swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Vaxneuvance
Extension of therapeutic indication

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: extension of therapeutic indication approved on 9 January 2024

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 (Prevenar 13)
PCV15	15-valent conjugated pneumococcal vaccine
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PPS	Post-primary series
PPV	Pneumococcal polysaccharide vaccine
PPV23	PNEUMOVAX™23 (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)
PTD	Post-toddler dose
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)
V114	Vaxneuvance
VT	Vaccine serotype

2 Background information on the procedure

2.1 Applicant's request(s)

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

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, pneumonia, and acute otitis media caused by *Streptococcus pneumoniae* in infants, children, and adolescents from 6 weeks to less than 18 years of age.

2.2.2 Approved indication

Vaxneuvance is indicated for active immunisation for the prevention of invasive disease, pneumonia, and acute otitis media caused by *Streptococcus pneumoniae* in infants and children from 6 weeks to 5 years of age.

2.2.3 Requested dosage

Summary of the requested standard dosage for the extension of indication:
Routine vaccination schedule in infants and children aged 6 weeks to less than 2 years:

Infants and children who have begun immunisation with another pneumococcal conjugate vaccine may switch to Vaxneuvance at any point in the schedule (see section "Properties/effects").

Two-dose primary series followed by a booster dose
The recommended immunisation regimen consists of 3 doses of Vaxneuvance, each of 0.5 mL. The first dose is given as early as 6 to 12 weeks of age, with a second dose administered 8 weeks later. The third (booster) dose is recommended between 11 and 15 months of age.

Three-dose primary series followed by a booster dose
An immunisation regimen consisting of 4 doses of Vaxneuvance, each of 0.5 mL, may be given. This primary series consists of 3 doses, with the first dose given as early as 6 to 12 weeks of age, with an interval of 4 to 8 weeks between doses in the primary series. The fourth (booster) dose is recommended between 11 and 15 months of age and at least 2 months after the third dose.

Preterm infants (<37 weeks gestation at birth)
The recommended immunisation regimen consists of a 3-dose primary series of Vaxneuvance followed by a fourth (booster) dose, each of 0.5 mL, as per the 3-dose primary series followed by a booster dose posology (see sections "Warnings and precautions" and "Properties/effects").

Catch-up vaccination schedule for children 7 months to less than 18 years of age

Unvaccinated infants 7 to less than 12 months of age:
3 doses, each of 0.5 mL, with the first two doses given at least 4 weeks apart. A third (booster) dose is recommended after 12 months of age, separated from the second dose by at least 2 months.

Unvaccinated children 12 months to less than 2 years of age:
2 doses, each of 0.5 mL, with an interval of 2 months between doses.

Unvaccinated or not fully vaccinated children and adolescents 2 to less than 18 years of age:
1 dose (0.5 mL).
If a previous pneumococcal conjugate vaccine was administered, at least 2 months should elapse before administering Vaxneuvance.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	20 February 2023
Formal objection	27 March 2023
List of Questions (LoQ)	12 July 2023
Response to LoQ	8 August 2023
Preliminary decision	25 October 2023
Response to preliminary decision	23 November 2023
Final decision	9 January 2024
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/836730/2022 - 15 September 2022, 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.

Rates of IPD are highest in children under 2(-5) years of age, adults over 65 years of age, and (especially) in 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.

Prevention of pneumococcal disease includes vaccination with pneumococcal conjugate vaccines (PCVs) and pneumococcal polysaccharide vaccines (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 some vaccine-type pneumococci in children.
There are three pneumococcal vaccines available in Switzerland: a polysaccharide vaccine containing capsular polysaccharides from 23 serotypes, and a 13-valent and 15-valent conjugated vaccine.

In Switzerland, the Federal Commission for Vaccination recommends pneumococcal vaccination for children under 5 years 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).

[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 Nonclinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable by Swissmedic.

5 Clinical aspects

5.1 Clinical pharmacology

No clinical pharmacology studies describing the pharmacokinetic properties or the pharmacodynamic profile of Vaxneuvance (V114) were conducted in support of this application.
The pharmacodynamic profile of PCV15 can be characterised by its immunogenicity profile (see clinical study results).
This is acceptable as clinical pharmacology studies are not routinely conducted as part of the evaluation of vaccines, and is in line with the CHMP “Guideline on Clinical Evaluation of New Vaccines” (EMEA/CHMP/VWP/164653/2005).

5.2 Dose finding and dose recommendation

No dose-finding studies were included in this submission. The same dose as approved for adults over 65 years of age was chosen for the subsequently conducted Phase 3 studies in children.

5.3 Efficacy

Overall, no efficacy or effectiveness data were provided for V114 in infants and children in this application. The clinical development programme of V114 was built on comparative immunology compared to PCV13, which is acceptable. 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 children from 6 weeks to 5 years of age can be extrapolated from available efficacy data in this age group. A surrogate of protection, IgG of 0.35 µg/mL, has been established for IPD in children, which can be used to infer protection against IPD.

The pivotal study V114-025 evaluated the non-inferiority of V114 against PCV13 when given in a 2+1 dosing regimen in infants from 6 to 12 weeks of age (and in a 3+1 regimen in preterm infants). All participants were also administered concomitant paediatric vaccines during the study. Overall, 1,184 participants were randomised to receive V114 or PCV13. V114 or PCV13 was administered to full-term participants at approximately 2, 4, and 11 to 15 months of age and to preterm infants at approximately 2, 3, 4, and 11 to 15 months of age.
The conclusion of non-inferiority for the 13 shared serotypes was based on the lower bound of the 95% confidence interval (CI) being > -10 percentage points for the difference in IgG response rates (V114 - PCV13) or > 0.5 for the IgG geometric mean concentration (GMC) ratio (V114/PCV13). A conclusion of superiority for the 2 additional serotypes was based on the lower bound of the 95% CI being > 10 percentage points for the difference in IgG response rates (V114 - PCV13) or > 2.0 for the IgG GMC ratio (V114/PCV13).
The primary immunogenicity objectives were met as non-inferiority to PCV13 for the 13 shared serotypes and superiority for the 2 unique serotypes in V114 were shown at 30 days post-toddler dose (PTD) both for IgG response rates and IgG GMCs. At 30 days PTD the vast majority of participants achieved the surrogate of protection of ≥0.35 µg/mL and percentages were comparable between both groups.
A lower immune reaction was observed after the 2+1-dose primary series compared to the 3+1-dose primary series.
For a tabular presentation of the immunogenicity data please refer to Table 3 and Table 4 of the information for healthcare professionals.

