EU RISK MANAGEMENT PLAN (RMP) FOR

CAPVAXIVE™

(Pneumococcal 21-valent Conjugate Vaccine)

RMP version to be assessed as part of this application:

RMP Version number: 1.0

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Rationale for submitting an updated RMP:

Not applicable.

Summary of significant changes in this RMP:

Not applicable.

Other RMP versions under evaluation:

Not applicable.

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QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

AE	Adverse Experience
ATC	Anatomical Therapeutic Chemical classification system
CAP	Community Acquired Pneumonia
CCDS	Company Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
deOAc	de-O-acetylated
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
GLP	Good Laboratory Practice
HIV	Human Immunodeficiency Virus
HSCT	Hematopoietic Stem Cell Transplant
INN	International Nonproprietary Name
IPD	Invasive Pneumococcal Disease
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
N/A	Not Applicable
PAES	Post-authorization Efficacy Study
PCV	Pneumococcal Conjugate Vaccine
PD	Pneumococcal Disease
PnP	Pneumococcal polysaccharides
PP	Pneumococcal Pneumonia
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

PART I: PRODUCT(S) OVERVIEW

Table I.1: Product Overview

Active substance(s) **(INN or Generic name)**	Pneumococcal polysaccharides for 21 serotypes conjugated to CRM197 carrier protein (Pneumococcal 21-valent Conjugate Vaccine)
Pharmacotherapeutic group(s) (ATC Code)	Vaccines, pneumococcal vaccines (J07AL)
Marketing Authorisation Applicant	Merck Sharp & Dohme B.V.
Number of medicinal products to which this RMP refers	One
Invented name(s) in the European Economic Area (EEA)	CAPVAXIVE™
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Protein conjugated polysaccharide vaccine
	Summary of mode of action CAPVAXIVE™ contains 21 pneumococcal capsular polysaccharides from *S. pneumoniae* (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, deOAc15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B), which are known to contribute to the pathogenicity of pneumococci in adults. Each serotype of activated polysaccharide is individually conjugated to a carrier protein (CRM197), and elicits antibodies that enhance opsonization, phagocytosis, and killing of pneumococci to protect against pneumococcal disease. CAPVAXIVE™ elicits a T-cell dependent immune response. Carrier protein specific helper T-cells support specificity, functionality, and maturation of serotype-specific B-cells.
	Important information about its composition **Active Ingredient** Each 0.5mL dose contains a total of 84mcg of pneumococcal polysaccharide antigen (4mcg each of polysaccharide serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, deOAc15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B) conjugated to approximately 65mcg of CRM197 carrier protein. CRM197 is a nontoxic mutant of diphtheria toxin (originating from *Corynebacterium diphtheriae* C7) expressed recombinantly in *Pseudomonas fluorescens*. **Inactive Ingredients (List of excipients)** Sodium Chloride, L-histidine, Polysorbate 20, and water for injection.
Hyperlink to the Prescribing Information	See proposed Prescribing information in Module 1.3.1
Indication(s) in the EEA	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.
Dosage in the EEA	1 dose (0.5 mL), administered by intramuscular injection

Table I.1: Product Overview

Pharmaceutical form(s) and strengths	CAPVAXIVE™ is a solution for injection available in 0.5 mL single dose prefilled syringes. The vaccine is a colourless, clear to opalescent solution.
Is/will the product be subject to additional monitoring in the EU?	Not assigned

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

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.

Incidence and Prevalence:

Humans are the only reservoir for *S. pneumoniae*, and pneumococcal nasal carriage isolates are the source of invasive strains in the individual. Pneumococcal disease (PD) is a serious condition, and a leading cause of vaccine-preventable disease in adults worldwide, resulting in considerable morbidity and mortality, particularly in older adults (≥65 years of age), immunocompromised adults ≥18 years of age (eg, human immunodeficiency virus [HIV], hematopoietic stem cell transplant patients [HSCT]), and adults ≥18 years of age with comorbid conditions that predispose to pneumococcal disease (eg, chronic lung disease, chronic liver disease, chronic heart disease, diabetes mellitus, asthma) [Ref. 5.4: 03QZM3] [Ref. 5.4: 05725M] [Ref. 5.4: 05725N]. PD incidence further varies by age, region, and race. PD is classified as invasive or non-invasive disease (IPD or non-IPD). IPD is defined by the isolation of S. pneumoniae in body fluids that are otherwise sterile and includes bacteremic pneumonia, bacteremia without focus, meningitis, pleuritis, and arthritis. Non-IPD mainly consists of nonbacteremic pneumococcal pneumonia (nonbacteremic PP), sinusitis, and acute otitis media (AOM) [Ref. 5.4: 04PNDT, 03QZM3, 05725N, 07XGKX].

