NATIONAL PHARMACEUTICAL REGULATORY DIVISION MINISTRY OF HEALTH MALAYSIA

TECHNICAL EVALUATION SUMMARY

PRODUCT NAME:
SII PNEUMOSIL Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10-Valent) SUSPENSION FOR INJECTION (SINGLE DOSE - 1 DOSE) (MAL20076002AZ)
SII PNEUMOSIL Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed) (10-Valent) SUSPENSION FOR INJECTION (MULTIDOSE - 5 DOSE) (MAL20076001AZ)

ACTIVE INGREDIENT:
Each 0.5mL dose contains:
Saccharide for serotypes 1, 5, 6A, 7F, 9V, 14, 19A, 19F and 23F: 2µg each
Saccharide for serotype 6B: 4µg
Conjugated to CRM 197 (carrier protein)

PRODUCT REGISTRATION HOLDER:
Pharmaniaga LifeScience Sdn Bhd

MANUFACTURER AND FINAL RELEASE:
Serum Institute of India, Pvt, Ltd, India

PRESENTATION:
Single dose vial (0.5 mL)
Multi doses vial (2.5 mL, containing thiomersal 25µg / dose as preservative)

APPROVAL DATE:
9 JULY 2020 (DCA 346)

1.0 BACKGROUND INFORMATION

1.1 Approved Indication

Active immunization for the prevention of 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. The use of vaccine should be determined on the basis of relevant recommendations and take into consideration the disease impact by age and regional epidemiology.

1.2 Approved Posology

The dose is 0.5 ml given intramuscularly, with care to avoid injection into or near nerves and blood vessels. The preferred sites are anterolateral aspect of the thigh in infants or the deltoid muscle of the upper arm in young children. The vaccine should not be injected in the gluteal area. Do not administer SII PNEUMOSIL (10-valent) intravascularly. The vaccine should not be injected intradermally, subcutaneously or intravenously, since the safety and immunogenicity of these routes have not been evaluated.

Vaccination Schedule

SII PNEUMOSIL (10-valent) is to be administered as a three-dose primary series at 6, 10, and 14 weeks of age or 2, 3 and 4 months of age or 2, 4 and 6 months of age, with or without, depending on recommended dosing schedule, a booster dose at 9-10 or 12-15 months of age. The minimum interval between doses should be 4 weeks. If a booster dose is given, it should be at least 6 months after the last primary dose.

Table 1: Vaccination Schedule for Infants and Toddlers

Dosage Schedules	Dose 1[a,b]	Dose 2[b]	Dose 3[b]	Dose 4[c]
3p+1	6 weeks	10 weeks	14 weeks	9 – 10 months or 12-15 months
3p+0	6 weeks	10 weeks	14 weeks	-

[a] Dose 1 may be given as early as 6 weeks or at 2 months of age
[b] The recommended dosing interval is 4 to 8 weeks
[c] A booster (fourth) dose is recommended at least 6 months after the last primary dose and may be given from the age of 9 months onwards (preferably between 12 and 15 months of age)

For children who are beyond the age of routine infant schedule, the following SII PNEUMOSIL (10-valent) schedule is proposed: The catch-up schedule, for children 7 months through 2 years of age who have not received SII PNEUMOSIL (10-valent):

Table 2: Vaccination Schedules for Unvaccinated Children 7 Months of Age Through 2 Years of Age

Age at first dose	Total Number of 0.5 ml doses
7-11 months of age	3[a]
12-24 months of age	2[b]

[a] The vaccination schedule consists of two primary doses of 0.5 ml with an interval of at least 1 month between doses. A booster (third) dose is recommended in the second year of life with an interval of at least 2 months after the last primary dose.
[b] The vaccination schedule consists of two doses of 0.5 ml with an interval of at least 2 months between doses.

1.3 Method of administration

For intramuscular injection only**.**

2.0 SUMMARY REPORT

2.1 Quality

2.1.1 Active Substance

The drug substances for SII Pneumosil are monovalent bulk conjugates which comprise of pneumococcal polysaccharides from 10 *Streptococcus pneumoniae* serotypes (1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, and 23F) individually conjugated to a non-toxic mutant of diphtheria toxin, CRM197 as a carrier protein. The average molecular weight of each monovalent bulk conjugates is roughly more than 2000 kDa inclusive of CRM197. Each pneumococcal serotype has structurally distinct capsular polysaccharide composed of repeating oligosaccharide units jointed by glycosidic linkages. Recombinant CRM197 comprises of 535 amino acids with an average molecular weight of 58.4 kDa.

