Unit: Technical Assessment Unit

Public assessment report for biological products

(Pneumosil 5 doses and Pneumosil 1 dose)

Administrative information:

Trade name of the medicinal product:	Pneumosil 1& 5 doses
INN (or common name) of the active substance(s):	Pneumococcal polysaccharide conjugate vaccine (10-valent, adsorbed)
Manufacturer of the finished product	SERUM INSTITUTE OF INDIA PVT. LTD. 212/2, Hadapsar, Pune 411028, INDIA.
Marketing Authorization holder	SERUM INSTITUTE OF INDIA PVT. LTD. 212/2, Hadapsar, Pune 411028, INDIA.
Applied Indication(s):	Active immunisation for the prevention of invasive disease, pneumonia and acute otitis media caused by Streptococcus pneumoniae 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F and 23F in infants and toddlers from 6 weeks up to 2 years of age.
Pharmaceutical form(s) and strength(s):	Suspension for injection in multi-dose container (5 doses). 1 dose (0.5 ml) contains Saccharide for serotypes 1, 5, 9V, 14, 19A, 19F, 23F, 7F, 6A 2 mcg each Saccharide for serotype, 6B 4 mcg Conjugated to non toxic diphtheria CRM197 carrier protein to form the glycol conjugate. Individual conjugates are compounded and then polysorbate 20 and aluminium phosphate are added to formulate the vaccine.
Route of administration	Intramuscular
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

CRM197	Cross Reactive Material 197
MDV	Multidose Vial
ELISA	Enzyme -linked immunosorbent assay
TSE	Transmissible Spongiform Encephalopathies
BSE	Bovine Spongiform Encephalopathy
MA	Marketing Authorization
BP	British pharmacopeia
WHO	World Health Organization
IP	Indian pharmacopeia
USP	United States Pharmacopeia
IPCs	In process Control
API	Active pharmaceutical ingredient
10V	10- Valent
AE	Adverse event
AOM	Acute Otitis Media
DTwP-HepB-Hib:	Diphtheria, Tetanus, Pertussis (whole cell), Hepatitis B Haemophilus influenzae type 'B'vaccine
IM	Intramuscular
IgG	Immunoglobulin G
Gavi	Global Alliance for Vaccine and Immunization
GMC	Geometric Mean Concentration
EPI	Expanded Program of Immunization
IPD	Invasive pneumococcal diseases

NZW	New Zealand white
SAE	Serious Adverse Event
OPA	Opsonophagocytic Assay
PCV	Pneumococcal conjugate vaccines
SC	Subcutaneous
SD	Sprague Dawley
TEAE	Treatment Emergent Adverse Event

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1. **Quality aspects:**

1.2.1 Introduction

-10-Valent Pneumococcal Conjugate (10vPnC) vaccine in Multidose vial (MDV) is a sterile liquid suspension for intramuscular administration of capsular polysaccharide antigens of Streptococcus pneumonia serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F and 23F with each saccharide individually conjugated to plasmid derived Diphtheria protein.

-Pneumosil 10 MDV is presented in vials containing 5x0.5ml doses (2.5mL) in multidose and 0.5 ml in single dose. Filled in USP type 1 glass vial and closed with chlorobutyl rubber stopper followed by capping with aluminium flip-off cap.
-0.005% thiomerthal is used as an antimicrobial preservative in multidose presentation.

1.2.2 Drug Substance (Active ingredient)

General information

Nomenclature:

INN : Pneumococcal polysaccharide conjugate vaccine (10-valent, adsorbed)

General Properties

Physicochemical Properties

The Monovalent Bulk conjugates are a clear liquid with no visible particles. The monovalent bulk conjugate from each serotype is produced conjugating the individual purified / modified polysaccharide from each of the ten serotypes with the carrier protein.

