swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

CAPVAXIVE

International non-proprietary name: *Streptococcus pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A,12F, 15A, 15B de-O-acetylated, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, 35B polysaccharide conjugated to *Corynebacterium diphtheriae* CRM197 protein

Pharmaceutical form:	solution for injection in pre-filled syringe
Dosage strength(s):	4 µg of each serotype / 0.5 ml
Route(s) of administration:	intramuscular use
Marketing authorisation holder:	MSD Merck Sharp & Dohme AG
Marketing authorisation no.:	69781
Decision and decision date:	approved on 23 September 2025

Note:

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

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AOM	Acute otitis media
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
COPD	Chronic obstructive pulmonary disease
CYP	Cytochrome P450
DDI	Drug-drug interaction
DT	Diphtheria toxin
EMA	European Medicines Agency
ERA	Environmental risk assessment
FAS	Full analysis set
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMC	Geometric mean concentration
GMT	Geometric mean titre
HIV	Human Immunodeficiency Virus
HPLC	High-performance liquid chromatography
HSCT	Haematopoietic stem cell transplantation
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IgG	Immunoglobulin G
INN	International non-proprietary name
IPD	Invasive pneumococcal disease
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
MBC	Monovalent bulk conjugate
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MOPA	Multiplex opsonophagocytic assay
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
OPA	Opsonophagocytic assay
PBPK	Physiology-based pharmacokinetics
PCV	Pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PCV15	15-valent pneumococcal conjugate vaccine
PCV20	20-valent pneumococcal conjugate vaccine
PCV21	21-valent pneumococcal conjugate vaccine

PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
Pn ECL	Pneumococcal electrochemiluminescence
PnPs	Pneumococcal Polysaccharide
PopPK	Population pharmacokinetics
PP	Per protocol
PPQ	Process Performance Qualification
PPV/PPSV	Pneumococcal polysaccharide vaccine
PPV23/PPSV23	23-valent pneumococcal polysaccharide vaccine
PSP	Pediatric study plan (US FDA)
QIV	Quadrivalent influenza vaccine
RMP	Risk management plan
SAE	Serious adverse event
SOC	System Organ Class
SOT	Solid organ transplant
ST/s	Serotype/s
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)
V116	21-valent pneumococcal conjugate vaccine/Capvaxive
WOCBP	Women of childbearing potential

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

New active substance status
The applicant requested new active substance status for *Streptococcus pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A,12F, 15A, 15B de-O-acetylated, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, 35B polysaccharide conjugated to *Corynebacterium diphtheriae* CRM197 protein in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

Capvaxive is indicated in individuals 18 years of age and older for the active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae*.
For information on protection against specific pneumococcal serotypes see 'Warnings and precautions' and 'Properties/effects'.
The use of Capvaxive should be based on official recommendations.

2.2.2 Approved indication

CAPVAXIVE 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 'Warnings and precautions' and 'Properties/Effects' for information on protection against specific pneumococcal serotypes.
The use of CAPVAXIVE should be based on official recommendations.

2.2.3 Requested dosage

Summary of the requested standard dosage:
Individuals 18 years of age and older: 1 dose (0.5 ml)
Paediatric population
The safety and effectiveness of Capvaxive in children under 18 years of age have not been demonstrated.
Mode of administration
This vaccine should only be administered by intramuscular injection. The preferred injection site in adults is the deltoid muscle of the upper arm. Capvaxive must not be administered intravascularly.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	31 October 2024
Formal control completed	5 November 2024
List of Questions (LoQ)	4 February 2025

Response to LoQ	24 March 2025
Preliminary decision	13 June 2025
Response to preliminary decision	28 July 2025
Informal labelling corrections and/or other aspects	12 September 2025
Response to labelling corrections and/or other aspects	16 September 2025
Final decision	23 September 2025
Decision	approval

3 Medical context

Streptococcus pneumoniae, also known as pneumococcus, causes a variety of infections, including acute otitis media (AOM), pneumonia, and invasive pneumococcal disease (IPD) such as septicaemia, meningitis or bacteraemic pneumonia.
Pneumococcal infections, including IPDs, are major causes of communicable disease morbidity and mortality in Europe and globally.
Pneumococcal infections are treated with antibiotics, and the choice of antibiotic should reflect local resistance patterns and national treatment guidelines.

The highest disease burden is found in infants/toddlers and in the elderly above 65 years of age.
In Switzerland, approximately 80% of fatal pneumococcal infections occur in adults of 65 years and older. In addition to age, there are other factors identified that increase the risk of pneumococcal disease also in younger populations. These risk factors include immunosuppression/immunodeficiencies (HIV infection), chronic lung/heart/liver/kidney disease, splenic dysfunction, diabetes mellitus, or smoking and alcohol abuse.
The polysaccharide capsule of pneumococci is an important virulence factor, which protects the organism from phagocytosis. Over 100 pneumococcal serotypes have been described based on the different capsule antigens.
The prevalence and distribution of invasive serotypes differ across populations and geographical areas. In Switzerland, between 2013-2017, the most common serotypes responsible for IPD were serotypes 3 (17%), 8 (10%), 22F (9%),19A (6%), 7F and 9N (both 5%).[1] The most common serotypes in 2020 were 8, 3, 22F, 19A, 9N.

In Switzerland, the Federal Commission for Vaccination recommends pneumococcal vaccination with a pneumococcal conjugated vaccines (PCVs) for children under 5 years of age, for older children and adults with health conditions entailing a high risk of invasive pneumococcal disease, and healthy adults aged 65 and over.
Currently available PCVs include PCV13 (Prevenar 13), PCV15 (Vaxneuvance), and PCV20 (Prevenar 20).

CAPVAXIVE (PCV21) contains purified capsular polysaccharides from *S. pneumoniae* serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, deOAc15B (de-O-acetylated serotype 15B), 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B conjugated to CRM197 carrier protein.
CAPVAXIVE contains 4 µg from each pneumococcal polysaccharide, which is a higher dose than for the other approved PCVs (generally 2-2.2 µg, except for 6B in PCV13 and PCV20). In contrast to the currently approved PCVs (PCV13, 15, and 20), CAPVAXIVE does not contain an adjuvant.

CAPVAXIVE includes serotypes that are relevant disease-causing serotypes in the adult population and are also represented in the approved vaccines (as serotypes 3, 7F, 8, 19A). It additionally includes 8 serotypes (15A, 15C [as deOAC15B], 16F, 23A, 23B, 24F, 31 and 35B) that are not represented in other currently available PCVs or in the 23-valent polysaccharide pneumococcal vaccine (PPV23). These additional serotypes have the potential to provide a broader serotype coverage.

[1] Pneumokokkenerkrankungen 2013–2017 BAG-Bulletin 3, 14 January 2019

4 Quality aspects

4.1 Drug substance

CAPVAXIVE is a pneumococcal conjugate vaccine (21-valent) containing 21 pneumococcal polysaccharide (PnPs) serotypes, each individually conjugated to CRM197 carrier protein to produce a distinct monovalent bulk conjugate (MBC). CRM197 is a nontoxic (enzymatically inactive) form of diphtheria toxin (DT). The polysaccharides are purified PnPs from 21 serotypes of *Streptococcus pneumoniae*. The MBC serotype designations are 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, deOAc15B, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F, 35B.
Of the 21 PnPs serotypes, 14 are shared with the applicant's Pneumovax23 (authorisation number 65675, the 23-valent non-conjugated pneumococcal vaccine) and/or Vaxneuvance (authorisation number 68752, the 15-valent pneumococcal conjugate vaccine, approved by Swissmedic in 2023).

The manufacturing process consists of pneumococcal bacteria fermentation and phenol inactivation steps. The inactivated bacteria are processed in clarification, membrane ultrafiltration, polishing and product recovery steps to produce purified PnPs. The manufacturing process and controls of the CRM197 are identical to those for Vaxneuvance (68752). The 21 PnPs serotypes are individually conjugated to CRM197 using a common manufacturing platform with three main processes (polysaccharide preparation, conjugation, and conjugate purification) to produce the MBC drug substances

The physicochemical and biological properties of the drug substance and its impurities were characterised using state-of-the-art methods.