The master cell culture of *Streptococcus pneumoniae* strains from each of the 10 serotypes were obtained from the Center for Disease Control and Prevention (CDC) Atlanta, USA. Each Master and Working Seed Lot complied with the specifications laid down in the WHO TRS 977, Annex 3. For recombinant CRM197, the pfenex expression technology in *Pseudomonas fluorescens* was used as a starting point for the development of strains expressing CRM197 protein.

The manufacturing process of monovalent bulk conjugates for all 10 serotypes are similar and broadly divided into four stages namely fermentation and harvest of pneumococcal polysaccharide, purification of polysaccharide, modification or sizing of purified pneumococcal polysaccharide, and lastly conjugation of polysaccharide with CRM197. In-process tests are conducted during multiple stages of manufacturing followed by final control release of the monovalent bulk conjugates.

Process validation and consistency using three commercial-scale drug substance batches demonstrated that the process is capable of producing reproducible and consistent monovalent bulk conjugate. The data from stability studies support the proposed shelf life of 36 months when stored at 2-8°C for each monovalent bulk conjugate.

2.1.2 Finished Product

The formulation process of SII Pneumosil finished product consists of five steps namely the preparation of buffer and stock solution, sequential addition of formulation components, adjustment of pH, mixing of blends, incubation and transfer of final vaccine bulk for filling. The final process includes filling into vials, sealing and visual inspection.

Process validation of the manufacturing process for three consecutive lots of multi-dose finished drug product (DP) and one single-dose finished DP at commercial scale have been performed. The results

obtained shows that the manufacturing process is robust and consistently meets the predetermined drug product quality characteristics.

The long term stability studies results for single- and multiple-dose showed that the finished product is stable at 36 months when stored refrigerated at the recommended storage condition (5°C ±3°C) with the container kept in the intended secondary packaging material to protect from light. Once opened, multiple-dose vials should be kept between 2°C to 8°C and may be used on conditions in subsequent immunization sessions for up to a maximum of 28 days.

SII Pneumosil is a sterile homogenous suspension (whitish turbid) of Pneumococcal capsular polysaccharides individually conjugated to a carrier protein (CRM197) and adsorbed on to aluminum phosphate. This ready to use liquid vaccine is presented in USP type I, tubular, transparent glass vials, stoppered with 13 mm, butylated, grey rubber stopper and sealed with 13 mm aluminum seal with Burgundy colored polypropylene flip-top cap. One-dose vaccine may be filled either in 30 mm or in 40 mm height vial whereas five-doses vaccine may be filled either in 35 mm or 40 mm height vial. A vaccine vial monitor (VVM) 30 is to be placed on top of the vial for 1-dose vaccine and on primary container label for 5-dose vaccine.

The product has passed the NPRA laboratory evaluation on analytical protocol and validation.

2.2 Efficacy/ Immunogenicity

A total of 4 studies ranging from Phase I, Phase I/II and Phase III were submitted to support the proposed indication. The studies are summarized as below:

- PCV-10-001: Phase I, first in human study in India to obtain preliminary information on the safety and tolerability profile of the vaccine in adults. (Pneumovax 23)
- PCV-10-002: Phase II, evaluation of the safety, tolerability and immunogenicity for catch-up vaccination of PCV-naïve Indian toddlers (12-15 months). (Prevenar 13)
- VAC-017: Phase I/II (in parallel with Phase I and II) age de-escalation trial evaluating the safety, tolerability and immunogenicity in PCV-naïve adults (Pneumovax 23), PCV (Prevenar 13) primed children, and PCV-naïve infants (Prevenar 13) in Gambia.
- VAC-056: Phase III, randomised, active controlled, double blind study conducted in infants in Gambia. (Synflorix)

