swissmedic

Date: 17 September 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Prevenar 20

International non-proprietary name: *Streptococcus pneumoniae* serotype 1 / 3 / 4 / 5 / 6A / 6B / 7F / 8 / 9V / 10A / 11A / 12F / 14 / 15B / 18C / 19A / 19F / 22F / 23F / 33F polysaccharide conjugated to *Corynebacterium diphteriae* CRM197 protein

Pharmaceutical form: suspension for injection in pre-filled syringe

Dosage strength(s): 2.2 µg of each serotype / 0.5 mL

Route(s) of administration: intramuscular

Marketing authorisation holder: Pfizer AG

Marketing authorisation no.: 69222

Decision and decision date: approved on 26 March 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.

Table of contents

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
GMR	Geometric mean ratio
GMT	Geometric mean titres
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
NDCMC	Newly diagnosed chronic medical conditions
NO(A)EL	No observed (adverse) effect level
OPA	Opsonophagocytosis assay
PBPK	Physiology-based pharmacokinetics
PCV	Pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PCV20	Pneumococcal conjugate vaccine containing 20 serotypes (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F)
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PPV	Pneumococcal polysaccharide vaccine
PPV23	23-valent pneumococcal polysaccharide vaccine
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SIIV	Seasonal inactivated influenza vaccine
SOC	System organ class

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

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for polysaccharides of *Streptococcus pneumoniae* serotype 1 / 3 / 4 / 5 / 6A / 6B / 7F / 8 / 9V / 10A / 11A / 12F / 14 / 15B / 18C / 19A / 19F / 22F / 23F / 33F conjugated to *Corynebacterium diphteriae* CRM197 protein in the above-mentioned medicinal product.

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

2.2 Indication and dosage

2.2.1 Requested indication

Active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in individuals 18 years of age and older.
For information on protection against specific pneumococcal serotypes, see "Warnings and Precautions" and "Properties/Effects".
Prevenar 20 should be used in accordance with official recommendations.

2.2.2 Approved indication

Active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in individuals 65 years of age and older.
Prevenar 20 does not protect against diseases caused by S. *pneumoniae* serotypes not contained in the vaccine.
For information on protection against specific pneumococcal serotypes, see "Warnings and Precautions" and"Properties/Effects".
Prevenar 20 should be used in accordance with official recommendations.

2.2.3 Requested dosage

Summary of the requested standard dosage:
Individuals 18 years of age and older
Prevenar 20 is to be administered as a single dose to individuals 18 years of age and older.
The need for revaccination with a subsequent dose of Prevenar 20 has not been established.
No data on sequential vaccination with other pneumococcal vaccines or a booster dose are available for Prevenar 20. Based on the clinical experience with Prevenar 13 (a pneumococcal conjugate vaccine consisting of 13 polysaccharide conjugates that are also in Prevenar 20), if the use of 23-valent pneumococcal polysaccharide vaccine (PPV23) is considered appropriate, Prevenar 20 should be given first (see "Properties/Effects").
[…]

Special populations
There are no data with Prevenar 20 in special populations.
Limited experience from clinical studies with Prevenar 13 (a pneumococcal conjugate vaccine consisting of 13 polysaccharide conjugates that are also in Prevenar 20) is available in adults at higher risk of pneumococcal infection (either immunocompromised individuals or following bone marrow transplantation; see "Warnings and precautions" and "Properties/Effects").
Based on these data the following posology was recommended for Prevenar 13:
- Individuals at higher risk of pneumococcal infection (e.g. individuals with sickle cell disease or HIV infection), including those previously vaccinated with 1 or more doses of PPV23, were recommended to receive at least 1 dose of Prevenar 13.

- In individuals with a haematopoietic stem cell transplant (HSCT), the recommended immunisation series with Prevenar 13 consisted of 4 doses of 0.5 mL each. The primary series consisted of 3 doses, with the first dose given 3 to 6 months after HSCT and with an interval of at least 1 month between doses. A booster dose was recommended 6 months after the third dose (see “Properties/Effects”).

Paediatric population
The safety and efficacy of Prevenar 20 in children and adolescents younger than 18 years of age have not been established. No data are available.

Method of administration
For intramuscular use only.
[…]

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	30 November 2022
Formal objection	23 December 2022
Response to formal objection	26 January 2023
Formal control completed	16 February 2023
List of Questions (LoQ)	23 May 2023
Response to LoQ	21 August 2023
Preliminary decision	17 November 2023
Response to preliminary decision	16 January 2024
Final decision	26 March 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 Apexxnar – EMA/12384/2022 – 14 February 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 old, adults over 65 years of age, and (especially) individuals with certain chronic health conditions including chronic pulmonary/heart/lung disease, diabetes, splenic dysfunction, immunosuppression/immunodeficiencies, cerebrospinal fluid leak, Cochlear implant, smoking, or alcoholism.

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

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

The polysaccharide (PS) capsule of pneumococci is an important virulence factor, which protects the organism from phagocytes. Over 90 pneumococcal serotypes have been described based on the different capsule antigens. The prevalence and distribution of invasive serotypes differ across populations and geographic areas.

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 the vaccine serotypes (VTs) in children.

In Switzerland, the Federal Commission for Vaccination recommends pneumococcal vaccination for children under 5 years of age and for older children and adults with health conditions with a high risk of 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 a major cause of vaccine-preventable infections in Switzerland. [1]

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

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

4 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The SwissPAR relating to quality aspects refers to the publicly available assessment report Apexxnar – EMA/12384/2022 – 14 February 2022, issued by the EMA.

5 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority, the EMA. The nonclinical aspects in this SwissPAR refer to the publicly available assessment report Apexxnar – EMA/12384/2022 – 14 February 2022, issued by the EMA.

6 Clinical aspects

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

6.1 Clinical pharmacology

No clinical pharmacology studies describing the pharmacokinetic properties or the pharmacodynamic profile of 20-valent pneumococcal conjugate vaccine (PCV20) 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 PCV20 can be characterised by its immunogenicity profile (see the clinical study results).

6.2 Dose finding and dose recommendation

There was 1 dose response study (B7471001), a Phase 1, first-in-human, randomised, controlled (2-arm parallel design), observer-blind trial to compare the safety and immunogenicity of PCV20 to a tetanus, diphtheria, and acellular pertussis (Tdap) vaccine in healthy adults aged 18-49 years. Overall, 66 adults aged 18 to 49 years with no history of pneumococcal vaccination were randomised 1:1 to receive a single dose of PCV20 or Tdap on Day 1.
The results showed an increase in opsonophagocytosis assay (OPA) geometric mean titres (GMTs) from Day 0 to 1 month after vaccination for all 20 serotypes in the PCV20 group. In the Tdap group, OPA GMTs for each serotype were similar between Day 0 and 1 month after vaccination. The results of this dose response study demonstrated that the PCV20 induced an immune response to all 20 serotypes.

6.3 Efficacy

No efficacy study was submitted in support of this application. The clinical development programme of PCV20 was built on comparative immunology to a 13-valent pneumococcal conjugate vaccine (PCV13) and a 23-valent pneumococcal polysaccharide vaccine (PPV23), which is acceptable.

