# PREVNAR 13™

## 1. PRODUCT NAME

**Prevnar 13** suspension for injection

Pneumococcal 13-valent Conjugate Vaccine (Diphtheria $CRM_{197}$ Protein)

## 2. NAME AND STRENGTH OF ACTIVE INGREDIENTS

Each dose (0.5 mL) contains:

| | |
|---|---|
| Pneumococcal polysaccharide serotype 1* | 2.2 µg |
| Pneumococcal polysaccharide serotype 3* | 2.2 µg |
| Pneumococcal polysaccharide serotype 4* | 2.2 µg |
| Pneumococcal polysaccharide serotype 5* | 2.2 µg |
| Pneumococcal polysaccharide serotype 6A* | 2.2 µg |
| Pneumococcal polysaccharide serotype 6B* | 4.4 µg |
| Pneumococcal polysaccharide serotype 7F* | 2.2 µg |
| Pneumococcal polysaccharide serotype 9V* | 2.2 µg |
| Pneumococcal polysaccharide serotype 14* | 2.2 µg |
| Pneumococcal polysaccharide serotype 18C* | 2.2 µg |
| Pneumococcal polysaccharide serotype 19A* | 2.2 µg |
| Pneumococcal polysaccharide serotype 19F* | 2.2 µg |
| Pneumococcal polysaccharide serotype 23F* | 2.2 µg |

* Conjugated to $CRM_{197}$ carrier protein and adsorbed on aluminium phosphate (0.125 mg aluminium).

## 3. PRODUCT DESCRIPTION

Pneumococcal 13-valent conjugate vaccine is a sterile solution of saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated by reductive amination to non-toxic diphtheria $CRM_{197}$ protein. The polysaccharides are chemically activated and then covalently linked to the protein carrier $CRM_{197}$ to form the glycoconjugate.

Individual conjugates are compounded and then polysorbate 80, 5 mM succinate buffer and aluminum phosphate are added to formulate the vaccine. The potency of the vaccine is determined by the quantity of the saccharide antigens and the saccharide-to-protein ratios in the individual glycoconjugates. Each dose (0.5 mL) is formulated to contain approximately 2.2 µg of each saccharide for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F and approximately 4.4 µg of saccharide for serotype 6B, conjugated to $CRM_{197}$ carrier protein, 0.02% polysorbate 80, and 0.125 mg of aluminum as aluminum phosphate adjuvant.

## 4. PHARMACODYNAMICS/PHARMACOKINETICS

### 4.1 Pharmacodynamics Properties

Pharmacotherapeutic group: pneumococcal vaccines; ATC code: J07AL02.

**Mechanism of Action**

**Prevnar 13** contains the 7 pneumococcal capsular polysaccharides that are in pneumococcal 7-valent conjugate vaccine (4, 6B, 9V, 14, 18C, 19F, 23F) plus 6 additional polysaccharides (1, 3, 5, 6A, 7F, 19A) all conjugated to $CRM_{197}$ carrier protein. The immune response to most antigens is T-dependent and involves the collaboration of CD4+ T cells and B cells, recognizing the antigen in a linked fashion. CD4+ T cells (T-helper cells) provide signals to B cells directly through cell surface protein interactions, and indirectly through the release of cytokines. These signals result in proliferation and differentiation of the B cells, and production of high-affinity antibodies. CD4+ T cell signaling is a requisite for the generation of long-lived B cells called plasma cells, which continuously produce antibodies of several isotypes (with an IgG component) and memory B cells that rapidly mobilize and secrete antibodies upon re-exposure to the same antigen.

Bacterial capsular polysaccharides (PS) are T-cell-independent antigens that stimulate mature B-lymphocytes, but not T-lymphocytes. In the absence of T-lymphocyte help, PS-stimulated B cells predominantly produce IgM antibodies, have no affinity maturation or generation of memory B cells (anamnestic or booster response). PS vaccines are associated with poor or absent immunogenicity in infants less than 24 months of age and failure to induce immunological memory at any age. Conjugation of a PS to a protein carrier changes the nature of the antibody response from T-cell-independent to T-cell-dependent. Such protein carrier-specific T-lymphocytes provide the signals needed for maturation of the B cell response and generation of B cell memory, allowing an anamnestic (booster) response on re-exposure to pneumococcal polysaccharides.

Based on serotype surveillance in Europe performed before the introduction of pneumococcal 7-valent conjugate vaccine, **Prevnar 13** is estimated to cover 83%-93% (depending on the country) of serotypes causing IPD (Invasive Pneumococcal Disease) among infants and young children.

**Prevnar 13** is estimated to cover over 90% of serotypes causing antibiotic-resistant IPD.

**Clinical Trials Data on Efficacy**

Disease Burden for Infants and Children

*S. pneumoniae* is an important cause of morbidity and mortality in persons of all ages worldwide. The organism causes invasive infections, such as bacteremia and meningitis, as well as pneumonia and upper respiratory tract infections, including otitis media and sinusitis. In children older than 1 month, *S. pneumoniae* is the most common cause of invasive disease. More than 90 different serotypes of *S. pneumoniae* have been identified, varying both by the composition of their seroreactive capsular polysaccharides and in their ability to cause disease, with the majority of invasive disease caused by relatively few serotypes. The relative frequencies of pneumococcal serotypes causing invasive disease in children vary geographically, but have been remarkably stable over time. In the US, the serotypes causing the majority of disease in the 1990s were the basis for the development of the pneumococcal 7-valent conjugate vaccine and included serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F.