The specifications for release include relevant tests and acceptance criteria, e.g. for appearance, identity, polysaccharide concentration, protein concentration, conjugate size, product-related substances, pH, endotoxin and bioburden control. Specifications are based on clinical experience, batch analysis data (release and stability data) and are in conformance with current compendial or regulatory guidelines. All analytical methods are described and non-compendial methods have been validated in accordance with ICH guidelines.

Batch analysis data for non-clinical batches, clinical batches, and Process Performance Qualification (PPQ) batches were provided. Comparable quality was shown throughout the clinical development. Comparability between PPQ batches, Phase 3 clinical batches and technical development was demonstrated.

No significant changes were observed under the proposed storage conditions for the MBC. Serotype-specific storage periods have been accepted.

4.2 Drug product

The drug product is prepared by pooling 21 MBCs together in histidine buffer, PS-20 and sodium chloride solution. All excipients are compliant with Ph. Eur. standards. Each 0.5mL dose contains a total of 84 µg of PnPs antigen conjugated to approximately 65 µg of CRM197. The volume per nominal dose is 0.5 ml.

The manufacturing process for the drug product consists of formulation, sterile filtration, aseptic filling, and visual inspection steps. Process validation studies were executed at commercial scale using validation batches.

The specifications for the drug product were set based on compendial requirements, experience from clinical trials, and commercial process capability. They include relevant tests and limits, e.g. for

appearance, identity, conjugated saccharide content, polysorbate 20 content, pH, osmolality, bacterial endotoxin, and sterility. All non-compendial methods are validated in accordance with ICH guidelines. Batch analysis data for process performance qualification batches have been provided. All batch release data comply with the commercial drug product specifications.

The drug product container closure system consists of a 1.5mL syringe barrel assembly (Luer lock adaptor and plastic tip cap) and plunger stopper. All components coming into contact with the finished product comply with Ph. Eur. requirements.

The drug product is stored at a temperature of 2–8 ºC (no freezing and protected from light). The product can support up to 24 months of storage at 2–8 ºC and up to 96 hours of time out of storage up to 25 °C. No significant changes were observed under the proposed storage conditions. A shelf life of 24 months has been accepted.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

Regarding the marketing authorisation application for Capvaxive, the Division Nonclinical Assessment conducted an abridged evaluation, which was based on the Health Canada assessment report (12.06.2024) provided by the applicant.
Overall, the submitted nonclinical documentation is considered appropriate to support the authorisation of Capvaxive in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. There were no safety issues identified in the nonclinical studies that would be of concern for human use. All nonclinical data that are relevant for safety are adequately mentioned in the Information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

No clinical pharmacology studies describing the pharmacokinetic properties or the pharmacodynamic profile of PCV21 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/164653/05 Rev. 1).

The pharmacodynamic profile of PCV21 can be characterised by its immunogenicity profile (see the clinical study results).

CAPVAXIVE, similarly to the other pneumococcal vaccines, induces protective, serotype-specific, anticapsular antibodies. Conjugation of polysaccharides to proteins induces a T cell-dependent immune response.

The opsonophagocytic assay (OPA) measures the capacity of the antibodies to opsonise the pneumococci. The level of OPA GMTs that would protect against IPD, pneumonia or any other pneumococcal disease is not set for adults and might be different for each STs and dependent on age/comorbidities.

In the V116 adult clinical programme, vaccine-induced, serotype-specific immune responses (OPA and IgG) were measured using a validated multiplex opsonophagocytic assay (MOPA) and a pneumococcal electrochemiluminescence (Pn ECL) assay, respectively.

The MOPA is an antibody-mediated killing assay that measures the ability of human serum to kill *S. pneumoniae* serotypes with the help of complement and phagocytic effector cells. The assay readout is the opsonisation index, which is the reciprocal of the highest dilution that gives ≥50% bacterial killing, as determined by comparison to assay background controls.

Evaluation of the serotype-specific OPA responses was the primary objective of the V116 Phase 3 studies, while evaluation of serotype-specific IgG GMCs was a key secondary objective.

6.2 Dose finding and dose recommendation

V116-001 was a randomised, double-blind, comparator-controlled, two-phase study to assess the safety, tolerability, and immunogenicity of V116 compared with the 23-valent pneumococcal polysaccharide vaccine (PPV23).
In phase 1, 90 pneumococcal vaccine-naïve adults aged 18–49 years were randomly assigned (1:1:1) to receive a single dose of V116-1 with 2 µg per pneumococcal polysaccharide (PnP) per 0.5 mL, V116-2 with 4 µg/1 mL, or PPV23 (0.5mL).
Both dose levels of V116 were immunogenic, eliciting immune responses to all serotypes contained in the vaccine, as assessed by OPA GMTs and IgG GMCs. Although a direct comparison of V116-1 and V116-2 was not an objective of the study, a dose-response was observed, and V116-2 elicited higher immune responses than V116-1 for nearly all serotypes. V116-2, with 4 µg/each PnP per dose was selected for further evaluation in the phase 2 part of the study.
In phase 2, 508 vaccine-naïve adults aged 50 years or older were randomly assigned (1:1) to receive one dose of V116 or PPV23.
Primary immunogenicity outcomes showed non-inferiority (using a 0.33 margin) of V116 compared with PPV23 as measured by serotype-specific OPA-GMT ratios for the serotypes common to the two vaccines at 30 days after vaccination and showed superiority (using a 1.0 margin) of V116 compared with PPV23 as measured by serotype-specific OPA-GMT ratios for the serotypes unique to V116 at 30 days after vaccination. The above margins are considered weaker than the usually used margins

(0.5-0.67 for non-inferiority and 2.0 for superiority), but can nevertheless be accepted for dose finding, especially as, based on the secondary endpoint, the non-inferiority was also met when a 0.5 margin was used.
There were no vaccine-related serious adverse events or vaccine-related deaths in either study phase. V116 showed a higher rate of solicited local and systemic reactions, and thus was more reactogenic than PPV23.
Based on the above results, the phase 3 studies were conducted with a dose of 4µg/each PnP.

6.3 Efficacy

No clinical efficacy studies were provided in support of this application.
The clinical development programme of V116 was based on the demonstration of non-inferior immunogenicity to currently approved pneumococcal vaccines. In Study V116-P003 (P003) PCV20 (Prevenar 20) was the comparator vaccine and in Study V116-P010 (P010) PPV23 (Pneumovax23).

An immunological correlate of protection is not established for IPD or pneumonia in adults. It is acceptable that the surrogate OPA responses are used for non-inferiority assessment.
Immunogenicity data alone, however, might not predict the clinical benefit of the vaccine against non-invasive diseases, as higher OPA GMTs might be needed as compared to the protection against IPD.
Furthermore, the clinical relevance of superiority compared to vaccines that do not include the same serotypes is not known.

Study P003 was a randomised, active comparator-controlled, parallel-group, multisite, double-blind study to evaluate the safety, tolerability, and immunogenicity of V116 in pneumococcal vaccine-naïve adults ≥18 years of age.
The comparator vaccine PCV20 is approved in Switzerland for the prevention of IPD and pneumonia in adults 65 years and older. PCV20 is approved by other regulatory agencies (EMA, FDA) also for younger adults from 18 years and above. The initial approval of PCV20 was based on immunological non-inferiority for the common serotypes to PCV13 and for the additional serotypes to PPV23.
Although PCV20 was shown to be non-inferior to PCV13 for the common STs, the OPA GMTs were numerically lower for all common serotypes. Clinical efficacy data are not available for PCV20.