Pivotal study
The pivotal study B7471007 aimed to demonstrate that in adults 60 years of age and older, the immune responses induced by PCV20 are non-inferior to the immune responses induced by PCV13 for the 13 shared serotypes, and that for the 7 additional serotypes the immune responses induced by PCV20 are non-inferior to the immune responses induced by PPV23. Subsequently, the aim was to demonstrate that the immune responses in younger adults 18 to 59 years of age are non-inferior to the immune responses induced by PCV20 in adults ≥60 years of age.

Adult patients with no history of pneumococcal vaccination were enrolled and assigned to 1 of 3 cohorts based on their age at enrolment and randomised to a PCV20 group or a control group.

- In Cohort 1, participants ≥60 years of age were stratified by age (60–64, 65–69, 70–79, or ≥80 years of age) and randomised (1:1) to receive either PCV20 or PCV13 at Vaccination 1. Participants who received PCV20 at Vaccination 1 received saline at Vaccination 2, and those who received PCV13 at Vaccination 1 received PPV23 at Vaccination 2.
- In Cohort 2, participants 50 to 59 years of age were enrolled and randomised (3:1) to receive a single dose of PCV20 or PCV13 at Visit 1.
- In Cohort 3, participants 18 to 49 years of age were enrolled and randomised (3:1) to receive a single dose of PCV20 or PCV13 at Visit 1.

The primary efficacy endpoint was non-inferiority of serotype-specific OPA titres induced by PCV20 compared to the comparator vaccines 1 month after vaccination. The chosen non-inferiority margin (the lower limit of the 95% CI for the OPA GMT ratio >0.5) is commonly used in vaccine comparative immunogenicity studies and can therefore be accepted. The applicant used OPA titres for the evaluation of immune response, which are commonly used as surrogate marker for a protective effect.

In Cohort 1, 3009 participants were enrolled, 2997 received PCV20 or PCV13, and 2835 (94.2%) completed the study. The disposition of participants in Cohort 1 was similar in the PCV20/saline and PCV13/PPV23 groups, with the most common reason for withdrawal being “lost to follow-up” in both groups.
In Cohort 2, 445 participants were enrolled and vaccinated and 432 (97.1%) completed the study. The disposition of participants in Cohort 2 was similar in the PCV20 and PCV13 groups; the most common reason for withdrawal in both groups was “lost to follow-up”.
In Cohort 3, 448 participants were enrolled, 447 were vaccinated, and 423 (94.4%) completed the study. The disposition of participants in Cohort 3 was similar in the PCV20 and PCV13 groups; the most common reason for withdrawal in both groups was “lost to follow-up”.
A total of 514 subjects older than 65 years received PCV20 in this pivotal study.

The defined non-inferiority criteria were met for all shared 13 serotypes included in PCV20 compared to PCV13 in Cohort 1. Nevertheless, a numerically lower immune response was observed for 11 serotypes. The clinical relevance of this difference is unclear, especially since no correlate of protection exists.
The defined non-inferiority criteria were met for 6 of the 7 additional serotypes in PCV20 compared to PPV23 in Cohort 1. The geometric meant ratios (GMRs) for these serotypes were clearly above 1, indicating a stronger immune response with PCV20 compared to PPV23, which has previously been seen with other PCVs compared to PPV23. However, serotype 8 missed the non-inferiority criterion. The potential reasons for the pronounced difference observed for serotype 8 compared to the other 6 serotypes are unknown. The clinical relevance of this finding and the impact on vaccine efficacy and protection against serotype 8 is not known, but serotype 8 is one of the most common serotypes responsible for IPD in Switzerland.

In Cohort 2, the immune responses to the 20 vaccine serotypes induced by PCV20 in adults 50 to 59 years of age were noninferior to those in adults 60 to 64 years of age.
In addition, in Cohort 3, the immune responses to the 20 vaccine serotypes induced by PCV20 in adults 18 to 49 years of age were non-inferior to those in adults 60 to 64 years of age.

Adult subjects with risk factors for IPD are an important target population for pneumococcal vaccines. Although such subjects were not explicitly recruited, about 1/3 of the enrolled subjects in the pivotal study had at least 1 risk factor (e.g. cardiovascular disease, chronic pulmonary disease, chronic liver disease). In general, the immune response in patients with risk factors was clearly detectable. However, the observed immune responses (OPA GMTs) were lower in subjects with risk factors compared to those without in all cohorts (GMT ratio ~ 60-80%, ≥ 4-fold rise ~5-10% difference).
No studies were performed in immunocompromised patients.

Based on a provided post-hoc analysis for patients ≥65 years of age, it was observed that the overall response measured by OPA GMTs was consistently lower in patients ≥65 years of age compared to the overall population. However, this was observed in both the PCV20/saline and the PCV13/PPV23 groups. The GMRs were similar in the age group ≥65 years of age compared to the overall results and the predefined non-inferiority criteria were met for all the 13 shared serotypes also in the age group ≥65 years of age.
The same pattern could be observed for the 7 additional serotypes with generally lower GMTs for all serotypes compared to the overall population; however, this was again the same for both vaccine arms.

Since the clinical development programme of PCV20 was based on comparative immunogenicity and did not include efficacy studies, efficacy of PCV20 can only be assumed for the age groups for which the comparator vaccine was approved and for which efficacy data were available.
As a consequence, efficacy against pneumococcal disease in adults ≥ 65 years can be extrapolated from the CAPiTA study conducted with PCV13 ("PCV13 was effective in preventing vaccine-type pneumococcal, bacteremic, and nonbacteremic community-acquired pneumonia and vaccine-type invasive pneumococcal disease but not in preventing community-acquired pneumonia from any cause."[2]). However, clinically proven efficacy/effectiveness data for adults <65 years of age were not available. Given the lack of an identified correlate of protection for pneumococcal disease in adults, the immunogenicity data do not directly support a clinical benefit.

Supportive studies

Study B7471002: This was a Phase 2, multicentre, randomised, active-controlled, double-blind study to evaluate the safety and immunogenicity of PCV20 in adults 60 to 64 years of age.
The study was conducted in 444 healthy, pneumococcal vaccine-naïve adults; 221 received PCV20 at Vaccination 1 and saline 1 month later; 222 received PCV13 at Vaccination 1 and PPV23 1 month later.
When comparing the humoral immune response 1 month after Vaccination 1, OPA GMTs against the 13 shared serotypes were numerically higher in subjects who had received PCV13 compared to PCV20. However, the 95% confidence intervals overlapped between the vaccine groups.
In comparison to PPV23, PCV20 induced higher OPA GMTs for all of the 7 additional serotypes, except for serotype 8. These results at 1 month after vaccination are generally in line with results from the pivotal study B7471007.
Data from 12 months after the first vaccination indicate that while OPA GMTs declined over time for both vaccination regimens (PCV20/saline or PCV13/PPV23), titres remained above baseline levels.

