swissmedic

Date: 14 March 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Vaxneuvance

International non-proprietary name: *Streptococcus pneumoniae* serotypes 1 / 3 / 4 / 5 / 6A / 6B / 7F / 9V / 14 / 18C / 19A / 19F / 22F / 23F / 33F polysaccharide conjugated to *Corynebacterium diphtheriae* CRM 197 protein

Pharmaceutical form: suspension for injection in pre-filled syringe

Dosage strength(s): 2 µg of each serotype / 0.5 mL

Route(s) of administration: intramuscular

Marketing authorisation holder: MSD Merck Sharp & Dohme AG

Marketing authorisation no.: 68752

Decision and decision date: approved on 14 February 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMC	Geometric mean concentration
GMT	Geometric mean titre
HAI	Haemagglutination inhibition
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
IPD	Invasive pneumococcal disease
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
OPA	Opsonophagocytic activity
PBPK	Physiology-based pharmacokinetics
PCV	Pneumococcal conjugate vaccine
PCV13	13-valent conjugated pneumococcal vaccine
PCV15	15-valent conjugated pneumococcal vaccine
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PPV	Pneumococcal polysaccharide vaccine
PPV23	Pneumococcal polysaccharide vaccine containing 23 serotypes (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F)
PSP	Pediatric study plan (US FDA)
QIV	Quadrivalent influenza vaccine
RMP	Risk management plan
SAE	Serious adverse event
ST	Serotype

SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
VT	Vaccine serotype

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for *Streptococcus pneumoniae* serotypes 1 / 3 / 4 / 5 / 6A / 6B / 7F / 9V / 14 / 18C / 19A / 19F / 22F / 23F / 33F polysaccharide conjugated to *Corynebacterium diphtheriae* CRM 197 protein in the above-mentioned medicinal product.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Vaxneuvance is indicated for active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in individuals 18 years of age and older.
See sections "Warnings and precautions" and "Properties/Effects" for information on protection against specific pneumococcal serotypes.
The use of Vaxneuvance should be in accordance with official recommendations.

2.2.2 Approved indication

Vaxneuvance is indicated for active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in individuals 65 years of age and older.
Vaxneuvance does not protect against diseases caused by *S. pneumoniae* serotypes that are not included in the vaccine.
See "Warnings and precautions" and "Properties/Effects" for information on protection against specific pneumococcal serotypes.
The use of Vaxneuvance should be based on official recommendations and consider the risk of invasive diseases and pneumonia in the different age groups, underlying conditions as well as epidemiologic variability of the serotypes in the different geographic areas.

2.2.3 Requested dosage

Summary of the requested standard dosage:

Individuals 18 years of age and older

1 dose (0.5 mL) i.m. The need for revaccination with a subsequent dose of Vaxneuvance has not been established.

Paediatric population

The safety and efficacy of Vaxneuvance in children and adolescents under 18 years of age have not been established.

Special populations

One dose of Vaxneuvance may be given to individuals who have 1 or more underlying conditions predisposing them to an increased risk of pneumococcal disease (e.g. adults living with human immunodeficiency virus (HIV) or immunocompetent adults 18 to 49 years of age with risk factors for pneumococcal disease).

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	12 November 2021
Formal objection	2 December 2021
List of Questions (LoQ)	19 April 2022
Response to LoQ	15 July 2022
Preliminary decision	3 October 2022
Response to preliminary decision	9 November 2022
Final decision	14 February 2023
Decision	approval

Swissmedic has only assessed parts of the primary data submitted with this application. As regards the remaining data, Swissmedic relies for its decision on the assessment of the foreign reference authority, the EMA. This SwissPAR relates to the publicly available assessment report Vaxneuvance - EMA/620380/2021 - 13 December 2021, issued by the EMA.

3 Medical context

Streptococcus pneumoniae (pneumococcus) is a common commensal bacterium and opportunistic pathogen. Asymptomatic nasopharyngeal colonisation is common and ranges from 20 to 40% in children and from 5 to 10% in adults. While carriage is typically asymptomatic, pneumococcus can cause a variety of infections including otitis media, sinusitis, and pneumonia. Invasive pneumococcal disease (IPD) occurs when pneumococcus enters normally sterile tissue sites, such as the bloodstream or cerebrospinal fluid, leading to septicaemia, meningitis, or bacteraemic pneumonia.

Other, less frequent infections include periorbital cellulitis, osteomyelitis, endocarditis, pericarditis, peritonitis, pyogenic arthritis, soft tissue infections, and neonatal septicaemia.

Rates of IPD are highest in children under 2(-5) years old, adults over 65 years of age, and (especially) individuals with certain chronic health conditions including chronic pulmonary/heart/lung disease, diabetes, splenic dysfunction, immunosuppression/immunodeficiencies, cerebrospinal fluid leak, Cochlear implant, smoking, or alcoholism. Crowded environments or poor socioeconomic conditions are also considered risk factors.

In Switzerland, approximately 80% of fatal pneumococcal infections occur in adults aged 65 years and older.[1]

Pneumococcal infections are treated with antibiotics and the choice of antibiotic should reflect local resistance patterns and national treatment guidelines.

The polysaccharide (PS) capsule of pneumococci is an important virulence factor, which protects the organism from phagocytes.

Over 90 pneumococcal serotypes have been described based on the different capsule antigens. The prevalence and distribution of invasive serotypes differs across populations and geographic areas.

Prevention of pneumococcal disease in adults includes vaccination with PCVs and PPVs and the prophylactic use of antibiotics in special populations. The mechanism of action of all licensed pneumococcal vaccines is the induction of protective, serotype-specific, anticapsular antibodies. Pneumococcal vaccines have demonstrated efficacy and effectiveness against invasive disease caused by the serotypes contained in those vaccines in both children and adults. Recommendations for pneumococcal vaccination in adults are typically based on age or risk for pneumococcal disease. Childhood immunisation against *S. pneumoniae* is the most effective public health measure for preventing IPD among both vaccine recipients (direct effect) and unvaccinated populations (indirect 'herd' effect) as children are the main reservoir, thus unvaccinated populations benefit from the reduction or even removal of the vaccine serotypes (VTs) in children.

In Switzerland, the Federal Commission for Vaccinations recommends pneumococcal vaccination for children under 5 and for older children and adults with health conditions with a high risk of an invasive pneumococcal disease. Vaccination of healthy adults over 65 years of age was not recommended at the time of this assessment.

With an annual incidence of approximately 10 cases per 100 000 individuals for IPD alone, pneumococcus remains an important cause of vaccine-preventable infections in Switzerland.[1]

In Switzerland, the impact of the infant immunisation programme has reduced most of the vaccine-type IPD cases in the vaccinated population; however, the rate of IPD in the elderly remained stable (until the COVID-19 pandemic restrictions were implemented.)

There is no immunological threshold level of antibody concentration that correlates with protection against pneumococcal disease in adults. Opsonophagocytic antibodies are surrogate markers for vaccine efficacy against pneumococcal disease and have been shown to correlate with vaccine-induced protection. Due to the difficulties in conducting an efficacy study with the PCVs, an immunobridging approach is acceptable to consider licensure.

