Taiwan Food and Drug Administration

Assessment Report

Trade Name：肺恩賜 肺炎鏈球菌十五價結合型疫苗 滅菌懸液注射劑/ VAXNEUVANCE Suspension for Injection

Active Ingredient：Pneumococcal 15-valent Conjugate Vaccine [CRM197 Protein]

License Number：MOHW-BI 001198

Applicant：美商默沙東藥廠股份有限公司台灣分公司

Approval Date：2022/9/26

Indication： Active immunization for the prevention of invasive pneumococcal disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 23F, 22F, 33F in adults 18 years of age and older.

「VAXNEUVANCE 適用於 18 歲以上成人的主動免疫接種，以預防肺炎鏈球菌血清型 1、3、4、5、6A、6B、7F、9V、14、18C、 19A、19F、22F、23F 及 33F 所引起的侵襲性疾病。」

Background Information

Trade Name	肺恩賜 肺炎鏈球菌十五價結合型疫苗 滅菌懸液注射劑/ VAXNEUVANCE Suspension for Injection
Active Ingredient(s)	Pneumococcal 15-valent Conjugate Vaccine [CRM197 Protein]
Applicant	美商默沙東藥廠股份有限公司台灣分公司
Dosage Form & Strengths	Suspension for injection (0.5 mL dose), containing 64 µg/mL of total Pneumococcal Polysaccharide (PnPs) antigens conjugated to CRM197 (~ 30 µg), supplied as a single-dose prefilled syringe.
Indication	Active immunization for the prevention of invasive pneumococcal disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 23F, 22F, 33F in adults 18 years of age and older.
Posology	Intramuscular injection with a single dose
Pharmacological Category **ATC Code**	J07AL02

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The active substance is manufactured by conjugation of CRM197 to the pneumococcal capsular polysaccharides.

The polysaccharides are the purified PnPs from 15 serotypes of *Streptococcus pneumoniae*. The serotype designations using the Danish naming system are 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F. All 15 serotypes are polymers of serotype-specific repeating units, the repeat units for eight serotypes are linear (1, 3, 4, 6A, 6B, 9V, 19A and 19F), while the repeat units for the other seven contain short branches (5, 7F, 14, 18C, 22F, 23F and 33F).

CRM_{197} is a nontoxic (enzymatically inactive) form of Diphtheria toxin (DT). CRM_{197} protein exists predominantly as monomeric protein molecules, with minimal higher order aggregates.

Reductive amination chemistry is used to link the aldehydes on activated polysaccharide molecules with primary amides on CRM197. Within each conjugate molecule, polysaccharide chains may contain carrying numbers of repeating units. Additionally, each conjugate molecule may contain different numbers of polysaccharide and protein molecules. Weight-average molecular masses measured by this assay range from approximately 800 to 6500 kDa across the 15 serotypes.

The specifications for monovalent bulk conjugate (MBC) are provided. The analytical methods for release included physicochemical attributes, appearance, identity, assays, impurities, microbial quality which are considered adequate. The methods have been described and validated. All analytical results of PPQ batches are within the acceptance criteria.

Stability studies for PPQ batches were studied at the long-term condition, the accelerated condition, and the stress condition. Three batches (PPQ) for each serotype were placed in stability studies and the results support claimed shelf-life of each serotype.

2.1.2 Drug product

Vaxneuvance DP is a sterile opalescent liquid suspension for injection and is filled into 1.5 mL glass syringe with 0.5 mL for a dose. The DP provides a total of 64 μg/ml of total Pneumococcal Polysaccharide (PnPs) antigens conjugated to CRM_{197} (~30 μg) as MBC in the final formulated bulk (FFB).

The analytical methods for Vaxneuvance DP release included physicochemical attributes, appearance and description, identification, assays, and microbial quality. The description of the analytical methods and validation results are acceptable. All results in batch analysis indicate the quality reproducibility of Vaxneuvance DP.

Stability data for Vaxneuvance DP stored at long-term and supporting conditions are provided. The submitted long-term stability data showed no significant quality change in terms of content, physicochemical properties, or purity of Vaxneuvance DP. The proposed shelf life of 24 months for Vaxneuvance DP stored at 2-8ºC is acceptable.

2.2 Preclinical Pharmacology/Toxicology Evaluation

V114 contains 15 distinct pneumococcal capsular polysaccharides individually conjugated to the CRM_{197} carrier protein. In vivo, V114 was immunogenic against each of the 15 serotypes

contained in the vaccine and capable of inducing functional antibodies with opsonophagocytic activity in rabbits and infant rhesus monkeys. In general, the vaccine formulations tested were well-tolerated, and no vaccine-related adverse events were noted in the immunogenicity studies. V114 Formulation B, the proposed marketing formulation, generated comparable antibody responses to Prevnar 13 for the 13 common serotypes.