Prior to the introduction of the pneumococcal 7-valent conjugate vaccine, the incidence of invasive pneumococcal disease (IPD) among children less than 2 years of age was approximately 180-200 cases/100,000/year, with an overall estimated case-fatality rate of 1.4%. The incidence of pneumococcal meningitis in this age group was estimated to be approximately 7-10 cases/100,000/year, with an associated mortality rate as high as 8%-25%. Of survivors, a significant proportion had serious sequelae, including developmental delay, seizure disorders, and deafness. Finally, while pneumonia is generally not considered to be invasive disease *per se*, it may be accompanied by bacteremia or may be complicated by local invasion into a normally sterile space with empyema; both of these invasive manifestations of pneumonia are more severe and carry considerably higher morbidity and mortality rates than do non-invasive pneumonia, even among children. Prior to the licensure of the pneumococcal 7-valent conjugate vaccine, the estimated incidence of pneumonia among children <2 years of age was 24/100,000. Children in group child care have an increased risk for IPD, as do individuals with asthma, diabetes mellitus, immunocompromised individuals with neutropenia, asplenia, sickle cell disease, disorders of

complement and humoral immunity, human immunodeficiency virus (HIV) infection or chronic underlying disease.

The pneumococcal 7-valent conjugate vaccine was licensed in the US for infants and children in 2000, following a randomized, double-blinded clinical trial in a multiethnic population at Northern California Kaiser Permanente (NCKP) from October 1995 through August 20, 1998, in which 37,816 infants were randomized to receive either the pneumococcal 7-valent conjugate vaccine or a control vaccine (an investigational meningococcal group C conjugate vaccine [MnCC]) at 2, 4, 6, and 12-15 months of age. In this study, the efficacy of the pneumococcal 7-valent conjugate vaccine against invasive disease due to *S. pneumoniae* in cases accrued during this period was 100% in both the per-protocol and intent-to-treat analyses (95% CI, 75.4%-100% and 81.7%-100%, respectively). Data accumulated through an extended follow-up period to April 20, 1999, resulted in similar efficacy estimates of 97.3% in the per-protocol analysis and 94.4% in the intent-to-treat analysis. Since the vaccine's introduction, a 98% reduction in IPD caused by vaccine serotypes has been observed among children younger than 5 years of age through 2005, attesting to the high effectiveness of the pneumococcal 7-valent conjugate vaccine in routine use. While the effect of routine use of the pneumococcal 7-valent conjugate vaccine in infants and young children has been dramatic, with a near-total elimination of the serotypes contained in this vaccine, a proportional increase in other serotypes causing IPD has been observed (as an increasing percentage of residual disease). Specifically, while serotype 19A was the ninth most commonly isolated serotype causing IPD in the US prior to the introduction of the pneumococcal 7-valent conjugate vaccine, according to both CDC and independent surveillance, as of 2005, serotype 19A had become the predominant pneumococcal serotype causing IPD in US children, accounting for approximately 30%-45% of the residual IPD in 2005 in children <5 years of age. Compounding the issue of the predominance of emerging serotype 19A is that it is increasingly likely to be non-susceptible to commonly used first-line antimicrobial agents. Furthermore, approximately 66% of the serotyped IPD cases occurring in children <5 years of age in 2006-2007 in the Centers for Disease Control and Prevention (CDC) Active Bacterial Core surveillance were due to serotypes 1, 19A, 7F, 3, 6A, and 5 included in **Prevnar 13**. In various recent US surveys conducted by other investigators, more than 45% and up to 60% of residual IPD cases in pediatric subjects were caused by these 6 additional serotypes.

Epidemiologic observations in the US since the introduction of the pneumococcal 7-valent conjugate vaccine have shown that not only has invasive disease been significantly reduced among vaccinated children, especially that caused by serotypes included in the vaccine, but it has also been reduced both among persons older than 5 years of age (a population for whom the conjugate vaccine is not

routinely recommended) and among infants too young to be eligible for immunization. It is generally believed that the reduction in disease among unvaccinated people is the result of herd immunity or indirect effect, a phenomenon that occurs via interruption of transmission of disease to otherwise susceptible populations, resulting in an observed reduction in disease overall. In this case, herd immunity is observed in unvaccinated populations due to the ability of the pneumococcal 7-valent conjugate vaccine to interrupt transmission of pneumococci from vaccinated children to their unvaccinated contacts. It is expected that there will be similar population responses related to **Prevnar 13** when used routinely.