[1] Zens KD, Baroutsou V, Fehr JS and Lang P (2022) Pneumococcal Vaccination Coverage and Uptake Among Adults in Switzerland: A Nationwide Cross-Sectional Study of Vaccination Records. Front. Public Health 9:759602. doi: 10.3389/fpubh.2021.759602

4 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The SwissPAR relating to quality aspects refers to the publicly available assessment report Vaxneuvance - EMA/620380/2021 - 13 December 2021 issued by the EMA.

5 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The nonclinical aspects in this SwissPAR refer to the publicly available assessment report Vaxneuvance - EMA/620380/2021 - 13 December 2021 issued by the EMA.

6 Clinical aspects

Swissmedic has assessed the primary data relating to clinical aspects submitted with this application as at the time of the submission the comparator product in the pivotal study, PCV13 was not approved for the proposed age and the EMA and FDA approved indications were slightly different.

6.1 Clinical pharmacology

No clinical pharmacology studies describing the pharmacokinetic properties or the pharmacodynamic profile of PCV15 were conducted in support of this application. This is acceptable as clinical pharmacology studies are not routinely conducted as part of the evaluation of vaccines and in line with the CHMP “Guideline on Clinical Evaluation of New Vaccines” (EMEA/CHMP/VWP/164653/2005).
The pharmacodynamic profile of PCV15 can be characterised by its immunogenicity profile (see the clinical study results).

6.2 Dose finding and dose recommendation

The proof-of-concept Phase 2 study (V114-002) in adults over 50 years of age was described. However, the formulation has since been changed due to the lower immune responses observed in infants compared to PCV13. Several modifications were made to the manufacturing of a subset of serotypes and final formulation of the drug product. Two new optimised formulations (Formulation A and B) were tested in infants and younger adults (V114-004, V114-005). Formulation B was selected for further development. Two Phase 2 studies (V114-006, V114-007) in adults and a larger Phase 2 study (V114-008) in infants were conducted to further evaluate Formulation B.

The selected dose was administered in the Phase 3 studies conducted subsequently. As no dose-finding studies were provided, there was uncertainty as to whether an adequate dose was chosen. In response to the LoQ, it was explained that the dose was selected based on preclinical dose-ranging animal studies and dose-ranging studies in infants and young adults. This is acceptable.

6.3 Efficacy

No efficacy study was submitted in support of this application. The clinical development programme of Vaxneuvance (V114) was built on comparative immunology, which is acceptable.

Study V114-019 was considered the pivotal study that tested the non-inferiority of the common serotypes (STs) and superiority of the unique STs (and ST3) between V114 and a 13-valent conjugated pneumococcal vaccine (PCV13). All other studies were descriptive and not powered to demonstrate differences in opsonophagocytic activity (OPA) and/or IgG responses across vaccination groups, and thus are considered supportive for the application.

Supportive studies investigated:

- Lot-to-lot consistency and safety and immunogenicity of vaccine-naïve, healthy adults ≥ 50 years (Study V114-020)
- Safety and immunogenicity of PPV23 vaccination 1 year after V114 in healthy adults ≥ 50 years (Study V114-016)
- Safety and immunogenicity of a single dose of V114 and PCV13 in adults ≥ 65 years previously vaccinated with PPV23 (Study V114-007)
- Safety and immunogenicity of V114 when administered concomitantly with influenza vaccine in healthy adults ≥ 50 years (Study V114-021)
- Safety and immunogenicity of adults with risk factors for pneumococcal disease vaccinated with V114 or PCV13 followed by PPV23 six months later (Study V114-017)
- Safety and immunogenicity of adults ≥18 years of age with HIV infection (Study V114-018)

Study V114-019 was a randomised, active-controlled, parallel-group, modified double-blind study of V114 in adults 50 years of age or older conducted in 5 countries (USA, Canada, Japan, Spain, and Taiwan). This study was a modified double-blind study as the study personnel administering the vaccines were unblinded, while the participant and the investigator involved in the assessment remained blinded.

One Protocol Amendment was issued on 13 February 2020, 6 weeks before the study completion date (30 March 2020). It added a secondary objective to demonstrate superiority for serotype 3 based on the OPA geometric mean titres (GMTs) and the proportion of participants with a ≥4-fold rise from pre-vaccination to 30 days post-vaccination. It also revised the statistical criterion for the evaluation of superiority for serotypes 22F and 33F to be >0.1 rather than >0 for the difference in proportions of participants with a ≥4-fold rise from pre-vaccination to 30 days post-vaccination for serotype-specific OPA responses (V114 - PCV13).

Eligible participants were healthy males or females ≥50 years without a history of invasive pneumococcal disease or prior administration of any pneumococcal vaccine. According to the inclusion criteria, any underlying chronic condition(s) had to be stable according to the investigator's judgment. Subjects with a history of IPD or a known history of other culture-positive pneumococcal disease within 3 years of Visit 1 were excluded. Other main exclusion criteria were: impairment of immunological function, receipt of any pneumococcal vaccine or expected to receive any pneumococcal vaccine during the study outside of the protocol, receipt of systemic corticosteroids exceeding physiologic replacement doses within 14 days before vaccination, and receipt of immunosuppressive therapy.

Eligible participants were randomly assigned in a ratio of 1:1 to a single dose of V114 or PCV 13. The vaccines were administered into the muscle.

Randomisation was stratified by participant age (50 to 64 years, 65 to 74 years, and ≥75 years). At least 800 participants ≥ 65 years of age were planned.

A total of 1,205 participants were randomised across 30 study sites, of whom 98% completed the study. Major protocol deviations were reported in 29 participants (2.4%).

Demographic characteristics were comparable for both groups. The median age of participants was 66 years (range: 50 to 92 years), with approximately 69% of participants 65 years of age or older (n=830), and approximately 12% over 75 years of age.

The majority of participants were female (57%), white (68%), and of non-Hispanic or Latino ethnicity (78%).

Baseline characteristics, medical history, prior medication, and concomitant medication were comparable in both groups.

The primary immunogenicity analyses were conducted using the per-protocol (PP) population, which was defined as all randomised participants without protocol deviations that could have substantially impacted the results of the immunogenicity analyses. Supportive immunogenicity analyses were conducted for the primary immunogenicity endpoint using the full analysis set (FAS) population. This approach was acceptable.

Primary immunogenicity endpoints

V114 met non-inferiority criteria for the 13 shared serotypes as assessed by serotype-specific OPA GMTs at 30 days post-vaccination with the lower bound of the 95% CI of the estimated OPA GMT ratio (V114/PCV13) >0.5 for all shared serotypes.

V114 met superiority criteria for the 2 unique serotypes as assessed by serotype-specific OPA GMTs at 30 days post-vaccination with the lower bound of the 95% CI of the estimated OPA GMT ratio (V114/PCV13) >2.0. Superiority criteria for the 2 unique serotypes were also met when assessed by the proportions of participants with a ≥4-fold rise from pre-vaccination to 30 days post-vaccination for serotype-specific OPA responses. Also, the lower bound of the 2-sided 95% CI of the difference in percentages [V114-PCV13] was >10% for both unique serotypes.