In study P003, eligible participants were enrolled in 1 of 2 cohorts based on age. In Cohort 1, approximately 2300 individuals ≥50 years of age were randomly assigned in a 1:1 ratio to receive a single dose of V116 or PCV20 on Day 1. Randomisation was stratified by participant age at enrolment (50 to 64 years, 65 to 74 years, 75 to 84 years, and ≥85 years). In Cohort 2, approximately 300 individuals 18 to 49 years of age were randomised in a 2:1 ratio to receive a single dose of V116 or PCV20 on Day 1.
This study included male or female adults ≥18 years of age with any underlying chronic conditions assessed to be stable per the investigator’s judgment, and WOCBP had to be not pregnant or breastfeeding.
Main exclusion criteria included a history of IPD or other culture-positive pneumococcal disease, a known or suspected impairment of immunological function, prior receipt of any pneumococcal vaccine, or receipt of systemic corticosteroids or immunosuppressive therapy.
The applicant stated that all hypotheses were tested individually for each serotype at a 1-sided 0.025 alpha-level. This approach controlled the 1-sided type 1 error rate at 0.025, and no multiplicity adjustment was required.
The study had >90% power to demonstrate non-inferiority in OPA GMTs between participants 18 to 49 years of age in the V116 group from Cohort 2 (approximately 200 participants) and participants 50 to 64 years of age in the V116 group from Cohort 1 (approximately 575 participants) at an overall 1-sided 2.5% alpha-level, which was one of the secondary endpoints of the study.
Overall, a total of 2663 participants were randomised, and 2656 participants received study intervention. The majority (>97%) of participants completed the study. The number of participants who discontinued the study and the reasons for discontinuation were generally comparable between intervention groups. The majority (77 of 91) of non-randomised participants were screen failures who

did not satisfy the inclusion or exclusion criteria. Important protocol deviations were reported for 222 (8.3%) participants.
Within both cohorts, most randomised participants were included in the OPA and IgG analyses for the per protocol (PP) population for at least 1 timepoint (>97%) and for both Day 1 and Day 30 timepoints (>89%). The reasons for exclusion from the PP population were generally comparable between intervention groups.
Supportive immunogenicity analyses were conducted for the primary immunogenicity endpoints using the full analysis set (FAS) population, defined as all randomised participants who received at least 1 vaccination and had at least 1 serology result.

Among all vaccinated participants (Cohort 1+2) the majority (72%) were white; approximately 10% of participants were black and approximately 14% were Asian. Approximately 59% of participants were female, and 22% of participants were of Hispanic or Latino ethnicity. Almost half of the subjects were recruited in the US.
The median age was 63.0 years (range: 18 to 97 years), and approximately 45% of participants were ≥65 years of age. Within each cohort, the proportions of participants by number of risk factors (0, 1, or ≥2) associated with an increased risk of pneumococcal disease and by specific risk factors were generally comparable between intervention groups.
In Cohort 1, approximately 36% of all vaccinated participants had ≥1 prespecified medical history condition. Diabetes (16.7%), smoking (11.5%) and chronic lung disease (11.3%) were the most frequently reported risk factors. As such, Cohort 1 enrolled mostly healthy elderly subjects.
In Cohort 2, even a higher rate of subjects were healthy, thus not at risk for IPD, and 77.7% did not have a risk factor. Smoking was the most reported risk factor with 10.3%, and chronic lung disease with 9.0%.

Results:
In adults ≥50 years of age (Cohort 1) V116 met the predefined criterion for non-inferiority to PCV20 (lower bound of 95% CI of the OPA GMT ratio [V116/PCV20] >0.5) for each of the 10 common serotypes at 30 days post-vaccination.
However, in case of serotypes 6A, 10A, and 22F, OPA GMTs were numerically lower, with the 95% CI not crossing 1.
V116 met the predefined criteria for superiority (lower bound of the 95% CI of the OPA GMT ratio [V116/PCV20] >2.0) for 10 of 11 serotypes unique to V116 at 30 days post-vaccination, however it did not meet the criteria for serotype 15C, as the lower bound of the 95%CI of the OPA GMT ratio was 1.77.

Furthermore, in Cohort 1 the predefined criteria for superiority to PCV20 (lower bound of 95% CI of the differences [V116 – PCV20] >0.1 [10 percentage points]) for 10 of 11 serotypes unique to V116 based on the proportion of participants with a ≥4-fold rise in serotype-specific OPA responses from baseline to 30 days post-vaccination were also met, but again were not met for ST 15C, as the lower bound of 95% CI of the percentage point difference [V116 –PCV20] was 5.6 percentage points.

Of note, for serotype 15C, the percentage of V116 participants with a ≥4-fold rise from baseline to 30 days post-vaccination was 83.4%.

See tabular presentation of the above results in Tables 2 and 3 of the Information for healthcare professionals.

The applicant chose to test all hypotheses at a 0.025 significance level without correcting for multiplicity that implies co-primary endpoints, and all co-primary endpoints need to reject the null hypothesis to claim “success”.

In both superiority hypotheses there was the 15C serotype, for which the null-hypothesis could not be rejected. It is therefore not possible for the applicant to claim superiority (with regards to primary hypotheses 2 and 3), as the applicant chose not to correct for multiplicity and otherwise the type 1 error is not controlled at 0.025.

In Cohort 1 V116 for serotype 15B (cross reactive to serotype 15C), the percentage of participants with a ≥4-fold rise in cross-reactive OPA responses from baseline to 30 days post-vaccination was 64.7% (95% CI: 61.4, 67.8), thus it met the predefined criterion for an acceptable antibody response (lower bound of the 95% CI of the proportion of participants with a ≥4-fold rise in OPA responses >0.5 [>50%]).

For serotype 6C (cross reactive to serotype 6A) the predefined criterion for an acceptable antibody response was not met, as the percentage of participants with a ≥4-fold rise in cross-reactive OPA responses from baseline to 30 days post-vaccination was 49.3% (95% CI: 46.0, 52.6).

For primary immunogenicity endpoints, serotype-specific OPA GMT ratios and the proportion of participants with a ≥4-fold rise in serotype-specific OPA responses at 30 days post-vaccination with V116 in Cohort 1 within each of the subgroup categories analysed (age, sex, race, ethnicity, number of risk factors) were generally consistent with the results observed in the overall population.

A trend toward lower immune responses (OPA GMTs) was observed in the older age groups (i.e. 65 to 74 years, and ≥75 years) compared with the younger age group (50 to 64 years) in Cohort 1.

The predefined criteria for immunobridging were met for V116 in participants 18 to 49 years of age (Cohort 2) compared with V116 in participants 50 to 64 years of age (Cohort 1) for all 21 serotypes (lower bound of the 95% CI of the OPA GMT ratio [V116 18 to 49 years group/V116 50 to 64 years group] >0.5) as assessed by serotype-specific OPA GMTs at 30 days post-vaccination.

This is not an unexpected result as a trend toward higher immune responses is generally seen in younger adults compared to older adults.

See tabular presentation of the above results in Table 6 of the Information for healthcare professionals.

As Cohort 2 mostly enrolled healthy young adults, the clinical relevance of this “immunobridging” for the younger adults with risk factors for IPD, who are the target population to be vaccinated in this age range, is not known.

Results for serotype-specific OPA GMTs at 30 days post-vaccination in the FAS population were consistent with those observed in the PP population.

For serotype 15B (cross-reactive to serotype 15C), V116 in participants 18 to 49 years of age (Cohort 2) met the predefined criterion for immunobridging to V116 in participants 50 to 64 years of age (Cohort 1) (lower bound of the 95% CI of the OPA GMT ratio [V116 18 to 49 years group/V116 50 to 64 years group] >0.5) as assessed by serotype-specific OPA GMTs at 30 days post-vaccination. The immunobridging hypothesis was not tested for serotype 6C (cross-reactive to serotype 6A) in accordance with the statistical analysis plan.

Study P010 was a randomised, active comparator-controlled, parallel-group, multisite, double-blind study to evaluate the safety, tolerability, and immunogenicity of V116 in pneumococcal vaccine-naïve adults ≥50 years of age or older.
Participants were enrolled in a 1:1 ratio to receive a single dose of either V116 or PPV23.
PPV23 is approved for subjects aged 2 years and older with an increased risk of pneumococcal disease. In general, a conjugated pneumococcal vaccine induces stronger immune/OPA responses than a polysaccharide vaccine, thus it is not the preferred comparator, although it is understood to have the highest serotype overlap with V116. Furthermore, although PPV23 has proven effectiveness against IPD, effectiveness against pneumonia based on literature data is controversial.