Study No/ Phase/ Location	Study Design	Study Population	Schedule of vaccination/ Control	No. of Subjects	
				Pneumosil	Control
PCV-10-001/ Phase 1/ India (first in human)	Prospective, Randomised (1:1), Active- Controlled, Double-Blind Study	PCV- naïve adults (18-40 years inclusive)	1 dose on Day 0/ Penumovax 23	17	17
PCV-10-002/ Phase 2/ India	Prospective, Multi-centre, Randomised (1:1), Active-Controlled, Double-Blind Study	PCV- naïve toddlers (12-15 months inclusive)	2 doses on Day 0 and Day 56/ Prevenar 13	57	57
VAC-017/ Phase 1/2/ Gambia	Prospective, Single-centre, Randomised (1:1), Active-Controlled	PCV-naïve adults (18-40 years inclusive)	1 dose on Day 0/ Pneumovax 23	17	17
	Double-Blind, Age De-escalation Study	PCV-primed toddlers (12-15 months inclusive)	1 dose on Day 0/ Prevenar 13	56	56
		PCV-naïve infants (6-8 weeks inclusive)	3 dose primary vaccination series (at Week 0, 4 and 8) plus booster vaccination at 10-14 months of age in a subset/ Prevenar 13	100 (49)	100 (47)
VAC-056/ Phase 3/ Gambia	Prospective, Single-centre, Randomised, Active-Controlled, Double Blind Study (Randomised 2:2:2:3 Pneumosil Lot 1: Pneumosil Lot 2: Pneumosil Lot 3: Synflorix) for evaluation of lot to lot consistency	PCV- naïve infants (6-8 weeks inclusive on Day 0)	3-dose primary vaccination series (at Week 0, 4 and 8) plus booster vaccination at 9-10 months of age in a subset/ Synflorix	1503 (428)	747 (213)

Study VAC-056 (Phase III):

Choice of comparator for VAC-056 Phase III:

- Synflorix, a WHO prequalified PCV at the time of product development is the only second generation PCV that has been evaluated in randomised controlled trials for both efficacy and effectiveness against invasive pneumococcal disease (IPD) and pneumonia in infants and children.
- The clinical development has been conducted in accordance to WHO TRS 977 (Recommendations to assure the quality, safety and efficacy of Pneumococcal conjugate vaccines). In brief, clinical studies should aim to evaluate the following:
    a. Manufacturing quality demonstrated by post lot-to-lot immunologic consistency

b. Vaccine efficacy based on immunogenic non-inferiority to a licensed and prequalified comparator vaccine post a 3-dose primary series
c. Immunologic non-interference with co-administered expanded programme for immunisation (EPI) vaccines
d. Immunologic memory as indicated by booster response
e. Adequate safety and tolerability profile after primary series and booster vaccination

- Immune responses to pneumococcal conjugate vaccines can be assessed (as primary endpoint) by:
  a. Determination of serotype-specific IgG antibody; geometric mean concentrations (GMCs) based on measurement of binding to polysaccharides (e.g. using an ELISA method) or
  b. Determination of serotype-specific functional antibody titres using an opsonophagocytic assay (OPA)

Study type & design (n)	**Study VAC-056**: A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety, Tolerability, Lot-to-Lot Consistency, Immunogenicity, and Non-Interference with Concomitant Vaccinations of Serum Institute of India's 10-Valent Pneumococcal Conjugate Vaccine (PNEUMOSIL®) in Healthy Infants in The Gambia A total of (n=2250) healthy infants, born full-term (ie, at gestational age ≥ 37 weeks), who were 6 to 8 weeks of age (ie, 42 to 56 days) inclusive, and who had a weight-to-height z-score of ≥ -2 (World Health Organization [WHO] child growth standard), and were ≥ 3.5 kg, were eligible for inclusion. <u>Randomised 2:2:2:3</u> • 1,503 subjects received PNEUMOSIL (Lot 1: 502 subjects, Lot 2: 501 subjects, Lot 3: 500 subjects) • 747 subjects received Synflorix
Treatment	**<u>SII PNEUMOSIL</u>** • 209Y7001AZ (Lot 1) • 209Y7002AZ (Lot 2) • 209Y7003AZ (Lot 3) **<u>SYNFLORIX</u>** (Intramuscular (IM) injection (0.5 mL dose) into the anterolateral aspect of the left thigh) • XSPNA828BB i. First phase: Priming: 3 doses at 6, 10, and 14 weeks of age. Intramuscular (IM) injection (0.5 mL dose) into the anterolateral aspect of the left thigh. ii. Second phase: Booster: 9 months of age (subset of subjects, n= 675) Intramuscular (IM) injection (0.5 mL dose) into the anterolateral aspect of the left thigh. iii. Third phase: Out of the 675 booster subjects, subjects who consented for further evaluation will participate for the assessment of immune persistence 12 (+1) months after the booster

	vaccination. Data for this is currently on-going. Standard EPI vaccinations in The Gambia were to be given concomitantly with all 4 doses of the study vaccines: • pentavalent – diphtheria, tetanus, whole-cell pertussis, hepatitis B, and Hib combined vaccine [DTwP-HepB-Hib], inactivated poliovirus vaccine [IPV], measles-rubella, and yellow fever virus vaccines)-injection • Rotavirus vaccine (RV) and oral poliovirus vaccine (OPV)- oral