Secondary immunogenicity endpoints

V114 met the superiority criterion for serotype 3 as assessed by the OPA GMTs at 30 days post-vaccination with the lower bound of the 95% CI of the OPA GMT ratio (V114/PCV13) >1.2.

The superiority criterion for serotype 3 was also met if assessed by the proportion of participants with a ≥4-fold rise from pre-vaccination to 30 days post-vaccination for OPA responses. The lower bound of the 2-sided 95% CI of the difference in percentages [V114- PCV13] was >0%.

Notably, the superiority criterion lower bound of the 2-sided 95% CI of the OPA GMT ratio [V114/ PCV13] >1.2 for ST3 is a rather low value and not scientifically established. The clinical relevance of the superior immunogenicity for ST3 remains unclear.

Relevant subgroup analysis:

Age

Within the pre-defined age subgroups (50 to 64, 65 to 74, and ≥ 75 years of age) serotype-specific OPA GMT ratios at 30 days post-vaccination were consistent with the ratios observed for the overall population. However, there was a trend towards lower values in older patients (≥ 65 years of age).

Immunogenicity results were also analysed in all participants ≥ 65 years of age. In this analysis, V114 met non-inferiority criteria for the 13 shared serotypes and met superiority criteria for the 2 unique serotypes. The superiority criteria for the 2 unique serotypes were also met based on the proportions of participants with a ≥4-fold rise of serotype-specific OPA responses 30 days post-vaccination. Thus, the findings are consistent with the overall results.

However, OPA GMTs for ST4 and 19A after PCV15 vaccination were numerically lower compared to PCV13.

Table 2 in the information for healthcare professionals presents the serotype-specific OPA GMTs at 30 days post-vaccination for pneumococcal vaccine-naïve subjects over 65 years of age.

V114-020 (PNEU-TRUE) was a Phase 3, multicentre, randomised, double-blind, active comparator-controlled, lot-to-lot consistency study to evaluate the safety, tolerability, and immunogenicity of V114 in healthy pneumococcal vaccine-naïve adults 50 years of age or older.

Eligible participants were randomly assigned in a 3:3:3:1 ratio to 1 of 4 intervention groups (3 different lots of V114 and PCV13.

Randomisation was stratified by participant age at enrolment (50 to 64 years, 65 to 74 years, and ≥75 years). Similarly to Study 019, this was also a modified double-blind study as the study personnel administering the vaccines were unblinded. The inclusion and exclusion criteria were mainly similar to the pivotal study.

A total of 2,340 participants were randomised across 55 study sites. Demographic characteristics were generally comparable for vaccinated participants across intervention groups. The median age of participants was 65.0 years (range: 50 to 92 years). Approximately 55% of participants were ≥65 years of age, and approximately 10% of participants were ≥75 years of age. The majority of participants were female, white, and of non-Hispanic or Latino ethnicity.

The 3 lots of V114 met equivalence criteria, as assessed by the serotype-specific OPA GMTs for the 15 serotypes in V114 at 30 days post-vaccination. For each pairwise lot-to-lot comparison, the lower and upper limits of the 95% CI of the GMT ratios were within the range of 0.5 to 2.0 for all 15 serotypes in V114.

Inter-group comparisons of IgG GMCs at 30 days post-vaccination with V114 (Lot 1, Lot 2, Lot 3) were consistent with the primary analysis of OPA GMTs.

Serotype-specific IgG GMCs at 30 days post-vaccination were comparable in the V114 (combined lots) and PCV13 intervention groups for the 13 shared serotypes, and higher following administration of V114 compared with PCV13 for the 2 serotypes unique to V114.

OPA and IgG antibody responses (geometric mean fold rise (GMFR) and proportions of participants with a ≥4-fold rise from pre-vaccination to 30 days post-vaccination with V114 were generally comparable across the 3 V114 lots for all 15 serotypes in V114.

Based on the ST-specific IgG GMCs and OPA titres at day 30 the combined lots elicited in general a comparable immune response to PCV13. Immune response seemed to be numerically lower for ST1 and 4 (upper limit of the 2 sided CI not including 1) compared to PCV13, and seems to be numerically higher for ST 3, 6B, 18C, 23 F and as expected for the unique STs 22F and 33F.

Study V114- 007 was a randomised, multi-site, double-blind descriptive Phase 2 clinical study comparing the safety, tolerability, and immunogenicity of a single dose of V114 and PCV13 in adults 65 years of age or older in good health who had been vaccinated previously with PPV23 1 year or more before study entry.

A total of 253 subjects were randomised in this study (127 in the V114 group and 126 in the PCV13 group). Randomisation was stratified by age (65 to 74 years of age versus ≥75 years of age) and time since prior PPV23 vaccination (1 to 3 years versus >3 years). None of the 253 randomised and vaccinated subjects discontinued the study.

The demographics and baseline characteristics between the groups were balanced. The median age was 72 years; 30% of the subjects were over 75 years of age.

IgG and OPA responses were generally similar for shared serotypes in subjects administered V114 as compared to PCV13 recipients. Similarly to previous studies, the OPA responses for ST4 and 5 were numerically lower for V114. In case of ST3, 18C a stronger OPA response could be observed for V114 compared to PCV13. In general, higher IgG and OPA antibody responses were observed in the older age group with longer time since PPV23 and primarily in the V114 group.

Study V114-016 was a randomised, multicenter, double-blind descriptive Phase 3 active comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of V114 followed by a PNEUMOVAX™23 one year later in healthy adults 50 years of age or older.

A total of 652 participants were randomized in a 1:1 ratio to receive either V114 or Prevnar 13™ on Day 1 and PPV23 at Month 12. Randomization was stratified by age (50 to 64 years, 65 to 74 years, and 75 years or older. The majority of participants completed the study. Notably, participants could have been considered as having completed the study without receipt of PPV23.

Demographic characteristics were generally comparable for vaccinated participants across intervention groups. The median age of participants was 65 years (range: 50 to 90 years). Approximately 12% of participants were ≥75 years of age.

Serotype-specific OPA GMTs at 30 days following vaccination with PPV23 (Month 13) were comparable between participants administered V114 or PCV13 12 months prior to receipt of PPV23 for all 15 serotypes in V114. IgG GMCs were consistent with the primary analysis of the OPA GMTs. For several STs the OPA GMTs at Month 13 were lower compared to 30 days following PCV vaccination (as in both vaccine groups for 6A, 6B) and similar for most STs.

Study V114-021(PNEU-FLU) was a phase 3, multicentre, randomised, double-blind, placebo-controlled study to evaluate the safety, tolerability, and immunogenicity of V114 when administered concomitantly with influenza vaccine in healthy adults 50 years of age or older.

Subjects with a history of IPD, prior PCV vaccination, prior PPV23 vaccination within 1 year, or with immunosuppressed conditions were excluded.

Participants were randomised in a 1:1 ratio to receive either V114 with concomitant quadrivalent influenza vaccine (QIV) or V114 with non-concomitant QIV. Randomisation was stratified by age (50 to 64 years, 65 to 74 years, and 75 years or older) and by history of prior PNEUMOVAX™23 vaccination.
Of the 1,200 randomised participants, 97.2% completed the study. Demographics and baseline characteristics including medical history/medications were generally comparable across intervention

groups. The median age was 65 years. Overall, 20.9% of participants reported prior administration of PPV23.