In this study randomisation was stratified by age at enrolment (50 to 64 years, 65 to 74 years, and ≥75 years), and at least 50% of participants were ≥65 years of age.

The study had the same main inclusion and exclusion criteria as Study P003. The same non-inferiority and superiority criteria were used as in Study P003 (except for the immunobridging to other age groups). Of note, the common and unique serotypes differed as the comparator was different.

The study was planned to randomise approximately 700 participants to the V116 group and 700 participants to the PPV23 group. The overall power for all the primary hypotheses was >90% at an overall 1-sided 2.5% alpha level.
All hypotheses were tested individually for each serotype at a 1-sided 0.025 alpha level.
This approach controlled the 1-sided type 1 error rate at 0.025, and no multiplicity adjustment was required.

Overall, a total of 1484 participants were randomised, and 1480 participants received the study intervention. The majority (>98%) of participants completed the base study.
The number of participants who discontinued the study and the reasons for discontinuation were generally comparable between the intervention groups.

The demographic characteristics were generally comparable between the intervention groups.
The majority (62.2%) of participants were white, 19.7% were Asian, and 16.4% were multiple races.
Approximately 55% of participants were female, and approximately 21% of participants were of Hispanic or Latino ethnicity.
The median age was 65.0 years (range: 50 to 90 years), and approximately 54% of participants were ≥65 years of age. A total of 142 subjects (9.6%) were ≥75 years of age.
The proportions of participants by number of risk factors (0, 1, or ≥2) associated with an increased risk of pneumococcal disease and by specific risk factors were generally comparable between the intervention groups.
Approximately 28% of all vaccinated participants had ≥1 prespecified medical history condition (alcoholism, chronic heart disease, chronic kidney disease, chronic liver disease, chronic lung disease, diabetes, or smoking). The most frequently reported risk factors were diabetes (11.9%), smoking (8.9%) and chronic lung disease (6.8%), and were balanced between the groups.
Medical history conditions, prior and concomitant medications were generally comparable between the groups.

V116 met the predefined criterion for non-inferiority to PPV23 (lower bound of 95% CI of the OPA GMT ratio [V116/PPV23] >0.5) for each of the 12 common serotypes at 30 days post-vaccination.
V116 also met the predefined criterion for superiority to PPV23 (lower bound of 95% CI of the OPA GMT ratio [V116/PPV23] >2.0) for each of the 9 serotypes unique to V116 at 30 days post-vaccination.
Results for serotype-specific OPA GMTs at 30 days post-vaccination in the FAS population were consistent with those observed in the PP population.

V116 met the predefined criterion for superiority to PPV23 (lower bound of 95% CI of the differences [V116 – PPV23] >0.1 [10 percentage points]) for 8 of the 9 STs unique to V116 based on the proportions of participants with a ≥4-fold rise in serotype-specific OPA responses from baseline to 30 days post-vaccination. V116 did not meet the predefined criterion for superiority to PPV23 for ST 15C as the lower bound of the 95% CI of the percentage point difference [V116 – PPV23] was 7.5 percentage points.

Supportive studies further assessed the immune response of PCV21 in different settings and populations.

In the lot-to-lot study V116-P004 with vaccine-naïve adults 18 to 49 years of age, the 3 lots of V116 met the safety and immunology equivalence criteria for all 21 serotypes demonstrating consistency in manufacturing.

In study V116-P005, V116 was immunogenic when administered concomitantly with QIV in vaccine-naïve and vaccine-experienced adults ≥50 years of age. There was a trend toward lower serotype-specific OPA GMT and IgG GMCs when co-administered; serotype 23B did not meet the prespecified non-inferiority criterion and, additionally, the influenza strain A/H3N2 also marginally missed it.

In the descriptive Study V116-P006 with pneumococcal vaccine-experienced adults 50 years and older, who received the previous pneumococcal vaccine more than 1 year prior, V116 was immunogenic for all 21 serotypes contained in the vaccine. However, when PPV23 was used as the prior vaccination immune response based on OPA GMTs/IgG, GMCs were lower than when PCV 13 was used previously.

In the descriptive Study V116-P007, V116 induced an acceptable immune response in adults living with HIV compared to PCV15 followed by PPV23 8 weeks later. The study population was mostly suppressed, with stable disease and with good immune function.

Study V116-P008 showed that V116, in adults 18 to 64 years of age with stable conditions and at increased risk for pneumococcal disease, induced similar immune response (for the common 13 STs) as PCV15+PPV23 given with an 8-week interval.

Immunogenicity data in patients with high-risk conditions, splenic disorders, HSCT and SOT patients, immunosuppression due to other reasons, and severe or other immunodeficiency as stable HIV positivity (Study P007) were not provided. Data on subjects with non-stable underlying medical conditions were not available and, as stated by the applicant in the response to the preliminary decision, studies in the above-mentioned populations are not ongoing or planned.

In the submitted studies immunogenicity was assessed 30 days post-vaccination, thus currently long-term persistence data are not available. The long-term immunogenicity sub-study of Study P010 will provide further information, with results expected at the end of 2025.

6.4 Safety

The safety data from 6 phase 3 studies were integrated by pooling the participants who received V116 into 1 group (V116-003, V116-004, V116-006, the sequential group in V116-005, V116-007, and V116-010) and by pooling the participants who received an active comparator (PCV15, PCV20, and/or PPV23) into 1 combined control group.
This integrated population included 7828 participants overall, of these 4914 received PCV21. This included 1919 adults 18-49 years of age (1896 vaccine-naïve and 23 vaccine-experienced) and 2995 adults older than 50 years (2300 vaccine-naïve and 695 vaccine-experienced).
A total of 2914 subjects received an active control, 9% PCV15, 44% PCV20 and 47% PPV23.
Most of the subjects (67%) did not have a risk factor for IPD.
The safety database is sufficient to characterise the safety profile of PCV21.

Solicited adverse events were reported in 61.1% of the PCV21 group and 60.1% of the control group.
There were slightly more solicited injection site reactions and systemic AEs after PCV21 (54.4% vs 52.0% and 35.0% vs 30.0%, respectively).
The most common solicited injection site reaction was injection site pain (52.9% vs 49.9%), injection site erythema (8.9% vs 6.7%), and injection site swelling (8.9% vs 7.6%).
The most commonly reported solicited systemic AEs were fatigue (25.3% vs 21.5%), headache (17.7% vs 14.5%), myalgia (10.4% vs 7.1%), and pyrexia (2.0% vs 1.5%).
The rate of unsolicited AEs was comparable between the groups (23.1% vs 22.5%).

All injection site AEs and pyrexia solicited from Day 1 through Day 5 post-vaccination were considered vaccine related.
The most frequently reported (≥5%) vaccine-related AEs in the integrated safety population were the solicited AEs of injection site pain, fatigue, headache, myalgia, injection site erythema, and injection

site swelling. The proportions of participants with vaccine-related AEs, including solicited AEs, were generally comparable between the V116 group and the combined control group.

Vaccine-related unsolicited AEs within 30 days after vaccination were more frequently reported in the PCV21 group compared to the combined active control group of PCV13, PCV20 and/or PPV23 (8.1% vs 5.5%). Lymphadenopathy, diarrhoea, nausea, chills, feeling hot, injection site erythema, pruritus, swelling, arthralgia, dizziness, headache, cough, and oropharyngeal pain contributed the difference.

The proportion of participants with SAEs was low (≤3%) and generally comparable for the V116 group and the combined control group in the integrated safety population for all time periods analysed (within 30 minutes, Day 1 through Day 30, and Day1 through Month 6 post-vaccination).

Among the SAEs up to 30 days and up to 6 months post-vaccination there were no MedDRA SOC where PCV21 had higher rates than in the control group, with the exception of respiratory, thoracic and mediastinal disorders, including acute respiratory failure, bronchospasm, COPD, dyspnoea, pneumothorax, and pulmonary embolism, which had one event each.