The pivotal study V114-029 evaluated the non-inferiority of V114 against PCV13 when given in a 3+1 dosing regimen in infants from 6 to 12 weeks of age. Participants received either V114 or PCV13 at approximately 2, 4, 6, and 12 to 15 months of age. All participants were also administered concomitant paediatric vaccines during the study. Overall, 1,720 participants were randomised to receive V114 or PCV13.
A conclusion of non-inferiority for the 13 shared serotypes was based on the lower bound of the 95% CI being > -10 percentage points for the difference in IgG response rates (V114 - PCV13) or > 0.5 for the IgG GMC ratio (V114/PCV13).
At 30 days post-primary series (PPS) (dose 3), non-inferiority to PCV13 was shown based on IgG response rate for all serotypes and for 14 out of 15 serotypes (excluding serotype 6A) based on IgG GMCs. At 30 days PPS, the vast majority of participants achieved the surrogate of protection of ≥0.35 µg/mL and percentages were comparable between both groups. At 30 days PTD (dose 4), all serotypes were non-inferior to PCV13 based on IgG GMCs.
The serotype-specific immune responses are presented in Table 5 and Table 6 of the information for healthcare professionals.

The immune response to the concomitantly administered routine childhood vaccines was comparable between the V114 and PCV13 groups in both pivotal studies. All responses for the concomitant vaccines showed a difference of within 5 percentage points between the treatment arms.

Study V114-027 investigated the interchangeability of both PCV13 and V114 in infants approximately 2 months of age. The study investigated the immune response after switching from PCV13 to V114 at different time points during the 3 + 1 regimen. IgG GMCs were comparable overall for the 13 shared serotypes between the groups which switched to V114. Response rates for the shared serotypes remained high in all groups.

Study V114-024 assessed the immunogenicity of catch-up vaccination with V114 in children aged 7 to 11 months, 12 to 23 months, and 2 to 17 years of age. The three catch-up vaccination schedules evaluated were 3 doses for children aged 7 to 11 months, 2 doses for children 12 to 23 months of age, and 1 dose for children 2 to 17 years of age. Overall, the data suggest that the catch-up schedules induce an immune response that is substantial and sufficient to ensure protection against IPD, as the proportion of subjects achieving IgG antibody levels of ≥0.35 µg/ml after vaccination with V114 was high (83.9% to 100%) for all serotypes and for all 3 age groups. This was comparable to the response rate seen in the PCV13 groups.

Study V114-031 was designed to evaluate the safety and tolerability of V114 administered at approximately 2, 4, 6, and 12 to 15 months of age compared with PCV13 in healthy infants and to evaluate the immunogenicity of V114 compared with PCV13 in preterm infants (as an immunogenicity substudy). This study enrolled 99 preterm infants, who received 4 doses of either V114 or PCV13. V114 elicited serotype-specific IgG responses in preterm infants that were generally comparable to Prevenar 13 for the 13 shared serotypes and higher than PCV13 for the two serotypes unique to V114 (22F and 33F).

All the available immunogenicity data for V114 in the age group from 6 weeks to 5 years of age refer to mostly healthy infants; there are no data in immunocompromised infants or those with underlying chronic disease in this age group.

5.4 Safety

To evaluate the safety of V114 when administered as a complete 3- or 4-dose regimen, safety data from the four Phase 3 studies (V114-025, V114-027, V114-029, and V114-031) were integrated based on similarities in study design, population, and dosing strategy (either V114 or PCV13 administered as a 2-dose or 3-dose primary series during the first 4 to 6 months of life followed by a toddler dose at 11 to 15 months of age). Participants who received both V114 and PCV13 either

inadvertently or based on study design were not included in the integrated analysis. In the integrated exposure, a total of 3,589 infants received at least one dose of V114 and 2,058 infants received at least one dose of PCV13.

The safety profile in the integrated safety population for V114 was generally comparable to the safety profile of PCV13. Adverse events (AEs) were experienced by a comparable proportion of participants in both treatment groups. The most commonly reported vaccine-related AEs were mostly solicited AEs and comparable in both the V114 and PCV13 groups: irritability (67.7% vs 62.8%), somnolence (48.5% vs 45.7%), injection-site pain (44.4% vs 39.4%), injection-site erythema (41.7% vs 40.5%), decreased appetite (29.8% vs 26.2%), pyrexia (29.8% vs 28.2%), injection-site induration (28.3% vs 30.8%), and injection-site swelling (28.2% vs 25.3%). In both intervention groups, the majority of participants had solicited AEs which were mild to moderate in intensity and of short duration (≤3 days).
In this integrated safety population, the proportions of participants experiencing serious adverse events (SAEs) were comparable across intervention groups.
The number of deaths in the integrated safety analysis was low, with two deaths (0.1%) in the V114 group and two deaths (0.1%) in the PCV13 group. The narratives of participants who died were reviewed and no indication of a causal relationship to the vaccine could be identified.