V116 consists of 21 capsular polysaccharides from serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, deOAc15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B each conjugated to CRM197 protein. V116 was designed, in part, based on global serotype epidemiology data in older adults in regions with high pediatric pneumococcal vaccination uptake and provides significantly broader disease coverage against the leading serotypes associated with pneumococcal disease in adults compared to currently licensed pneumococcal vaccines.

Invasive Pneumococcal Disease (IPD)

Incidence and Prevalence:

IPD follows a seasonal pattern, with the number of cases peaking in the winter months.

In the EU, the notification rate of IPD in adults ≥65 years of age was 16.1 cases per 100,000 in 2019 [Ref. 5.4: 08GKPP]. The overall case fatality rate of IPD was 15% in the EU in 2017. The case fatality rate increased with age: 3% in children <15 years of age, 6% in 15 to 44-year-olds, 11% in 45 to 64-year-olds, and 22% in adults ≥65 years of age [Ref. 5.4: 05G56D]. The case fatality rate was as high as 10% to 30% among patients with

pneumococcal meningitis [Ref. 5.4: 08GKW4]. In France, the incidence of IPD was 27.3 per 100,000 in adults ≥65 years of age in 2019 [Ref. 5.4: 08GKYF]. Between 2014 and 2017, the non-meningitis IPD case fatality rate among hospitalized adults in France was 21%, ranging from 8% in adults 18 to 49 years of age to 35% among adults ≥85 years of age [Ref. 5.4: 05LF3S]. In Spain, the incidence of IPD among adults was 4.7 cases per 100,000 in adults 18 to 64 years of age and 18.1 cases per 100,000 in adults ≥65 years of age in 2018/2019 [Ref. 5.4: 08GKPQ].

In the US, the incidence of IPD in adults ≥65 years of age was 23.6 cases per 100,000 in 2019 [Ref. 5.4: 07YD35] while in Canada, it was 23.2 per 100,000 that year [Ref. 5.4: 08CNXX]. Case fatality rate of bacteremic pneumococcal pneumonia, the most common presentation of IPD in adults, ranged from 5% to 7%, being higher in elderly persons [Ref. 5.4: 08CT5X]. The overall case fatality rate of IPD was approximately 11% in the US in 2019 [Ref. 5.4: 07YD35]. Mortality is highest among adults ≥50 years of age, ranging from 15% to 25%, with higher mortality observed in adults >85 years of age [Ref. 5.4: 07YD35]. In adults 50 to 64 years of age, 67% of IPD cases are in adults with underlying medical conditions [Ref. 5.4: 06CQT7]. Among adults, the incidence rates of IPD are 2 to 8-fold higher in persons with chronic illnesses (e.g. chronic heart disease, chronic lung disease, diabetes, cancer, HIV and alcoholism) than in healthy individuals, and rates increase with the number of concurrent chronic illnesses present [Ref. 5.4: 03QTFW]. The risk of IPD is increased further in individuals considered high-risk or immunocompromised [Ref. 5.4: 03RMXB].

The overall incidence of IPD due to serotypes covered by vaccines currently licensed for routine use in children has decreased significantly in all age groups in regions where PCVs have been introduced into infant immunization schedules, with the exception of IPD due to serotype 3 [Ref. 5.4: 04KW8S, 043MRP, 04KVRV, 04KW88, 04KTFC, 04KW8B, 04KSQ3, 04KTF2, 04KW7F, 04KVRL, 04KTDB]. However, in some regions and countries, after implementation of PCV, the burden of vaccine-type IPD decreased while the burden of IPD due to non-vaccine serotypes has increased, especially in adult populations [Ref. 5.4: 04XFWW, 03RKY7].

Despite the widespread use of pneumococcal vaccines, *S. pneumoniae* continues to cause disease worldwide, resulting in considerable morbidity and mortality. Infection with *S. pneumoniae* can lead to IPD and non-IPD. Treatment of these conditions places a significant burden on healthcare systems, requiring treatment with antibiotics and, in some cases, hospitalizations. Furthermore, some strains of *S. pneumoniae* have been shown to be resistant to first-line antibiotic therapy, which could result in greater morbidity and mortality and substantial healthcare utilization and cost [Ref. 5.4: 06D5Q0].