V114 Formulation B was generally well-tolerated in GLP repeated-dose toxicity studies in rats at the proposed human dose. The immunogenicity was confirmed, and the vaccine-related findings were limited to localized inflammatory response at the injection sites and draining lymph nodes, consistent with an expected response to vaccination without manifesting unexpected effects for an adjuvanted vaccine. The NOAEL provides a 200-fold safety margin on a BW-adjusted basis.

An EFD and preweaning toxicity study and a postnatal developmental toxicity study were conducted in rats. The data from these DART studies generally showed no V114-related maternal or developmental toxicity at the proposed human dose, which provides a 200-fold safety margin on a BW-adjusted basis.

Local tolerance was assessed as part of the repeated-dose studies in rats. No unexpected tissue response at the IM or SC injection sites and in the draining lymph nodes was noted.

Consistent with the WHO's guidelines, secondary pharmacodynamics, safety pharmacology, genotoxicity, and carcinogenicity studies are generally not required for vaccines. The totality of nonclinical data indicates that V114 had no effect on physiological functions other than the expected immune responses.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In this submission, the Sponsor provided six well-controlled studies (p016, p017, p018, p019, p020 and p021) to support the immunogenicity of Vaxneuvance for the claimed indication. The major design features and results of those studies were summarized as follows:

- ***Study p016***

Serotype-specific OPA GMTs at 30 days following vaccination with PPV23 (Month 13) were comparable between participants administered Vaxneuvance or Prevnar 13™ 12 months priorto receipt of PPV23 for all 15 serotypes in Vaxneuvance, as assessed by OPA GMT ratios. Results showed that Serotype-specific OPA GMTs at 30 days following vaccination with PPV23 were comparable between participants administered Vaxneuvance or Prevnar 13™ 12

months prior to receipt of PPV23 with the exception of Serotypes 1, 14, 22F and 23F (95% CIs do not contain the value 1), as assessed by OPA GMT ratios.

- ***Study p017***

Vaxneuvance was immunogenic in pneumococcal vaccine-naïve, immunocompetent adults 18 to 49 years of age with or without risk factors for pneumococcal disease as assessed by OPA GMTs at 30 days postvaccination (Day 30) for all 15 serotypes contained in the vaccine. Prevnar 13™ was immunogenic as assessed by OPA GMTs at 30 days postvaccination for all 13 serotypes contained in the vaccine.

Results showed that the upper bound of the 95% CI of OPA GMTs in the Vaxneuvance group was less than the lower bound of 95% CI of OPA GMTs in the Prevnar 13™ group for serotypes 4 and 7F.

- ***Study p018***

Vaxneuvance was immunogenic in pneumococcal vaccine-naïve adults infected with HIV as assessed by OPA GMTs at 30 days postvaccination (Day 30) for all 15 serotypes contained in the vaccine. Prevnar 13™ was immunogenic as assessed by OPA GMTs at 30 days postvaccination for all 13 serotypes contained in the vaccine

Results showed the upper bound of the 95% CI of OPA GMTs and IgG GMCs in the Vaxneuvance group was less than the lower bound of 95% CI of OPA GMTs and IgG GMCs in the Prevnar 13™ group for serotype 4.

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- ***Study p019***

This was a randomized, active-controlled, parallel-group, multisite, double-blind study of Vaxneuvance in adults 50 years of age or older. The primary immunogenicity endpoints were Serotype-specific OPA GMTs at 30 days postvaccination (Day 30) for the 15 serotypes contained in Vaxneuvance and proportion of participants with a ≥4-fold rise from pre-vaccination to 30 days postvaccination for OPA responses for the 2 unique serotypes contained in Vaxneuvance.

Vaxneuvance met non-inferiority criteria [lower bound of the 95% CI of the estimated OPA GMT ratio (Vaxneuvance /Prevnar 13™) was >0.5] for the 13 shared serotypes as assessed by serotype-specific OPA GMTs at 30 days postvaccination.

Vaxneuvance met superiority criteria [lower bound of the 95% CI of the estimated OPA GMT ratio (Vaxneuvance /Prevnar 13™) was >2.0] for the 2 serotypes unique to V114 as assessed by serotype specific OPA GMTs at 30 days postvaccination.

Vaxneuvance met superiority criteria [lower bound of the 2-sided 95% CI of the difference in percentages Vaxneuvance -Prevnar 13™) was >10 percentage points] for the 2 serotypes unique to Vaxneuvance as assessed by the proportions of participants with a ≥4-fold rise from pre-vaccination to 30 days postvaccination for serotype-specific OPA responses.