Study B7471004: This was a Phase 3, randomised, double-blind trial to evaluate the safety and immunogenicity of PCV20 when co-administered with seasonal inactivated influenza vaccine (SIIV) in adults ≥65 years of age.
A total of 1796 participants were randomised in a 1:1 ratio to either the co-administration or the separate administration group. The co-administration group received SIIV and PCV20 at the same visit (Visit 1), followed 1 month later by administration of saline (Visit 2). The separate administration group received SIIV and saline at Visit 1, followed 1 month later by PCV20 administered at Visit 2.
Non-inferiority of PCV20: non-inferiority for a serotype was declared if the lower bound of the 2-sided 95% CI for the GMR of the co-administration group over the separate administration group exceeded 0.5. The non-inferiority criteria were met for all 20 serotypes of PCV20. However, for all serotypes, OPA GMTs were numerically lower in the co-administration group compared to the separate administration group.
Non-inferiority of SIIV: non-inferiority for a strain was declared if the lower bound of the 2-sided 95% CI for the GMR of the co-administration group over the separate administration group exceeded 0.67. The non-inferiority criteria were met for the immune response to all 4 influenza strains.

Study B7471006: This Phase 3, randomised, open-label study aimed to describe the immune responses to PCV20 in adults ≥65 years of age previously vaccinated with PPV23, PCV13, or PCV13 followed by PPV23.
Subjects ≥ 65 years of age were enrolled into different cohorts based on their previously received pneumococcal vaccination (PCV13, PPV23, or both sequentially (PCV13/PPV23)).
Overall, PCV20 elicited immune responses across all serotypes and cohorts but the immune responses differed considerably between the different cohorts. Overall, the data indicate that PCV20

[2] Bonten, M.J.M.; Huijts, S.M.; Bolkenbaas, M.; Webber, C.; Patterson, S.; Gault, S.; van Werkhoven, C.H.; van Deursen, A.M.M.; Sanders, E.A.M.; Verheij, T.J.M.; et al. Polysaccharide Conjugate Vaccine against Pneumococcal Pneumonia in Adults. N. Engl. J. Med. 2015, 372, 1114–1125.

achieved higher immune responses after prior vaccination with the conjugate vaccine PCV13 compared to prior vaccination with the unconjugated vaccine PPV23, either alone or after prior vaccination with PCV13.

Study B7471008: This was a Phase 3, multi-centre, randomised, double-blind, lot-to-lot consistency study with a 4-arm parallel design in adults 18 to 49 years of age with no history of pneumococcal vaccination.
A total of 1710 participants were included in this study. The pre-defined equivalence criteria were met for comparisons between all PCV20 lots, i.e. each of the CI for the GMR of OPA titres 1 month after vaccination were within the pre-specified interval (0.5, 2.0) for each of the 20 serotypes.

6.4 Safety

Across the 3 Phase 3 studies (B7471006, B7471007, B7471008), 6470 subjects were vaccinated; 4263 subjects received PCV20 and 2207 received a control vaccine. Results were summarised separately by age group for individuals who were naïve to pneumococcal vaccine at trial enrolment, and by prior pneumococcal vaccination status (naïve or previously vaccinated with PCV13, PPV23, or both) for individuals ≥65 years of age.

The proportion of subjects administered PCV20 who reported local reactions within 10 days after vaccination and systemic events within 7 days after vaccination was similar to those administered PCV13 or PPV23.
After PCV20, the most commonly reported local reaction was injection site pain (44% to 79% of subjects), followed by injection site erythema (4.8% to 8.6%), and swelling (4.0% to 9.9%).
The most commonly reported systemic events after PCV20 were muscle pain (32% to 63% of subjects), fatigue (29% to 47%), and headache (13% to 37%); fever was reported in 0.0% to 1.5% of subjects.

Among subjects naïve to pneumococcal vaccine (B7471007 and B7471008), the proportions of subjects reporting any adverse event (AE) within 1 month after vaccination were similar across age groups and were similar for subjects who received PCV20 (8.4% to 10%) and PCV13 (7.3% to 11%). The most frequently reported AEs were in the Infections and Infestations system organ class (SOC).
Among subjects ≥65 years of age, the proportions of subjects by prior pneumococcal vaccination status (B7471006 and B7471007) reporting any AE within 1 month after vaccination were similar for subjects who received PCV20 (4.9% to 10%) or control vaccines (9.0% to 12%). The most frequently reported AEs were in the ‘Infections and Infestations’ SOC (1.2% to 3.2% after PCV20; 1.6% to 4.9% after control vaccines).

Among subjects naïve to pneumococcal vaccine, the proportions of subjects reporting any AE occurring within 1 month after vaccination and considered by the investigator to be related to the study vaccine were low and were similar after PCV20 (≤0.9%) or PCV13 (≤1.5%) and across age groups. The most frequently reported types of AEs considered by the investigator to be related to the study vaccine were injection site reactions in the General isorders and administration site conditions SOC.
Among subjects ≥65 years of age by prior pneumococcal vaccination status, AEs considered related to study vaccine were reported for ≤1.6% of subjects after PCV20 and for ≤2.4% after control vaccines.

The proportions of subjects reporting newly diagnosed chronic medical conditions (NDCMCs) was low, both among subjects naïve to pneumococcal vaccine (≤ 2.3% after both PCV20 and PCV13) and among subjects ≥65 years of age by prior pneumococcal vaccination status (≤ 4.0% after PCV20; ≤ 2.4% after control vaccines). Overall, the NDCMCs reported were generally diseases and conditions often observed in adults in these age groups.

In subjects naïve to pneumococcal vaccine, the proportions of subjects reporting one or more serious adverse events (SAEs) within 6 months after vaccination were low and similar after PCV20 (≤2.4%) or PCV13 (≤1.9%). SAEs were reported at a slightly higher frequency among subjects ≥60 years of age (2.4% after PCV20, 1.9% after PCV13) than in younger age groups (≤0.9% after either vaccine). The most frequently reported SAEs were in the Infections and Infestations SOC.
In subjects ≥65 years of age by prior pneumococcal vaccination status, the proportions of subjects reporting one or more SAEs within 6 months after vaccination were low and similar after PCV20 (≤3.7% in naïve and 2.4% in previously vaccinated) or control vaccine (≤2.8% in naïve or 1.6% in previously vaccinated).

Over the course of the clinical studies, 2 participants died. Neither of the deaths was considered related to study interventions.

In summary, the safety profile of PCV20 was comparable to the safety profile of PCV13. Furthermore, no major safety differences between PCV20 and PPV23 were observed.
An updated safety assessment for subjects over 65 years of age was additionally provided. The safety profile in patients over 65 years of age was generally comparable to the overall population. However, there were slightly more cardiac events in the first month after vaccination in the PCV20 group compared to the PCV13 group (0.8% for PCV20, 0.2% for PCV13) and a similar number compared to the PPV23 group (0.8%). However, this finding may also be due to the unequal sample sizes of the different groups. In addition, as the difference in cardiac events also diminished after 6 months, this is not considered prohibitive.