The exact contribution of *S. pneumoniae* to childhood pneumonia is unknown, as it is often not possible to identify the causative organisms. In studies of children <5 years of age with community-acquired pneumonia (CAP), where diagnosis was attempted using serological methods, antigen testing, or culture data, 30% of cases were classified as bacterial pneumonia, and 70% of these (21% of total CAP) were found to be due to *S. pneumoniae,* making it the most common bacterial cause of pneumonia in this age group. Observations since the introduction of the pneumococcal 7-valent conjugate vaccine, however, suggest that *S. pneumoniae*, and in particular those pneumococcal serotypes included in the vaccine, are responsible for a considerable burden of CAP among children, and that the pneumococcal 7-valent conjugate vaccine is effective in preventing CAP in children. In particular, reviews of hospital utilization databases in the US found a 39%-52.4% reduction in hospitalizations for all-cause pneumonia, and a 57.6%-65% reduction in hospitalizations coded as pneumococcal pneumonia, in children younger than 2 years of age. While uncomplicated pneumonia is generally considered non-invasive disease, pneumococcal pneumonia may be complicated by both bacteremia and locally invasive manifestations, including pleural empyema and pulmonary necrosis. Observations in the US since the introduction of the pneumococcal 7-valent conjugate vaccine suggest that complicated, invasive pneumonia may be increasing, and that these more severe manifestations of pneumonia are more likely to be associated with serotypes included in **Prevnar 13** (1, 3, 19A, and 7F); serotype 3 in particular has been associated with necrotizing pneumonia.

*Streptococcus pneumoniae* is also a major cause of non-invasive disease in children, particularly of acute otitis media (AOM). AOM is a common childhood disease, with more than 60% of children experiencing an episode by 1 year of age, and more than 90% of children experiencing an episode by age 5. Prior to the US introduction of the pneumococcal 7-valent conjugate vaccine in the year 2000, approximately 24.5 million ambulatory care visits and 490,000 procedures for myringotomy with tube placement were attributed to otitis media annually. The peak incidence of AOM is 6-18

months of age. Otitis media is less common, but occurs, in older children. In a 1990 surveillance report by the CDC, otitis media was the most common principal illness diagnosis in children 2-10 years of age. Complications of AOM include persistent middle-ear effusion, chronic otitis media, transient hearing loss, or speech delays and, if left untreated, may lead to more serious diseases such as mastoiditis and meningitis. *S. pneumoniae* is an important cause of AOM. It is the bacterial pathogen most commonly isolated from middle-ear fluid, identified in 20%-40% of middle-ear fluid cultures in AOM. Pneumococcal otitis media is associated with higher rates of fever and is less likely to resolve spontaneously than AOM due to either non-typeable *H. influenzae* or *M. catarrhalis*.

The efficacy of the pneumococcal 7-valent conjugate vaccine against otitis media was assessed in 2 clinical trials: a trial in Finnish infants at the National Public Health Institute and the pivotal efficacy trial in US infants at Northern California Kaiser Permanente (NCKP). The Finnish Otitis Media (FinOM) trial was a randomized, double-blind trial in which 1,662 infants were equally randomized to receive either pneumococcal 7-valent conjugate vaccine or a control vaccine (Hepatitis B vaccine [Hep B]) at 2, 4, 6, and 12-15 months of age. In this study, parents of study participants were asked to bring their children to the study clinics if the child had respiratory infection or symptoms suggesting AOM. If AOM was diagnosed, tympanocentesis was performed, and the middle-ear fluid was cultured. If *S. pneumoniae* was isolated, serotyping was performed; the primary endpoint was efficacy against AOM episodes caused by vaccine serotypes in the per-protocol population. In the NCKP trial, the efficacy of the pneumococcal 7-valent conjugate vaccine against otitis media was assessed from the beginning of the trial in October 1995 through April 1998. The otitis media analysis included 34,146 infants randomized to receive either the pneumococcal 7-valent conjugate vaccine (N=17,070), or the control vaccine (N=17,076), at 2, 4, 6, and 12-15 months of age. In this trial, no routine tympanocentesis was performed, and no standard definition of otitis media was used by study physicians. The primary otitis media endpoint was efficacy against all otitis media episodes in the per-protocol population.

The vaccine efficacy against AOM episodes due to vaccine serotypes assessed in the Finnish trial was 57% (95% CI, 44%-67%) in the per-protocol population and 54% (95% CI, 41%-64%) in the intent-to-treat population. The vaccine efficacy against AOM episodes due to vaccine-related serotypes (6A, 9N, 18B, 19A, 23A), also assessed in the Finnish trial, was 51% (95% CI, 27, 67) in the per-protocol population and 44% (95% CI, 20, 62) in the intent-to-treat population. There was a non-significant increase in AOM episodes caused by serotypes unrelated to the vaccine in the per-protocol population, suggesting that children who received the pneumococcal 7-valent conjugate vaccine appeared to be at increased risk of otitis media due to pneumococcal serotypes not