Results	
Objective	**Primary efficacy endpoint**
1. <u>Immunogenicity:</u> a. To demonstrate that the immune responses to the 10 pneumococcal serotypes in SII PNEUMOSIL (1,5, 6A, 6B, 7F, 9V, 14, 19A, 19F, 23F) induced by 3 different lots of SII PNEUMOSIL are equivalent when measured 4 weeks after a 3-dose primary series. [(lot-to-lot consistency); First phase]	Lot-to-lot consistency; Serotype-specific IgG GMC measured 4 weeks post vaccination 3 Immunologic equivalence was demonstrated for the 3 lots of SII PNEUMOSIL. For each of the 10 serotypes in the SII PNEUMOSIL group and each pair of lots, the 95% CIs for IgG GMC ratios between lots lay within the interval (0.5, 2).
b. To demonstrate non-inferior immune responses for at least 7 of the 10 serotypes in SII PNEUMOSIL in comparison to matched serotypes (for 1, 5, 6B, 7F, 9V, 14, 19F, 23F) or the lowest responder (for 6A, 19A) in Synflorix; First phase	Non-inferior immune responses for at least 7 of the 10 serotypes in SII PNEUMOSIL in comparison to matched serotypes (for 1, 5, 6B, 7F, 9V, 14, 19F, 23F) 4 weeks post primary vaccination series looking at: a. % immunoglobulin (Ig) G response ≥ 0.35 µg/mL or (Non-inferiority was shown if the two-sided 97.5% CI for the difference in proportions of responders, as defined above, had a lower limit > -10%) b. IgG geometric mean concentrations (IgG GMCs) measured 4 weeks after a 3-dose primary series (Non-inferiority was shown if the two-sided 97.5% CI for the GMC ratio, as defined above, had a lower limit > 0.5 Immunologic non-inferiority was demonstrated for both IgG responses ≥ 0.35 µg/mL and IgG GMCs for all 10 serotypes in the SII PNEUMOSIL group in comparison to the responses induced by the matched serotypes (1, 5, 6B, 7F, 9V, 14, 19F and 23F) or serotypes with the lowest IgG seroresponse rate (6A and 19A) in the Synflorix group.

c. To demonstrate that the immune responses induced by routine pediatric vaccines (pentavalent, polio and rotavirus) when co-administered with a 3-dose primary series of SII PNEUMOSIL are noninferior to those induced by these vaccines when co-administered with Synflorix (subset of subjects); First phase	**Non-interference with routinely administered paediatric vaccines** Non-inferiority was to be shown if the lower limit of the 95% CI exceeded -10% (for comparisons based on the difference in proportions of antibody responders to EPI vaccines between SII PNEUMOSIL and Synflorix) or if the lower limit of the 95% CI for the GMC ratio exceeded 0.5 (for pertussis antigens). Non-inferiority of the immune responses was demonstrated for all EPI vaccines co-administered with the 3-dose primary series. The proportion of antibody responders to rotavirus was low but similar in both vaccine groups.
d. To demonstrate the immune responses (antibody concentrations and functional responses) to Pneumosil in comparison to Synflorix, from 4 weeks after a 3-dose primary series to 4 weeks after a booster dose (subset of patients); Second phase	**Booster immune response** Booster immune response was demonstrated for all 10 serotypes in both vaccine groups. For both SII PNEUMOSIL and Synflorix, a significant booster immune response was demonstrated for 9 out of 10 serotypes based on IgG GMCs (no booster effect for serotype 5), and for all 10 serotypes based on OPA GMTs.

2.3.2 Safety

- Majority of the reactions observed following vaccination were of mild or moderate severity and were of short duration. Overall, the most common adverse reactions observed after primary vaccination were tenderness at the injection site, fever and irritability, which were reported for approximately 49%, 52% and 32% of all infants, respectively.
- No increase in the incidence or severity was observed following subsequent doses of the primary vaccination course. Following booster vaccination, the most common adverse reaction was tenderness at the injection site, which was reported for approximately 8% of all infants.
- The safety and reactogenicity profile of SII Pneumosil can be concluded to show similarity (in terms of frequency, severity and the nature of the solicited adverse reactions) with currently available pneumococcal vaccines for infants.

3.0 CONCLUSION

- Drug Control Authority (DCA) on the 346th meeting on 9th July 2020 has decided to approve the registration of this product (conditional registration of 2 years) with the following information:

  Active immunization for the prevention of 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. The use of vaccine should be determined on the basis of relevant recommendations and take into consideration the disease impact by age and regional epidemiology.