Biological Activity

The biological properties of pneumococcal polysaccharide-specific antibody is characterized by the following in vitro methods: -ELISA - Opsonophagocytic Assay (OPA) - multiplex bead based competitive inhibition assay (BBCIA) Purity and Impurities As per ICH Q6B all process and product related impurities are evaluated and controlled during manufacturing process to an acceptable limit.

Manufacture, process controls and characterization:

Manufacturing site

S.No.	Name and address of manufacturing site	Function(s)
1	**SERUM INSTITUTE OF INDIA PRIVATE LIMITED,** Off Soli-Poonawalla Road, 212/2 Hadapsar, Pune- 411 0028, **INDIA.**	Manufacturing, testing and stability study of Monovalent bulk conjugate of serotypes

Description of Manufacturing Process and Process Controls.

-Analytical method validation summary reports of the testing methods is provided and Validation of analytical procedures has been mentioned in the MA file

Batch analysis.

-Quality assessment of all batches shows close similarity of all analytical results and demonstrate consistency in quality. The details of the used batches are tabulated in the MA file.

Reference Standards or Materials.

-Reference standards used in various tests performed on drug substances are tabulated in MA file.
-Some of the standards are outsourced and some are developed in-house.

-The in-house developed reference standards are calibrated against respective available standards.
Container closure system

-Monovalent bulk conjugates (drug substance) from all ten pneumococcal serotypes are stored in bottles.

-Summarized Leachability assessment: has been mentioned in the MA file.

Stability of drug substance

-The shelf life and storage conditions are Based on available stability data and fully detailed in MA file
Shelf Life: 3 years ,
Storage of active substance: store at refrigerator (2-8) ºC
-The accelerated stability studies are done for 6 months at temperature (25°C + 2°C/60 ± 5% RH)
-The long-term stability studies are done for 36 months at temperature (2-8°C) on the following batches

.**2.2.3 Drug product:**

SERUM INSTITUTE OF INDIA PVT. LTD. 212/2, Hadapsar, Pune 411028, INDIA.

Description and Composition of the Drug Product:

-The Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10-Valent) is a sterile homogenous suspension of Pneumococcal capsular polysaccharides individually conjugated to a carrier protein and adsorbed on to aluminum phosphate and supplied in vials.

- The drug product composition has been fully detailed, including the active substance and accompanying excipients along with their respective functions.

Pharmaceutical Development including brief description on Components of drug product.

-Pneumococcal Polysaccharide Conjugate Vaccine is composed of 10 different pneumococcal capsular polysaccharides purified from S. pneumoniae serotypes (1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F and 23F) which are individually conjugated to a carrier protein

- These conjugates are adsorbed on to the aluminum phosphate adjuvant gel in the presence of formulation excipients.

-It is manufactured as a liquid formulation single dose without thiomersal and is to be administered intramuscularly as 0.5 mL single dose.

Formulation Development

-There is no change in the qualitative and quantitative formula since its initial development and use in manufacture of non-clinical batches.

- Formulation ingredients and their quantity for different scales described in MA file.

Physicochemical and Biological Properties

-The physicochemical and biological properties are tabulated and described in the MA file.

Manufacturing Process Development..

- Detailed description for process development is mentioned in the MA file.

Container closure system and their compatibility.

-Pneumococcal Polysaccharide conjugate vaccine (Adsorbed) (10-Valent) is filled in USP type 1 glass vial and closed with chlorobutyl rubber stopper followed by capping with aluminium flip-off cap

-Specification for all materials used in packing is well provided in MA file

Microbiological Attributes.

Critical quality attributes of drug substance

1. Saccharide content
2. Protein content for serotypes
3. Saccharide to protein ratio for serotypes
4. Free saccharide content , Free protein content , Molecular size distribution .

Manufacture of the drug product:

Description of manufacturing process and process controls along with manufacturers and responsibilities.

-The DP is produced using standard manufacturing steps, such as solution preparation and transfer, Blend A Formulation Process, Blend B Formulation Process, Preparation of Final Bulk, filling, capping and screening of vaccine vials.