In total 221 pre-term infants were exposed to V114. The safety profile in preterm infants was largely comparable to that for the healthy infants. The most frequently reported vaccine-related AEs were identical in the preterm infants as compared to the total population. There was a slight numerical increase in the percentage of participants who experienced at least one AE in both treatment arms compared to the total healthy infant population, indicating a slight increase in reactogenicity in preterm infants. The percentage of participants experiencing SAEs was comparable between both groups and none of the SAEs was considered related to the vaccine.

The safety of V114 in healthy children was assessed in a study that included 226 participants from 2 to 5 years of age (inclusive), of whom 114 received a single dose of V114. The most commonly reported vaccine-related AEs occurred at a similar or somewhat lower percentage compared to the integrated safety population.

5.5 Final clinical benefit-risk assessment

The submitted data demonstrated that V114 is immunogenic in children. The non-inferior immunogenicity compared to PCV13 is considered proven for children. Thus, the existing clinical efficacy of PCV13 for children from 6 weeks to 5 years of age can be bridged to V114 for the same age group. However, no conclusion on the additional serotypes (22F and 33F) can be drawn regarding clinical benefit. In addition, in the lack of efficacy data for children and adolescents from 5 to 18 years of age no firm conclusion can be drawn regarding the clinical benefit of Vaxneuvance in children and adolescents from 5 to 18 years of age. Clinical efficacy can only be extrapolated to age ranges with available efficacy data. As no clinical efficacy data are available for children and adolescents from 5 to 18 years of age, further justification was requested to support indication for children and adolescents from 5 to 18 years of age. The responses have not provided relevant additional data confirming efficacy in these subjects; thus, the indication has been restricted to children from 6 weeks to 5 years of age.
The safety profile of V114 was comparable to the safety profile of PCV13 and no new safety concerns were identified.
As a conclusion, V114 can be approved for children from 6 weeks to 5 years of age for the prevention of IPD, pneumonia, and acute otitis media.

6 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.

7 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, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* in infants and children from 6 weeks to 5 years of age.
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

Routine vaccination schedule in infants and children aged 6 weeks to less than 2 years of age
Infants and children who have begun immunisation with a lower-valency pneumococcal conjugate vaccine may switch to Vaxneuvance at any point in the schedule (see section «Properties/Effects»).

Two dose primary series followed by a booster dose
The recommended immunisation regimen consists of 3 doses of Vaxneuvance, each of 0.5 mL. The first dose is given as early as 6 to 12 weeks of age, with a second dose administered 8 weeks later. The third (booster) dose is recommended between 11 through 15 months of age.

Three dose primary series followed by a booster dose
An immunisation regimen consisting of 4 doses of Vaxneuvance, each of 0.5 mL, may be given. This primary series consists of 3 doses, with the first dose given as early as 6 to 12 weeks of age, with an interval of 4 to 8 weeks between doses in the primary series. The fourth (booster) dose is recommended between 11 through 15 months of age and at least 2 months after the third dose.

Preterm infants (<37 weeks gestation at birth)
The recommended immunisation regimen consists of a three-dose primary series of Vaxneuvance followed by a fourth (booster) dose, each of 0.5 mL, as per three-dose primary series followed by a booster dose posology (see sections «Warning and Precautions» and «Properties/Effects»).

Catch-up vaccination schedule for children 7 months to 5 years of age

Unvaccinated infants aged 7 to less than 12 months of age
3 doses, each of 0.5 mL, with the first two doses given at least 4 weeks apart. A third (booster) dose is recommended after 12 months of age, separated from the second dose by at least 2 months.

Unvaccinated children aged 12 months to less than 2 years of age
2 doses, each of 0.5 mL, with an interval of 2 months between doses.

Unvaccinated or not fully vaccinated children 2 to 5 years of age
1 dose (0.5 mL).
If a previous pneumococcal conjugate vaccine was administered, at least 2 months should elapse before administering Vaxneuvance.

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.

Mode of administration

The vaccine should be administered by intramuscular injection. The preferred site is the anterolateral aspect of the thigh in infants or the deltoid muscle of the upper arm in children and adults.
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.

Apnoea in premature infants

The potential risk of apnoea and the need for respiratory monitoring for 48-72 hours should be considered when administering the primary immunisation series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination generally should not be withheld or delayed.

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

Different injectable vaccines should always be administered at different injection sites.
Immunosuppressive therapies may reduce the immune responses to vaccines.

Infants and children aged 6 weeks to 23 months

Vaxneuvance can be given concomitantly with any of the following vaccine antigens, either as monovalent or combination vaccines: diphtheria, tetanus, pertussis, poliomyelitis (serotypes 1, 2 and 3), hepatitis A, hepatitis B, *Haemophilus influenzae* type b, measles, mumps, rubella, varicella and rotavirus vaccine.

Children 2 to 5 years of age

There are no data on the concomitant administration of Vaxneuvance with other vaccines.

Data from a post-marketing clinical study evaluating the impact of prophylactic use of antipyretics (ibuprofen and paracetamol) on the immune response to other pneumococcal vaccines suggest that administration of antipyretics concomitantly or within the same day of vaccination may reduce the immune response after the infant series. Responses to the booster dose administered at 12 months were unaffected. The clinical significance of this observation is unknown.

Adults

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.

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

Paediatric population

Infants and children aged 6 weeks to 23 months

The safety of Vaxneuvance in healthy infants aged 6 weeks to 23 months of age (inclusive), including preterm infants (from 6 weeks of age at first vaccination) and children (11 through 15 months of age) was assessed as a 3 dose or 4 dose regimen in 5 clinical studies with a total of 7,229 participants.
All 5 studies evaluated the safety of Vaxneuvance when administered concomitantly with other routine paediatric vaccines. In these studies, 4,286 participants received a complete regimen of Vaxneuvance, 2,405 participants received a complete regimen of the 13-valent pneumococcal conjugate vaccine (PCV) and 538 participants received Vaxneuvance when used to complete a regimen initiated with the 13-valent PCV (mixed dose regimen).