Demographics of the population in the proposed indication and risk factors for the disease:

IPD is a serious condition, and the majority of cases are reported in young children < 5 years and older adults, with the highest incidence occurring in adults 65 years or older [Ref. 5.4: 05J8JP]. In addition, individuals living in crowded, closed settings (eg, shelters, long-term care facilities), immunocompromised individuals (eg, patients with HIV, recipients

of HSCT, immunosuppressive medication, or asplenia) and adults ≥18 years of age with certain chronic illnesses (eg, chronic lung disease, chronic liver disease, chronic heart disease, diabetes mellitus, asthma, and alcoholism) are at increased risk of PD, and IPD in particular [Ref. 5.4: 04VSTX, 04VSHL, 04NK7X]. In adults, the incidence rates of IPD are approximately 2 to 8-fold higher in persons with chronic illnesses (e.g., chronic heart disease, chronic lung disease, diabetes, cancer, HIV and alcoholism) than in healthy individuals, and rates increase with the number of conditions present [Ref. 5.4: 03QTFW]. Similarly, among at-risk children, rate ratios for IPD (vs children without at-risk/high-risk conditions) are approximately 1.8 (95% CI, 1.4–2.3) in children <5 years of age and 3.3 (95% CI, 2.4–4.4) in children 5 to 17 years of age [Ref. 5.4: 05R6YJ]. The risk of IPD is increased further in individuals considered high risk or immunocompromised [Ref. 5.4: 03RMXB].

Mortality due to IPD is higher in older adults and in those with chronic medical conditions compared to younger adults and healthy older adults. The highest mortality is among adults ≥50 years of age, ranging from 15% to 25%, with higher mortality observed in adults ≥85 years of age [Ref. 5.4: 07YD35]. Risk of death from IPD is 2 to 3 times higher in adults with underlying chronic diseases and alcoholism, respectively, compared to adults without these conditions [Ref. 5.4: 08D75W]. Adults with HIV infection are 4 times more likely to die from IPD than those without HIV.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

IPD is associated with significant morbidity and mortality in both children and adults worldwide. Serious manifestations of IPD include meningitis, septicemia and bacteremic pneumonia. Pneumococcal meningitis (PM) is a bacterial infection of the central nervous system. The bacteria enter the cerebrospinal fluid in the subarachnoid space by crossing the blood-brain barrier. Once the pathogen reaches the brain, an often uncontrolled inflammatory response occurs contributing to high rates of complications, morbidity and mortality [Ref. 5.4: 08D79C]. Bacteremia can cause serious clinical manifestations if immune response mechanisms fail or if untreated. The case fatality ratio of bacteremia is approximately 12% in adults [Ref. 5.4: 07XGKX]. Bacteremic infection can result in sepsis. Sepsis is a dysregulated immune response from infection that can be severe and potentially fatal, characterized by inflammation, multiorgan dysfunction, altered cognition, and possible amputation of limbs or phalanges. Approximately 30-50% of sepsis cases result in death [Ref. 5.4: 04J9XK].

In Europe in 2019, the case fatality rate of IPD was 15% and increased with age, reaching 21% in adults 65 years and older [Ref. 5.4: 05M4CV]. In the US, the case fatality rate of IPD is approximately 11%, accounting for approximately 3,500 deaths annually. Mortality rates are higher in older adults and in adults with certain comorbid conditions, especially conditions associated with immune impairment [Ref. 5.4: 03RBPW, 05J8JP].

Pneumococcal Pneumonia

Incidence and Prevalence:

Pneumococcal pneumonia (PP) consists of bacteremic PP and non-bacteremic PP and remains one of the most important causes of death from infection in many world regions. The incidence of PP without bacteremia is difficult to estimate due to the lack of available diagnostic tests for use in routine clinical practice. Clinically defined cases of pneumonia, chest x-ray confirmed pneumonia, and hospitalizations due to pneumonia have been used as surrogates to estimate the incidence. In adults 50 to 64 years of age, 71% of PP cases were in adults with underlying medical conditions [Ref. 5.4: 06CQT7]. Community-acquired pneumonia (CAP) has a high incidence in the general population [Ref. 5.4: 05G4DK, 05G4BF, 03RBQ0]and is responsible for a substantial hospitalization burden [Ref. 5.4: 05GPX5].

The pathogen causing CAP is only identified in 30% to 40% of all CAP cases. However, *S. pneumoniae* is one of the most commonly identified pathogens. Studies have found that *S. pneumoniae* causes 10% to 37% of CAP requiring hospitalization in adults in the EU and the US [Ref. 5.4: 05GLGB, 05GLGV, 05GLG8].