6.5 Final clinical benefit-risk assessment

Streptococcus pneumonia, or pneumococcus, causes community-acquired pneumonia, otitis media, sinusitis, and invasive pneumococcal disease (IPD), such as bacteraemia, sepsis, or meningitis. Pneumococcal infections and IPDs are among the major causes of morbidity and mortality in Europe and globally, despite available antibiotic treatments. The disease burden is highest in infants/toddlers and in the elderly over 65 years of age. Apart from age, other factors such as immune deficiencies (e.g. HIV infection), chronic diseases, smoking, and alcohol abuse increase the risk of pneumococcal disease. More than 90 *Streptococcus pneumoniae* serotypes (STs) are classified based on the polysaccharide capsule. The distribution and prevalence of the serotypes differ across geographic areas and seasons. Currently, three pneumococcal vaccines are available in Switzerland: a 13-valent conjugated pneumococcal vaccine (PCV13), a 15-valent conjugated pneumococcal vaccine (PCV15) and a polysaccharide vaccine containing 23 STs (PPV23). Higher-valency PCVs might provide better coverage of the pneumococcal diseases compared with lower-valent PCVs; however, the clinical benefit is highly dependent on the local epidemiological situation. With an annual incidence of approximately 10 cases per 100,000 individuals for IPD alone, pneumococcus remains an important cause of vaccine-preventable infections in Switzerland. The impact of the infant immunisation programme has reduced most of the vaccine-type IPD cases in the vaccinated population. However, the rate of IPD in the elderly remained stable until the COVID-19 pandemic. The most common STs responsible for IPD are ST8, ST3, ST23B, 22F, and 9N. Between 2013 and 2021 ST22F was responsible for 5-11% of the analysed IPD cases. Between 2020 and 2021 this rate was 7%. ST33F was found in fewer cases: around 2% between 2017 and 2021.

<u>Beneficial effects and respective uncertainties</u>
The pivotal study B7471007 demonstrated that the immune responses to the shared 13 serotypes with PCV13 induced by PCV20 in adults 60 years of age and older were non-inferior to the immune response induced by PCV13. Nevertheless, numerically lower immune responses were observed for 11 serotypes.
The study also showed that the immune responses to 6 out of 7 additional serotypes induced by PCV20 in adults 60 years of age and older were non-inferior to the immune response induced by PPV23. Serotype 8 missed the non-inferiority margin.

Based on the provided post-hoc analysis for patients ≥65 years of age, it was observed that the overall response measured by OPA GMTs was consistently lower in patients ≥65 years of age compared to the overall population. However, this was observed in both the PCV20/saline and also the PCV13/PPV23 groups.

Undesirable effects and respective uncertainties

The safety profile of PCV20 was comparable to the safety profile of PCV13 as measured by the percentage of subjects reporting local reactions, systemic events, AEs, SAEs, and NDCMCs. Furthermore, no major safety differences between PCV20 and PPV23 were observed. In addition, the safety profile in patients over 65 years of age was comparable to the overall population. As expected, reactogenicity slightly decreased with age, especially for solicited local and systemic reactions. There were slightly more cardiac events in the first month after vaccination in the PCV20 group compared to the PCV13 group, but this difference diminished after 6 months.
Over the course of the clinical studies, 2 participants died. Neither of these deaths was considered related to study interventions.

Final benefit-risk assessment

Overall, the submitted data demonstrated that PCV20 is immunogenic in the elderly population with stable underlying disease. The non-inferior immunogenicity compared to PCV13 is considered proven for adults. However, a reduced immune response of 11 out of the 13 shared serotypes compared to PCV13 was observed and the non-inferiority to serotype 8 compared to PPV23 was not met; the clinical relevance of this is unknown.
As this application was based on immunobridging, no new efficacy studies were provided. Clinical efficacy can only be extrapolated for adults ≥ 65 years based on the results of the CAPiTA study, showing less VT IPD and VT community-aquired pneumonia after vaccination with PCV13.

The safety profile of PCV20 appears to be comparable to the safety profile of PCV13. Furthermore, no major safety differences between PCV20 and PPV23 were observed.

In conclusion, the totality of the submitted data only result in a positive benefit-risk assessment for adults ≥ 65 years. The indication has therefore been restricted to adults ≥ 65 years.

7 Risk management plan summary

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

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Prevenar 20 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.

Prevenar 20®

Composition

Active substances

Polysaccharida streptococci pneumoniae (serotype 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F) conjugatum cum proteinum corynebacteriae diphteriae CRM_{197}.

Adjuvant

Aluminii phosphas.

Excipients

Natrii chloridum (corresp. 1.73 mg sodium), acidum succinicum, polysorbatum 80, aqua ad iniectabilia.

Pharmaceutical form and active substance quantity per unit

Suspension for i.m. injection in pre-filled syringe.

One dose (0.5 ml) contains 2.2 µg of each pneumococcal polysaccharide of the serotypes 1, 3, 4, 5, 6A, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F as well as 4.4 µg of serotype 6B (in total 46.2 µg of polysaccharides) conjugated to CRM_{197} carrier protein (approximately 51 µg per dose) and adsorbed on aluminium phosphate (0.125 mg aluminium per dose).

The vaccine is a homogeneous white suspension.

Indications/Uses

Active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in individuals 65 years of age and older.

Prevenar 20 does not protect against diseases caused by S. *pneumoniae* serotypes not contained in the vaccine.

For information on protection against specific pneumococcal serotypes, see «Warnings and Precautions» and «Properties/Effects».

Prevenar 20 should be used in accordance with official recommendations.

Dosage/Administration

Usual dosage

Individuals 65 years of age and older

Prevenar 20 is to be administered as a single dose to individuals 65 years of age and older.

The need for revaccination with a subsequent dose of Prevenar 20 has not been investigated.

No data on sequential vaccination with other pneumococcal vaccines or a booster dose are available for Prevenar 20. Based on the clinical experience with Prevenar 13 (a pneumococcal conjugate vaccine consisting of 13 polysaccharide conjugates that are also in Prevenar 20), if the use of 23-valent pneumococcal polysaccharide vaccine (PPSV23) is considered appropriate, Prevenar 20 should be given first (see «Properties/Effects»).

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Special dosage instructions

There are no data with Prevenar 20 in special populations.

Children and adolescents

The safety and efficacy of Prevenar 20 in children and adolescents younger than 18 years of age have not been established. No data are available.

Mode of administration

For intramuscular use only.

The dose (0.5 ml) of Prevenar 20 should be administered intramuscularly, preferably in the deltoid muscle, with care to avoid injection into or near nerves and blood vessels.

For instructions on the handling of the vaccine before administration, see section («Other Information», «Instructions for handling»).

Contraindications

Hypersensitivity to the active substances, to any of the excipients, or to diphtheria toxoid.

Warnings and precautions

Do not inject Prevenar 20 intravascularly.

Hypersensitivity

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

Concurrent illness

Vaccination should be postponed in individuals suffering from acute severe febrile illness. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

Thrombocytopenia and coagulation disorders

The vaccine must be administered with caution to individuals with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration.

The risk of bleeding in patients with coagulation disorders needs to be carefully evaluated before intramuscular administration of any vaccine, and subcutaneous administration should be considered if the potential benefit clearly outweighs the risks.

