

Company

Pfizer Inc.

Drug or Device Name

PREVNAR 20™

Category

Biotechnology

Compound/Technical Name

Pneumococcal 20-valent Conjugate Vaccine), suspension for intramuscular injection

Trade Name

PREVNAR 20™

Date of Approval

06/08/2021

Therapeutic Categories

Infectious Disease

Indications

Prevnar 20 is a vaccine indicated for active immunization for the prevention of pneumonia and invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F in adults 18 years of age and older.

Background

Streptococcus pneumoniae causes disease syndromes in adults that range from mucosal infections such as sinusitis and lower respiratory infections including pneumonia, to invasive infections like septicemia and meningitis. Before the onset of the COVID-19 pandemic, pneumonia has been the most common manifestation of lower respiratory infections, a leading cause of death worldwide in adults, accounting for an estimated one million deaths in 2016. Among these deaths, around half were attributed to *S. pneumoniae* (1). The greatest burden of adult disease is among those 50 years of age and older and among those with certain underlying medical conditions.

Protective immunity to the pneumococcal bacterium is mediated by antibody responses against the polysaccharide capsule that surrounds the bacterium. Early pneumococcal vaccines were comprised of serotype-specific purified capsular polysaccharide antigens. The most recent were comprised of 23 different serotypes and were licensed in 1983: (e.g., Pnu-Imune® and Pneumovax®) of which only Pneumovax is still marketed today. These vaccines have largely been replaced by conjugated polysaccharide vaccines (PCVs). Unconjugated polysaccharide vaccines elicit a T-cell-independent immune response preventing the induction of robust responses in certain populations (e.g., immunocompromised adults), and do not generate immunologic memory, which leads to waning effectiveness over time (i.e., 2-5 years) (2). Additionally, pneumococcal polysaccharide vaccines have

limited protection against mucosal disease, including nonbacteremic pneumonia. Conjugated pneumococcal vaccines overcome these challenges by eliciting a T-cell-dependent immune response that induce an enhanced antibody response and generate memory B cells, including among immunocompromised adults, allowing for an anamnestic (booster) response upon re-exposure (2, 5). While there are over 100 serotypes of *S. pneumoniae* identified to date, a limited number are responsible for the majority of disease. Prevnar 20® targets prevention of disease caused by 20 serotypes, and includes the capsular polysaccharide conjugates of the seven serotypes in the original pneumococcal conjugate vaccine, Prevnar® (first licensed for infants and young children in 2000); the additional six conjugates in Prevnar 13® (first licensed in pediatric and adult populations in 2010 and 2011, respectively); and conjugates for seven additional serotypes: 8, 10A, 11A, 12F, 15B, 22F and 33F. The seven additional Prevnar 20® serotypes account for 23.2% and 34.3% of invasive disease in US and European adults ≥65 years, respectively (4, 10, 12). In Europe, serotype 8 is of particular concern, causing 14% of all invasive disease in older adults in 2018, followed by 22F (7.4%), 12F (4.0%), 11A (2.8%), 33F (2.5%), and 10A (2.3%) (Table 1) (12). Overall, the serotypes included in Prevnar 20 represent seven of the 10 most prevalent serotypes that caused IPD in adults ≥65 years of age (3, 4, 5). In addition, these serotypes have characteristics of medical importance, including antibiotic resistance (11A, 15B), association with outbreaks (8, 12F), and a tendency to cause more severe disease (e.g., association with meningitis and/or increased mortality rate) (10A, 11A, 22F) (3).

Among adults with pneumonia, the seven additional Prevnar 20® serotypes account for around 3-5% of all disease in U.S. and European adults. Among these serotypes, 8, 11A, and 22F ranked among the most prevalent that were detected (11). Pneumococcal pneumonia is associated with complications and long-term sequelae in all age groups, including respiratory failure requiring hospitalization, empyema, and necrotizing pneumonia exacerbations of chronic medical conditions, declines in quality of life, and with a significant increased risk of death within 30 days (acute) and one-year (long-term) after the event (4). In recent studies of older adults hospitalized with pneumococcal pneumonia in the US, 7.6% experienced a cardiovascular event after hospitalization, 58% continued to experience cognitive impairment six-months after hospitalization, and quality of life remained lower at six-months post-hospitalization compared with before hospitalization (11).