The true burden of PP remains underestimated in Europe [Ref. 5.4: 04T4G5]. A meta-analysis of 77 studies conducted between 1997 and 2011 including a total of 24,410 patients with CAP estimated that *S. pneumoniae* was a cause for 6.5% of CAP in Southern Europe [Ref. 5.4: 04T4G5]. In Germany, the burden of all-cause pneumonia was greatest in older adults and those with chronic medical conditions. In 2015, incidence rates of all-cause CAP were 551 and 2,032 cases per 100,000 person-years in adults aged 16 to 59 years and ≥60 years, respectively [Ref. 5.4: 082D3G]. A recent study conducted in Germany between 2012 and 2017 reported that *S. pneumoniae* was responsible for 10.7% of CAP in adults ≥18 years of age [Ref. 5.4: 05GPX4]. In Sweden, in adults ≥18 years, the proportion of CAP caused by *S. pneumoniae* was 24.3% between 2016 and 2018 [Ref. 5.4: 08GKQ4]. In Spain, CAP incidence among adults was 463 cases per 100,000 person-years between 2009–2013, ranging from 190 cases per 100,000 person-years among adults aged 20 to 25 years to 2374 cases per 100,000 person-years in adults aged ≥90 years [Ref. 5.4: 08GKQ6]. In Italy, the incidence of CAP increases with age, ranging from 91.5 per 100,000 population in patients aged 15 to 44 years to 333.8 per 100,000 in patients aged ≥65 years [Ref. 5.4: 08GN0G]. In Italian adults ≥65 years, *S. pneumoniae* was responsible for an estimated 31.7% of CAP in those hospitalized or seen at outpatient visits for CAP in the Apulia region [Ref. 5.4: 08GKQ0] and 58.3% of hospitalized adults with CAP in Milan between 2013 and 2015 [Ref. 5.4: 08GKPT]. In 2012, the British Lung Foundation estimated that the incidence of all-cause pneumonia in the overall population was 345 per100,000 persons in the UK, an increase from 307 per 100,000 in 2004 [Ref. 5.4: 08GKPN]. Among adults in Nottingham hospitalized with CAP in 2008-2013, *S. pneumoniae* caused 28.9% of cases [Ref. 5.4: 055NPC].

The World Health Organization estimates that about 11% of CAP in the US is caused by *S. pneumoniae* [Ref. 5.4: 07ZG8H]. In 2017, pneumococcal pneumonia contributed an estimated 103,000 hospitalizations in the US [Ref. 5.4: 07XY2V]. In 2016, an estimated 4.9

million patients suffered from all-cause pneumonia in the US. The mean rate of all-cause pneumonia was 45.0 per 1000 person-years between 2008 and 2014 among US adults ≥65 years of age [Ref. 5.4: 07ZG8B]. A cohort study conducted in the US between 2014 and 2016 reported that 12.3% of radiologically confirmed CAP hospitalizations identified *S. pneumoniae,* with approximately half of the cases occurring in adults 18 to 64 years of age and half occurring in adults ≥65 years of age. This includes *S. pneumoniae* identified in urine antigen assays including serotype-specific urinary antigen detection assays [Ref. 5.4: 07ZG86]. In Canada, a recent study by LeBlanc et al presented updated data from active surveillance of PP in hospitalized adults from 2010 to 2017. Laboratory testing identified that a high proportion (>90%) of bacteremic PP, non-bacteremic PP, and IPD (non-CAP) cases in adults were due to *S. pneumoniae* serotypes in current and investigational vaccines. Approximately half of the PP cases were seen in adults ≥65 years of age, whereas 30% of the cases were seen in adults 50 to 64 years of age. Risk factors for death among PP patients included age ≥75 years, immunocompromising conditions, and being underweight. Among all PP cases, the most commonly identified serotypes were 3, 7F, 9N, 11A, 19A, and 22F, all of which are included in V116 [Ref. 5.4: 0800ZR].

In summary, even with the availability of pneumococcal vaccines for adults as well as the indirect protection afforded from pediatric immunization, there is a substantial burden of disease due to IPD and non-IPD in adults that represents a serious public health concern and an unmet medical need in adults.

Demographics of the population in the proposed indication and risk factors for the disease:

PP is responsible for significant morbidity and mortality. The incidence of PP increases with age, with the highest rates reported in adults 80 years or older [Ref. 5.4: 04M5ZZ, 05GLGB]. The risk factors for PP are similar to those for IPD, and include older age, immunocompromising conditions and treatments (eg, HIV infection, HSCT and solid organ transplant, primary immunodeficiency, cancer chemotherapy, chronic corticosteroid use and other immunosuppressive therapies), and certain chronic illnesses (eg, chronic respiratory disease, chronic renal disease, liver disease, heart disease, diabetes, and alcoholism) [Ref. 5.4: 05M74F].