- A flow diagram is clearly presented giving the steps of the process and showing where materials enter the process. A narrative description of the manufacturing process, including packaging, which represents the sequence of steps undertaken are provided.

Control of critical steps and intermediates

- Tests and acceptance criteria for critical manufacturing steps and intermediate steps are clearly identified, with defined action and acceptance limits.

Process validation and / or evaluation.

- Process validation is described in the file.

-Process validation report on formulated bulk of three lots are provided

Product specification:

Description of the product specifications (state the reference whether compendial or in-house) and the excipients (mention excipient specifications) as well.

- The proposed specifications are in the strict sense In house

Justify the specification if needed.

Most of the tests in the pharmacopeia do not mention any specifications

Highlight whether human or animal origin are present and novel excipients as well.

No substance of Human or animal origin are used as an excipient.

No Novel excipients are added during formulation.

Characterization of impurities.

The potential impurities which may introduce during manufacture of drug product are contaminating microorganism and particulate matter, which are being controlled by filtration of final bulk of vaccine .

Further tests for sterility, bacterial endotoxin and particulate matter are being carried out on every batch of Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10-Valent) before release to ensure the absence of contaminating microorganism and particulate matter.

Reference Standards or Materials.

-Reference standards used in various tests are provided. -Some of the standards are outsourced and some are developed in-house. -The in-house developed reference standards are calibrated against respective

available standard. Requalification period of Identity of carrier protein and Total Protein content are under establishment

Container closure system.

Pneumococcal Polysaccharide conjugate vaccine (Adsorbed) (10-Valent) is filled in USP type 1 glass vial and closed with chlorobutyl rubber stopper followed by capping with aluminium flip-off cap Specification for all materials used in packing is well provided in MA file

Stability of the drug product.

1-Pneumosil 5 doses:

-Shelf life 36 months After opening the vial: approved for use for up to 28 days ,The vaccine should be stored at 2 - 8°C -Do not freeze, discard if the vaccine has been frozen -After opening the vial: stored at 2 - 8°C

- The accelerated stability study: is done on 3 batches for 6 months at Temperature (25°C + 2°C/60 ± 5% RH) -The long-term stability study: is done on 3 batches for 42 months at Temperature (5°C ± 3°C)

-The In-Use stability study: is done on for 28 days at Temperature (2°C - 8°C).

2-Pneumosil 1 dose: -shelf life 3 years - The vaccine should be stored at (2-8 ºC) -Do not freeze, discard if the vaccine has been frozen. -After opening the vial, store at (2-8 ºC)

- The accelerated stability study: is done on 3 batches for 6 months at Temperature (25°C + 2°C/60 ± 5% RH) -The long-term stability study: is done on 3 batches for 42months at Temperature (2 ºC - 8 ºC).

2. Non –clinical aspect:

- Pneumosil 1 dose is a Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10-Valent) is a sterile suspension of saccharides of the capsular antigens of Streptococcus pneumoniae serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F and 23F individually conjugated by using 1-cyano-4-dimethylamino pyridinium tetrafluoroborate chemistry to non-toxic diphtheria CRM197 protein.
- **Pharmacology:** No dedicated studies were conducted to assess the efficacy of Pneumosil 1 dose. However, the immunogenicity endpoints were evaluated as part of the repeated dose toxicity studies in SD rats and NZW rabbits. The total IgGs and functional antibodies were estimated in the serum samples, showing that Pneumosil 1 dose vaccine has the ability to induce anti-pneumococcal polysaccharide specific antibodies against all the vaccine serotypes.

- **Pharmacokinetics:** Not applicable according to WHO guidelines on nonclinical evaluation of vaccines Annex 1 (TRS, No. 927, 2005).

- **Toxicology:** Single- and repeat-dose administration of Pneumococcal Pneumosil 1 dose via IM or SC routes to SD rats and NZW rabbits was well tolerated and the observed changes that were not adverse but rather a consequence of its pharmacological activity of the vaccine as they were reported across all treatment groups, including the comparator Prevenar 13® vaccine.