Development

Prevnar 20® is the result of more than 30 years of research by Pfizer scientists on pneumococcal conjugate vaccines, starting with preclinical work in the early 1990s and with the first licensure in the U.S. of the original Prevnar® (7-valent) in children in February 2000. This was followed by Prevnar 13® with six additional serotypes to broaden protection in children in 2009. In 2011, Prevnar 13® was approved for use in the adult population in the U.S. Now with the licensure in late 2021 of Prevnar 20® for use in adults, the product includes an additional seven serotypes relative to Prevnar 13® resulting in 20 different polysaccharide conjugates with excipients. Prevnar 13® was licensed in adults for the prevention of pneumococcal invasive disease and pneumonia after clinical studies demonstrated an acceptable safety profile and comparable immunogenicity to the Pneumovax®23 (PPSV23), the only licensed pneumococcal vaccine for adults at the time. A randomized, placebo-controlled study to measure the efficacy of Prevnar 13® against pneumonia was conducted as a post approval commitment in >80,000 adults 65 years of age⁵. This study definitively demonstrated the efficacy of Prevnar 13® against vaccine-type pneumonia (non-bacteremic and bacteremic) and invasive pneumococcal disease. Real-world vaccine effectiveness on Prevnar 13® in US adults further supported these findings¹⁰.

Prevnar 20® is based on and builds from the Prevnar 13® program. Based on the success in showing efficacy of Prevnar 13® in adults, it became infeasible and ethically questionable to conduct a placebo-

controlled efficacy study of a new pneumococcal conjugate vaccine. In regulatory agency discussions it was agreed that licensure for Prevnar 20® for the adult population could be based on demonstration of an acceptable safety profile and of immune responses comparable to Prevnar 13® (for the 13 matched serotypes) and to PPSV23 (for the seven additional serotypes). In the adult clinical program, Prevnar 20® exhibited an acceptable safety profile^{6,7,8}, substantially similar to Prevnar 13®. The pivotal clinical study demonstrated that the responses elicited by Prevnar 20® for all 20 serotypes were comparable to those of Prevnar 13® for the 13 matched serotypes and to PPSV23 for the seven additional serotypes⁹. These data, along with additional characterization of immunogenicity elicited by Prevnar 20® allowed effectiveness to be inferred and has supported approvals for its adult indication in the United States, the European Union, United Kingdom and Canada to date. Thus, the success in developing Prevnar 20® continues Pfizer's leadership in helping to protect lives from pneumococcal disease.

[Note: On April 27, 2023, Prevnar 20® was further approved by CBER for use in the

- active immunization for the prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F in individuals 6 weeks of age and older.
- active immunization for the prevention of otitis media caused by *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F in individuals 6 weeks through 5 years of age.]

Prevnar 20® vaccine is one of the most complex biotechnology products brought to licensure yet requiring production of 20 drug substance intermediates (polysaccharides), a carrier protein (CRM), 20 drug substances (conjugates) and one drug product, all in the context of clinical and regulatory agreements and assumptions from decades of pneumococcal vaccine development. This complexity has resulted in innovative thinking across all functions supporting the successful development of the vaccine.

Innovation

Clinical/Regulatory

Proof-of-concept in adults was achieved with a pilot study that reflected the design of the planned Phase 3 trial, gaining early regulatory approvals for Phase 3 design. This positioned the program to complete three Phase 3 trials in adults that supported the BLA filing for the adult indication in record time. To accomplish this, the multifunctional team implemented innovative clinical/regulatory approaches on many fronts, while simultaneously maintaining Pfizer's standards of quality and patient safety:

- An innovative clinical design used an efficient sequential vaccination with Prevnar 13®/PPSV23 to allow for a single control group to provide relevant and contemporaneous comparisons between licensed pneumococcal vaccines and Prevnar 20®.
- Cutting-edge statistical modeling was used to establish proof-of-concept criteria for 20 different clinical endpoints, that were stringent enough to indicate whether the vaccine could be expected to work in providing protection against all serotypes, but would not result in the rejection of an efficacious vaccine.
- Early regulatory submission of Phase 3 protocols not only facilitated early and efficient study starts, but also helped to establish a basis for licensure that has included use of supplemental immunogenicity characterizations to support the continued inclusion of vaccine serotypes, a totality of data approach that is key to managing the clinical assessment of an unprecedented number of antigens in a vaccine.
- Approximately 6,500 subjects, age 18 to over 90 years who were healthy or with chronic medical conditions, and with varying pneumococcal vaccine backgrounds, were enrolled in three Phase 3 trials

over 9 months. Analysis of sera collected before and after vaccination required the generation of more than 270,000 biological (opsonophagocytic activity antibody) assays results. Optimization of clinical assays using liquid-handling robotics and high-throughput multiple-well plate formats has been key to rapidly providing an unprecedented number of analyses in support of pivotal immunogenicity data that was the basis for determining efficacy.