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Complications occur in approximately 40%-50% of those hospitalized with PP [Ref. 5.4: 053DW5, 053DWB] and can include bacteremia, IPD, pleural effusion, empyema, lung abscess, pneumothorax, and necrotizing pneumonia (particularly with serotypes 3 and 19A). Long-term outcomes for patients with empyema exhibit high rates of readmission and repeated intervention [Ref. 5.4: 08D78T].

CAP, including PP, is a leading cause of infection-related death among adults. Studies have shown case fatality rates of pneumococcal pneumonia ranging from 2 to 7%, with higher rates among older adults [Ref. 5.4: 04M5ZZ, 04QTVG, 05M747]. A 2015 prospective study in Northern Spain found that, among adults hospitalized for non-bacteremic PP, 12.8% had a

poor outcome, defined as need for mechanical ventilation and/or shock and/or in-hospital death [Ref. 5.4: 05M747].

Important comorbidities:

- Coronary heart disease/Ischemic heart disease
- Congestive heart failure
- Chronic obstructive pulmonary disease and asthma
- Chronic liver disease
- Chronic renal failure
- Diabetes
- Sickle cell disease (SCD), especially sickle cell anemia (SCA) subtype (hemoglobin SS)
- HIV
- Congenital immunodeficiency
- Malignancy

The main existing treatment options for pneumococcal disease (PD):

Treatment options:

Treatment of disease caused by *S. pneumoniae* is based on clinical presentation and antimicrobial susceptibility data. Most cases with clinical symptoms consistent with IPD and PP require initiation of empiric antibiotic therapy before bacterial culture results are known. Initial treatment generally includes broad-spectrum antibacterials that have efficacy against *S. pneumoniae* as well as other likely pathogens [Ref. 5.4: 05MGY8]. The increasing rate of pneumococcal resistance to penicillin and other commonly used antimicrobial agents complicates treatment decisions and may lead to treatment failures with subsequent increased morbidity and health care costs [Ref. 5.4: 05MGYD]. Before the introduction of PCV7, the proportion of *S. pneumoniae* isolates resistant to penicillin and other antibiotics was increasing in Europe and the US. After the introduction of PCV7, PCV10, and PCV13, there have been steady and substantial declines in pneumococcal resistance in children vaccinated with PCVs and unvaccinated older children and adults. This is likely due to a reduction in transmission of resistant strains from vaccinated children to unvaccinated children and adults, and decreased use of empiric broad-spectrum antibiotics as the incidence of IPD declined due to PCV use [Ref. 5.4: 04PPWT, 05LT6N]. As V116 is being developed to target residual disease in adults and includes unique serotypes not in any currently licensed vaccine, it has the potential to prevent a greater proportion of cases of PD and can be expected to further decrease empiric use of broad-spectrum antibiotics and associated pressure on antimicrobials that selects for multidrug resistant organisms.

Prevention options:

Prevention of PD in pediatrics and adults includes vaccination 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 IPD and non-IPD caused by the serotypes contained in those vaccines in both children [Ref. 5.4: 04WSBX] and adults [Ref. 5.4: 04NFHD, 05LX25, 05HVTT].

The introduction of infant vaccination with PCV7 and later with PCV10 and PCV13 has significantly reduced the overall incidence of IPD caused by vaccine serotypes in children and has resulted in decreased incidence of vaccine serotype disease in adults through indirect effects (herd protection). Prior to the licensure of PCV7, the crude annual incidence rates of IPD in the US in 1998-1999 were highest among children <5 years of age (98.7 cases per 100,000 population) and older adults ≥65 years of age (60.1 cases per 100,000 population) [Ref. 5.4: 03R5S4].

Following implementation of PCV7 in 2000 and PCV13 in 2010 in US children, a substantial decrease in the overall incidence of IPD was observed among children <5 years of age, from 71.8 cases per 100,000 in 2000 to 7 cases per 100,000 in 2019. Two years after the introduction of PCV13 in US children, a significant reduction in hospital admissions for IPD and non-invasive pneumococcal pneumonia was observed in children <2 years of age (64% and 40% reduction, respectively) and adults ≥65 years of age (29% and 34% reduction respectively) [Ref. 5.4: 04KVRV]. Following the recommendations to directly vaccinate adults with PCV13, modest additional decreases were seen in the adult populations: in adults ≥65 years of age with universal recommendation (from 36 cases per 100,000 in 2010 to 24 cases per 100,000 in 2018) and in high-risk adults 50 to 64 years of age also recommended to be vaccinated (from 18.1 cases per 100,000 in 2010 to 16.6 cases per 100,000 per year in 2018) [Ref. 5.4: 05K9XY], [Ref. 5.4: 05J8JP].