Primary immunogenicity analyses were conducted using the per-protocol population, which was assessed as acceptable.

Serotype-specific OPA responses 30 days following vaccination with V114 were non-inferior in the concomitant group compared with the non-concomitant group based on the analysis of GMT ratios (lower limit of 95% CI >0.50) for all STs. Although the pre-specified non-inferiority criteria were fulfilled for all STs, the OPA GMTs in the concomitant group were lower for almost all STs (with the exception of ST19F). The clinical relevance of this observation is not clear.

Strain-specific haemagglutination inhibition (HAI) GMTs at 30 days post-vaccination were non-inferior in the concomitant group compared with the non-concomitant group, as the HAI GMT ratios were above the non-inferiority criteria of the lower limit of 95% CI >0.50.

One of the secondary endpoints also evaluated the proportions of participants with an HAI titre ≥1:40 at 30 days post-vaccination with QIV. The rates of subjects with an HAI titre over 1:40 were similar between the groups.

6.4 Safety

The overall safety database included 7 studies (1 pivotal and 6 supportive). Safety was similarly evaluated in all submitted studies. Post-vaccination safety findings were reported on a Vaccination Report Card (VRC) by the participants for up to 14 days and were reviewed by the study investigator based on protocol-specified criteria and medical judgement. All safety analyses were performed in all randomised participants as treated (vaccination with PCV15 or PCV13 *All participants as treated* (APaT)).

Overall, 7,438 participants ≥18 years received either PCV15 or PVC13. Of these, 5,630 subjects received PCV 15 and 1,808 subjects PCV13. The population was diverse with respect to age, gender, race, ethnicity, and geographic region.

The median age was 62 years (range: 18 to 98 years) with approximately:

- 23% of subjects 18 to 49 years old
- 77% of subjects ≥50 years of age
- 45% of subjects ≥65 years of age
- 9% of subjects ≥75 years of age.

Overall, 54.6% of participants were female. The majority (72.3%) of participants were white. Most of the participants were immunocompetent. Only 302 (4.1%) were considered immunocompromised due to HIV infection (V114-018).

An additional pooled analysis was performed including vaccine-naïve adults over 50 years of age from the pivotal study (V114-019) and two supportive studies: Study V114-020, lot-to-lot consistency and safety and immunogenicity of vaccine-naïve healthy adults ≥ 50 years, and Study V114-016, Safety and immunogenicity of PNEUMOVAX™23 vaccination 1 year after V114 in healthy adults ≥ 50 years.

There was a higher proportion of participants with AEs in the V114 group compared with the PCV13 group, and in particular a higher proportion of participants with injection-site AEs.

The proportion of participants who experienced SAEs was low and comparable in both vaccine groups. None of the SAEs were considered by the investigator to be vaccine-related.

The percentage of deaths was also low and similar in both intervention groups. None of the deaths were considered by the investigator to be vaccine-related.

The most frequently reported (≥5%) AEs in both intervention groups were the solicited events. The 3 most common solicited AEs following V114 vaccination were: injection-site pain, fatigue, and myalgia.

Of the unsolicited AEs after vaccination with V114, injection-site pruritus was the most common (≥1%).

The proportions of participants with solicited AEs were generally comparable across intervention groups, with the exception of injection-site pain, which was reported in a higher proportion of participants in the V114 group (difference >10%). The proportion of participants with solicited AEs by maximum intensity or size and duration was generally comparable across intervention groups.

Safety aspects in special populations

Supportive Study 016 included healthy adults ≥ 50 years. The first vaccination with V114 or PCV 13 was followed by the second vaccination with PPV23 1 year later.

The safety findings following the first vaccination with PCV are part of the integrated safety analysis. The second vaccination with PPV23 was well tolerated. The proportions of participants with AEs (injection-site, systemic, and vaccine-related AEs) were generally comparable between the groups.

A trend towards lower proportions of participants with AEs was observed in older age groups (65 to 74, and ≥75 years of age) compared with the younger age group (50 to 64 years of age).

The proportions of participants who experienced SAEs were low and comparable. None of the SAEs were considered by the investigator to be related to the study vaccine. No participants died during the study.

In Study 021 V114 was administered concomitantly with influenza vaccine in healthy adults 50 years of age or older.

Concomitant and non–concomitant intervention groups had comparable proportions of participants with AEs, injection-site AEs, systemic AEs, and vaccine-related systemic AEs. There was no difference in results if prior PPV23 vaccination was considered. The results were also consistent with findings from other studies in pneumococcal vaccine-naïve adults ≥ 50 years of age.

However, there were more SAEs in the concomitant vaccination group. In particular, more patients developed cardiac disorders: 1.2% vs 0.2% (8 vs. 1 cases), of which 1 was fatal, in the concomitant group. None of the cardiac disorders (congestive heart failure, myocardial infarction, and coronary artery disease) were considered vaccine-related by the investigator.

In supportive Study 007 adults ≥ 65 years previously vaccinated with PPV23 received a single dose of V114 or PCV13

The proportions of participants with AEs, systemic AEs, and vaccine-related systemic AEs were generally comparable in both intervention groups. The proportion of participants with injection-site AEs was higher following vaccination with V114 compared with PCV13. The difference was generally due to higher proportions of participants with solicited injection-site pain and injection-site swelling in the V114 group. These differences were not considered clinically meaningful, as the majority of the AEs were transient and mild in intensity.

No participants in the V114 group experienced an SAE. Also, no participants died during the study. No difference could be observed based on the time since the PPV23 vaccination (within or over 3 years).

6.5 Final clinical benefit-risk assessment

Streptococcus pneumonia, or pneumococcus, causes community-acquired pneumonia, otitis media, sinusitis, and invasive pneumococcal disease (IPD), such as bacteraemia, sepsis, or meningitis.

Pneumococcal infections and IPDs are among the major causes of morbidity and mortality in Europe and globally, despite available antibiotic treatments. The disease burden is highest in infants/toddlers and in the elderly over 65 years of age. Apart from age, other factors such as immune deficiencies (e.g. HIV infection), chronic diseases, smoking, and alcohol abuse increase the risk of pneumococcal disease.

More than 90 *Streptococcus pneumoniae* serotypes are classified based on the polysaccharide capsule. The distribution and prevalence of the serotypes (STs) differ across geographic areas and seasons.

Currently, 2 pneumococcal vaccines are available in Switzerland. A 13-valent conjugated pneumococcal vaccine (PCV13) is approved for infants from 6 weeks to children 5 years of age for the prevention of invasive pneumococcal disease, pneumonia, and otitis media. During the review process a variation for adults ≥ 65 years of age was also approved. The second available vaccine is the polysaccharide vaccine containing 23 STs, which is approved for active immunisation against pneumococcal disease for subjects over 2 years of age with risk factors.

This application concerns a 15-valent PCV including STs 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F. The two subtypes 22F and 33F are the additional STs in comparison to the already authorised PCV13. However, these STs are included in the 23-valent polysaccharide pneumococcal vaccine.