Protection against pneumococcal disease

Prevenar 20 will only protect against *Streptococcus pneumoniae* serotypes included in the vaccine, see «Clinical efficacy», and will not protect against other microorganisms that cause invasive disease or pneumonia. As with any vaccine, Prevenar 20 may not protect all individuals receiving the vaccine from pneumococcal invasive disease or pneumonia.

Immunocompromised individuals

Safety and immunogenicity data on Prevenar 20 are not available for individuals in immunocompromised groups. Vaccination should be considered on an individual basis.

Based on experience with pneumococcal vaccines, some individuals with altered immunocompetence may have reduced immune responses to Prevenar 20.

Individuals with impaired immune response, whether due to the use of immunosuppressive therapy, a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunization. The clinical relevance of this is unknown.

Excipients of particular interest

This medicinal product contains less than 1 mmol sodium (23 mg) in each dose of vaccine (0.5 ml suspension for injection), i.e. it is almost «sodium-free».

Interactions

Concomitant administration of Prevenar 20 with a seasonal influenza vaccine (QIV; surface antigen, inactivated, adjuvanted) was investigated in a study with adults aged 65 years and older. In subjects with underlying conditions associated with a high risk of developing life-threatening pneumococcal disease, consideration may be given to separating administrations of QIV and Prevenar 20 (e.g., by approximately 4 weeks). In a double-blind, randomised study (B7471004) in adults 65 years of age and older, the immune response was formally non-inferior, however numerically lower titres were observed for all pneumococcal serotypes included in Prevenar 20 when given concomitantly with seasonal influenza vaccine (QIV, surface antigen, inactivated, adjuvanted) compared to when Prevenar 20 was given alone. The clinical relevance of this finding is unknown.

Concomitant administration of Prevenar 20 with COVID-19 mRNA vaccine (nucleoside modified) was investigated in a study with adults aged 65 years and older. Thereby, the immune response was comparable between participants receiving Prevenar 20 and saline placebo versus participants receiving Prevenar 20 and the Covid-19 mRNA vaccine (nucleoside modified.

There are no data on the concomitant administration of Prevenar 20 with other vaccines.

Different injectable vaccines should always be given at different vaccination sites.

Do not mix Prevenar 20 with other vaccines/medicinal products in the same syringe.

Pregnancy, lactation

Pregnancy

There are no data on the use of Prevenar 20 in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Administration of Prevenar 20 in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

Lactation

It is unknown whether Prevenar 20 is excreted in human milk.

Fertility

No human data on the effect of Prevenar 20 on fertility are available. Animal studies do not indicate direct or indirect harmful effects with respect to female fertility (see «Preclinical data»).

Effects on ability to drive and use machines

Prevenar 20 has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section «Undesirable effects» may temporarily affect the ability to drive or use machines.

Undesirable effects

Summary of the safety profile

The safety of Prevenar 20 was evaluated in 4552 participants 18 years of age and older in six clinical trials (two Phase 1, one Phase 2, and three core Phase 3), and 2496 participants in the control groups. Of these, one Phase 2 included 443 participants 60 to 64 years of age with 221 who received Prevenar 20 and 222 in the control group. Two of the core Phase 3 trials had 4315 participants that were 50 years of age and older with 2465 in Prevenar 20 and 1850 in the control groups.

In the core Phase 3 trials, 2465 participants 50 years of age and older received Prevenar 20. This included 334 participants 50 through 59 years of age, and 2131 participants 60 years of age and older (1138 were 65 years of age and older). Of the participants, 50 years of age and older who received Prevenar 20 in the core Phase 3 trials, 1841 were naïve to pneumococcal vaccines, 253 had previously received PPSV23 (≥1 to ≤5 years prior to enrollment), 246 had previously received Prevenar 13 only (≥6 months prior to enrollment), and 125 had previously received Prevenar 13 followed by PPSV23 (the dose of PPSV23 ≥1-year prior to enrollment).

Participants in the Phase 3 trial B7471007 (Pivotal Study 1007) were evaluated for adverse events for 1 month after vaccination, and serious adverse events through 6 months after vaccination. This study included 445 participants 50 to 59 years of age, 1985 participants 60 to 64 years of age,

624 participants 65 to 69 years of age, 319 participants 70 to 79 years of age, and 69 participants ≥80 years of age.

In participants 50 to 59 years of age in Study 1007, the most frequently reported adverse reactions were pain at injection site (72.5%), muscle pain (49.8%), fatigue (39.3%), headache (32.3%), and joint pain (15.4%). In participants ≥60 years of age in Study 1007, the most frequently reported adverse reactions were pain at injection site (55.4%), muscle pain (39.1%), fatigue (30.2%), headache (21.5%), and joint pain (12.6%). These were usually mild or moderate in intensity and resolved within a few days after vaccination.

Safety data from a pooled analysis of adults ≥65 years of age including both pneumococcal naïve participants (Study 1007) and participants with prior pneumococcal vaccination (Study 1006) included 1885 participants; among these 1138 received Prevenar 20 and 747 received control vaccine. The safety profile of Prevenar 20 in adults 65 years of age and older with or without prior pneumococcal vaccination was generally similar to control vaccine. MedDRA system organ class (SOC) adverse events for cardiac disorders 1 month after vaccination in participants 65 years of age and older were similar for Prevenar 20 (9 events in 1138 participants (0.8%)) and PPSV23 (1 event in 127 participants (0.8%)), but higher than Prevenar 13 (1 event in 620 participants (0.2%)). At 6 months after vaccination, cardiac events in the SOC were reported for 0.5% of participants (6 events in 1138 participants) who received Prevenar 20.

Phase 3 Study B7471006 (Study 1006) evaluated Prevenar 20 in participants ≥65 years of age with varying prior pneumococcal vaccination status (prior PPSV23, prior Prevenar 13 or prior Prevenar 13 followed by PPSV23). In this study, the most frequently reported adverse reactions for participants were similar in frequency to those described for participants ≥60 years of age in Study 1007, with slightly higher injection site pain (61.2%) in participants with prior Prevenar 13, and joint pain (16.8%) in participants with prior Prevenar 13 followed by PPSV23.

List of adverse reactions

The adverse reactions from the Phase 3 clinical trials and post-marketing experience are presented below.

The adverse reactions are listed according to MedDRA system organ classes in decreasing order of frequency and seriousness. The frequency is defined as follows: «very common» (≥1/10), «common» (≥1/100, <1/10), «uncommon» (≥1/1000, <1/100), «rare» (≥1/10’000, <1/ 1000), «very rare» (<1/10’000) and «not known» (frequency cannot be estimated from the available data).

Adverse reactions from clinical trials

Prevenar 20

As Prevenar 20 contains the same 13 serotype-specific capsular polysaccharide conjugates and the same vaccine excipients as Prevenar 13, the adverse reactions already identified for Prevenar 13 have been adopted for Prevenar 20. Listed below are the adverse reactions reported in Phase 3 trials of Prevenar 20, based on the highest frequency among adverse reactions, local reactions, or systemic events after vaccination in any Prevenar 20 group. In clinical trials, the safety profile of Prevenar 20 was similar to that of Prevenar 13. No new adverse reactions were identified as compared to Prevenar 13.