Through prevention of pneumococcal infections and subsequent decreased transmission, PCVs have reduced the circulation of antibiotic-resistant serotypes/strains. Prior to PCV introduction, the serotypes in PCV7 accounted for a substantial proportion of PD and 83% of antibiotic-resistant IPD in children. Since PCV introduction in 2000, the rates of antibiotic-resistant IPD caused by vaccine strains have decreased by 97% among children younger than 5 years and by more than 60% among adults [Ref. 5.4: 0850WB].

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

V116 was evaluated in a GLP repeat-dose intramuscular (IM) toxicity study in rats that included complete toxicity, local tolerability, and immunogenicity assessments. A robust immune response was demonstrated confirming species relevance. There were no adverse vaccination-related findings at 100-fold multiples over the adult clinical dose on a per kg basis. In a GLP IM developmental and reproductive toxicity study, female rats were administered V116 at a dose providing a 100-fold margin over the adult clinical dose on a per kg basis. A sustained immune response across generations was observed, confirming species relevance. Overall, V116 had no effects on mating performance, fertility, embryonic/fetal or pre-weaning development.

Table SII.1: Summary of Important Safety Findings from Non-clinical Studies

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
None	Not Applicable

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

The clinical program to support V116 licensure in adults includes 7 completed studies [1 Phase 2 study (V116-001) and 6 Phase 3 studies (V116-003, V116-004, V116-005, V116-006, V116-007, V116-010)] that enrolled and treated over 8,800 adults across 366 clinical sites in 26 countries. Approximately 5,700 adults received V116 across these studies.

In the phase 2 study, pneumococcal vaccine naïve adults 50 years of age or older received a single V116 dose containing 4 µg of each pneumococcal polysaccharide (PnPs) antigen per 1.0 mL. The single dose of V116 containing 4 µg of each PnPs antigen per 0.5 mL was administered in all the Phase 3 studies.

The Phase 3 clinical studies enrolled adults ≥18 years of age and specifically targeted enrollment of individuals ≥65 years of age who have an increased risk of PD due to age. The population enrolled in the Phase 3 program was diverse and included individuals across different races and ethnicities, with and without prior pneumococcal vaccine exposure, and with and without increased risk of PD due to chronic medical conditions.

- V116-003: Study comparing the safety and immunogenicity of V116 with PCV20 in vaccine naïve adults ≥18 years of age,
- V116-004: Clinical lot consistency study comparing the safety and immunogenicity of 3 manufacturing lots of V116 in vaccine naïve adults 18 to 49 years of age,
- V116-005: Concomitant use of V116 with influenza vaccine in adults ≥50 years of age,
- V116-006: Safety and immunogenicity of V116 in vaccine experienced adults ≥50 years of age.
- V116-007: Safety and immunogenicity of V116 in adults ≥18 years of age living with HIV
- V116-010: Study comparing the safety and immunogenicity of V116 with PPSV23 in vaccine naïve adults ≥50 years of age.

Exposure to V116 by age group and gender, dose and race/ethnic origin in the clinical trials are shown in Tables SIII.1 to SIII.3 below. Duration of exposure is not applicable for vaccines.

Table SIII.1: Age Group and Gender

Age Group	Patients	
	M	F
Adults (18 to 49 years)	818	1,101
Adults ≥50 years	1,688	2,097
50 to 64 years	744	1,074
65 to 74 years	741	801
≥75 years	203	222
Total	2,506	3,198
Participants from completed studies V116-001 Phase 2, V116-003, V116-004, V116-005, V116-006, V116-007, V116-010		

Table SIII.2: Dose

Dose of Exposure	Patients
V116 (4 µg of each PnPs antigen per 1.0 mL)	254
V116 (4 µg of each PnPs antigen per 0.5 mL)	5,450
Total	5,704
Participants from completed studies V116-001 Phase 2, V116-003, V116-004, V116-005, V116-006, V116-007, V116-010	

Table SIII.3: Race/Ethnic Origin

Race/Ethnic Origin	Patients
Race	
American Indian Or Alaska Native	28
Asian	564
Black Or African American	581
Multiple	234
Native Hawaiian Or Other Pacific Islander	33
White	4,258
Missing	5
Ethnic origin	
Hispanic Or Latino	1,237
Not Hispanic Or Latino	4,422
Not Reported/Unknown	46
Participants from completed studies V116-001 Phase 2, V116-003, V116-004, V116-005, V116-006, V116-007, V116-010	