Manufacturing

The production of the original heptavalent pneumococcal vaccine (Prevnar®) was a technical tour de force that had never been attempted in the industry. The combination of 7 uniquely manufactured drug substances being formulated into a single vaccine that maintained the immunogenicity of each of those components was one part of the challenge. Another was the implementation, coordination and control of a highly complex and robust manufacturing process that could support the supply demands of the vaccine. Addressing these manufacturing and control challenges required 1) developing a fundamental understanding of the chemistry of the polysaccharide component of each glycoconjugate to assure appropriate antigenicity; 2) developing scalable and reproducible conjugate chemistry specific for each polysaccharide; and 3) understanding the immunological “structure” for each of the components of the vaccine in combination to assure the appropriate immunogenicity of the final vaccine.

The team that developed Prevnar 13® took this challenge considerably further by nearly doubling the number of individual polysaccharide-carrier conjugates in the vaccine. Each new conjugate required the development of individualized conjugation chemistries, and the final vaccine used a novel production method to achieve a stable formulation. At this point, Prevnar 20® is the most complex biological product in production. It is composed of 20 individually produced and released polysaccharides that are then each individually conjugated to a protein carrier. These 20 uniquely manufactured drug substances are then formulated into a single drug product. Further additional novel manufacturing processes were implemented to assure the consistent high-level production of the vaccine at volumes of tens of millions of doses per year.

Manufacturing process development innovations that brought yet more added efficiency to the production of Prevnar 20® include those developed for Prevnar® and Prevnar 13®, as well as innovations in several new unit operations and chemistries that enable a robust controlled strategy for ensuring reproducible processes that meet the critical quality attributes for the product. They include the following:

- Quenching of oxidation reactions: This innovation provides a process for preparing an activated *Streptococcus pneumoniae* serotype 10A, 22F or 33F capsular polysaccharide that is critical for controlling the final size of the conjugate. The process involves reacting an isolated serotype 10A, 22F or 33F capsular polysaccharide with an oxidizing agent, followed by addition of a quenching agent that results in an activated *Streptococcus pneumoniae* serotype 10A, 22F or 33F polysaccharide.
- eTEC chemistry for conjugation of the saccharide conjugation to the carrier protein: This innovation is directed towards methods of producing glycoconjugates whereby a purified saccharide is covalently conjugated to a carrier protein through a bivalent, heterobifunctional linker referred to herein as a (2-(2-oxoethyl)thio)ethyl)carbamate (eTEC) spacer. The eTEC spacer includes seven linear atoms (i.e., —C(O)NH(CH₂)₂SCH₂C(O)—) and provides stable thioether and amide bonds between the saccharide and carrier protein. This novel chemistry enhances stability of the Serotype 33F conjugate and maintains its immunogenicity in Prevnar 20®.
- TEMPO oxidation: To improve the stability of serotype 12F-CRM197 glycoconjugates, alternative chemistries were explored using 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) and N-chlorosuccinimide (NCS) as the co-oxidant to oxidize primary alcohols to aldehyde groups. CC/MS analysis showed that the sites of oxidation were different from that of the periodate mediated

oxidation used previously. In general, the production of serotype 12F glycoconjugates was carried out in several phases, including activation of serotype 12F polysaccharide with TEMPO/NCS. This novel chemistry enhances stability of the serotype 12F conjugate while maintaining immunogenicity of the conjugate in Prevnar 20®.

- Mechanical sizing of polysaccharide: The process includes sizing the purified *Streptococcus pneumoniae* serotypes 11A, 15B, and 22F capsular polysaccharide by high pressure homogenization. Mechanical sizing controls the sizing of the polysaccharide and ensures robust and consistent processability of the final conjugate.
- Use of flocculation for polysaccharide purification: This innovation introduced during purification of the bacterial polysaccharides removes impurities from cellular lysates of bacteria (host cell proteins and DNA) and replaces several tedious precipitation/resolubilization steps simplifying the process and reducing the number of unit operations from 15 to seven.