The most frequent adverse reactions were pyrexia ≥ 38°C (75.2%), irritability (74.5%), somnolence (55.0%), injection-site pain (44.4%), injection-site erythema (41.7%), decreased appetite (38.2%), injection-site induration (28.3%) and injection-site swelling (28.2%) based on results in 3,589 participants (Table 1), excluding participants who received a mixed dose regimen. The majority of solicited adverse reactions were mild to moderate (based on intensity or size) and of short duration (≤ 3 days). Severe reactions (defined as being extremely distressed or unable to do usual activities or size > 7.6 cm) occurred in ≤ 3.5% of infants and children following any dose, with the exception of irritability which occurred in 11.4% of participants.

Preterm infants (<37 weeks of gestation)

The safety of VAXNEUVANCE was evaluated in preterm infants (<37 weeks gestation at birth) enrolled within 4 double-blind, active comparator-controlled studies (Protocol 025, Protocol 027, Protocol 029 and Protocol 031). In these studies, 174 participants were randomized to receive VAXNEUVANCE. The safety profile in preterm infants receiving 4 doses of VAXNEUVANCE was generally consistent with those observed in the overall healthy infant population in these studies (including preterm and term infants).

Children 2 to 5 years of age

The safety of Vaxneuvance in healthy children was assessed in a study that included 226 participants 2 to 5 years of age (inclusive), of whom 114 received a single dose of Vaxneuvance. In this age cohort, 101 (28.7%) of all participants had a history of previous vaccination with a lower valency pneumococcal conjugate vaccine across both vaccination groups.

The most frequent adverse reactions were injection-site pain (37.7%), injection-site swelling (21.1%), injection-site erythema (21.1%), pyrexia (≥ 38°C) (8.8%), fatigue (7.9%), irritability (6.1%) and myalgia (5.3%) (Table 1). The majority of solicited adverse reactions were mild to moderate (based on intensity or size) and of short duration (≤ 3 days); severe reactions (defined as being extremely distressed or unable to do usual activities or size >7.6 cm) occurred in ≤ 2.6% of children.

Mixed dose regimen of different pneumococcal conjugate vaccines

The safety profiles of mixed 4-dose regimens of Vaxneuvance and the 13-valent PCV in healthy infants and children were generally comparable to those of complete 4-dose regimens of either Vaxneuvance or the 13-valent PCV (see section «Properties/Effects»).

Catch-up vaccination schedule

Safety was also assessed as a catch-up vaccination schedule in 126 healthy infants and children from 7 months to 23 months of age (inclusive) who received 2 or 3 doses of Vaxneuvance based on age at enrollment. The safety profile of the catch-up vaccination schedule was generally consistent with the safety profile of the routine vaccination schedule initiated from 6 to 12 weeks of age (see section «Properties/Effects»).

Adults 50 years of age and older

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%) (Table 2). 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

In clinical studies of adults local and systemic adverse reactions were solicited daily after vaccination for 5 and 14 days, respectively and in infants and children up to 14 days after vaccination. In all populations, 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 in adults 50 years of age and older 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.

Adverse reactions reported for all age groups are listed in this section per system organ class, in decreasing order of frequency and seriousness. The frequency is defined as follows: 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 in infants and children 6 weeks to 5 years of age

System Organ Class	Adverse Reactions	Frequency	
		Infants/Children	
		6weeks to 23 months†	2 years to 5 years§
Metabolism and nutrition disorders	Decreased appetite	Very Common (38.2%)	Common
Psychiatric disorders	Irritability	Very Common (74.5%)	Common (6.1%)
Nervous system disorders	Somnolence	Very Common (55.0%)	Common
	Headache	-	Common
Skin and subcutaneous tissue disorders	Urticaria	Common	Common
	Rash	Common	Not known‡
Gastrointestinal disorders	Nausea	-	Uncommon
	Vomiting	Common	Uncommon
Musculoskeletal and connective tissue disorders	Myalgia	-	Common (5.3%)
General disorders and administration site conditions	Pyrexia⊥	Very Common (75.2%)	Common (8.8%)
	≥39°C	Very Common	Common
	≥40 °C	Common	-
	Injection-site pain	Very Common (44.4%)	Very Common (37.7%)
	Injection-site erythema	Very Common (41.7%)	Very Common (21.1%)
	Injection-site swelling	Very Common (28.2%)	Very Common (21.1%)
	Injection-site induration	Very Common (28.3%)	Common
	Injection-site bruising/haematoma	Common	Uncommon
	Injection-site urticaria	Uncommon	Uncommon
	Fatigue	--	Common (7.9%)

†Inclusive

§Different systemic adverse events were solicited for participants 2 to <3 years of age, than for participants ≥3 to 5 years of age. For participants <3 years of age (Vaxneuvance N=32, 13-valent PCV N=28), decreased appetite, irritability, somnolence and urticaria were solicited from Day 1 through Day 14 following vaccination. For participants ≥3 to 5 years of age, fatigue, headache, myalgia, and urticaria were solicited from Day 1 through Day 14 following vaccination.

‡In clinical trials, no events were observed following Vaxneuvance in healthy children and two events were observed in special populations (sickle cell disease and HIV).