Higher-valency PCVs might provide better coverage of the pneumococcal diseases compared with PCV13; however, the clinical benefit is highly dependent on the local epidemiological situation.

With an annual incidence of approximately 10 cases per 100,000 individuals for IPD alone, pneumococcus remains an important cause of vaccine-preventable infections in Switzerland. The impact of the infant immunisation programme has reduced most of the vaccine-type IPD cases in the vaccinated population. However, the rate of IPD in the elderly remained stable until the COVID-19 pandemic.

The most common STs responsible for IPD are ST8, ST3, ST23B, 22F, and 9N. Between 2013 and 2021 ST22F was responsible for 5-11% of the analysed IPD cases. Between 2020 and 2021 this rate was 7%. ST33F was found in fewer cases: around 2% between 2017 and 2021.

The clinical development of PCV15 is based on the comparable immunogenicity with PCV13. It aims to demonstrate non-inferiority of the immune response to 13 shared serotypes and superiority to 2 unique serotypes. Clinical efficacy against pneumococcal disease in adults ≥ 65 years can be extrapolated from the CAPiTA study conducted with PCV13 ("PCV13 was effective in preventing vaccine-type pneumococcal, bacteremic, and nonbacteremic community-acquired pneumonia and vaccine-type invasive pneumococcal disease but not in preventing community-acquired pneumonia from any cause."[2])

The proposed indication was "*for active immunisation for the prevention of invasive disease and pneumonia caused by Streptococcus pneumoniae in adults 18 years of age and older".* The applicant requested a marketing authorisation in accordance with Art. 13 TPA, with the EMA as the reference authority. At the time of submission, the comparator product PCV13, was not approved for the proposed age indication in Switzerland, and the indications approved by EMA and FDA differ slightly. For these reasons, a full clinical review took place.

Pivotal Study 019 enrolled healthy pneumococcal vaccine-naïve adults 50 years of age and older with stable underlying conditions who did not have history of IPD and were not immunosuppressed.

The study met its primary endpoints. It demonstrated non-inferiority for the common STs and superiority for the 2 unique STs based on the OPA GMT ratios at Day 30 post-vaccination. The non-inferiority margin was not justified (the lower limit of the 95% CI for the GMT ratio >0.5). However, it is commonly used in vaccine studies for regulatory approval and thus can be accepted.

Notably, 7 of the common STs (1, 4, 5,7F, 9V, 14, 19A, 19F) in PCV15 elicited numerically lower OPA GMTs compared to PCV13. On the other hand, the immune response to ST3 was higher. Although ST3 is one of the most common causes of breakthrough infection after PCV 13 vaccination, the clinical relevance of the higher OPA GMTs is not known.

Study 019 also provided evidence in participants 65 years of age and older. PCV15 met non-inferiority criteria for the 13 shared serotypes and met superiority criteria for the 2 serotypes unique to PCV15,

[2] Bonten et al N Engl J Med 2015; 372:1114-1125

as assessed by serotype-specific OPA GMT ratios at 30 days post-vaccination, consistent with results observed in the overall population. This analysis was pre-specified in the country-specific study amendment for Japan as requested by the Pharmaceuticals and Medicinal Devices Agency (PMDA).

Supportive Study 020 evaluated lot consistency and immunogenicity (ST specific OPA GMTs and IgG geometric mean concentration (GMCs)) of the 3 combined lots for PCV15 and PCV 13 in healthy pneumococcal vaccine-naïve adults 50 years of age or older. The study was descriptive, thus no strong conclusion on the comparability can be drawn.

Study 016 showed a similar immune response in adults ≥ 50 years who were vaccinated with PPV23 1 year after the initial vaccination with PCV15 or PCV13.

Another descriptive study (007) reported the immune response after previous vaccination with PPV23 in healthy adults ≥ 65 years.

In Study 021 the co-administration of a quadrivalent split, inactivated influenza vaccine with PCV15 in adults over 50 years of age induced similar immunogenicity compared to non-concomitant vaccination.

Study 017 showed a similar immune response in adults 18 to 49 years of age with risk factors for pneumococcal disease vaccinated with PCV15 and PCV13 followed by PPV3 6 months later.

Study 018 assessed the immunogenicity of PCV15 in pneumococcal vaccine-naïve adults ≥18 years of age with HIV infection (CD4+ T-cell count ≥50 cells/µL).

Pivotal Study 019 in pneumococcal-naïve healthy adults ≥ 50 years is the only study that tested the non-inferiority for the common STs and superiority of the unique STs between V114 and PCV 13. All other studies were descriptive, and were not powered to investigate non-inferiority or superiority. Comparable immunogenicity was therefore only demonstrated for adults ≥ 50 years.

The superiority analysis of ST3 as a secondary endpoint was added to the protocol late in the study, just 6 weeks before study completion. Furthermore, the superiority margin was low and not established in medical science (the lower limit of the 2-sided 95% CI of the OPA GMT ratio > 1.2). The applicant explained that the superiority analysis of ST3 including chosen margin was added at the request of the FDA. Taking the FDA request into consideration, inclusion of the superiority results in the information for healthcare professionals was accepted, provided the exact margins are described.

Although the above-detailed non-inferiority and superiority were met in the pre-specified sub-group analysis in elderly subjects ≥ 65 years, there was a trend towards numerically lower serotype-specific OPA GMTs in older subjects (65 to 74 and ≥75 years of age) compared with the younger age group (50 to 64 years of age). The clinical implication of these findings is unknown.

Overall, the immunogenicity data without an established correlate of protection are not sufficient to allow a conclusion on the protective clinical effect. Clinical efficacy can only be extrapolated for adults ≥ 65 years based on the results of the CAPiTA study, showing less VT IPD and VT after vaccination with PCV13. As no clinical efficacy data are available for adults < 65 years, further justification was requested to support indication below 65 years of age. The responses have not provided relevant additional data confirming efficacy in these subjects, thus the indication has been restricted to adults ≥ 65 years.

Further limitations of the clinical development include a lack of data on the immune response in subjects with non-stable medical conditions, immunosuppression, or immunodeficiency other than HIV.

Several supportive studies provide descriptive results on the immune response in different age groups, special populations, with sequential administration of PPV23, and with co-administration of influenza vaccine. These descriptive data suggest that PCV15 may induce a weaker immune response for ST4 compared to PCV13.

Immune persistence data are limited to 1 study (Study 016). In this study OPA GMTs and IgG GMCs were lower 12 months post-vaccination compared to 30 days post-vaccination, but higher than at baseline and similar for PCV13 and PCV15 vaccines. There is a lack of longer-term immune persistence results.

The effect of co-administration was only evaluated for influenza vaccine (QIV). Although non-inferior immunogenicity was shown, the OPA GMTs and IgG GMCs were lower for several STs in the co-vaccination group, which must be mentioned in the information for healthcare professionals.

A total of 5,630 subjects received PCV 15 in the submitted studies. PCV15 consistently induced a higher rate of solicited AEs, including injection-site and systemic reactions, compared to PCV13.

