Unit: Technical Assessment Unit

Public assessment report for biological products

Prevenar 13 multidose

Administrative information:

Trade name of the medicinal product:	Prevenar 13 Multidose.
INN (or common name) of the active substance(s):	Pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)
Manufacturer of the finished product	Pfizer
Marketing Authorization holder	Pfizer Europe MA EEIG, Boulevard de la Plaine 17, 1050 Bruxelles-Belgium
Applied Indication(s):	Active immunization 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 immunization for the prevention of invasive disease and pneumonia caused by Streptococcuspneumoniae in adults ≥ 18 years of age and the elderly.
Pharmaceutical form(s) and strength(s):	Suspension for injection in multi-dose container (4 doses). 1 dose (0.5 ml) contains approximately 32 µg CRM_{197} carrier protein and 0.125 mg aluminium.
Route of administration	IM injection
Type of registration (EMA/FDA – Local)	EMA

List of abbreviations

EMA	European Medicines Agency
MDV	Multidose vial
CRM_{197}	Cross-reacting Material 197
13vPnC	13-valent pneumococcal conjugate
AlPO4	Aluminum Phosphate
EEA	European Economic Area
Ph.Eur.	European Pharmacopoeia
MA	Marketing Authorization

CTM	Clinical Trial Material
MBC	Monovalent Bulk Conjugate
ENRA	Egyptian National Regulatory Authority
GMT	Geometric mean titre
OPA	Opsonophagocytic activity against Streptococcus pneumoniae
23 vPS	23-valent pneumococcal polysaccharide vaccine

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1. **General introduction about the product including brief description of the AI, its mode of action and indications:**
   13-Valent Pneumococcal Conjugate (13vPnC) vaccine in Multidose vial (MDV) is a sterile liquid suspension for intramuscular administration of capsular polysaccharide antigens of Streptococcus pneumonia 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.
2. **Quality aspects:**

2.2.1 Introduction

As mentioned in the aforementioned section.

2.2.2 Drug Substance (Active ingredient)

- **General information**

-The physicochemical, biological, and immunological characterization of purified Pneumococcal Polysaccharide for each Serotype and Pneumococcal Saccharide-CRM197 Conjugate for each Serotype is detailed in the M.A. file
-Each conjugate induces a protective immune response against each pneumococcal serotype bacteria in immunized individuals

- **Nomenclature**

a) Nomenclature for each Pneumococcal Polysaccharide Serotype: Pneumococcal Polysaccharide Serotype 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14,18C, 19A, 19F and 23F.

- **Manufacture, process controls and characterization:**
- **Manufacturer:**

Pneumococcal polysaccharides are manufactured at two Wyeth manufacturing facilities within the United States; Andover, MA (Wyeth Pharmaceuticals Inc. 1 Burtt Road Andover, MA 01810 United States) and Pearl River, NY (Wyeth Pharmaceuticals Inc.401 North Middletown Road Pearl River, NY 10965 United States)

- **Description of Manufacturing Process and Process Controls.**

Four-stage fermentation process followed by inactivation plus a harvest step, each stage is detailed in M.A. file

- **Control of Materials**

Internal in-process tests (e.g. bioburden testing) are performed at various stages).

- **Controls of Critical Steps and Intermediates**

For strain and master cell bank and working cell bank, Pneumococcal Polysaccharide, activated polysaccharide, conjugated polysaccharide are included in details in the M.A. file.

- **Process Validation**

The key intent of the process validation is to demonstrate that:
1) The process steps and related critical process parameters are controlled within defined ranges
2) The performance indicator(s) for each process step can demonstrate process effectiveness.

- **Manufacturing Process Development.**

The changes represent process improvements, scale-up from pilot to commercial scale, changes in dispensing of the purified polysaccharide, the generation of a new master and working cell bank prior to commercial scale Phase 3 clinical trial material (CTM) production, and the addition of a new production site are described in M.A file.
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- **Characterization**

-After completion of the filling phase of the cell banking process, all cell bank vials were frozen at ≤ -65°C. Gram stain, purity, viable cell count, and identity were tested on representative samples of the fill. Additional characterization testing for growth suitability for MCB and WCB and addition test is genotypic/phenotypic identity for MCB was also performed.
-The main impurities arising from the fermentation and purification of Pneumococcal cellular proteins and nucleic acids.
Additional process related impurities are introduced during the production process.

- **Specification and Analytical Procedures**

The analytical methods used for the analysis of Pneumococcal cell Banks are described in details with the release and stability specification in the M.A. file.

- **Batch analysis**

Quality control data for Pneumococcal Saccharide-CRM197 Conjugate for each Serotype batches used in non-clinical studies, clinical trials , process validation consistency and commercial batches to support specifications and expiry date

- **Reference Standards or Materials**

There are no product-related reference standards or reference materials required for the release tests used in the quantitation of the pneumococcal polysaccharides, activated pneumococcal polysaccharides, or monovalent bulk conjugates.