⊥defined as temperature ≥38 °C

Table 2: Tabulated list of adverse reactions in adults 50 years of age and older

System Organ Class	Adverse Reactions	Frequency Adults ≥50 Years
Immune system disorders	Hypersensitivity reaction including tongue oedema, flushing, and throat tightness	Rare
Nervous system disorders	Headache	Very Common (14.5%)
	Dizziness	Uncommon
Skin and subcutaneous tissue disorders	Rash	Uncommon
Gastrointestinal disorders	Nausea Vomiting	Uncommon
Musculoskeletal and connective tissue disorders	Myalgia	Very Common (19.5%)
	Arthralgia	Common (6.3%)
General disorders and administration site conditions	Injection-site pain Fatigue Injection-site swelling Injection-site erythema	Very Common (63.3%) Very Common (20.2%) Very Common (14.5%) Very Common (11.1%)
	Injection-site pruritus	Common
	Pyrexia[+] Injection-site warmth Injection-site bruising/haematoma Chills	Uncommon Uncommon Uncommon Uncommon

[+]defined as temperature ≥38 °C

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 and 23F, with the additional serotypes 22F and 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.
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 and is considered an important immunologic surrogate measure of protection against pneumococcal disease in adults. In children, a serotype-specific IgG antibody level corresponding to ≥0.35 µg/mL using the WHO enzyme linked immunosorbent assay (ELISA) has been used as the threshold value for the clinical evaluation regarding invasive disease of pneumococcal conjugate vaccines.

Pharmacodynamics

Not applicable.

Clinical efficacy

No efficacy studies have been conducted with Vaxneuvance.
The assessment is based on comparing the immune responses of the thirteen common serotypes contained in both Vaxneuvance and Prevenar 13. Immune responses to the two additional serotypes were also measured.
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”).

Clinical immunogenicity in healthy infants and children

Immunogenicity was assessed by serotype-specific IgG response rates (the proportion of participants meeting the serotype-specific IgG threshold value of ≥0.35 µg/mL) and IgG geometric mean concentrations (GMCs) at 30 days following the primary series and/or following the toddler (booster) dose. In a subset of participants, OPA geometric mean titres (GMTs) were also measured at 30 days following the primary series and/or following the toddler dose.

Infants and children receiving a routine vaccination schedule

3-dose regimen (2-dose primary series + 1 toddler dose)

In the double-blind, active comparator-controlled study (Protocol 025), 1,184 participants were randomised to receive Vaxneuvance or the 13-valent PCV in a 3-dose regimen. The first two doses were administered to infants at 2 and 4 months of age (primary series) and the third dose was administered to children at 11 through 15 months of age (toddler dose). Participants also received other paediatric vaccines concomitantly, including Rotavirus vaccine (live) with the infant primary series and Diphtheria, Tetanus, Pertussis (acellular), Hepatitis B (rDNA), Poliomyelitis (inactivated), *Haemophilus influenzae* type b conjugate vaccine (adsorbed) with all 3 doses in the complete regimen.

Vaxneuvance elicits immune responses, as assessed by IgG response rates, IgG GMCs and OPA GMTs, for all 15 serotypes contained in the vaccine. At 30 days following the two-dose primary series, serotype-specific IgG response rates and GMCs were generally comparable for the 13 shared serotypes and higher for the 2 additional serotypes (22F and 33F) in Vaxneuvance recipients, compared to the 13-valent PCV recipients. At 30 days following the toddler dose, Vaxneuvance is noninferior to the 13-valent PCV for the 13 shared serotypes and superior for the 2 additional serotypes, as assessed by IgG response rate and IgG GMCs (Table 3).

Table 3: Serotype-specific IgG response rates and IgG GMCs at 30 days following the 2-dose primary series (3-dose regimen, Protocol 025)

Pneumococcal Serotype	IgG response rates ≥0.35 µg/mL			IgG GMCs		
	Vaxneuvance (n=497)	13-valent PCV (n=468-469)	Percentage Point Difference* (Vaxneuvance - 13-valent PCV) (95% CI)*	Vaxneuvance (n=497)	13-valent PCV (n=468-469)	GMC Ratio** (Vaxneuvance/ 13-valent PCV) (95% CI)**
	Observed Response Percentage	Observed Response Percentage		GMC	GMC	
13 Shared Serotypes†						
1	95.6	97.4	-1.9 (-4.3, 0.5)	1.30	1.60	0.81 (0.74, 0.89)
3	93.2	66.1	27.1 (22.3, 31.9)	0.87	0.45	1.91 (1.75, 2.08)
4	93.8	96.8	-3.0 (-5.9, -0.4)	1.40	1.25	1.12 (1.01, 1.24)
5	84.1	88.1	-4.0 (-8.3, 0.4)	0.88	1.03	0.86 (0.76, 0.97)
6A	72.6	92.3	-19.7 (-24.3, -15.1)	0.64	1.39	0.46 (0.40, 0.53)
6B	57.7	50.2	7.5 (1.2, 13.8)	0.43	0.33	1.31 (1.11, 1.56)
7F	97.8	98.9	-1.1 (-3.0, 0.5)	2.03	2.42	0.84 (0.76, 0.92)
9V	88.3	95.3	-7.0 (-10.5, -3.6)	1.23	1.39	0.88 (0.78, 0.99)
14	96.8	97.2	-0.4 (-2.7, 1.8)	3.81	4.88	0.78 (0.68, 0.90)
18C	92.2	92.5	-0.4 (-3.8, 3.0)	1.16	1.30	0.89 (0.80, 0.99)
19A	96.2	97.2	-1.1 (-3.4, 1.3)	1.68	2.09	0.81 (0.72, 0.90)
19F	98.8	99.4	-0.6 (-2.0, 0.8)	2.63	3.35	0.79 (0.71, 0.87)
23F	77.9	70.1	7.8 (2.3, 13.3)	0.75	0.58	1.30 (1.14, 1.50)
2 Additional Serotypes in Vaxneuvance‡						
22F	95.6	5.3	90.2 (87.1, 92.6)	2.74	0.05	57.67 (50.95, 65.28)
33F	48.1	3.0	45.1 (40.4, 49.7)	0.30	0.05	6.11 (5.32, 7.02)

* Estimated difference and CI for the percentage point difference are based on the Miettinen & Nurminen method.

** GMC ratio and CI are calculated using the t-distribution with the variance estimate from a serotype-specific linear model utilising the natural log-transformed antibody concentrations as the response and a single term for vaccination group.