Reproductive and Developmental Toxicity Are usually not necessary for vaccines indicated for immunization during childhood, according to the WHO Guideline on non-clinical testing of vaccines and Guideline on Adjuvants in Vaccines for Human Use (EMEA/CHMP/VEG/134716/2004).

No Stand-alone **local tolerance** study was performed but investigated within the toxicity studies.

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

3. **Clinical aspect:**

Clinical Development Programme included 4 completed clinical studies conducted with Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10- Valent) (Phase I, II & III). The safety and immunogenicity of Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10- Valent) have been evaluated in adults, children and infants in 2 trials in India and 2 in Africa. The data from these studies are provided to support the use of Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10- Valent) for active immunization against IPD, pneumonia and acute otitis media (AOM) caused by S. pneumoniae serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F and 23F in infants and children from 6 weeks up to 2 years of age.

<u>Clinical Efficacy:</u> (Clinical Immunogenicity analysis)

- The immune response induced by Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10- Valent) was demonstrated to be non-inferior to a licensed and WHO prequalified comparator vaccine (Synflorix™) for all 10 vaccine serotypes after a 3-dose primary vaccination series, based on both the percentage of IgG responders and IgG GMC criteria.
- Non-inferiority was shown following vaccination on a 6-, 10- and 14-week schedule, which is the most relevant schedule for Gavi countries. This schedule is also the most stringent for evaluation of the immune response to vaccination and, as stated in WHO TRS 977 Annex 3, it can be anticipated that a robust immune response would be elicited by Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10- Valent) when used on other less stringent schedules.
- The IgG and OPA immune responses following a booster dose of Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10- Valent) established that immune memory had been induced to all serotypes present in the vaccine.

- The effects of concurrent administration of Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10- Valent) and Expanded Program of Immunization (EPI) vaccines were studied with vaccines which are routinely given at the same clinic visits as PCVs i.e., pentavalent DTwP-HepB-Hib, polio, and rotavirus vaccines during the primary course and measles-rubella and yellow fever vaccines at the time of the booster dose. No immune interference was observed with any co-administered vaccine. Immune responses to

vaccines co-administered with Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10- Valent) were shown to be non-inferior to the responses to these vaccines when co-administered with Synflorix™.

- Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10- Valent) was shown to be immunogenic in both infants and children in their second year of life and is thus indicated for both primary and catch-up vaccination. Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10- Valent) elicited robust immune responses in 2 racially diverse populations in different geographic settings (India and The Gambia). These data can therefore be considered as predictive of protective responses in other populations.

Clinical Safety:

- PCV 10V was demonstrated to have an acceptable safety profile and be well-tolerated when co-administered with routine pediatric vaccines through 4 weeks after a booster vaccination.
- The most commonly reported adverse reaction directly attributable to Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10- Valent) was injection site tenderness, which was reported for approximately one-half of all subjects. Erythema/redness and induration/swelling were less frequently observed.
- The majority of the local reactions were mild to moderate in intensity and resolved spontaneously.
- The incidence and severity of the systemic AEs for subjects who received Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10- Valent) and routine EPI vaccines were not different in a way that was clinically relevant for subjects who received either of the licensed comparator PCVs. Importantly, all events reported were in line with what can be expected following routine vaccination of infants and children.
- None of the SAEs reported during the studies was considered to be related to Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10- Valent) administration. No safety signals were raised following vaccination with Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10- Valent) in any of the age cohorts studied.

Benefit/ Risk discussion:

Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10- Valent) is thus expected to be as safe and effective as currently licensed and prequalified PCVs in providing protection against IPD, pneumonia and AOM caused by S. pneumoniae serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F and 23F.

In conclusion, the overall benefit/risk of PCV 10V (Pneumosil single dose) is favorable in Active immunization against invasive disease, pneumonia and acute otitis media caused by Streptococcus pneumoniae serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F and 23F in infants and toddlers from 6 weeks up to 2 years of age.

4. General Conclusion and Recommendations if any:

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