There were 2 vaccine-related SAEs in the PCV21 group: bronchospasm and injection site cellulitis. The SAE of bronchospasm in the sequential group of V116-005 occurred within 30 minutes following vaccination with V116, required medical intervention and resolved after approximately 24 hours. The SAE of injection site cellulitis with an onset on Day 5 post-vaccination with V116 in V116- required hospitalisation and resolved on Day 16.

There were 10 deaths in the integrated safety population. None of the deaths were considered to be vaccine related by the investigator, which is supported based on the narratives.

As Study P008V116 (P008) was not included in the pooled safety analyses, its findings are presented separately. Study P008 included participants aged 18-64 years with stable underlying risk conditions as diabetes mellitus, chronic heart disease, chronic lung disease, chronic kidney and liver disease.
The proportion of participants with AEs was lower in the V116+Placebo group (68.7%), compared with the PCV15+PPV23 group (90.8%). Following any vaccination, the most frequently reported (≥5%) AEs in both intervention groups were the solicited AEs of injection site pain, fatigue, injection site swelling, headache, injection site erythema, and myalgia.
The proportions of participants with solicited injection site and systemic AEs were lower in the V116+Placebo group (52.6% and 40.7%, respectively), compared with the PCV15+PPSV23 group.
Of the participants with solicited AEs, the majority experienced AEs that were mild (Grade 1) or moderate (Grade 2) and of short duration (≤3 days) in both intervention groups.
The proportion of participants with SAEs was low (≤5.4%) and generally comparable in both intervention groups. None of the SAEs were considered by the investigator to be related to the study vaccine. In summary, the safety findings in Study P008 did not raise any concerns, the safety profile was in line with the findings of the integrated safety analyses.

The safety profile observed after concomitant administration of V116 with inactivated influenza vaccine was generally consistent with the safety profile observed for V116 administered alone.

6.5 Final clinical benefit risk assessment

Streptococcus pneumoniae causes community-acquired pneumonia, otitis media, sinusitis and invasive pneumococcal disease, such as bacteraemia, sepsis or meningitis.
Pneumococcal infections, including invasive pneumococcal infections (IPDs), are major causes of communicable disease morbidity and mortality in Europe and globally.
The highest disease burden is found in infants/toddlers and in the elderly above 65 years of age.
In Switzerland, approximately 80% of fatal pneumococcal infections occur in adults 65 years and older.

In addition to age, there are other identified factors that increase the risk of pneumococcal disease, including in younger populations. These risk factors include immunosuppression / immunodeficiencies (HIV infection), chronic lung/heart/liver/kidney disease, splenic dysfunction, diabetes mellitus, or smoking and alcohol abuse.

The totality of the submitted data demonstrated that PCV21 is immunogenic in the mostly healthy, immunocompetent adult population over 18 years of age.
The provided pivotal immunogenicity data in vaccine-naïve subjects over 50 years of age showed non-inferior immune response to an approved conjugated pneumococcal vaccine (PCV20).

In the lack of an established correlate of protection for pneumococcal disease in adults, the immunogenicity data do not allow a firm conclusion on efficacy.
Non-inferior OPA responses compared to PCV20 were demonstrated for the 10 common serotypes and to the polysaccharide pneumococcal vaccine (PPV23) for the 12 common serotypes, although uncertainties remain for the benefit of the unique STs. The exact protective effect against disease caused by the additional 8 serotypes not included in other pneumococcal vaccines based on the immune response without a correlate of protection is hard to predict, although there is no biological reason to believe that it would not translate into a clinical benefit for the protection against IPD. However, it is more difficult to predict the effectiveness against non-bacteraemic pneumonia, as it is likely that higher OPA GMTs are needed for protection.
Efficacy data with PCV20 are not available, and the effectiveness of PPV23 is demonstrated for IPD, but is controversial against pneumonia.
Efficacy against IPD and CAP for adults aged 65 years and older through (serial) immunobridging can only be inferred for 4 STs common with PCV13, the only PCV with proven efficacy against IPD and CAP in adults over 65 years and older.

A post-marketing observation study is planned to confirm the overall effectiveness of PCV21 against vaccine-type community-acquired pneumonia. The study results are requested to be submitted as a post-marketing requirement.

PCV 21 has an acceptable safety profile, which is generally comparable to other PCVs, but with somewhat higher reactogenicity.

The totality of the provided data is considered sufficient to accept the proposed indication for adults 18 years of age and above, in line with the currently published *Swissmedic Position zu konjugierten Pneumokokken-Impfstoffen,* which included the reconsiderations of the previous regulatory approach concerning the approval of PCVs for younger adults (18-64 years of age).

The role of CAPVAXIVE in the armamentarium of pneumococcal disease prevention might be its use (complementing the infant immunisation programme) in at-risk and elderly subjects, however, its benefit will be highly dependent on the actual serotype distribution.

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 CAPVAXIVE 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.

CAPVAXIVE®

Composition

Active substances

Pneumococcal polysaccharide conjugate vaccine (21-valent)

Excipients

Sodium chloride (corresp. 1.77 mg sodium), L-histidine, Polysorbate 20, Hydrochloric Acid (for pH adjustment), water for injections and CRM_{197} carrier protein.

Pharmaceutical form and active substance quantity per unit

Solution for injection in pre-filled syringe.
The vaccine is a colourless, clear to opalescent solution.
1 dose (0.5 mL) contains:

Pneumococcal polysaccharide serotype 3[1]	4 µg
Pneumococcal polysaccharide serotype 6A[1]	4 µg
Pneumococcal polysaccharide serotype 7F[1]	4 µg
Pneumococcal polysaccharide serotype 8[1]	4 µg
Pneumococcal polysaccharide serotype 9N[1]	4 µg
Pneumococcal polysaccharide serotype 10A[1]	4 µg
Pneumococcal polysaccharide serotype 11A[1]	4 µg
Pneumococcal polysaccharide serotype 12F[1]	4 µg
Pneumococcal polysaccharide serotype 15A[1]	4 µg
Pneumococcal polysaccharide from deOAc15B (de-O-acetylated serotype 15B)[1]	4 µg
Pneumococcal polysaccharide serotype 16F[1]	4 µg
Pneumococcal polysaccharide serotype 17F[1]	4 µg
Pneumococcal polysaccharide serotype 19A[1]	4 µg
Pneumococcal polysaccharide serotype 20A[1]	4 µg
Pneumococcal polysaccharide serotype 22F[1]	4 µg
Pneumococcal polysaccharide serotype 23A[1]	4 µg
Pneumococcal polysaccharide serotype 23B[1]	4 µg
Pneumococcal polysaccharide serotype 24F[1]	4 µg
Pneumococcal polysaccharide serotype 31[1]	4 µg
Pneumococcal polysaccharide serotype 33F[1]	4 µg

Pneumococcal polysaccharide serotype 35B[1] 4 µg

[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*.

1 dose (0.5 mL) contains approximately 65 µg CRM_{197} carrier protein.

Indications/Uses

CAPVAXIVE 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 «Warnings and precautions» and «Properties/Effects» for information on protection against specific pneumococcal serotypes.

The use of CAPVAXIVE should be based on official recommendations.

Dosage/Administration

Posology

Individuals 18 years of age and older

1 dose (0.5 mL).

The need for revaccination with a subsequent dose of Capvaxive has not been established.

Paediatric population

The safety and efficacy of CAPVAXIVE in children younger than 18 years of age have not been established.

Mode of administration

This vaccine should be administered by intramuscular injection only. The deltoid muscle of the upper arm is the preferred site for injection in adults. CAPVAXIVE must not be administered intravascularly.

For instructions on the handling of the vaccine before administration, see «Other information, *Instructions for handling*».

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Contraindications

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

Warnings and precautions

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 illnesses

Vaccination should be postponed in persons suffering from acute severe febrile illness or acute infection. The presence of a mild infection and/or mild 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

Based on experience with pneumococcal vaccines, immunocompromised individuals, including those receiving immunosuppressive therapy, may have a reduced immune response to CAPVAXIVE.