Reactogenicity decreased with age, as is usually seen with other vaccines. Importantly, the proportion of participants, who experienced SAEs was low and comparable in both vaccine groups. None of the SAEs were considered by the investigator to be vaccine-related. There were few deaths in either vaccine group; none were considered by the investigator to be vaccine-related.

The safety profile was consistent in special populations investigated in the supportive studies (HIV-infected subjects, subjects 18-49 years of age, and subjects previously vaccinated with PPV23).

Safety following subsequent PPV23 vaccination after a PCV15 dose (8 weeks in HIV-positive subjects, 6 months in subjects 18-49 years old, and 1 year later in healthy adults 50 years of age or older) was comparable to the safety observed for PCV13.

Safety was not assessed in elderly subjects with risk factors, in subjects with unstable underlying medical conditions, or in subjects with immunosuppression/severe immunodeficiency other than HIV.

In addition, very limited safety data were available for pregnant women, and no safety data were available for breastfeeding women.

The data submitted demonstrated that PCV15 is immunogenic in the elderly population with stable underlying disease. The non-inferior immunogenicity compared to PCV13 is considered proven for adults over 50 years of age. Thus, the clinical efficacy of PCV13 which is established for adults over 65 years of age can also be expected with PCV15 for the same age group. However, no conclusion on the additional STs (22F and 33F) can be drawn regarding clinical benefit. In addition, in the lack of efficacy data for the younger adults below 65 years of age no firm conclusion can be drawn regarding the clinical benefit of Vaxneuvance in adults 50-65 years of age. For adults **below** 50 years of age no statistically confirmed comparability to PCV13 could be demonstrated as the studies were descriptive, not designed to test hypothesis. Furthermore, clinically proven efficacy/effectiveness data for this age group were not available. In the lack of an identified correlate of protection for pneumococcal disease in adults, the immunogenicity data do not directly support a clinical benefit.

The safety profile of PCV15 is acceptable, although the vaccine is more reactogenic compared to PCV13.

In conclusion, the data only result in a positive benefit-risk assessment for adults ≥ 65 years.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Vaxneuvance was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

VAXNEUVANCE®

Composition

Active substances

Pneumococcal polysaccharide conjugate vaccine (15-valent, adsorbed)

Excipients

Sodium chloride (NaCl, 1.77 mg sodium), L-histidine, Polysorbate 20, water for injections, aluminum phosphate adjuvant and CRM_{197} carrier protein.

Pharmaceutical form and active substance quantity per unit

Suspension for injection in pre-filled syringe.
The vaccine is an opalescent suspension.
1 dose (0.5 mL) contains:

Pneumococcal polysaccharide serotype 1[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 3[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 4[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 5[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 6A[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 6B[1,2]	4.0 micrograms
Pneumococcal polysaccharide serotype 7F[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 9V[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 14[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 18C[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 19A[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 19F[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 22F[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 23F[1,2]	2.0 micrograms
Pneumococcal polysaccharide serotype 33F[1,2]	2.0 micrograms

[1]Conjugated to CRM_{197} carrier protein. CRM_{197} is a nontoxic mutant of diphtheria toxin (originating from *Corynebacterium diphtheriae* C7) expressed recombinantly in *Pseudomonas fluorescens*.
[2]Adsorbed on aluminium phosphate adjuvant.
1 dose (0.5 mL) contains 125 micrograms aluminium (Al^{3+}) and approximately 30 micrograms CRM_{197} carrier protein.

Indications/Uses

Vaxneuvance is indicated for active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in individuals 65 years of age and older.
Vaxneuvance does not protect against diseases caused by *S. pneumoniae* serotypes that are not included in the vaccine.
See «Warnings and precautions» and «Properties/Effects» for information on protection against specific pneumococcal serotypes.
The use of Vaxneuvance should be based on official recommendations and consider the risk of invasive diseases and pneumonia in the different age groups, underlying conditions as well as epidemiologic variability of the serotypes in the different geographic areas.

Dosage/Administration

Posology

Individuals 65 years of age and older

1 dose (0.5 mL).
The need for revaccination with a subsequent dose of Vaxneuvance has not been established.
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Children and adolescents

The safety and efficacy in children and adolescents less than 18 years of age have not been demonstrated.

Mode of administration

The vaccine should be administered by intramuscular injection. The preferred site is the deltoid muscle of the upper arm.
No data are available for administration via the subcutaneous or intradermal routes.
For instructions on the handling of the vaccine before administration, see «Other information, *Instructions for handling*».

Contraindications

Hypersensitivity to the active substances, to any of the excipients listed in section «Composition» or to any diphtheria toxoid-containing vaccine.

Warnings and precautions

Precaution related to route of administration

Vaxneuvance must not be administered intravascularly.

Anaphylaxis

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders

As with other intramuscular injections, the vaccine should be given with caution to individuals receiving anticoagulant therapy, or to those with thrombocytopenia or any coagulation disorder such as haemophilia. Bleeding or bruising may occur following an intramuscular administration in these individuals.

Immunocompromised individuals

Immunocompromised individuals, whether due to the use of immuno-suppressive therapy, a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunisation.

Protection

As with any vaccine, vaccination with Vaxneuvance may not protect all vaccine recipients. Vaxneuvance will only protect against Streptococcus pneumoniae serotypes included in the vaccine (see «Composition» and «Properties/Effects»).

Sodium

This medicinal product contains less than 1 mmol sodium (23 milligrams) per dose, i.e. essentially ‘sodium-free’.

Interactions

In a study in adults 50 years and older the concomitant administration of Vaxneuvance with quadrivalent inactivated influenza vaccine (split vaccine, inactivated, (QIV)) was investigated. Immune responses to all 4 QIV strains were non-inferior when Vaxneuvance and QIV were administered concomitantly compared to QIV alone (see “Properties/Effects”).
There are no data on the concomitant administration of Vaxneuvance with other vaccines.
Different injectable vaccines should always be administered at different injection sites.
Immunosuppressive therapies may reduce the immune responses to vaccines.

Pregnancy, lactation

Pregnancy

There is limited experience with the use of Vaxneuvance in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see «Preclinical data»).
Administration of Vaxneuvance in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and the foetus.

Lactation

It is unknown whether Vaxneuvance is excreted in human milk.

Fertility

No human data on the effect of Vaxneuvance on fertility are available. Animal studies in female rats do not indicate harmful effects (see «Preclinical data»).

Effects on ability to drive and use machines

Vaxneuvance has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under «Undesirable effects» may temporarily affect the ability to drive or use machines.