The determinations for the intermediates and drug substance are independent of a reference standard or reference material

- **Container closure system**

Pneumococcal Polysaccharide is dispensed into 50L stainless steel containers.
The monovalent bulk conjugate (MBC) is dispensed into an engineered-film, 2 L flexible container closure system.
The material of container closure system has been demonstrated to be compatible with the Pneumococcal Polysaccharide through stability studies.

- **Stability of drug substance**

Storage condition of DS: 2-8°C

2.2.3 Drug product:

- **Description and Composition of the Drug Product:**

13-Valent Pneumococcal Conjugate (13vPnC) vaccine is composed of capsular polysaccharide antigens of Streptococcus pneumonia 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 and aluminum phosphate as an adjuvant. 2-phenoxyethanol is used as an antimicrobial preservative.

- Pharmaceutical Development including brief description on Components of drug product.

The Prevenar 13 vaccine is comprised of thirteen Drug Substances consisting of pneumococcal polysaccharide each individually conjugated to diphtheria CRM_{197}.

- Formulation Development

The Prevenar 13 vaccine formulation with preservative was developed based on the formulation of 13vPnC vaccine with the addition of 2-Phenoxyethanol as preservative

- Overages

There are no overages in the formulation of the13vPnC vaccine.

- Physicochemical and Biological Properties

The antigenicity of the vaccine is tightly controlled for each of the conjugates.

- Manufacturing Process Development.

To increase capacity, a second formulation booth (Booth II) was introduced.
A comparative assessment was performed to prove that the formulation process of 13vPnC in Booth I and II is identical, there are no changes in the formulation process steps or equipment.

- Container closure system and their compatibility.

The container closure system for 13vPnC is a 2 mL glass vial, stoppered with a latex-free rubber stopper and sealed with an aluminum flip-off seal with a polypropylene flip-off cap.
Safety testing of the stoppers, including toxicity testing of extractable, was performed. The testing demonstrated that the extractable were non-toxic.
- **Microbiological Attributes:** Container closure integrity testing was performed to demonstrate the integrity of the container closure system
- Compatibility.
The stability data demonstrate that the vaccine maintains its quality attributes throughout stability testing to date in the final filled vials at the recommended storage conditions of 2-8 °C.

- **Manufacture of the drug product:**
- Description of manufacturing process and process controls along with manufacturers and responsibilities
Manufacturer:
**Pfizer Manufacturing Belgium NV Rijksweg 12 B-2870 Puurs*, Belgium is responsible for:
-$AlPO_4$ manufacture and Quality control testing.
-13vPnC vaccine formulation and vial filling
- Final labeling and packaging of Drug Product multidose vials.
-Release testing of Drug Product multidose vials (except Aluminum testing and Antigenicity testing).
* *Pfizer Ireland Pharmaceuticals Grange Castle Business Park Clondalkin Dublin 22, Ireland* is responsible for:
-$AlPO_4$ manufacture and Quality control testing.
-Release and stability testing of Drug Product multidose vials.

*Contract Testing Site: *Charles River Laboratories Preclinical Services Ireland Ltd, Carrentrila, Ballina, Co. Mayo, Ireland* is responsible for Stability testing (Efficacy of Antimicrobial Preservation) of Drug Product multidose vials

*Disposition Site (Legal Address): *Pfizer Manufacturing Belgium NV Rijksweg 12 B-2870 Puurs, Belgium* is responsible for Batch Release by Qualified Person in the EEA.

- Control of critical steps and intermediates
The manufacturing process is controlled through critical process parameters, in process testing and release testing. A summary of the critical process parameters and tests for the finished product is provided in the dossier.
- Process validation and / or evaluation.
The manufacturing process results of all test items were met with the predefined acceptance criteria.

According to the results, this process validation provided consistency and reproducibility of manufacturing process.

- **Product specification:**

The 13vPnC multidose vial complies with the Ph.Eur. monograph for Pneumococcal Polysaccharide Conjugate Vaccine (adsorbed) (2150).
The specifications are based on compendial requirements, clinical trial experiences, and data obtained from manufacturing runs.

Each dose is formulated in succinate buffer with sodium chloride, with aluminum phosphate as adjuvant and polysorbate 80 as excipients.
2-phenoxyethanol is used as an antimicrobial preservative.

All of the excipients used are compendial except for aluminum phosphate, its release and stability specification are mentioned in the file.

Impurities are predominantly derived from the manufacture of the thirteen pneumococcal conjugates, and from degradation of the conjugates to release protein and saccharide breakdown products.
Both protein and saccharide levels are monitored during stability testing, and the results obtained demonstrate that there are no significant decreases in protein levels or saccharide antigenicity through expiry.