Protection

As with any vaccine, vaccination with CAPVAXIVE may not protect all vaccine recipients. CAPVAXIVE will only protect against *Streptococcus pneumoniae* serotypes included in the vaccine and shows a cross-reactive OPA response to serotype15B (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.

A study in adults aged 50 years and older evaluated the co-administration of CAPVAXIVE with quadrivalent influenza vaccine (QIV; split virion, inactivated) (see «Properties/Effects»).

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

Pregnancy, lactation

Pregnancy

There is no experience with the use of CAPVAXIVE in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see «Preclinical data»).

Administration of CAPVAXIVE in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and the foetus.

Breast-feeding

It is unknown whether CAPVAXIVE is excreted in human milk.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for CAPVAXIVE and any potential adverse effects on the breastfed child from CAPVAXIVE or from the underlying maternal condition.

Fertility

No human data on the effect of CAPVAXIVE 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

CAPVAXIVE 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 CAPVAXIVE was assessed in 6 clinical studies, conducted across the Americas, Europe, Asia Pacific and Africa, which included approximately 8 400 individuals ranging in age from 18 to 97 years. Each study included adults with stable underlying medical conditions. Across all 6 studies approximately 5,500 adults received CAPVAXIVE and approximately 2 900 adults received an active comparator.

Across the six Phase 3 clinical studies, the most commonly reported (> 10%) solicited adverse reactions in individuals 18 to 49 years of age who received CAPVAXIVE were injection-site pain (72.1%), fatigue (35.2%), headache (27.1%), myalgia (16.1%), injection-site erythema (13.1%), and injection-site swelling (12.9%).Across the six Phase 3 clinical studies, the most commonly reported (> 10%) solicited adverse reactions in individuals 50 years of age and older who received CAPVAXIVE were injection-site pain (40.6%), fatigue (18.9%), and headache (11.6%).

In each of the six Phase 3 clinical studies in individuals 18 years of age and older, the majority of local and systemic solicited adverse reactions for individuals who received CAPVAXIVE were mild or moderate (based on intensity or size) and of short duration (≤ 3 days); severe events (defined as an event that prevents normal daily activity or size > 10 cm) occurred in ≤ 1.0% of adults (see Table 1).

List of adverse reactions

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

System Organ Class	Adverse Reactions	Frequency	
		Adults 18 to 49 years of age	**Adults > 50 years of age**
Immune system disorders	Hypersensitivity reaction, including bronchospasm	Rare	Rare
Blood and lymphatic system disorders	Lymphadenopathy	Uncommon	Uncommon
Gastrointestinal disorders	Nausea	Uncommon	Uncommon
	Diarrhoea	Uncommon	Uncommon
General disorders and administration site conditions	Injection-site pain‡	Very common (72.1%)	Very common (40.6%)
	Fatigue‡	Very common (35.2%)	Very common (18.9%)
	Injection-site erythema‡	Very common (13.1%)	Common
	Injection-site swelling‡	Very common (12.9%)	Common
	Pyrexia‡	Common	Common
	Injection-site pruritus	Uncommon	Uncommon
	Chills	Uncommon	Uncommon
Musculoskeletal and connective tissue disorders	Myalgia ‡	Very common (16.1%)	Common
	Arthralgia	Uncommon	Uncommon
Nervous system disorders	Headache‡	Very common (27.1%)	Very common (11.6%)
	Dizziness	Uncommon	Uncommon

‡indicates the specific terms solicited from Day 1 through Day 5 postvaccination in clinical studies of adults

Safety in individuals 65 years of age and older

Overall, there were no clinically meaningful differences of CAPVAXIVE in the safety profile observed in individuals 65 to 74 years and 75 years of age and older when compared to individuals less than 65 years of age (see section «Properties/Effects»).

Safety in adults living with HIV

The safety profile of CAPVAXIVE in adults living with HIV was generally comparable to the safety profile of pneumococcal 15-valent conjugate vaccine (PCV15) followed by pneumococcal 23-valent polysaccharide vaccine (PPV23) (see section «Properties/Effects»).

Safety with concomitant influenza vaccine administration

The safety profile of CAPVAXIVE when administered concomitantly with QIV was generally comparable to the safety profile of CAPVAXIVE (see section «Properties/Effects»).

Safety in Adults with Increased Risk for Pneumococcal Disease

An additional study, Protocol 008, was conducted to evaluate CAPVAXIVE in pneumococcal vaccine-naïve adults 18 to 64 years of age with one or more prespecified chronic medical conditions known to increase the risk of pneumococcal disease. The safety profile of CAPVAXIVE was generally comparable to PCV15 followed by PPV23. Following vaccination with CAPVAXIVE, the most frequently reported (>10%) solicited adverse reactions were: injection-site pain (49.5%), fatigue (24.6%), and headache (15.8%). The proportion of individuals with SAEs were comparable between vaccine groups, and none were assessed by the investigator to be related to CAPVAXIVE.

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 is no data of administration of higher than the recommended dose of CAPVAXIVE.

Properties/Effects

ATC code

J07AL02

Mechanism of action

CAPVAXIVE contains 21 pneumococcal capsular polysaccharides from *S.pneumoniae*each conjugated to a carrier protein (CRM197). CAPVAXIVE elicits a T-cell dependent immune response to induce antibodies that enhance opsonization, phagocytosis and killing of pneumococci to protect against pneumococcal disease. Carrier protein-specific helper T-cells support specificity, functionality, and maturation of serotype-specific B cells.

Immune responses following natural exposure to S. pneumoniae or following pneumococcal vaccination can be determined through the assessments of opsonophagocytic activity (OPA) responses and immunoglobulin G (IgG) titers. OPA representsfunctional antibodies capable of opsonizing pneumococcal capsular polysaccharides for presentation to phagocytic cells for engulfment and subsequent killing. OPA responses are considered an important immunologic surrogate measure of protection against pneumococcal disease in adults.. There is a positive correlation between OPA responses and anti-capsular Immunoglobulin G (IgG) responses. Specific thresholds correlating with protection in adults have not been defined.

Serotype-specific immune responses (OPA and IgG) for the 21 serotypes contained in CAPVAXIVE and the cross-reactive serotype 15B were measured using a validated multiplexed opsonophagocytic assay (MOPA) and pneumococcal electrochemiluminescence (Pn ECL) assay. Serotype 15C represents the immune response to the deOAc15B polysaccharide as the molecular structure for deOAc15B and 15C are similar.

Pharmacodynamics

Not applicable.

Clinical efficacy

No efficacy studies have been conducted with CAPVAXIVE.

Immunogenicity data

Immunogenicity in individuals 18 years of age and older

Six Phase 3, clinical studies (Protocol 003, Protocol 004, Protocol 005, Protocol 006, Protocol 007, and Protocol 010) conducted across the Americas, Europe, Asia Pacific and Africa, evaluated the immunogenicity of CAPVAXIVE in approximately 8 400 individuals 18 years of age and older, of whom approximately 5 500 received CAPVAXIVE. Participants enrolled in the Phase 3 studies included adults across different age groups; approximately 32% were 18 to 49 years of age, 32% were 50 to 64 years of age, 29% were 65 to 74 years of age, and 8% were 75 years of age and older. Of those vaccinated, 14% had received other prior pneumococcal vaccines, 33% had risk factors for pneumococcal disease (e.g., alcoholism, chronic heart disease, chronic liver disease, chronic lung disease including asthma, diabetes, renal disorders, smoking) and approximately 4% were adults living with HIV, which is associated with high risk of pneumococcal disease.

In each study, immunogenicity was assessed by serotype-specific OPA and IgG responses at 1-month postvaccination. Study endpoints included OPA geometric mean titers (GMTs) and IgG geometric mean concentrations (GMCs).

Clinical trials conducted in pneumococcal vaccine-naïve adults

The immunogenicity of CAPVAXIVE in adults was demonstrated based on the pre-specified statistical comparison with licensed pneumococcal vaccines (pneumococcal 20-valent conjugate vaccine (PCV20) and PPV23).