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Participant has a history of IPD or known history of other culture-positive pneumococcal disease within 3 years of study start	May confound immunogenicity evaluation of V116.	No	No unique safety findings are anticipated in this population.
Has a known hypersensitivity to any component of V116, including diphtheria toxoid.	For participant safety. May confound safety evaluation of V116.	No	History of hypersensitivity to a product is a well-recognized risk for adverse reactions associated with use of that product.
Participant has known or suspected impairment of immunological function; including participants who have received: • Systemic corticosteroids (prednisone equivalent of ≥20 mg/day) for ≥14 consecutive days and has not completed intervention at least 14 days before study entry; • Systemic corticosteroids exceeding physiologic replacement doses (approximately 5 mg/day prednisone equivalent) within 14 days before vaccination; • Immunosuppressive therapy.	May confound immunogenicity evaluation of V116.	No	No unique safety findings are anticipated in these populations. In general, individuals with altered immunocompetence, including those receiving immunosuppressive therapy, may have a reduced immune response to vaccination.
Participant is pregnant	Safety of V116 in pregnant women has not been established	No	Vaccination in a pregnant woman can be postponed. The decision to vaccinate a woman who is pregnant should consider the woman's risk of pneumococcal disease; V116 should be administered only if clearly needed.

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Participant has a coagulation disorder contraindicating intramuscular vaccinations	May confound safety evaluation of V116.	No	The risk of bleeding in persons with underlying coagulation disorders exists for any vaccine that is administered intramuscularly, is well characterized, and considered common medical knowledge, as is medical management of this risk [Ref. 5.4: 05MBMT],
Participant has a history of malignancy <3 years prior to signing informed consent, except for adequately treated basal cell and/or squamous cell carcinoma of the skin, or carcinoma in situ	May confound immunogenicity evaluation of V116.	No	No unique safety findings are anticipated in this population.
Participant had a recent febrile illness (defined as oral or tympanic temperature ≥100.4°F [≥38.0°C] or axillary or temporal temperature ≥99.4°F [≥37.4°C]) or received antibiotic therapy for any acute illness occurring within 72 hours before receipt of study vaccine.	May confound safety evaluation of V116.	No	Deferral of vaccination in persons with acute illness is considered common medical knowledge based on best practice guidelines for immunization as it avoids the potential for causing confusion between manifestations of the underlying illness and possible adverse effects of vaccination [Ref. 5.4: 05MFWR].
Participant has received: A blood transfusion or blood products, including immunoglobulin, within the 6 months before receipt of study vaccine or is scheduled to receive a blood transfusion or blood product within 30 days of receipt of study vaccine	May confound immunogenicity evaluation of V116.	No	No unique safety findings are anticipated in these populations.
Participants <18 years of age	The safety and efficacy of V116 in individuals <18 years of age has not been established. This population was excluded pending demonstrated safety and efficacy in the adult population ≥>18 years of age.	No	A pediatric indication is not being sought at this time.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Program

Based on a sample size of 5,704 participants who received V116 in the clinical development program, there is a 95% chance of observing an adverse reaction with an underlying incidence of 0.05% or greater.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program

Table SIV.3.1: Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Pregnant women were excluded from studies in the clinical development program and participants of childbearing potential were to use effective birth control methods for 6 weeks postvaccination. Participants who were breastfeeding were excluded from studies in the clinical development program.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials • Adults living with HIV.	The risk for invasive and noninvasive pneumococcal disease is higher in persons with chronic illness and the risk increases with the number of conditions present [Ref. 5.4: 04NFHN] [Ref. 5.4: 06CQT7] [Ref. 5.4: 03QTFW]. The phase 3 clinical program (V116-003, V116-004, V116-005, V116-006, V116-010) enrolled adults ≥18 years of age with stable underlying chronic medical conditions (including chronic heart disease, chronic kidney disease (CKD), chronic liver disease, chronic lung disease, or diabetes), as well as alcoholism or smoking, Participants with CKD Stage 4 or 5 (end stage renal disease) were not included in the clinical development program. A total of 2,760 (33%) had at least 1 or more chronic medical conditions associated with an increased risk of pneumococcal disease: 2,219 (26.5%) of participants had one chronic medical condition, and 541(6.5%) had 2 or more chronic medical conditions. V116-007 enrolled 313 adults with HIV infection. Individuals immunocompromised due to congenital or acquired immunodeficiencies (other than HIV) were not included in the clinical development program. Refer to Table SIV.1.1
Population with relevant different ethnic origin	Included, see Table SIII.3
Subpopulations carrying relevant genetic polymorphisms	There are no known genetic polymorphisms relevant to vaccination with V116.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 Post-Authorisation Exposure

As of the DLP, this product is not marketed in any country worldwide.