- ***Study p020***

This was a randomized, active-controlled, parallel-group, multisite, double-blind study of Vaxneuvance in healthy adults. The primary immunogenicity endpoints are the serotype-specific OPA GMTs at 30 days postvaccination (Day 30).

The 3 lots of Vaxneuvance met criteria for equivalence, as assessed by the serotype-specific OPA GMTs for the 15 serotypes in Vaxneuvance at 30 days postvaccination. The lower and upper limits of the 95% CI of the serotype-specific OPA GMT ratios between any 2 lots were within the equivalence margin (0.5 to 2.0) for all 15 serotypes.

- ***Study p021***

This was a randomized, placebo-controlled, parallel-group, multisite, double-blind study of Vaxneuvance in healthy adults. The primary immunogenicity analysis endpoints were Serotype-specific OPA GMTs at 30 days postvaccination with Vaxneuvance and Strain-specific HAI GMTs at 30 days postvaccination with Quadrivalent influenza vaccine (QIV).

Vaxneuvance administered concomitantly with QIV was noninferior to Vaxneuvance administered nonconcomitantly with QIV as assessed by serotype-specific OPA GMTs at 30 days postvaccination with Vaxneuvance. The lower bound of the 2-sided 95% CI of the OPA GMT ratio was >0.50 for all 15 serotypes.

QIV administered concomitantly with Vaxneuvance was noninferior to QIV administered non-concomitantly with Vaxneuvance as assessed by strain-specific HAI GMTs at 30 days postvaccination with QIV. The lower bound of the 2-sided 95% CI of the HAI GMT ratio was >0.50 for all 4 strains.

2.4.2 Safety Results

Among the pneumococcal vaccine-naïve vaccinees 50 years of age and older, a higher proportion of participants with AEs was observed in Vaxneuvance group compared with the Prevnar 13 group, mainly due to more injection-site AEs reported following vaccination with Vaxneuvance. The majority of these events were mild in a maximum intensity. The higher proportion of injection site AEs following Vaxneuvance vaccination compared to Prevar13

was driven by injection site pain.. The proportions of participants with systemic AEs and vaccine-related systemic AEs were generally comparable across the intervention groups. The 3 most common AEs following Vaxneuvance vaccination were injection-site pain, fatigue, and myalgia. The proportions of participants who experienced SAEs were low and comparable across intervention groups. There were few deaths in either intervention group. None of the deaths were considered by the investigator to be vaccine-related. Safety results observed for each age subgroup (50 to 64, 65 to 74, and ≥75 years of age) were generally consistent with those observed in the overall senior population. The safety and tolerability of sequential administration of PPV23 administered 12 months following Vaxneuvance or Prevnar13 were generally comparable. The safety and tolerability of Vaxneuvance concomitant use with Flu vaccine was acceptable.

Among pneumococcal vaccine-naïve adults 18 to 49 years of age, the proportions of participants with AEs, injection-site AEs, systemic AEs, vaccine-related systemic AEs and SAEs were generally comparable across intervention groups. The safety and tolerability following sequential vaccination with PPV23 is also comparable across intervention groups. Overall, the safety observed at the younger population was consistent with the senior population.

Among HIV-positive adult vaccinees, Vaxneuvance was well tolerated with safety results that were generally consistent with those observed in immunocompetent, pneumococcal vaccine-naïve adults. There were no clinically meaningful changes from baseline in CD4+ T-cell count and plasma HIV RNA 30 days postvaccination with Vaxneuvance.

2.5 Bridging Study Evaluation

The sponsor provided evidence of East Asian participants from the Phase 3 studies (p016 and p019) to support the BSE. A total of 285 (23.7%) East Asian participants (including 40 Taiwanese) were randomized and vaccinated with PCV in Study p019. A total of 201(30.8%) East Asian participants (including 101 Taiwanese) were randomized in Study p016. The results revealed Vaxneuvance is immunogenic at the East Asian population, consistent with the efficacy of Global population. In addition to injection-site AEs, the incidence of systemic AEs in Vaxneuvance group was higher than that in Prevnar13 group among East Asian participants, which was not observed at Global population. However, Vaxneuvance is well tolerated at East Asian population with lower solicited AE rate than the rate at Global population.

In summary, no ethnic difference with clinical impact was observed. Bridging study waive was recommended.

2.6 Conclusion

The multidiscipline review concluded Vaxneuvance demonstrates a favorable risk-benefit profile with enough evidence to recommend regular approval for the following indication: **Active immunization for the prevention of invasive pneumococcal disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, 23F, 22F, 33F in adults 18 years of age and older.**

3. Post-Marketing Requirements

NA