Pneumococcal vaccine-naïve adults 50 years of age and older

In a double-blind study (Protocol 003), 2 362 pneumococcal vaccine-naïve individuals 50 years of age and older were randomised to receive either CAPVAXIVE or PCV20. The study demonstrated that CAPVAXIVE was noninferior to PCV20 for the 10 common serotypes as assessed by the OPA-GMT

ratio (CAPVAXIVE/PCV20) where the noninferiority statistical criteria were met if the lower bounds of the 2-sided 95% Confidence Interval (CI) were > 0.5.

CAPVAXIVE induced statistically significantly stronger OPA responses (as measured by the GMT ratio (CAPVAXIVE/PCV20)) in 10 of 11 additional serotypes contained only in Capvaxive compared to PCV20. Serotype 15C did not meet the criterion for statistical significance (see Table 2).

Table 2: Serotype-Specific OPA GMTs in Pneumococcal Vaccine-Naïve Individuals ≥50 Years of Age (Protocol 003)

Pneumococcal Serotype	CAPVAXIVE (N=1 179)		PCV 20 (N=1 177)		GMT Ratio* (CAPVAXIVE/PCV20) (95% CI)*
	n	GMT*	n	GMT*	
10 Common Serotypes†					
3	1 154	274.0	1 161	176.7	1.55 (1.40, 1.72)
6A	1 148	2 302.0	1 153	2 972.5	0.77 (0.68, 0.88)
7F	1 152	3 637.4	1 158	3 429.9	1.06 (0.95, 1.18)
8	1 155	2 501.3	1 158	1 811.1	1.38 (1.25, 1.53)
10A	1 161	3 893.4	1 159	4 678.0	0.83 (0.75, 0.93)
11A	1 145	3 232.6	1 150	2 092.8	1.54 (1.39, 1.72)
12F	1 160	2 641.2	1 161	2 499.6	1.06 (0.92, 1.21)
19A	1 159	2 136.1	1 162	2 871.8	0.76 (0.69, 0.84)
22F	1 147	3 874.5	1 154	4 770.1	0.81 (0.72, 0.92)
33F	1 154	13 558.9	1 157	11 742.1	1.15 (1.01, 1.32)
11 Additional Serotypes in CAPVAXIVE‡					
9N	1 147	7 470.7	1 150	1 640.4	4.55 (4.12, 5.04)
15A	1 107	5 237.2	1 102	1 589.0	3.30 (2.91, 3.74)
15C	1 153	4 216.2	1 158	2 072.3	2.03 (1.77, 2.34)
16F	1 151	4 868.2	1 153	846.3	5.75 (5.16, 6.41)
17F	1 148	7 764.9	1 156	460.4	16.86 (14.90, 19.09)
20A	1 161	6 099.2	1 155	631.1	9.66 (8.66, 10.79)
23A	1 132	3 737.2	1 104	461.5	8.10 (6.86, 9.55)
23B	1 160	1 082.5	1 160	107.3	10.09 (8.48, 12.00)
24F	1 153	2 728.6	1 130	70.5	38.71 (33.87, 44.25)
31	1 153	3 132.5	1 154	144.4	21.69 (18.68, 25.18)
35B	1 153	8 527.8	1 159	1 383.0	6.17 (5.59, 6.80)
1 Cross-Reactive Serotype					
15B	1 140	4 400.6	1 141	4 640.0	0.95 (0.84, 1.07)

* GMTs, GMT ratio, and 95% CI were estimated from a constrained Longitudinal Data Analysis model.

† A conclusion of non-inferiority for the common serotypes was based on the lower bound of the 2-sided 95% CI for the estimated OPA-GMT ratio (CAPVAXIVE/PCV20) being > 0.5.

‡A statistically significant OPA response for the additional serotypes in CAPVAXIVE was defined as the lower limit of the 2-sided 95% CI for the estimated GMT ratio (CAPVAXIVE/PCV20) of > 2.0.

N=Number of individuals randomized and vaccinated; n=Number of individuals contributing to the analysis.

CAPVAXIVE demonstrated statistically significant stronger OPA responses compared to PCV20 for 10 of 11 additional serotypes, as assessed by the proportion of individuals who achieved a ≥ 4-fold rise from prevaccination to 1-month postvaccination for OPA responses. The statistical criterion was defined

as the difference between CAPVAXIVE and PCV20 being > 10 percentage points (see Table 3). Serotype 15C did not meet the criterion for statistical significance

Table 3: Pneumococcal Vaccine-Naïve Individuals ≥ 50 Years of Age With a ≥ 4-Fold Rise in OPA Responses for Serotypes Additional to CAPVAXIVE (Protocol 003)

Pneumococcal Serotype	CAPVAXIVE (N=1 179)	PCV20 (N=1 177)	Percentage Point Difference (CAPVAXIVE/PCV20)
	Observed Response Percentage (m/n)	Observed Response Percentage (m/n)	Estimate (95% CI) *, †
9N	64.7 (595/920)	19.9 (195/978)	44.7 (40.7, 48.6)
15A	66.7 (462/693)	35.8 (253/706)	30.9 (25.8, 35.8)
15C	83.4 (794/952)	74.2 (695/937)	9.2 (5.6, 12.9)
16F	71.9 (654/910)	20.8 (200/961)	51.1 (47.1, 54.9)
17F	75.8 (653/862)	9.5 (90/952)	66.3 (62.8, 69.6)
20A	67.3 (675/1003)	9.6 (97/1011)	57.7 (54.2, 61.1)
23A	78.9 (598/758)	36.8 (270/734)	42.2 (37.6, 46.6)
23B	85.5 (873/1021)	49.6 (506/1021)	35.9 (32.1, 39.6)
24F	80.5 (745/925)	6.3 (55/872)	74.2 (71.1, 77.1)
31	76.5 (698/912)	17.9 (171/954)	58.6 (54.8, 62.1)
35B	60.0 (550/917)	6.8 (67/988)	53.2 (49.6, 56.6)

* Estimated difference and CI were based on the stratified Miettinen & Nurminen method.

†A statistically significant OPA response was based on the lower bound of the 2-sided 95% CI of the differences [CAPVAXIVE/PCV20] between the percentages of individuals with a ≥ 4-fold rise from prevaccination to 1-month postvaccination being > 10 percentage points.

N=Number of individuals randomized and vaccinated; m=Number of individuals with the indicated response. n=Number of individuals contributing to the analysis.

In a double-blind study (Protocol 010), 1 484 pneumococcal vaccine-naïve individuals 50 years of age and older were randomized to receive either CAPVAXIVE or PPV23. The study demonstrated that CAPVAXIVE was noninferior to PPV23 for the 12 common serotypes as assessed by the GMT ratio (CAPVAXIVE/ PPV23) where the noninferiority statistical criteria were met if the lower bounds of the 2-sided 95% CI were > 0.5. CAPVAXIVE was superior to PPV23 for the 9 serotypes additional to CAPVAXIVE as assessed by the GMT ratio (CAPVAXIVE/ PPV23) where the superiority statistical criteria were met if the lower bound of the 2-sided 95% CI were > 2.0.

Immunobridging in pneumococcal vaccine-naïve individuals 18 to 49 years of age

In a double-blind study (Protocol 003) pneumococcal vaccine-naïve individuals 18 to 49 years of age were randomized in a 2:1 ratio to receive CAPVAXIVE or PCV20.

The group aged 18 to 49 years who received CAPVAXIVE (N = 200) was compared with the group aged 50 to 64 years (N = 589) who also received CAPVAXIVE to investigate OPA responses.

CAPVAXIVE immunobridged serotype-specific immune responses to each of the 21 vaccine serotypes in individuals 18 to 49 years of age to individuals 50 to 64 years of age, as the lower bound of the 2-sided 95% CI for the GMT ratio for each serotype was > 0.5 (see Table 4).