Summary

The licensure of Prevnar 20® for use in adults addresses the need to substantially expand the coverage of an effective vaccine that helps to protect against disease caused by *S. pneumoniae*.¹⁰ Innovative approaches to the clinical evaluation of the vaccine, and to the development of robust processes for maintaining the consistent manufacture and supply of the vaccine, have made it possible to provide that coverage throughout the world. The consistency of the manufacturing process is being proven by the ability to supply the rapidly expanding worldwide demand for the vaccine. The design of the vaccine and its associated manufacturing processes will ensure that effective anti-pneumococcal immunization can and will continue to be made available for all the world's human populations.

Pubmed

1. GBD 2016 Lower Respiratory Infections Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect Dis* 2018; 18: 1191-2100
2. Iyer AS, Ohtola JA, Westerink MA. Age-related immune response to pneumococcal polysaccharide vaccination: lessons for the clinic. *Expert Rev Vaccines* 2015;14(1):85-97.
3. van Hoek AJ, Andrews N, Waight PA, et al. Effect of serotype on focus and mortality of invasive pneumococcal disease: coverage of different vaccines and insight into vaccine serotypes. *PLoS One* 2012;7(7):e39150.
4. Drikkoningen JJ, Rohde GG. Pneumococcal infection in adults: burden of disease. *Clin Microbiol Infect* 2014;20 Suppl 5:45-51.
5. Bonten MJ, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *N Engl J Med*. 2015;372(12):1114-25.
6. Hurley D, Griffin C, Young M, Scott DA, Pride MW, Scully IL, Ginis J, Severs J, Jansen KU, Gruber WC, Watson W. Safety, tolerability, and immunogenicity of a 20-Valent pneumococcal conjugate vaccine (PCV20) in adults 60 to 64 years of age. *Clin Infect Dis* 2021; 73(7):e1489-e1497.
7. Klein NP, Peyrani P, Yacisin K, Caldwell N, Xu X, Scully IL, Scott DA, Jansen KU, Gruber WC, Watson W. A phase 3, randomized, double-blind study to evaluate the immunogenicity and safety of 3 lots of 20-

valent pneumococcal conjugate vaccine in pneumococcal vaccine-naïve adults 18 through 49 years of age. *Vaccine* 2021; 39(38):5428-5435.

8. Cannon, K, Elder C, Young M, Scott DA, Scully IL, Baugher G, Peng Y, Jansen KU, Gruber WC, Watson W. A trial to evaluate the safety and immunogenicity of a 20-valent pneumococcal conjugate vaccine in populations of adults >65 years of age with different prior pneumococcal vaccination. *Vaccine* 2021; 39(51): 7494-7502.

9. Essink B, Sabharwal C, Cannon K, Frenck R, Lal H, Xu X, Sundaraiyer V, Peng Y, Moyer L, Pride MW, Scully IL, Jansen KU, Gruber WC, Scott DA, Watson W. Pivotal phase 3 randomized clinical trial of the safety, tolerability, and immunogenicity of 20-valent pneumococcal conjugate vaccine in adults 18 years and older. *Clin Infect Dis* 2022; 75 (3): 390–398.

10. McLaughlin JM, Jiang Q, Isturiz RE, Sings HL, Swerdlow DL, Gessner BD, Carrico RM, Peyrani P, Wiemken TL, Mattingly WA, Ramirez JA, Jodar L. Effectiveness of 13-Valent Pneumococcal Conjugate Vaccine Against Hospitalization for Community-Acquired Pneumonia in Older US Adults: A Test-Negative Design. *Clin Infect Dis*. 2018;67(10):1498-1506.

11. Grant L, Begier E, Barry R, et al., Contribution of Serotypes Covered by Pneumococcal Conjugate Vaccines Among Adults with Community-Acquired Pneumonia. ISPPD-12, Toronto, Canada, June 19-23. Abstract #389.

12. European Centre for Disease Prevention and Control. Surveillance Atlas for Infectious Diseases, Invasive Pneumococcal Disease, 2018. Available: <https://www.ecdc.europa.eu/en/data-tools>. Accessed 17 July 2020.

Attachments

- 1654093089Prevnar20_PrixGalienUSAFinal.docx
- 1654093105Prevnar20_PrixGalienUSAFinal.docx
- 1654093075Prevnar20_PrixGalienUSAFinal.docx
- 1654093131Prevnar20_PrixGalienUSAFinal.docx
- Prevnar20 PrixGalienUSA 2023.docx

Submit