represented in the vaccine, compared to children who received the control vaccine. However, vaccination with the pneumococcal 7-valent conjugate vaccine reduced pneumococcal otitis media episodes overall. In the NCKP trial, in which the endpoint was all otitis media episodes regardless of etiology, vaccine efficacy was 7% (95% CI, 4%-10%) and 6% (95% CI, 4%-9%), respectively, in the per-protocol and intent-to-treat analyses. Several other otitis media endpoints were also assessed in the 2 trials. Recurrent AOM, defined as 3 episodes in 6 months or 4 episodes in 12 months, was reduced by 9% in both the per-protocol and intent-to-treat populations (95% CI, 3%-15% in per-protocol and 95% CI, 4%-14% in intent-to-treat) in the NCKP trial; a similar trend was observed in the Finnish trial. The NCKP trial also demonstrated a 20% reduction (95% CI, 2, 35) in the placement of tympanostomy tubes in the per-protocol population and a 21% reduction (95% CI, 4, 34) in the intent-to-treat population. Data from the NCKP trial accumulated through an extended follow-up period to April 20, 1999, in which a total of 37,866 children were included (18,925 in the pneumococcal 7-valent conjugate vaccine group and 18,941 in the MnCC control group), resulted in similar otitis media efficacy estimates for all endpoints.

Similar to the experience with IPD, reductions in AOM have been observed in the US since the introduction of the pneumococcal 7-valent conjugate vaccine as a routine infant vaccine. Since diagnostic tympanocentesis is not routinely performed in the US, less information is available on shifts in the distribution of causative pneumococcal serotypes. However, results of several recent studies suggest that non-pneumococcal 7-valent conjugate vaccine serotypes are also emerging as important causes of AOM or its complications in children (including mastoiditis, which now accounts for 12% of all IPD in the US Pediatric Multicenter Pneumococcal Surveillance Study, all of it caused in 2006-2007 by serotype 19A), and that these non-pneumococcal 7-valent conjugate vaccine serotypes are likely to be resistant to commonly used antimicrobial agents. Another series of pneumococcal isolates from tympanocentesis samples collected from 5 centers across the United States identified serotype 3 most commonly, with a smaller percentage accounted for by serotypes 1 and 7.

Disease Burden for Adults

*Streptococcus pneumoniae* is a significant threat to world health. The World Health Organization (WHO) estimates that each year 1.6 million people die from pneumococcal disease, of which 600,000 to 800,000 are adults. Pneumococcal disease can be classified by the degree of bacterial invasion, which is predictive of complications and mortality. IPD is defined by the isolation of pneumococcus from a normally sterile site such as blood, cerebrospinal fluid, pleural fluid, or peritoneal fluid. In adults, the major clinical presentations of IPD are meningitis, bacteremia, or bacteremic pneumonia. Pneumonia without bacteremia is the most common serious manifestation of non-IPD.

Adults older than 50 years of age, especially those older than 65 years of age, are at increased risk for developing pneumococcal infections and are more likely to develop IPD with its associated increased mortality, morbidity and complications. Additional risk factors for serious pneumococcal disease include living circumstances and underlying medical conditions which may also concern younger adults, e.g., 18 years and above. Living conditions can increase the individual risk of pneumococcal disease, particularly residence in a nursing home or other long-term care facility. Significant medical risk conditions include: congenital or acquired immunodeficiency; sickle cell disease; asplenia; human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS); malignant hematological diseases, chronic heart, lung (including asthma), renal, or liver diseases; cancer; cerebrospinal fluid (CSF) leak; diabetes; chronic alcoholism or cigarette smoking; organ or hematopoietic cell transplantation; and cochlear implants. Among hospitalized patients in the United States, the all-case fatality rate from IPD remains high (12%-16%) and is much higher in many subgroups including those with increased age, comorbidities, complications of IPD and admission to intensive care units. Despite advances in medical science over the last decades, there has been little change in mortality rates since penicillin’s introduction.

The reported incidence of IPD worldwide ranges from 45 to 90 per 100,000. Prior to the introduction of pneumococcal 7-valent conjugate vaccine into National Immunization Programs (NIP), the IPD incidence for Canadian adults aged 65 years and older ranged from 16 to 31 per 100,000, while for US residents of the same age, the IPD incidence ranged from 60 to 65 per 100,000 (with rates of 190/100,000 documented among members of the Navajo Nation). The IPD incidence for older Europeans in the same age group ranged from 41 in Sweden to 66 per 100,000 in Denmark, with a particularly high rate documented in the older age groups beyond 65 years, for instance, in The Netherlands or the UK. In the United States, a decrease in adult disease after the initiation of childhood vaccination has been noted, presumably due to reduction of pneumococcal colonization

in infants and spread to susceptible adults (herd protection). However, the incidence of IPD in adults, especially the elderly, has remained high ranging from 23 per 100,000 to 29.4 per 100,000. Although the incidence estimates among adults younger than 65 are lower than those among adults older than 65, IPD represents a major public health burden among younger adults as well.