† A conclusion of non-inferiority for the 13 shared serotypes is based on the lower bound of the 95% CI being > -10 percentage points for the difference in IgG response rates (Vaxneuvance – 13-valent PCV) or > 0.5 for the IgG GMC ratio (Vaxneuvance/13-valent PCV).

‡ A conclusion of superiority for the 2 additional serotypes is based on the lower bound of the 95% CI being > 10 percentage points for the difference in IgG response rates (Vaxneuvance – 13-valent PCV) or > 2.0 for the IgG GMC ratio (Vaxneuvance/13-valent PCV).

n=Number of participants randomised, vaccinated and contributing to the analysis.

CI=confidence interval; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G.

Table 4: Serotype-specific IgG response rates and IgG GMCs at 30 days following the toddler dose (3-dose regimen, Protocol 025)

Pneumococcal Serotype	IgG response rates ≥0.35 µg/mL			IgG GMCs		
	Vaxneuvance (n=510-511)	13-valent PCV (n=504-510)	Percentage Point Difference* (Vaxneuvance - 13-valent PCV) (95% CI)*	Vaxneuvance (n=510-511)	13-valent PCV (n=504-510)	GMC Ratio** (Vaxneuvance/ 13-valent PCV) (95% CI)**
	Observed Response Percentage	Observed Response Percentage		GMC	GMC	
13 Shared Serotypes†						
1	96.5	99.4	-2.9 (-5.0, -1.3)	1.28	2.05	0.62 (0.57, 0.68)
3	91.8	83.7	8.1 (4.1, 12.1)	0.84	0.66	1.29 (1.18, 1.41)
4	95.7	97.8	-2.1 (-4.5, 0.0)	1.29	1.74	0.74 (0.67, 0.82)
5	99.0	100.0	-1.0 (-2.3, -0.2)	1.98	3.01	0.66 (0.60, 0.72)
6A	98.4	98.8	-0.4 (-2.0, 1.2)	3.09	4.53	0.68 (0.61, 0.76)
6B	97.3	99.0	-1.8 (-3.7, -0.1)	4.15	4.33	0.96 (0.85, 1.08)
7F	99.8	99.8	0.0 (-0.9, 0.9)	3.08	3.89	0.79 (0.73, 0.86)
9V	98.8	100.0	-1.2 (-2.5, -0.4)	2.14	2.97	0.72 (0.66, 0.78)
14	99.8	100.0	-0.2 (-1.1, 0.6)	5.22	6.90	0.76 (0.68, 0.84)
18C	98.8	99.2	-0.4 (-1.8, 1.0)	1.93	2.18	0.89 (0.81, 0.97)
19A	99.0	100.0	-1.0 (-2.3, -0.2)	4.65	5.61	0.83 (0.75, 0.92)
19F	99.6	100.0	-0.4 (-1.4, 0.4)	4.06	4.59	0.89 (0.81, 0.97)
23F	96.9	97.2	-0.4 (-2.6, 1.8)	1.52	1.69	0.90 (0.81, 1.00)
2 Additional Serotypes in Vaxneuvance‡						
22F	99.6	5.9	93.7 (91.2, 95.5)	5.97	0.08	71.76 (64.88, 79.38)
33F	99.0	4.4	94.7 (92.3, 96.3)	3.38	0.07	46.38 (41.85, 51.40)

* Estimated difference and CI for the percentage point difference are based on the Miettinen & Nurminen method.

** GMC ratio and CI are calculated using the t-distribution with the variance estimate from a serotype-specific linear model utilising the natural log-transformed antibody concentrations as the response and a single term for vaccination group.

† A conclusion of non-inferiority for the 13 shared serotypes is based on the lower bound of the 95% CI being > -10 percentage points for the difference in IgG response rates (Vaxneuvance – 13-valent PCV) or > 0.5 for the IgG GMC ratio (Vaxneuvance/13-valent PCV).

‡ A conclusion of superiority for the 2 additional serotypes is based on the lower bound of the 95% CI being > 10 percentage points for the difference in IgG response rates (Vaxneuvance – 13-valent PCV) or > 2.0 for the IgG GMC ratio (Vaxneuvance/13-valent PCV).

n=Number of participants randomised, vaccinated and contributing to the analysis.

CI=confidence interval; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G.

Additionally, Vaxneuvance elicits functional antibodies, as assessed by serotype-specific OPA GMTs at 30 days following the toddler dose, that are generally comparable but slightly lower for the 13 serotypes shared with 13-valent PCV. The clinical relevance of this slightly lower response is unknown.

OPA GMTs for both 22F and 33F were higher in Vaxneuvance recipients compared to the 13-valent PCV recipients.

4-dose regimen (3-dose primary series + 1 toddler dose)

A 4-dose regimen was evaluated in healthy infants in one phase 2 and three phase 3 studies. The primary series were administered to infants at 2, 4, and 6 months of age and the toddler dose was administered to children at 12 through 15 months of age.

In a double-blind, active comparator-controlled study (Protocol 029), 1,720 participants were randomised to receive Vaxneuvance or the 13-valent PCV. Participants also received other paediatric vaccines concomitantly, including HBVaxPro (Hepatitis B Vaccine [Recombinant]), RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent) and Diphtheria, Tetanus Toxoids, Acellular Pertussis Adsorbed, Inactivated Poliovirus, *Haemophilus* b Conjugate (Tetanus Toxoid Conjugate) Vaccine in the infant series. *Haemophilus* b Conjugate Vaccine (Tetanus Toxoid Conjugate), M-M-RvaxPro (Measles, Mumps, and Rubella Virus Vaccine Live), Varivax (Varicella Virus Vaccine Live) and Vaqta (Hepatitis A Vaccine, Inactivated) were administered concomitantly with the toddler dose of Vaxneuvance.