Immune system disorders

Uncommon: Hypersensitivity reaction, including face oedema, dyspnoea, bronchospasm.

Metabolism and nutrition disorders

Not known: Decreased appetite[a].

Nervous system disorders

Very common: Headache (36.7%)

Gastrointestinal disorders

Uncommon: Diarrhoea[a], nausea, vomiting[a].

Skin and subcutaneous tissue disorders

Uncommon: Rash[a], angioedema.

Musculoskeletal and connective tissue disorders

Very common: Muscle pain (62.9%), joint pain (16.8%).

General disorders and administration site conditions

Very common: Vaccination-site pain/tenderness (79.2%), fatigue (46.7%).

Common: Vaccination-site induration/swelling[a], vaccination-site erythema[a], pyrexia.

Uncommon: Vaccination-site pruritus, lymphadenopathy, vaccination-site urticaria, chills[a].

Not known: Limitation of arm movement[a].

[a] Event reported in clinical trials with Prevenar 13 with very common frequency (≥1/10). Decreased appetite and limitation of arm movement were not reported in the adult Phase 3 trials of Prevenar 20; therefore, the frequency is not known.

Safety with concomitant vaccine administration in adults

When Prevenar 20 was administered to adults aged ≥65 years together with the third (booster) dose of a COVID-19 mRNA vaccine (nucleoside modified), the tolerability profile generally resembled that of the COVID-19 mRNA vaccine (nucleoside modified) administered alone. There were a few differences in the safety profile when compared to administration of Prevenar 20 alone. In the phase 3 trial B7471026 (Study 1026), pyrexia (13.0%) and chills (26.5%) were reported as «very common» with co-administration. There was also one report of dizziness (0.5%) in the co-administration group.

Prevenar 13

Adults ≥65 years in the clinical efficacy study CAPiTA

The CAPiTA study compared 42’240 individuals ≥65 years vaccinated with Prevenar 13 to 42’256 individuals ≥65 years under placebo.

Among the 84’496 subjects, 58’072 (68.7%) were ≥65 to <75 years of age, 23’481 (27.8%) were ≥75 and <85 years of age, and 2’943 (3.5%) were ≥85 years of age. In the total safety population, more males (55.9%) were enrolled than females. Adults with immunocompromising conditions or receiving immunosuppressive therapy and adults residing in a long-term care facility or requiring semiskilled nursing care were excluded. Adults with pre-existing medical conditions, as well as subjects with a history of smoking were eligible for enrollment. In the safety population, 42.3% of subjects had pre-existing medical conditions including heart disease (25.4%), lung disease or asthma (15.1%) and type 1 and type 2 diabetes mellitus (12.5%). Smoking was reported at baseline by 12.3% of the subjects.

For a subset of 2011 subjects (1006 Prevenar 13 recipients and 1005 placebo recipients), solicited adverse reactions were monitored by recording local and systemic events using electronic diaries for 7 days after vaccination; unsolicited adverse events were collected for 28 days after vaccination, and serious adverse events were collected for 6 months after vaccination. For the remaining 41’231 Prevenar 13 and 41’250 placebo vaccinated subjects, serious adverse events were collected for 28 days after vaccination.

In the CAPiTA study (subjects 65 years and older), serious adverse events within 1 month of vaccination were reported in 327 of 42’237 (0.8%) Prevenar 13 recipients (352 events) and in 314 of 42’225 (0.7%) placebo recipients (337 events). In the subset of subjects where serious adverse events were monitored for 6 months, 70 of 1006 (7%) Prevenar 13 vaccinated subjects (90 events) and 60 of 1005 (6%) placebo vaccinated subjects (69 events) reported serious adverse events.

During the follow-up period (average of 4 years) for case accumulation there were 3006 deaths (7.1%) in the Prevenar 13 group and 3005 deaths (7.1%) in the placebo group. There were 10 deaths (<0.1%) in the Prevenar 13 group and 10 deaths (<0.1%) in the placebo group within 28 days of vaccination. There were 161 deaths (0.4%) in the Prevenar 13 group and 144 deaths (0.3%) in the placebo group within 29 days – 6 months following vaccination.

These data do not provide evidence for a causal relationship between deaths and vaccination with Prevenar 13.

Undesirable effects from the post-marketing phase

Listed below are the adverse experiences that have been spontaneously reported during the post-marketing use of Prevenar 13, which may also occur with Prevenar 20. The postmarketing safety experience with Prevenar 13 is relevant to Prevenar 20, as Prevenar 20 contains all components (polysaccharide conjugates and excipients) of Prevenar 13. These events were reported voluntarily from a population of uncertain size. Therefore, it is not possible to reliably estimate their frequency or to establish, for all events, a causal relationship to vaccine exposure.

Immune system disorders

Not known: Anaphylactic/anaphylactoid reaction, including shock.

Skin and subcutaneous tissue disorders

Not known: Erythema multiforme.

General disorders and administration site conditions

Not known: Vaccination-site dermatitis.

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

Overdose with Prevenar 20 is unlikely due to its presentation as a pre-filled syringe.

Properties/Effects

ATC code

J07AL02

Mechanism of action

Prevenar 20 contains 20 pneumococcal capsular polysaccharides all conjugated to a CRM_{197} carrier protein, which modifies the immune response to the polysaccharide from a T-cell independent response to a T-cell dependent response. The T-cell dependent response leads to both an enhanced antibody response and generation of memory B-cells, allowing for an anamnestic (booster) response on re-exposure to the bacterium.

Vaccination with Prevenar 20 induces serum antibody production and immunologic memory against the serotypes contained within the vaccine. In adults, the levels of circulating antibodies that correlate with protection against pneumococcal disease have not been clearly defined.

Pharmacodynamics

No information.

Clinical efficacy

No efficacy studies have been performed with Prevenar 20. The protective efficacy of Prevenar 20 in adults aged 65 years and older is based on the efficacy demonstrated in the adult immunisation study against community-acquired pneumonia immunisation trial in adults, CAPiTA with 13-valent pneumococcal polysaccharide conjugate vaccine (see «Comparison of immune responses of Prevenar 20 to Prevenar 13»).

For serotypes 8, 10A, 11A, 12F, 15B, 22F and 33F, the indication is approved based on immune responses as measured by opsonophagocytic activity (OPA) assay.

Immunogenicity data

Prevenar 20 clinical trials in adults

Three core Phase 3 clinical trials, B7471006, B7471007 and B7471008 (Study 1006, Study 1007, and Study 1008), were conducted in the United States and Sweden evaluating the immunogenicity of Prevenar 20 in different adult age groups, and in participants who were either pneumococcal vaccine-naïve, or previously vaccinated with Prevenar 13, PPSV23 or both.