Pneumonia is one of the most common infectious diseases and the most common clinical presentation of pneumococcal disease in adults. *S. pneumoniae* is the most frequent cause of CAP, and is estimated to be responsible for approximately 30% of all CAP cases requiring hospitalization in adults in developed countries. The incidence of non-bacteremic pneumonia caused by *S. pneumoniae* is difficult to ascertain, because the causative pathogen is not identified in the majority of cases. In the United States, during 2006, over 4 million cases of pneumonia due to all causes were reported in adults. In Europe, rates of CAP vary by country and by age group and setting studied. Higher rates of CAP have been noted in the developing world, within specific genetic groups, in populations with lower socioeconomic status and in groups with less access to health care. Mortality from all-cause CAP range from 5%-15% and CAP contributes to a significant proportion of intensive care unit (ICU) admissions. Patients with pneumonia caused by *S. pneumoniae* tend to have more severe illness including greater likelihood of bacteremia, longer hospitalization, greater need for intensive care, and higher mortality. As for IPD, the risk of pneumococcal pneumonia increases with age from 50 years and is highest in individuals aged ≥65 years of age. Risk also increases with chronic underlying medical conditions, specifically, anatomical or functional asplenia, diabetes mellitus, asthma, chronic cardiovascular, pulmonary, kidney or liver disease, and it is highest in those who are immune-suppressed such as those with malignant hematological diseases or HIV infection.

While host factors such as age and comorbid conditions contribute to the likelihood of IPD and poor outcomes, there has been increasing appreciation that pathogen virulence and antimicrobial resistance play an important role. Although more than 90 different serotypes of *S. pneumoniae* have been identified, human disease is caused by a relatively small group of serotypes possessing poorly defined virulence factors that allow them to cause disease. According to a meta-analysis of serotype-specific disease outcomes for patients with pneumonia, serotypes 3, 6A, 6B, 9N, and 19F were statistically significantly associated with increased mortality when compared to serotype 14, used as a reference. For serotypes 19A and 23F, there was a trend towards increased mortality which did not reach statistical significance. Despite some regional variations in rate and mortality, these observations appeared to be a relatively stable characteristic of the serotype and appeared to be independent of antimicrobial resistance.

Antimicrobial resistance increases the difficulty of initially treating some serotypes of *S. pneumoniae* with an effective antibiotic. Despite great geographic variability of serotype distribution and prevalence of antimicrobial resistance, serotypes 6A, 6B, 9V, 14, 15A, 19F, 19A and 23F were most likely to demonstrate resistance to both penicillin and erythromycin.

**Prevnar 13** provides an immune response against prevalent strains of *S. pneumoniae* including those most likely to cause disease, be antimicrobial resistant, and result in poor outcomes.

**Table 1: Mortality and Resistance of Selected Serotypes in Adults**

| Serotype | 3 | 6A | 6B | 9N | 9V | 14 | 15A | 19A | 19F | 23F |
|---|---|---|---|---|---|---|---|---|---|---|
| Mortality | + | + | + | + | | | | +/- | + | +/- |
| Resistance | | + | + | | + | + | + | + | + | + |

**Prevnar 13 Immunogenicity Clinical Studies in Infants and Children**

The World Health Organization (WHO) has recommended a serum anti-capsular polysaccharide antibody concentration of 0.35 µg/mL measured 1 month after the primary infant series as a single antibody reference concentration to estimate the efficacy of new pneumococcal conjugate vaccines against IPD. This recommendation is largely based upon the observed correlation between immunogenicity and IPD efficacy from 3 placebo-controlled trials with either pneumococcal 7-valent conjugate vaccine or the investigational 9-valent $CRM_{197}$ conjugate polysaccharide vaccine. This reference concentration is only applicable on a population basis and cannot be used to predict protection against IPD on an individual basis.

Immune Responses Following a 3-Dose Primary Infant Series

Clinical trials have been conducted in a number of European countries, Canada and the US using a range of primary vaccination schedules. The percentage of infants achieving pneumococcal anti-capsular polysaccharide IgG antibody concentrations $\geq$0.35 µg/mL 1 month after a 3-dose primary series in representative studies are presented below (Table 2):

**Table 2: Percentage of Subjects with Pneumococcal Anti-capsular Polysaccharide IgG Antibody Concentrations ≥0.35 µg/mL 1 Month After the Infant Series**