Table 4: Comparison of Serotype-Specific OPA GMTs in Pneumococcal Vaccine-Naïve Individuals 18-49 Years of Age to 50-64 years of age who received CAPVAXIVE (Protocol 003)

Pneumococcal Serotype	18-49 years N=200		50-64 years N=589		GMT Ratio*† (18-49 years/50-64 years) (95% CI)*
	n	GMT	n	GMT	
3	194	308.6	572	282.7	1.09 (0.90, 1.33)
6A	196	5 289.6	569	2 572.9	2.06 (1.61, 2.62)
7F	198	6 447.2	571	4 278.8	1.51 (1.23, 1.84)
8	197	4 516.0	571	3 004.7	1.50 (1.26, 1.79)
9N	197	17 283.2	570	8 791.4	1.97 (1.59, 2.43)
10A	197	6 808.1	575	4 382.6	1.55 (1.26, 1.92)
11A	196	5 871.6	564	3 785.8	1.55 (1.26, 1.91)
12F	196	6 150.4	574	3 561.2	1.73 (1.37, 2.17)
15A	184	11 319.2	550	5 901.2	1.92 (1.55, 2.37)
15C	195	10 194.0	570	5 708.0	1.79 (1.36, 2.35)
16F	193	8 877.0	571	5 720.0	1.55 (1.26, 1.91)
17F	194	16 070.6	568	10 068.0	1.60 (1.26, 2.02)
19A	198	2 773.2	574	2 374.6	1.17 (0.97, 1.40)
20A	197	13 150.0	575	7 562.7	1.74 (1.39, 2.18)
22F	198	9 299.6	568	4 683.6	1.99 (1.58, 2.49)
23A	192	8 848.7	561	4 739.5	1.87 (1.43, 2.44)
23B	198	2 140.1	575	1 420.0	1.51 (1.11, 2.04)
24F	197	4 137.6	570	3 047.2	1.36 (1.10, 1.67)
31	195	8 005.6	570	3 820.7	2.10 (1.63, 2.69)
33F	197	34 805.5	570	17 607.4	1.98 (1.52, 2.57)
35B	198	13 933.4	573	9 053.9	1.54 (1.26, 1.87)

* GMTs, GMT ratio, and 95% CI were estimated from a Longitudinal Data Analysis model.

† A conclusion of immunobridging was based on the lower bound of the 95% CI for the estimated GMT ratio (18-49 years / 50-64 years) being > 0.5.

N=Number of individuals randomized and vaccinated; n=Number of individuals contributing to the analysis.

Clinical trials conducted in adults with prior pneumococcal vaccination

A descriptive Phase 3 study (Protocol 006), enrolled individuals ≥ 50 years of age who were previously vaccinated with other pneumococcal vaccines at least 1 year prior to study entry.

Adults who previously received PPV23 (double-blind cohort) were randomized to receive a single dose of either CAPVAXIVE or PCV15. CAPVAXIVE elicited comparable immune responses as compared with PCV15 for the 6 common serotypes, and higher immune responses for the additional 15 serotypes.

Adults who previously received pneumococcal 13-valent conjugate vaccine (PCV13) (double-blind cohort) were randomized to receive either CAPVAXIVE or PPV23. CAPVAXIVE elicited comparable immune responses as compared with PPV23 for the 12 common serotypes, and higher immune responses for the 9 additional serotypes.

Adults who received other prior pneumococcal vaccines (PCV13 + PPV23, PCV15 + PPV23, PPV23 + PCV13, or PCV15) were allocated to receive CAPVAXIVE (open-label cohort). CAPVAXIVE was demonstrated to be immunogenic for all serotypes included in the vaccine, based on OPA GMTs and the proportion of individuals with ≥ 4-fold rise in OPA responses from baseline to 1-month postvaccination.

Concomitant vaccination

In a double-blind study (Protocol 005), 1 080 adults 50 years of age and older with or without a history of prior pneumococcal vaccination were randomized to receive CAPVAXIVE and QIV concomitantly, followed by placebo 1-month later (concomitant group), or to receive QIV and placebo concomitantly, followed by CAPVAXIVE 1-month later (sequential group).

CAPVAXIVE administered concomitantly with QIV is non-inferior to CAPVAXIVE administered sequentially after QIV(concomitant group/sequential group) for 20 of 21 serotypes contained in the vaccine as the lower bound of the 2-sided 95% CI of the GMT ratio (concomitant group/sequential group) was >0.5; the lower bound for serotype 23B was 0.44. QIV administered concomitantly with CAPVAXIVE was non-inferior to QIV administered sequentially as assessed by influenza strain-specific hemagglutination inhibition (HAI) GMTs at 1-month postvaccination with QIV for 3 of 4 influenza strains. The lower bound of the 2-sided 95% CIs for HAI GMT ratios (concomitant group/sequential group) was >0.67 (the noninferiority margin) for 3 of 4 influenza strains in QIV; the lower bound was 0.67 for the A/H3N2 influenza strain.

Special Populations

Adults living with HIV

In a descriptive, double-blind study (Protocol 007), 313 individuals 18 years of age and older living with HIV, with CD4+ T-cells/µL ≥ 50 and plasma HIV ribonucleic acid (RNA) < 50 000 copies/mL, with or without a history of prior pneumococcal vaccination, were randomized in a 1:1 ratio to receive either CAPVAXIVE followed by placebo 8 weeks later, or PCV15 followed by PPV23 (PCV15 + PPV23) 8 weeks later. At screening, of the participants vaccinated 6.7% had a CD4 T-cell counts ≥ 50 to < 350 cells/µL, 18.6% had CD4+ T-cell counts ≥ 350 to < 500 cells/µL and 74.7% had a CD4+ T-cell counts ≥ 500 cells/µL; 83% had an undetectable HIV viral load (< 20 copies/mL).

CAPVAXIVE was immunogenic for all 21 serotypes contained in the vaccine, as assessed by serotype specific OPA GMTs at 1-month postvaccination with CAPVAXIVE. CAPVAXIVE elicited immune responses that were generally comparable to PCV15 + PPV23 for the 13 common serotypes and higher for the 8 serotypes additional to CAPVAXIVE as assessed by OPA GMTs at 1-month postvaccination with CAPVAXIVE and 1-month postvaccination with PCV15 + PPV23.

Adults at risk for pneumococcal disease
In a descriptive, double-blind study (Protocol 008), 518 individuals 18 to 64 years of age with one or more prespecified stable chronic medical conditions known to increase the risk of pneumococcal disease were randomized in a 3:1 ratio to receive either CAPVAXIVE followed by placebo 8 weeks later, or PCV15 followed by PPV23 (PCV15 + PPV23) 8 weeks later. Among the vaccinated participants, 194 (37.6%) had diabetes mellitus only, 84 (16.3%) had chronic heart disease only, 23 (4.5%) had chronic kidney disease only, 34 (6.6%) had chronic liver disease only, 99 (19.2%) had chronic lung disease only, and 82 (15.9%) had ≥2 increased-risk conditions. CAPVAXIVE was immunogenic for all 21 serotypes contained in the vaccine, as assessed by serotype-specific OPA GMTs at 1-month postvaccination with CAPVAXIVE. CAPVAXIVE elicited immune responses that were generally comparable to PCV15 + PPV23 for the 13 common serotypes and higher for the 8 serotypes unique to CAPVAXIVE as assessed by OPA GMTs at 1-month postvaccination with CAPVAXIVE and 1-month postvaccination with PCV15 + PPV23.

Pharmacokinetics

Not applicable.

Preclinical data

Conventional non-clinical studies of repeated dose toxicity and toxicity to reproduction and development revealed no hazards for humans.

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.
CAPVAXIVE should be administered as soon as possible after being removed from the refrigerator.
In the event of temporary temperature excursions, stability data indicate that CAPVAXIVE is stable at temperatures up to 25° C for 96 hours.
Keep out of the reach of children.

Instructions for handling

- The vaccine should be used as supplied.
- Inspect the solution 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 only, preferably in the deltoid area of the upper arm in adults.

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

Authorisation number

69781

Packs

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

Marketing authorisation holder

MSD Merck Sharp & Dohme AG
Lucerne

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