Each study included participants who were healthy or immunocompetent with stable underlying conditions, including chronic cardiovascular disease, chronic pulmonary disease, renal disorders, diabetes mellitus, chronic liver disease, and medical risk conditions and behaviours (e.g., smoking) that are known to increase the risk of serious pneumococcal pneumonia and IPD. In the pivotal study (Study 1007), these risk factors were identified in 34% of participants 60 years of age and over. A stable medical condition was defined as a medical condition not requiring significant change in therapy in the previous 6 weeks (i.e., change to new therapy category due to worsening disease), or any hospitalization for worsening disease within 12 weeks before receiving the study vaccine.

In each study, immune responses elicited by Prevenar 20 and the control pneumococcal vaccines were measured by an opsonophagocytic activity (OPA) assay. OPA assays measure functional antibodies to *S. pneumoniae*.

Comparison of immune responses of Prevenar 20 to Prevenar 13 and PPSV23

In a randomised, active-controlled, double-blind, non-inferiority clinical trial (Pivotal Study 1007) of Prevenar 20, pneumococcal vaccine-naïve participants 18 years of age and older were enrolled into 1 of 3 cohorts based on their age at enrollment (18 to 49, 50 to 59, and ≥60 years of age), and randomised to receive Prevenar 20 or control. Participants 60 years of age and older were randomised in a 1:1 ratio to receive Prevenar 20 (n=1507) followed 1 month later with the administration of saline placebo or Prevenar 13 (n=1490), and with the administration of PPSV23 1 month later.

Serotype-specific OPA geometric mean titres (GMTs) were measured before the first vaccination and 1 month after each vaccination. Non-inferiority of immune responses, OPA GMTs 1 month after vaccination, with Prevenar 20 to a control vaccine for a serotype was declared if the lower bound of the 2-sided 95% confidence interval (CI) for the GMT ratio (Prevenar 20/Prevenar 13; Prevenar 20/PPSV23) for that serotype was greater than 0.5.

In participants 60 years of age and older, the immune responses to all 13 matched serotypes elicited by Prevenar 20 were non-inferior to those elicited by Prevenar 13 for the same serotypes 1 month

after vaccination. In general, numerically lower geometric mean titres were observed with Prevenar 20 in the matched serotypes compared to Prevenar 13 (Table 1), however the clinical relevance of these findings is unknown.

The immune responses induced by Prevenar 20 to 6/7 additional serotypes were non-inferior to those induced by PPSV23 to the same serotypes 1 month after vaccination. The response to serotype 8 missed the pre-specified statistical non-inferiority criterion (the lower bound of the 2-sided 95% CI for the GMT ratio is 0.49 instead of >0.50) (Table 1). The clinical relevance of this observation is unknown. Supportive analyses for other serotype 8 endpoints in the Prevenar 20 group showed favourable outcomes. These include a geometric mean fold rise (GMFR) of 22.1 from before vaccination to 1 month post-vaccination, 77.8% of participants achieved a ≥4-fold rise in OPA titres from before vaccination to 1 month after vaccination, and 92.9% of participants achieved OPA titres ≥LLOQ 1 month after vaccination.

Table 1: OPA GMTs 1 month after vaccination in participants 60 years of age and older given Prevenar 20 compared to Prevenar 13 for the 13 matched serotypes and to PPSV23 for the 7 additional serotypes (Study 1007)[a,b,c,d]

	Prevenar 20 (N=1157–1430)	*Prevenar 13 (N=1390–1419)*	*PPSV23 (N=1201–1319)*	*Vaccine Comparison*	
	GMT[e]	*GMT*[e]	*GMT*[e]	*GMT Ratio*[e]	*95% CI*[e]
Serotype					
1	123	154		0.80	0.71, 0.90
3	41	48		0.85	0.78, 0.93
4	509	627		0.81	0.71, 0.93
5	92	110		0.83	0.74, 0.94
6A	889	1165		0.76	0.66, 0.88
6B	1115	1341		0.83	0.73, 0.95
7F	969	1129		0.86	0.77, 0.96
9V	1456	1568		0.93	0.82, 1.05
14	747	747		1.00	0.89, 1.13
18C	1253	1482		0.85	0.74, 0.97
19A	518	645		0.80	0.71, 0.90
19F	266	333		0.80	0.70, 0.91
23F	277	335		0.83	0.70, 0.97
Additional Serotypes					
8	466		848	0.55	0.49, 0.62
10A	2008		1080	1.86	1.63, 2.12
11A	4427		2535	1.75	1.52, 2.01
12F	2539		1717	1.48	1.27, 1.72
15B	2398		769	3.12	2.62, 3.71
22F	3666		1846	1.99	1.70, 2.32
33F	5126		3721	1.38	1.21, 1.57

Abbreviations: CI=confidence interval; GMT=geometric mean titre; LLOQ=lower limit of quantitation; N=number of participants; OPA=opsonophagocytic activity; PPSV23=pneumococcal polysaccharide vaccine (23-valent).

[a] Study 1007 was conducted in the United States and in Sweden.

[b] Non-inferiority for a serotype was met if the lower bound of the 2-sided 95% CI for the GMT ratio (ratio of Prevenar 20/comparator) was greater than 0.5 (2-fold criterion for non-inferiority).

[c] Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

[d] Evaluable immunogenicity population.

[e] GMTs and GMT ratios as well as the associated 2-sided CIs were based on analysis of log-transformed OPA titres using a regression model with vaccine group, sex, smoking status, age at vaccination in years, and baseline log transformed OPA titres.

A post hoc analysis in Study 1007 participants ≥65 years of age was conducted to evaluate serotype-specific OPA titers 1 month after Prevenar 20 compared to Prevenar 13 for the 13 matched serotypes, and PPSV23 for the 7 additional serotypes in that group. The OPA GMR for each serotype was summarized using the same linear regression model, as in the analysis of the primary immunogenicity objectives in the study population ≥60 years of age. If a 2-fold noninferiority margin (lower bounds of the 2-sided 95% CIs for the model-based OPA GMRs >0.5) as in the primary analysis were applied to the results, all 20 serotypes would have met the statistical noninferiority of Prevenar 20 to Prevenar 13 (or PPSV23) in participants ≥65 years of age.

Immunogenicity of Prevenar 20 in adults previously vaccinated with pneumococcal vaccine

A Phase 3 randomised, open-label clinical trial (Study 1006) described immune responses to Prevenar 20 in participants 65 years of age and older previously vaccinated with PPSV23, with Prevenar 13, or with Prevenar 13 followed by PPSV23. Participants previously vaccinated with Prevenar 13 (Prevenar 13 only or followed by PPSV23) were enrolled at sites in the United States, whereas participants and previously vaccinated with PPSV23 only were also enrolled from Swedish sites (35.5% in that category).

Prevenar 20 elicited immune responses to all 20 vaccine serotypes in participants 65 years of age and older with prior pneumococcal vaccination (Table 2). Immune responses were lower in participants in both groups who received prior PPSV23 vaccinations.