| Serotype | 2, 3, 4 months Germany (6096A1-006) | 2, 3, 4 months Poland (6096A1-3000 Manufacturing) | 2, 4, 6 months Spain (6096A1-501) | 2, 4, 6 months US (6096A1-004) | 2, 4, 6 months US Lot 1 (6096A1-3005) | 2, 4, 6 months US Lot 2 (6096A1-3005) | 2, 4, 6 months US Lot 3 (6096A1-3005) | 2, 4, 6 months Canada (6096A1-3008) |
|---|---|---|---|---|---|---|---|---|
| | (N=282 - 285) | (N=106 - 128) | (N=261 - 273) | (N=249 - 252) | (N=387 - 399) | (N=398 - 413) | (N=387 - 404) | (N=272 - 277) |
| 1 | 96.1 | 93.0 | 99.3 | 95.6 | 98.5 | 97.8 | 97.0 | 95.7 |
| 3 | 98.2 | 93.7 | 90.3 | 63.5 | 79.1 | 68.5 | 72.4 | 79.6 |
| 4 | 98.2 | 97.7 | 98.9 | 94.4 | 98.5 | 97.6 | 95.5 | 97.1 |
| 5 | 93.0 | 90.6 | 97.3 | 89.7 | 94.4 | 94.2 | 90.3 | 87.0 |
| 6A | 91.9 | 85.2 | 97.4 | 96.0 | 98.2 | 98.1 | 95.5 | 96.4 |
| 6B | 77.5 | 77.3 | 98.5 | 87.3 | 94.4 | 94.9 | 89.5 | 93.1 |
| 7F | 98.6 | 100.0 | 100.0 | 98.4 | 99.7 | 99.8 | 99.0 | 98.6 |
| 9V | 98.6 | 98.4 | 99.3 | 90.5 | 96.5 | 95.4 | 95.5 | 95.3 |
| 14 | 98.9 | 92.9 | 97.4 | 97.6 | 98.2 | 99.2 | 99.0 | 98.2 |
| 18C | 97.2 | 96.1 | 98.1 | 96.8 | 98.0 | 97.8 | 95.8 | 96.4 |
| 19A | 99.3 | 99.2 | 99.6 | 98.4 | 98.7 | 98.1 | 99.0 | 97.8 |
| 19F | 95.8 | 98.4 | 99.3 | 98.0 | 99.2 | 97.8 | 97.5 | 98.5 |
| 23F | 88.7 | 82.8 | 94.6 | 90.5 | 87.2 | 91.2 | 88.1 | 90.2 |

In **Prevnar 13** recipients, antipolysaccharide binding IgG antibody for each of the 13 serotypes has been demonstrated to be correlated with functional antibacterial opsonophagocytic activity (biologically-active antibody). Clinical trials also demonstrated that the response to **Prevnar 13** was non-inferior to that of pneumococcal 7-valent conjugate vaccine for all 13 serotypes using a set of pre-defined immunological non-inferiority criteria. Immune responses elicited by **Prevnar 13** to the 6 additional serotypes were quantitatively greater, for both polysaccharide-binding and opsonophagocytic antibodies, than the responses elicited by pneumococcal 7-valent conjugate vaccine.

Immune Responses Following a 2-Dose Primary Series

The immunogenicity after 2 doses in infants has been documented in 4 studies. The proportion of infants achieving a pneumococcal anti-capsular polysaccharide IgG concentration ≥0.35 µg/mL 1 month after the second dose ranged from 79.6% to 98.5% across 11 of the 13 vaccine serotypes. Smaller proportions of infants achieved this antibody concentration threshold for serotype 6B (27.9% to 58.4%) and 23F (55.8% to 68.6%). Compared to a 3-dose infant series, pneumococcal anti-capsular polysaccharide IgG GMCs were lower after a 2-dose infant series for most serotypes. The clinical effectiveness of a 2-dose primary series against AOM or pneumonia has not been established.

Booster Responses Following 2-Dose and 3-Dose Primary Series

Post-booster antibody concentrations were higher for 12 serotypes than those achieved after the infant primary series, which is consistent with adequate priming (the induction of immunologic memory). For serotype 3, antibody concentrations following the infant primary series and booster dose were similar. Antibody responses to booster doses following 2-dose or 3-dose infant primary series were comparable for all 13 vaccine serotypes.

For children aged 7 months to 5 years, age appropriate catch-up immunization schedules (as described in sections 6 and 7) result in levels of anti-capsular polysaccharide IgG antibody responses to each of the 13 serotypes that are at least comparable to those of a 3-dose primary series in infants.

Booster Responses to **Prevnar 13** Following a 3-Dose Primary Infant Series of Pneumococcal 7-valent Conjugate Vaccine or **Prevnar 13**

In a randomized, double-blind, active-control study in France (6096A1-008) infants were randomly assigned to 3 groups in a 2:1:1 ratio: (1) **Prevnar 13** at 2, 3, 4 and 12 months or (2) pneumococcal 7-valent conjugate vaccine at 2, 3 and 4 months followed by **Prevnar 13** at 12 months or (3) pneumococcal 7-valent conjugate vaccine at 2, 3, 4 and 12 months. Geometric mean concentrations of anti-capsular polysaccharide IgG antibody responses to each of the 13 serotypes in the 3 groups are shown in Table 3. GMCs to the 7 pneumococcal 7-valent conjugate vaccine serotypes did not differ in the 3 groups. Although the GMCs to the 6 additional serotypes in the pneumococcal 7-valent conjugate vaccine/**Prevnar 13** recipients were lower than those observed with the 4 dose **Prevnar 13** regimen (except for serotype 3), they were at least comparable to those of a 3-dose primary series in infants in studies (6096A1-004) and (6096A1-3005). This comparison

to infant series responses is similar to what was done with pneumococcal 7-valent conjugate vaccine to establish the immunization schedules in older infants and children.