Vaxneuvance elicits immune responses, as assessed by IgG response rates, IgG GMCs and OPA GMTs for all 15 serotypes contained in the vaccine. At 30 days following the primary series, Vaxneuvance is noninferior to the 13-valent PCV for the 13 shared serotypes, as assessed by IgG response rates (Table 5). Vaxneuvance is noninferior for the 2 additional serotypes, as assessed by the IgG response rates for serotypes 22F and 33F in recipients of Vaxneuvance compared with the response rate for serotype 23F in recipients of the 13-valent PCV (the lowest response rate for any of the shared serotypes, excluding serotype 3), with percentage point differences of 6.7% (95% CI: 4.6, 9.2) and -4.5% (95% CI: -7.8, -1.3), respectively.

At 30 days following the primary series, serotype-specific IgG GMCs are noninferior to the 13-valent PCV for 12 of the 13 shared serotypes. The IgG response to serotype 6A narrowly missed the prespecified noninferiority criteria by a small margin (0.48 versus >0.5) (Table 5). Vaxneuvance is noninferior to the 13-valent PCV for the 2 additional serotypes, as assessed by serotype-specific IgG GMCs for serotypes 22F and 33F in recipients of Vaxneuvance compared with the IgG GMCs for serotype 4 in recipients of the 13-valent PCV (the lowest IgG GMC for any of the shared serotypes, excluding serotype 3) with a GMC ratio of 3.64 and 1.24, respectively.

Table 5: Serotype-specific IgG response rates and IgG GMCs at 30 days following the 3-dose primary series (4-dose regimen, Protocol 029)

Pneumococcal Serotype	IgG response rates ≥0.35 µg/mL			IgG GMCs		
	Vaxneuvance (n=698-702)	13-valent PCV (n=660-665)	Percentage Point Difference* (Vaxneuvance - 13-valent PCV) (95% CI)*	Vaxneuvance (n=698-702)	13-valent PCV (n=660-665)	GMC Ratio** (Vaxneuvance/ 13-valent PCV) (95% CI)**
	Observed Response Percentage	Observed Response Percentage		GMC	GMC	
13 Shared Serotypes†						
1	95.7	99.1	-3.4 (-5.2, -1.8)	1.21	1.89	0.64 (0.59, 0.69)
3	94.7	79.2	15.6 (12.1, 19.2)	1.08	0.62	1.73 (1.61, 1.87)
4	96.4	98.6	-2.2 (-4.0, -0.6)	1.29	1.35	0.95 (0.88, 1.03)
5	95.3	97.4	-2.1 (-4.2, -0.2)	1.63	2.25	0.72 (0.66, 0.80)
6A	93.7	98.6	-4.9 (-7.1, -3.0)	1.55	2.95	0.52 (0.48, 0.58)
6B	88.6	92.0	-3.4 (-6.6, -0.3)	1.60	1.97	0.81 (0.71, 0.93)
7F	99.0	99.8	-0.8 (-1.9, -0.1)	2.48	3.23	0.77 (0.71, 0.83)
9V	97.1	98.2	-1.0 (-2.8, 0.6)	1.73	1.89	0.91 (0.84, 1.00)
14	97.9	97.9	-0.0 (-1.6, 1.6)	4.78	6.80	0.70 (0.63, 0.78)
18C	97.4	98.3	-0.9 (-2.6, 0.7)	1.53	2.00	0.76 (0.70, 0.83)
19A	97.9	99.7	-1.8 (-3.2, -0.8)	1.63	2.29	0.71 (0.65, 0.77)
19F	99.0	100.0	-1.0 (-2.1, -0.4)	2.01	2.72	0.74 (0.69, 0.79)
23F	91.5	91.8	-0.3 (-3.2, 2.7)	1.31	1.47	0.89 (0.80, 0.99)
2 Additional Serotypes in Vaxneuvance						
22F	98.6	3.5	95.1 (93.1, 96.5)	4.91	0.05	92.03 (83.47, 101.47)
33F	87.3	2.1	85.2 (82.3, 87.7)	1.67	0.06	29.50 (26.16, 33.26)

* Estimated difference and CI for the percentage point difference are based on the Miettinen & Nurminen method.

** GMC ratio and CI are calculated using the t-distribution with the variance estimate from a serotype-specific linear model utilising the natural log-transformed antibody concentrations as the response and a single term for vaccination group.

† A conclusion of non-inferiority for the 13 shared serotypes is based on the lower bound of the 95% CI being > -10 percentage points for the difference in IgG response rates (Vaxneuvance – 13-valent PCV) or > 0.5 for the IgG GMC ratio (Vaxneuvance/13-valent PCV)

.n=Number of participants randomised, vaccinated and contributing to the analysis.

CI=confidence interval; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G.

At 30 days following the toddler dose, serotype-specific IgG GMCs for Vaxneuvance are noninferior to the 13-valent PCV for all 13 shared serotypes and for the 2 additional serotypes as assessed by the IgG GMCs for serotypes 22F and 33F in Vaxneuvance recipients compared with the IgG GMC for serotype 4 in the 13-valent PCV recipients (the lowest IgG GMC for any of the shared serotypes, excluding serotype 3) with a GMC ratio of 4.69 and 2.59, respectively (Table 6).