Table 2: Pneumococcal OPA GMTs before and 1 month after Prevenar 20 in participants 65 years of age and older with prior pneumococcal vaccination (Study 1006)[a,b,c,d]

	Prior PPSV23 only		*Prior Prevenar 13 only*		*Prior Prevenar 13 and PPSV23*	
	Before vaccination (N=208–247)	*After vaccination (N=216–246)*	*Before vaccination (N=210-243)*	*After vaccination (N=201–243)*	*Before vaccination (N=106–121)*	*After vaccination (N=102-121)*
	GMT (95% CI)[e]	*GMT (95% CI)*[e]	*GMT (95% CI)*[e]	*GMT (95% CI)*[e]	*GMT (95% CI)*[e]	*GMT (95% CI)*[e]
Serotype						
1	24 (20, 28)	51 (42, 62)	34 (28, 41)	115 (96, 138)	42 (32, 56)	82 (61, 110)
3	13 (11, 15)	31 (27, 36)	15 (13, 18)	54 (47, 63)	20 (17, 25)	39 (32, 48)
4	29 (23, 35)	150 (118, 190)	67 (53, 84)	335 (274, 410)	73 (53, 101)	194 (143, 262)
5	27 (24, 31)	63 (53, 75)	38 (32, 44)	87 (73, 104)	47 (37, 59)	83 (65, 108)
6A	57 (46, 70)	749 (577, 972)	125 (99, 158)	1081 (880, 1327)	161 (116, 224)	1085 (797, 1478)
6B	107 (86, 133)	727 (574, 922)	174 (138, 219)	1159 (951, 1414)	259 (191, 352)	1033 (755, 1415)
7F	156 (132, 184)	378 (316, 452)	210 (175, 251)	555 (467, 661)	206 (164, 258)	346 (277, 432)
9V	203 (171, 241)	550 (454, 667)	339 (282, 408)	1085 (893, 1318)	352 (270, 459)	723 (558, 938)
14	212 (166, 270)	391 (315, 486)	282 (224, 356)	665 (554, 798)	336 (238, 473)	581 (434, 777)
18C	173 (137, 218)	552 (445, 684)	219 (177, 272)	846 (693, 1033)	278 (209, 369)	621 (470, 821)
19A	82 (66, 100)	239 (197, 288)	124 (100, 153)	365 (303, 440)	182 (141, 235)	341 (264, 439)
19F	61 (52, 71)	159 (131, 192)	89 (74, 107)	242 (199, 294)	120 (94, 154)	218 (168, 282)
23F	23 (18, 28)	152 (115, 199)	48 (37, 62)	450 (358, 566)	66 (46, 94)	293 (204, 420)
Additional Serotypes						
8	55 (45, 67)	212 (172, 261)	28 (24, 33)	603 (483, 753)	139 (99, 195)	294 (220, 392)
10A	212 (166, 269)	1012 (807, 1270)	141 (113, 177)	2005 (1586, 2536)	400 (281, 568)	1580 (1176, 2124)
11A	510 (396, 656)	1473 (1192, 1820)	269 (211, 343)	1908 (1541, 2362)	550 (386, 785)	1567 (1141, 2151)
12F	147 (112, 193)	1054 (822, 1353)	53 (43, 65)	1763 (1372, 2267)	368 (236, 573)	1401 (1002, 1960)
15B	140 (104, 189)	647 (491, 853)	74 (56, 98)	1480 (1093, 2003)	190 (124, 291)	1067 (721, 1578)
22F	167 (122, 230)	1773 (1355, 2320)	60 (45, 82)	4157 (3244, 5326)	286 (180, 456)	2718 (1978, 3733)
33F	1129 (936, 1362)	2026 (1684, 2437)	606 (507, 723)	3175 (2579, 3908)	1353 (1037, 1765)	2183 (1639, 2908)

Abbreviations: CI=confidence interval; GMT=geometric mean titre; LLOQ=lower limit of quantitation; N=number of participants; OPA=opsonophagocytic activity; PPSV23=pneumococcal polysaccharide vaccine (23-valent).

[a] Study 1006 was conducted in the United States and in Sweden.

[b] Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

[c] Evaluable immunogenicity population.

[d] Open-label administration of Prevenar 20.

[e] 2-sided CIs based on the Student t distribution.

Pharmacokinetics

Evaluation of pharmacokinetic properties is not required for vaccines.

Absorption

Not applicable

Distribution

Not applicable.

Metabolism

Not applicable.

Elimination

Not applicable.

Preclinical data

Non-clinical data revealed no special hazard for humans based on conventional studies of repeated-dose toxicity and reproduction and developmental toxicity.

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 the refrigerator (2-8 °C). Pre-filled syringes should be stored in the refrigerator horizontally to minimise the resuspension time.

Do not freeze. Discard if the vaccine has been frozen.

From a microbiological point of view, once removed from the refrigerator, the vaccine should be used immediately.

Stability data indicate that the vaccine is stable for 96 h when stored at temperatures from 8 °C to 25 °C, or 72 h when stored at temperatures from 0 °C to 2 °C. At the end of these time periods Prevenar 20 should be used or discarded. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

Keep out of the reach of children.

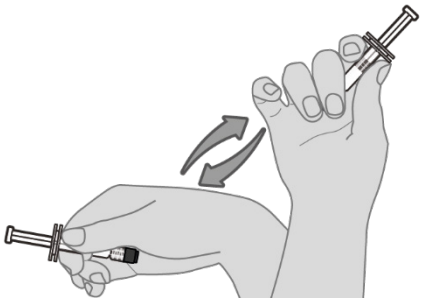
Instructions for handling

During storage, a white deposit and clear supernatant may be observed in the pre-filled syringe containing the suspension. Pre-filled syringes should be stored horizontally to minimise the resuspension time.

Preparation for administration

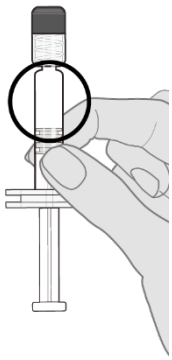
Step 1. Vaccine resuspension

Hold the pre-filled syringe horizontally between the thumb and the forefinger and shake vigorously until the contents of the syringe are a homogeneous white suspension. Do not use the vaccine if it cannot be resuspended.



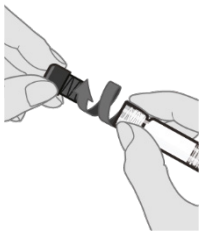
Step 2. Visual inspection

Visually inspect the vaccine for large particulate matter and discolouration prior to administration. Do not use if large particulate matter or discolouration is found. If the vaccine is not a homogenous white suspension, repeat steps 1 and 2.



Step 3. Remove syringe cap

Remove the syringe cap from the Luer lock adapter by slowly turning the cap counter clockwise while holding the Luer lock adapter.



Note: Care should be taken to ensure that the extended plunger rod is not depressed while removing the syringe cap.

Step 4. Attach a sterile needle

Attach a needle appropriate for intramuscular administration to the pre-filled syringe by holding the Luer lock adapter and turning the needle clockwise.

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

Authorisation number

69222 (Swissmedic).

Packs

1 pre-filled syringe of 0.5 ml and 1 needle. [B]

10 pre-filled syringes of 0.5 ml and 10 needles. [B]

Marketing authorisation holder

Pfizer AG, Zürich.

Date of revision of the text

November 2023