**Table 3: Pneumococcal Anti-capsular Polysaccharide IgG Antibody Geometric Mean Concentrations (µg/mL) 1 Month After Vaccination**

| Serotype | 13v/13v Post-Toddler (6096A1-008) N=233-236 | 7v/13v Post-Toddler (6096A1-008) N=108-113 | 7v/7v Post-Toddler (6096A1-008) N=111-127 | 13v Post-Infant (6096A1-004) N=249-252 | 13v Post-Infant (6096A1-3005) N=1172-1213 |
|---|---|---|---|---|---|
| 1 | 4.08 | 1.83 | 0.04 | 2.03 | 1.78 |
| 3 | 0.99 | 1.32 | 0.10 | 0.49 | 0.56 |
| 4 | 4.20 | 4.04 | 4.85 | 1.31 | 1.46 |
| 5 | 3.30 | 1.14 | 0.53 | 1.33 | 1.24 |
| 6A | 6.14 | 2.60 | 1.54 | 2.19 | 2.21 |
| 6B | 8.99 | 10.33 | 9.63 | 2.10 | 2.51 |
| 7F | 4.52 | 3.71 | 0.05 | 2.57 | 2.57 |
| 9V | 2.59 | 2.29 | 3.24 | 0.98 | 1.09 |
| 14 | 9.52 | 7.81 | 10.83 | 4.74 | 5.09 |
| 18C | 2.30 | 2.43 | 2.81 | 1.37 | 1.37 |
| 19A | 9.50 | 5.33 | 3.98 | 2.07 | 1.91 |
| 19F | 5.18 | 3.73 | 4.11 | 1.85 | 2.15 |
| 23F | 3.01 | 3.12 | 3.69 | 1.33 | 1.18 |

Preterm Infants (B1851037 [6096A1-4001])

Safety and immunogenicity of **Prevnar 13** given at 2, 3, 4 and 12 months was assessed in 100 prematurely born infants (estimated gestational age [EGA] mean, 31 weeks; range, 26 to 36 weeks) and compared with 100 infants born at term (EGA mean, 39 weeks; range, 37 to 42 weeks). More than 85% of subjects in the preterm group in the evaluable immunogenicity population achieved a pneumococcal polysaccharide IgG binding antibody concentration ≥0.35 µg/mL 1 month after the infant series for all serotypes except serotypes 5 (71.7%), 6A (82.7%), and 6B (72.7%) in the preterm group. For these 3 serotypes, the proportion of responders among preterm infants was significantly lower than among term infants. One (1) month after the toddler dose, evidence of priming was observed as the proportion of subjects in each group in the evaluable toddler immunogenicity population achieving this same antibody concentration threshold was >97%, except

for serotype 3 (70.6% in preterm infants and 79.3% in term infants). In general, serotype-specific IgG GMCs were lower for preterm infants than term infants.

Previously Unvaccinated Older Infants and Children

In an open-label study of **Prevnar 13** in Poland (6096A1-3002), children 7-11 months of age, 12-23 months and ≥24 months to 5 years of age (prior to the 6th birthday) who were naive to pneumococcal conjugate vaccine, were given 3, 2 or 1 dose of **Prevnar 13** according to the age-appropriate schedules (see sections 6 and 7). Serum IgG concentrations were measured 1 month after the final dose in each age group and the data are shown in Table 4.

These age appropriate catch-up immunization schedules result in levels of anti-capsular polysaccharide IgG antibody responses to each of the 13 serotypes that are at least comparable to those of a 3-dose primary series in infants.

**Table 4: Pneumococcal Anti-capsular Polysaccharide IgG Antibody Geometric Mean Concentrations (µg/mL) 1 Month After Vaccination (in Study 6096A1-3002)**

| Serotype | 7-11 months of age (N=83-84) | 12-23 months of age (N=104-110) | ≥24 months to 5 years of age (N=135-152) |
|---|---|---|---|
| 1 | 2.88 | 2.74 | 1.78 |
| 3 | 1.94 | 1.86 | 1.42 |
| 4 | 3.63 | 4.28 | 3.37 |
| 5 | 2.85 | 2.16 | 2.33 |
| 6A | 3.72 | 2.62 | 2.96 |
| 6B | 4.77 | 3.38 | 3.41 |
| 7F | 5.30 | 5.99 | 4.92 |
| 9V | 2.56 | 3.08 | 2.67 |
| 14 | 8.04 | 6.45 | 2.24 |
| 18C | 2.77 | 3.71 | 2.56 |
| 19A | 4.77 | 4.94 | 6.03 |
| 19F | 2.88 | 3.07 | 2.53 |
| 23F | 2.16 | 1.98 | 1.55 |

Simultaneous Administration with Other Vaccines in Infants and Children

In studies 6096A1-004, 6096A1-3005, and 6096A1-3008, routine pediatric vaccines were administered at the same visit as **Prevnar 13**. Immune responses to selected concomitant vaccine antigens were compared in infants receiving pneumococcal 7-valent conjugate vaccine and **Prevnar 13**. The proportion of responders at pre-specified antibody levels is shown in Table 5. Responses to all antigens in **Prevnar 13** recipients were similar to those in pneumococcal 7-valent conjugate vaccine recipients and met formal criteria for non-inferiority. Varicella responses as measured by a commercial whole cell ELISA kit, designed to detect immunity after natural infection, were low in both groups, but there was no evidence of interference with the immune response by concomitantly administered **Prevnar 13**.