- **Reference Standards or Materials.**

A reference standard for the Nephelometry assay is the only reference standard or material used for testing 13vPnC Drug Product.

- **Container closure system.**

The vial container closure system consists of:

-Vial (2 mL Schott or Medical Glass vials constructed of clear, Type I borosilicate glass).
- Stopper (The closure for the vials is a stopper composed of latex-free grey chlorobutyl rubber).
- Cap and seal (The seal is an aluminum flip-off seal with a polypropylene flip-off cap. They do not contact the product)

- **Stability of the drug product.**

-Based on available stability data,
approved Shelf Life: 24 months
approved Storage Conditions: 2-8ºC

- **Adventitious agents**

13-Valent Pneumococcal Conjugate Vaccine (13vPnC) is composed of components derived from bacterial fermentation, and is not a viral product.
The animal derived ingredients used in 13vPnC production are excluded from the scope of the TSE guideline
In addition to the precautions taken to ensure TSE-free donor animals are used, some steps in the production of the vaccine component and the final conjugate vaccine have adventitious agents elimination potential.

3. Non –clinical aspect:

➢ **Prevenar®**, a Pneumococcal 13-valent Conjugate Vaccine (13vPnC) is a sterile liquid formulation of Pneumococcal capsular polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, individually conjugated to Diphtheria CRM197 protein (CRM197) with aluminum phosphate as an adjuvant. It is indicated for active immunization against disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F in adults, infants and children from 2 months up to 5 years of age.

➢ **Pharmacology:** The immunogenicity and safety pharmacology were evaluated as part of the non-clinical toxicity studies. Adult and juvenile rats, rabbits, and cynomolgus monkeys were assessed for the pneumococcal serotype specific antibody response to 13vPnC; in addition, cynomolgus monkeys were assessed for antibody response to diphtheria toxoid. The analysis of results demonstrated the expected immune response. No 13vPnC-related effects were observed in either the CNS or respiratory system in both rats and monkeys tested.

➢ **Pharmacokinetics:** As described in the WHO Guideline on non-clinical testing of vaccines and Guideline on Adjuvants in Vaccines for Human Use (EMEA/CHMP/VEG/134716/2004), PK studies was not conducted.

➢ **Toxicology:** an acceptable dose for nonclinical toxicity studies for vaccines is considered to be equal to the clinical dose, on a per dose basis. Repeat SC or IM administration of 13vPnC in the rat, rabbit, and cynomolgus monkey toxicity studies and the fertility and developmental IM toxicity study in rabbits showed a significant immune response against all 13 of the serotypes contained in 13vPnC & there aren't any significant adverse local or systemic toxic or reproductive effects.

➢ **Overall conclusion:** Based on the toxicology data, the non-clinical evaluation of this product supports its efficient and safe use in the proposed patient population.

4. Clinical aspect:

➢ **<u>Clinical Efficacy including Immunogenicity:</u>**

Prevenar 13 has demonstrated robust immunogenicity across various age groups, with efficacy against invasive pneumococcal disease caused by Streptococcus pneumoniae. In infants, the vaccine showed slightly lower immunogenicity compared to the earlier 7-valent formulation (Prevenar), particularly for serotypes 6B and 9V. While the clinical significance of this difference remains uncertain, it is unlikely to impact protection against the seven common serotypes included in both vaccines.
Clinical trial data also indicated that the functional immune response—measured by opsonophagocytic activity (OPA) was relatively low for three of the six additional serotypes introduced in Prevenar 13. Although the implications of low OPA geometric mean titers (GMTs) for individual serotypes are not fully understood, they may suggest reduced efficacy against invasive disease caused by these strains. Therefore, post-marketing surveillance is essential to assess real-world effectiveness.
In adults aged 50 years and older, Prevenar 13 has been shown to elicit a strong immune response and provide protection against pneumococcal infections. For individuals requiring both the 13-valent pneumococcal conjugate vaccine (13vPnC) and the 23-valent pneumococcal polysaccharide vaccine (23vPS), current guidelines recommend administering 13vPnC first to optimize immunological priming.

- **Clinical Safety conclusion:**
  The safety profile of Prevenar 13 is consistent with that of its predecessor, Prevenar (7-valent), with no new or unexpected safety concerns identified during clinical trials. The vaccine is commonly associated with mild to moderate local and systemic reactions, such as injection site pain, redness, swelling, fever, and irritability. These adverse events are generally transient and self-limiting, and their frequency and severity do not contraindicate the use of Prevenar 13 for primary series, booster doses, or catch-up immunization schedules.

- **Overall Conclusion:**
  Overall, Prevenar 13 maintains a favorable benefit-risk profile and continues to be a key component of pneumococcal disease prevention strategies across age groups.

5. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.

Prevenar 13 : EPAR - Product Information

https://www.ema.europa.eu/en/documents/product-information/prevenar-13-epar-product-information_en.pdf