SV.1.1 Method Used to Calculate Exposure

Not applicable

SV.1.2 Exposure

Not applicable

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

Pneumococcal 21-valent Conjugate Vaccine is available only through prescribing physicians and other health care providers with prescriptive authority. Neither Pneumococcal 21-valent Conjugate Vaccine nor its components are known to possess addictive properties.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Risks with minimal clinical impact on patients

- Injection site pain, fatigue, headache, myalgia, injection site swelling, injection site erythema, pyrexia, injection site pruritus, nausea, chills, dizziness, diarrhoea, lymphadenopathy, arthralgia

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the prescribing information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Severe allergic reactions

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table SVII.1.2.1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety concern	Benefit risk impact
Important identified risks	None
Important potential risks	None
Missing information	None

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

There are no important identified or potential risks for Pneumococcal 21-valent Conjugate Vaccine.

SVII.3.2 Presentation of the Missing Information

There is no missing information for Pneumococcal 21-valent Conjugate Vaccine.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

The Company maintains systems and standard practices for routine pharmacovigilance activities to collect reports of suspected adverse reactions (including spontaneous reports, reports from clinical studies, reports of pregnancy/lactation exposures, overdoses and medication errors); prepare reports for regulatory authorities (e.g. individual case safety reports, Periodic Safety Update Reports (PSURs), etc.), and maintain continuous monitoring of the safety profile of approved products (including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities). The Company maintains a Pharmacovigilance System Master File which contains details of these systems and standard practices.

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

Other Forms of Routine Pharmacovigilance Activities

The Company will collect and report information on breakthrough disease and serotype replacement which will include:

- Review of post-marketing spontaneous reports of vaccination failure
- Relevant data on serotype distribution from invasive pneumococcal disease (IPD) surveillance from the US Centers for Disease Control and Prevention (US CDC), European Centre for Disease Prevention (ECDC) and/or available European single country data as they become available and as CAPVAXIVE™ is used.
- A summary of emerging antibiotic resistance trends/surveillance data

These topics will be summarized in the PSURs.

III.2 Additional Pharmacovigilance Activities

There are no ongoing or planned additional pharmacovigilance studies that are required for Pneumococcal 21-valent Conjugate Vaccine.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table III.3.1: On-Going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Required Additional pharmacovigilance activities				
None	N/A	N/A	N/A	N/A

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no ongoing or proposed post-authorization efficacy studies (PAES) for Pneumococcal 21-valent Conjugate Vaccine.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

The safety information in the proposed prescribing information is aligned to the reference medicinal product.

Table V.1.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
None	Not applicable

V.2 Additional Risk Minimisation Measures

No additional risk minimisation measures are needed. Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table V.3.1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
None	Not applicable	Not Applicable

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Summary of risk management plan for CAPVAXIVE™ (Pneumococcal 21-valent Conjugate Vaccine)

This is a summary of the risk management plan (RMP) for CAPVAXIVE™. The RMP details important risks of CAPVAXIVE™, and how more information will be obtained about CAPVAXIVE™ risks and uncertainties (missing information).

CAPVAXIVE™ summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how CAPVAXIVE™ should be used.

This summary of the RMP for CAPVAXIVE™ should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR)].

Important new concerns or changes to the current ones will be included in updates of CAPVAXIVE™ RMP.

I. The Medicine and What it is Used for

CAPVAXIVE™ is authorised for active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in individuals 18 years of age and older (see SmPC for the full indication). It contains pneumococcal polysaccharides for 21 serotypes conjugated to CRM197 carrier protein as the active substance and it is given by intramuscular injection.

Further information about the evaluation of CAPVAXIVE™ benefits can be found in CAPVAXIVE™ EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to product's EPAR summary landing page on the EMA webpage>.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of CAPVAXIVE™, together with measures to minimise such risks and the proposed studies for learning more about CAPVAXIVE™ risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of CAPVAXIVE™ are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of CAPVAXIVE™. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table II.A.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of Important Risks

The safety information in the proposed Prescribing Information is aligned to the reference medicinal product.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of CAPVAXIVE™.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for CAPVAXIVE™.

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ANNEXES

ANNEX 4 – SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable

ANNEX 6 – DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable; there are no additional risk minimisation activities.