Undesirable effects

Summary of the safety profile

The safety of Vaxneuvance was assessed in 6 clinical studies in 5,708 adults ≥ 50 years of age. Vaxneuvance was administered to 4,389 adults; 1,911 were 50 to 64 years of age, and 2,478 were 65 years of age and older.
The safety of Vaxneuvance in pneumococcal vaccine-naïve adults 50 years of age and older (3,032 of whom received Vaxneuvance), including a subgroup of adults 65 years of age and older (1,750 of whom received Vaxneuvance), was assessed based on data from a pool of 3 studies. The safety of Vaxneuvance in adults 65 years of age and older with prior pneumococcal vaccination (127 of whom received Vaxneuvance) was assessed based on data from a separate study.
The most frequently reported adverse reactions following vaccination with Vaxneuvance were solicited. In the pooled analysis of the 3 studies in pneumococcal vaccine-naïve adults 50 years of age and older, the most frequent adverse reactions were injection-site pain (63.3%), fatigue (20.2%), myalgia (19.5%), headache (14.5%), injection-site swelling (14.5%), injection-site erythema (11.1%) and arthralgia (6.3%). The majority of solicited adverse reactions were mild (based on intensity or size) and of short duration (≤ 3 days); severe reactions (defined as an event that prevents normal daily activity or size > 10 cm) occurred in ≤ 0.5% of older adults.
The safety profile of Vaxneuvance in adults 65 years of age and older with or without prior pneumococcal vaccination is generally consistent with the safety profile in vaccine-naïve adults 50 years of age and older.

List of adverse reactions

Local and systemic adverse reactions were solicited daily after vaccination for 5 and 14 days, respectively. Unsolicited adverse reactions were reported for 14 days after vaccination. The duration of the safety follow-up period for serious adverse events postvaccination with Vaxneuvance was 6 months in the pool of 3 studies and 1 month in the study that evaluated adults 65 years of age and older with prior pneumococcal vaccination. The table presented below is based on the pooled analysis of 3 studies in pneumococcal vaccine-naive adults 50 years of age and older.

Frequencies are reported as:

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), Very rare (<1/10,000), Not known (cannot be estimated from the available data).

Table 1: Tabulated list of adverse reactions

System Organ Class	Frequency	Adverse Reactions
Immune system disorders	Rare	Hypersensitivity reaction including tongue oedema, flushing, and throat tightness
Nervous system disorders	Very Common	Headache (14.5%)
	Uncommon	Dizziness
Skin and subcutaneous tissue disorders	Uncommon	Rash
Gastrointestinal disorders	Uncommon	Nausea Vomiting
Musculoskeletal and connective tissue disorders	Very Common	Myalgia (19.5%)
	Common	Arthralgia(6.3%)
General disorders and administration site conditions	Very Common	Injection-site pain (63.3%) Fatigue (20.2%) Injection-site swelling (14.5%) Injection-site erythema (11.1%)
	Common	Injection-site pruritus
	Uncommon	Pyrexia Injection-site warmth Injection-site bruising/haematoma Chills

Safety in adults 65 years of age and older

Pneumococcal vaccine-naïve adults 65 years of age and older have consistent frequencies of adverse reactions, except that rash was rare and hypersensitivity reaction including tongue oedema, flushing, and throat tightness was not reported.

Adults 65 years of age and older with prior pneumococcal vaccination have consistent frequencies of adverse reactions, except that dizziness, injection-site erythema and injection-site warmth were common and injection-site pruritus was uncommon. Rash, nausea, vomiting and hypersensitivity reaction including tongue oedema, flushing, and throat tightness were not reported.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There are no data with regard to overdose.

Properties/Effects

ATC code

J07AL02

Mechanism of action

Vaxneuvance contains 15 purified pneumococcal capsular polysaccharides from *Streptococcus pneumoniae* (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F), each conjugated to a carrier protein (CRM_{197}). Vaxneuvance elicits a T-cell dependent immune response to induce antibodies that enhance opsonisation, phagocytosis, and killing of pneumococci to protect against pneumococcal disease.

Pharmacodynamics

Not applicable.

Clinical efficacy

No efficacy studies have been conducted with Vaxneuvance.
The protective efficacy of Vaxneuvance in adults over 65 years of age is based on efficacy demonstrated in the Community-Acquired Pneumonia Immunization Trial in Adults, CAPiTA with 13-valent pneumococcal polysaccharide conjugate vaccine (see “Pneumococcal vaccine naive adults”).
Immunogenicity in immunocompetent adults 65 years of age and older
Immune responses following natural exposure to *Streptococcus pneumoniae* or following pneumococcal vaccination can be determined by measuring opsonophagocytic activity (OPA) and immunoglobulin G (IgG) responses. OPA represents functional antibodies capable of opsonizing pneumococcal capsular polysaccharides for presentation to phagocytic cells for engulfment and subsequent killing. The OPA titre that correlates with protection from pneumococcal diseases is not yet clearly defined in adults. OPA titres are expressed as the reciprocal of the highest serum dilution that reduces the survival of the pneumococci by at least 50%. A validated multiplex opsonophagocytic assay (MOPA) was used to measure serotype-specific OPA titres for each of the 15 serotypes in Vaxneuvance.
Four clinical studies (Protocol 007, Protocol 016, Protocol 019, and Protocol 021) conducted in the Americas, Europe and Asia Pacific evaluated the immunogenicity of Vaxneuvance in healthy and immunocompetent adults across different age groups including individuals with or without previous

pneumococcal vaccination. Each clinical study included adults with stable underlying medical conditions (e.g., diabetes mellitus, renal disorders, chronic heart disease, chronic liver disease, chronic lung disease including asthma) and/or behavioural risk factors (e.g., current tobacco use, increased alcohol consumption) that are known to increase the risk of pneumococcal disease.

In each study, immunogenicity was assessed by serotype-specific OPA and IgG responses at 30 days postvaccination. Study endpoints included OPA geometric mean titres (GMTs) and IgG geometric mean concentrations (GMCs).

Pneumococcal vaccine-naïve adults

In the pivotal, double-blind, active comparator-controlled study (Protocol 019), 1,205 immunocompetent pneumococcal vaccine-naïve participants ≥ 50 years of age were randomised to receive Vaxneuvance or the 13-valent pneumococcal polysaccharide conjugate vaccine (13-valent PCV). The median age of participants ≥ 50 years of age was 66 years (range: 50 to 92 years), with approximately 69% over 65 years of age, and approximately 12% over 75 years of age. 57.3% were female and 87% reported history of at least one underlying medical condition.

The study demonstrated that Vaxneuvance is noninferior to the 13-valent PCV for the 13 shared serotypes (the lower bound of the 95% CI for the estimated GMT ratio (Vaxneuvance/13-valent PCV) being > 0.5) and superior for the 2 additional serotypes (lower bound of the 95% CI for the estimated GMT ratio (Vaxneuvance/13-valent PCV) being > 2.0). Similarly, Vaxneuvance is superior to the 13-valent PCV for the shared serotype 3 (the lower bound of the 95% CI for the estimated GMT ratio (Vaxneuvance/13-valent PCV) being > 1.2).

Within this study, 830 participants were ≥ 65 years of age. The median age of participants in this subgroup was 69 years (range: 65 to 92 years) and 55.9% were female. The racial distribution was as follows: 61.0% were White, 34.1% were Asian, 4.3% were Black or African American, 0.5% were Multiracial and 0.1% were Native Hawaiian or Other Pacific Islander. In these participants, Vaxneuvance is noninferior to the 13-valent PCV for the 13 shared serotypes and superior for the 2 additional serotypes (Table 2).