Table 6: Serotype-specific IgG response rates and IgG GMCs at 30 days following the toddler dose (4-dose regimen, Protocol 029)

Pneumococcal Serotype	IgG response rates ≥0.35 µg/mL			IgG GMCs		
	Vaxneuvance (n=712-716)	13-valent PCV (n=677-686)	Percentage Point Difference* (Vaxneuvance - 13-valent PCV) (95% CI)*	Vaxneuvance (n=712-716)	13-valent PCV (n=677-686)	GMC Ratio** (Vaxneuvance/ 13-valent PCV) (95% CI)**
	Observed Response Percentage	Observed Response Percentage		GMC	GMC	
13 Shared Serotypes†						
1	96.6	99.4	-2.8 (-4.4, -1.4)	1.35	2.03	0.66 (0.62, 0.72)
3	94.0	86.9	7.1 (4.0, 10.2)	0.96	0.71	1.35 (1.25, 1.46)
4	95.1	97.5	-2.4 (-4.5, -0.4)	1.23	1.60	0.77 (0.71, 0.84)
5	99.2	99.9	-0.7 (-1.7, 0.1)	2.49	3.95	0.63 (0.58, 0.69)
6A	98.7	99.3	-0.5 (-1.7, 0.6)	3.70	6.21	0.60 (0.54, 0.65)
6B	98.7	99.3	-0.5 (-1.7, 0.6)	4.76	6.43	0.74 (0.67, 0.81)
7F	99.6	99.9	-0.3 (-1.1, 0.4)	3.42	4.85	0.70 (0.65, 0.77)
9V	99.4	99.7	-0.3 (-1.2, 0.6)	2.40	3.29	0.73 (0.67, 0.80)
14	99.3	99.6	-0.3 (-1.2, 0.7)	5.61	6.95	0.81 (0.73, 0.89)
18C	99.7	99.6	0.2 (-0.6, 1.0)	2.62	3.08	0.85 (0.78, 0.93)
19A	99.9	99.9	0.0 (-0.7, 0.7)	4.10	5.53	0.74 (0.68, 0.80)
19F	99.7	99.7	0.0 (-0.8, 0.8)	3.55	4.47	0.79 (0.74, 0.86)
23F	98.6	99.0	-0.4 (-1.7, 0.9)	2.04	3.32	0.61 (0.56, 0.68)
2 Additional Serotypes in Vaxneuvance						
22F	99.6	7.2	92.4 (90.1, 94.2)	7.52	0.11	68.80 (63.10, 75.02)
33F	98.9	6.2	92.7 (90.4, 94.4)	4.15	0.09	44.91 (41.04, 49.14)

* Estimated difference and CI for the percentage point difference are based on the Miettinen & Nurminen method.

** GMC ratio and CI are calculated using the t-distribution with the variance estimate from a serotype-specific linear model utilising the natural log-transformed antibody concentrations as the response and a single term for vaccination group.

† A conclusion of non-inferiority for the 13 shared serotypes is based on the lower bound of the 95% CI being > -10 percentage points for the difference in IgG response rates (Vaxneuvance – 13-valent PCV) or > 0.5 for the IgG GMC ratio (Vaxneuvance/13-valent PCV).

n=Number of participants randomised, vaccinated and contributing to the analysis.

CI=confidence interval; GMC=geometric mean concentration (µg/mL); IgG=immunoglobulin G.

Vaxneuvance elicits functional antibodies, as assessed by serotype-specific OPA GMTs at 30 days following the primary series and following the toddler dose, that are generally comparable but slightly lower for the 13 serotypes shared with 13-valent PCV. The clinical relevance of this slightly lower response is unknown. OPA GMTs for both 22F and 33F were higher in Vaxneuvance recipients compared to the 13-valent PCV recipients.

Infants and children receiving a mixed dose regimen of different pneumococcal conjugate vaccines

In a double-blind, active comparator-controlled, descriptive study (Protocol 027), 900 participants were randomised in a 1:1:1:1:1 ratio to one of five vaccination groups to receive a complete or mixed dosing regimen of pneumococcal conjugate vaccines. In two vaccination groups, participants received a 4-dose regimen of either Vaxneuvance or the 13-valent PCV. In the three other vaccination groups, the vaccination series were initiated with the 13-valent PCV and changed to Vaxneuvance at Dose 2, Dose 3 or Dose 4. Participants also received other paediatric vaccines concomitantly, including HBVaxPro (Hepatitis B Vaccine [Recombinant]) and RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent). Serotype-specific IgG GMCs at 30 days following the toddler dose were generally comparable for participants administered mixed regimens of Vaxneuvance and the 13-valent PCV and for participants administered a complete dosing regimen of the 13-valent PCV for the 13 shared serotypes, as assessed by IgG GMC ratios.
Higher antibodies to serotypes 22F and 33F were only observed when at least one dose of Vaxneuvance was administered during primary infant series and at the toddler age.

Immunogenicity in preterm infants

The immune responses (serotype-specific IgG and OPA) in preterm infants receiving 4 doses of pneumococcal conjugate vaccine in 4 double-blind, active comparator-controlled studies (Protocol 025, Protocol 027, Protocol 029 and Protocol 031), were generally consistent with those observed in the overall healthy infant population in these studies (including preterm and term infants).

Infants, children and adolescents receiving a catch-up vaccination schedule

In a double-blind, active comparator-controlled, descriptive study (Protocol 024), 606 children who were either pneumococcal vaccine-naïve or not fully vaccinated or completed a dosing regimen with lower valency pneumococcal conjugate vaccines were randomised to receive 1 to 3 doses of Vaxneuvance or the 13-valent PCV in three different age cohorts (7 through 11 months, 12 through 23 months and 24 months to less than 18 years of age), according to an age-appropriate schedule. Catch-up vaccination with Vaxneuvance elicited immune responses in children 7 months to less than 18 years of age that are comparable to the 13-valent PCV for the shared serotypes and higher than the 13-valent PCV for the additional serotypes 22F and 33F. Within each age cohort, serotype-specific IgG GMCs at 30 days following the last dose of vaccine were generally comparable between the vaccination groups for the 13 shared serotypes and higher in Vaxneuvance for the 2 additional serotypes.

Immunogenicity in immunocompetent adults 65 years of age and older

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 7).

Table 7: 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 23-valent pneumococcal polysaccharide vaccine (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 additional 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 additional 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 anterolateral aspect of the thigh in infants or in the deltoid area of the upper arm in children and adults.
- 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.

Authorisation number

68752 (Swissmedic)

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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