema greater than 7,0 cm	

Children and adolescents Aged 5 to 17 Years:

The most common adverse reactions in children and adolescents 5 to 17 years of age were:

Adverse Reactions Table		
System Organ Class	**Very Common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**
Metabolism and nutrition disorders	Decreased appetite	
Psychiatric disorders	Irritability	
Nervous system disorders	Drowsiness/ increased sleep; restless, sleep/ decreased sleep	Headache
Gastro-intestinal disorders		Diarrhoea; vomiting

Adverse Reactions Table		
System Organ Class	**Very Common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**
Skin and subcutaneous tissue disorders		Rash, urticaria or urticaria-like rash
General disorders and administration site conditions	Any injection-site erythema, induration/ swelling or pain/ tenderness; Injection-site tenderness (including impaired movement)	Fever

Other adverse reactions observed in other age groups may also be applicable in this age group but due to the small sample size, were not seen in the study.

Adults aged 18 years and older:

Adverse Reactions Table			
System Organ Class	**Very Common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1 000 to < 1/100**
Immune system disorders			Hypersensitivity reaction including face oedema, dyspnoea, bronchospasm
Metabolism and nutrition disorders	Decreased appetite		
Nervous system disorders	Headache		
Gastrointestinal disorders	Diarrhoea, vomiting (in adults aged 18 to 49 years)	Vomiting (in adults aged 50 years and older)	Nausea
Skin and subcutaneous tissue disorders	Rash		
Musculoskeletal, ~~and~~ connective tissue and bone disorders	Generalised new/aggravated joint pain; generalised new/aggravated muscle pain.		

Adverse Reactions Table			
System Organ Class	**Very Common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1 000 to < 1/100**
General disorders and administration site conditions	Chills; fatigue; injection-site erythema, injection-site induration/swelling; injection-site pain/tenderness; limitation of arm movement	Fever	Lymphadenopathy localized to the region of the injection site

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

Solicited adverse reactions in adult studies with PREVENAR 13 and TIV (trivalent inactivated influenza vaccine):

The safety of concomitant administration of PREVENAR 13 with TIV was assessed in 2 studies in PPSV23 unvaccinated adults. Frequencies of local reactions in adults aged 50-59 years and in adults aged ≥ 65 years were similar after PREVENAR 13 was administered with TIV compared to PREVENAR 13 administered alone.
Higher frequency in some solicited systemic reactions was observed when PREVENAR 13 was administered concomitantly with TIV compared to TIV given alone (headache, chills, rash, decreased appetite, muscle and joint pain) or PREVENAR 13 given alone (headache, fatigue, chills, decreased appetite, and joint pain).

Adverse Reactions from PREVENAR 13 Post-marketing Experience:

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

Adverse Reactions Table	
System Organ Class	**Frequency not known (cannot be estimated from available data)***
Blood and Lymphatic System Disorders	Lymphadenopathy localised to the region of the injection site
Immune System Disorders	Anaphylactic/anaphylactoid reaction including shock
Skin and Subcutaneous Tissue Disorders	Angioedema; erythema multiforme
General Disorders and Administration Site Conditions	Injection-site dermatitis; injection-site urticaria; injection-site pruritus
* ADR identified post-marketing	

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF TREATMENT:

Overdose with PREVENAR 13 is unlikely due to its presentation as a pre-filled syringe. However, in infants and children, there have been reports of overdose with PREVENAR 13 defined as subsequent doses administered closer than recommended to the previous dose. In general, adverse events reported with overdose are consistent with those that have been reported with doses given in the recommended schedules of PREVENAR 13.

IDENTIFICATION:

After shaking the vaccine is a white, homogenous suspension.

PRESENTATION:

PREVENAR 13 is presented as a ready-to-use suspension and is supplied as a 0,5 ml transparent glass pre-filled syringe.

PREVENAR 13 is available in pack size of 1 and 10, with or without needles and a multipack of 5 packs of 10 transparent 0,5 ml glass pre-filled syringes, with or without needles.

Not all pack sizes may be marketed.

STORAGE INSTRUCTIONS:

Store refrigerated at 2 °C – 8 °C.

DO NOT FREEZE.

Discard if the vaccine has been frozen.

Keep out of reach of children

Gently shake the vaccine before administration to ensure a uniform suspension of particles.

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

REGISTRATION NUMBER:

PREVENAR 13: 44/30.1/0002

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pfizer Laboratories (Pty) Ltd.

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2196

South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:

26 November 2015

BOTSWANA: S2

Reg. No.: BOT1101869

NAMIBIA: NS1

Reg. No.: 10/30.1/0365

ZIMBABWE: PP

Reg. No.: 2014/18.2/4856