Table 2: Serotype-specific OPA GMTs at 30 days Postvaccination in Pneumococcal Vaccine-Naïve Adults ≥ 65 Years of age (Protocol 019)[#]

Pneumococcal Serotype	**Vaxneuvance (N = 416)**		**13-valent PCV (N =414)**		**GMT Ratio* (Vaxneuvance/13-valent PCV) (95% CI)***
	n	**GMT***	**n**	**GMT***	
13 Shared Serotypes[†]					
1	412	228.7	412	270.8	0.84 (0.67, 1.07)
3	412	221.8	412	129.2	1.72 (1.44, 2.05)
4	412	1076.3	412	1453.5	0.74 (0.60, 0.91)
5	412	414.5	412	483.2	0.86 (0.67, 1.10)

6A	410	4808.4	412	4615.0	1.04 (0.84, 1.30)
6B	412	3590.2	412	2745.2	1.31 (1.04, 1.65)
7F	412	4232.8	412	5269.0	0.80 (0.68, 0.95)
9V	412	1681.7	411	1937.8	0.87 (0.73, 1.04)
14	412	1804.5	412	2086.5	0.86 (0.71, 1.06)
18C	412	2519.1	412	2379.7	1.06 (0.87, 1.29)
19A	412	2957.1	412	3681.1	0.80 (0.67, 0.96)
19F	412	1584.1	412	1763.5	0.90 (0.75, 1.08)
23F	412	1956.0	412	1476.5	1.32 (1.04, 1.69)
2 additional serotypes in Vaxneuvance[§]					
22F	408	2319.9	405	65.3	35.52 (27.05, 46.64)
33F	412	7453.0	411	1016.8	7.33 (6.02, 8.93)

[#]Based on a subgroup analysis in adults ≥65 years of age.

*GMTs, GMT ratio, and 95% CI are estimated from a cLDA model.

[†]A conclusion of non-inferiority for the 13 shared serotypes is based on the lower bound of the 95% CI for the estimated GMT ratio (Vaxneuvance/13-valent PCV) being > 0.5.

[§]A conclusion of superiority for the 2 additional serotypes is based on the lower bound of the 95% CI for the estimated GMT ratio (Vaxneuvance/13-valent PCV) being > 2.0.N=Number of participants randomised and vaccinated; n=Number of participants contributing to the analysis. CI=confidence interval; cLDA=constrained longitudinal data analysis; GMT=geometric mean titre (1/dil); OPA=opsonophagocytic activity; PCV=pneumococcal conjugate vaccine.

Sequential administration of pneumococcal vaccines in adults

In a double-blind, active comparator-controlled study (Protocol 016), 652 pneumococcal vaccine-naïve participants ≥ 50 years of age were randomised to receive Vaxneuvance or the 13-valent pneumococcal polysaccharide conjugate vaccine, followed by PPV23 one year later. Of these, 326 participants were ≥ 65 years of age.

Following vaccination with PPV23, OPA GMTs and IgG GMCs were comparable between the two vaccination groups for all 15 serotypes in Vaxneuvance.

Immune responses elicited by Vaxneuvance persisted up to 12 months postvaccination as assessed by OPA GMTs and IgG GMCs. Serotype-specific OPA GMTs declined over time, as they were lower at Month 12 than Day 30, but remained above baseline levels for all the serotypes contained in either Vaxneuvance or the 13-valent pneumococcal polysaccharide conjugate vaccine. OPA GMTs and IgG GMCs were generally comparable between the intervention groups at Month 12 for the 13 shared serotypes and higher for the 2 unique serotypes among recipients of Vaxneuvance.

Adults with prior pneumococcal vaccination

In a double-blind, descriptive study (Protocol 007), 253 participants ≥ 65 years of age who were previously vaccinated with PPV23 at least one year prior to study entry were randomised to receive Vaxneuvance or the 13-valent pneumococcal polysaccharide conjugate vaccine.
IgG GMCs and OPA GMTs were generally comparable between the two vaccination groups for the 13 shared serotypes and higher in the Vaxneuvance group for the 2 unique serotypes.
In a clinical study, in which another PCV was administered ≤ 1 year after PPV23, reduced immune responses were observed for the common serotypes compared to immune responses observed when PCV was given either alone or before PPV23. The clinical significance of this is unknown.
Concomitant administration with inactivated influenza vaccine
In a double-blind, randomized study (Protocol 021), 1,200 adults 50 years of age and older, with or without a history of prior PPV23 vaccination, were randomized to receive Vaxneuvance concomitantly or nonconcomitantly with quadrivalent inactivated influenza vaccine (split vaccine, inactivated (QIV)). One vaccination group received Vaxneuvance and QIV concomitantly, followed by placebo 30 days later. A second vaccination group received QIV and placebo concomitantly, followed by Vaxneuvance 30 days later.
Vaxneuvance administered concomitantly with QIV is non-inferior to Vaxneuvance administered nonconcomitantly with QIV (based on a 2-fold non-inferiority margin), as assessed by pneumococcal OPA GMTs at 30 days postvaccination with Vaxneuvance for all 15 serotypes contained in the vaccine. OPA GMTs were slightly lower for some serotypes when Vaxneuvance was administered concomitantly with QIV compared to Vaxneuvance administered alone. QIV administered concomitantly with Vaxneuvance is non-inferior to QIV administered nonconcomitantly (based on a 2-fold non-inferiority margin) as assessed by influenza strain-specific hemagglutination inhibition (HAI) GMTs at 30 days postvaccination with QIV for all 4 influenza strains.

Pharmacokinetics

Absorption

Not applicable.

Distribution

Not applicable.

Metabolism

Not applicable.

Elimination

Not applicable.

Preclinical data

Non-clinical study data revealed no hazard for humans based on conventional studies of repeated dose toxicity and toxicity to reproduction and development.
Vaxneuvance administered to female rats had no effects on mating performance, fertility, embryonic/foetal development, or development of the offspring.
Vaxneuvance administered to pregnant female rats resulted in detectable antibodies to all 15 serotypes in offspring. This was attributable to the acquisition of maternal antibodies via placental transfer during gestation and possibly via lactation.

Other information

Incompatibilities

In the absence of compatibility studies, this vaccine must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.
Vaxneuvance should be administered as soon as possible after being removed from the refrigerator.
In the event of temporary temperature excursions, stability data indicate that Vaxneuvance is stable at temperatures up to 25 °C for 48 hours.
Keep out of the reach of children.

Instructions for handling

- The vaccine should be used as supplied.
- Immediately prior to use, hold the pre-filled syringe horizontally and shake vigorously to obtain an opalescent suspension. Do not use the vaccine if it cannot be resuspended.
- Inspect the suspension visually for particulate matter and discolouration prior to administration. Discard the vaccine if particulates are present and/or if it appears discoloured.
- Attach a needle with Luer lock connection by twisting in a clockwise direction until the needle fits securely on the syringe.
- Inject immediately using the intramuscular (IM) route, preferably in the deltoid area of the upper arm.
- Exercise care to avoid harm from an accidental needle stick.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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Packs

Pack sizes of 1 or 10 pre-filled syringes in carton box with 2 separate needles.
0.5 mL suspension in pre-filled syringe (Type I glass) with a plunger stopper (latex-free bromobutyl rubber) and a tip cap (latex-free styrene-butadiene rubber). [B]

Marketing authorisation holder

MSD Merck Sharp & Dohme AG
Lucerne

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