**Table 5: Subjects Achieving a Pre-specified Antibody Level for Concomitant Vaccine Antigens (in Study 6096A1-004, Study 6096A1-3005, and Study 6096A1-3008)**

| **Vaccine Name/Vaccine Antigen (Pre-specified Antibody Level)** | **Prevnar 13 % Responders ($n^a/N^b$)** | **Pneumococcal 7-valent Conjugate Vaccine % Responders ($n^a/N^b$)** |
|---|---|---|
| **Pediarix (DTaP-IPV-HepB) Responses After the 3-dose Infant Series** | | |
| Dip (≥0.1 IU/mL) | 95.7 (223/233) | 96.1 (221/230) |
| Tet (≥0.1 IU/mL) | 98.4 (181/184) | 98.5 (193/196) |
| PT ≥16.5 EU/mL | 94.1 (225/239) | 95.0 (228/240) |
| FHA ≥40.5 EU/mL | 96.7 (231/239) | 95.0 (228/240) |
| PRN ≥26 EU/mL | 93.7 (224/239) | 95.8 (230/240) |
| Polio Type 1 (titer ≥1:8) | 100.0 (183/183) | 100.0 (187/187) |
| Polio Type 2 (titer ≥1:8) | 98.9 (181/183) | 99.5 (186/187) |
| Polio Type 3 (titer ≥1:8) | 100.0 (182/182) | 99.5 (186/187) |
| HBV | 100.0 (153/153) | 100.0 (173/173) |

| **Table 5: Subjects Achieving a Pre-specified Antibody Level for Concomitant Vaccine Antigens (in Study 6096A1-004, Study 6096A1-3005, and Study 6096A1-3008)** | | |
|---|---|---|
| **Vaccine Name/Vaccine Antigen (Pre-specified Antibody Level)** | **Prevnar 13 % Responders ($n^a/N^b$)** | **Pneumococcal 7-valent Conjugate Vaccine % Responders ($n^a/N^b$)** |
| ≥10.0 mIU/mL | | |
| **ActHIB (PRP) Responses After the Infant Series** | | |
| Hib (PRP) (≥0.15 µg/mL) | 97.9 (232/237) | 97.8 (225/230) |
| Hib (PRP) (≥1.0 µg/mL) | 77.6 (184/237) | 78.3 (180/230) |
| **Pentacel (DTaP-IPV-Hib) Responses After the Infant Series** | | |
| Hib (PRP) (≥0.15 µg/mL) | 97.8 (266/272) | 99.6 (265/266) |
| Hib (PRP) (≥1.0 µg/mL) | 81.6 (222/272) | 84.6 (225/266) |
| PT ≥12.0 EU/mL | 98.6 (278/282) | 96.0 (266/277) |
| FHA ≥20.0 EU/mL | 99.3 (281/283) | 95.7 (266/278) |
| PRN ≥7.0 EU/mL | 96.8 (274/283) | 96.0 (266/277) |
| FIM ≥4.0 EU/mL | 93.6 (264/282) | 95.3 (262/275) |
| **PedvaxHIB (PRP-OMP) Responses at 12-15 Months Following Infant Series with ActHIB** | | |
| Hib (PRP) (≥0.15 µg/mL) | 100.0 (230/230) | 100.0 (214/214) |
| Hib (PRP) (≥1.0 µg/mL) | 90.4 (208/230) | 92.1 (197/214) |
| **ProQuad (MMR-Varicella) Responses at 12-15 Months** | | |
| Measles (≥1.10 I.V.) | 96.4 (213/221) | 97.1 (204/210) |
| Mumps | 76.5 (169/221) | 72.9 (153/210) |

**Table 5: Subjects Achieving a Pre-specified Antibody Level for Concomitant Vaccine Antigens (in Study 6096A1-004, Study 6096A1-3005, and Study 6096A1-3008)**

| Vaccine Name/Vaccine Antigen (Pre-specified Antibody Level) | Prevnar 13 % Responders ($n^a/N^b$) | Pneumococcal 7-valent Conjugate Vaccine % Responders ($n^a/N^b$) |
|---|---|---|
| (≥1.10 I.V.) | | |
| Rubella (≥15 IU/mL) | 91.9 (192/209) | 90.7 (185/204) |
| Varicella (≥1.09 I.V.) | 26.7 (59/221) | 21.9 (46/210) |

[a] Number of subjects achieving the pre-specified antibody level.

[b] Number of subjects in the evaluable immunogenicity population.

Children and Adolescents 5-17 years of age

In Study 6096A1-3011 in the US, in children 5 to <10 years of age previously vaccinated with at least 1 dose of pneumococcal 7-valent conjugate vaccine, and in pneumococcal vaccine-naïve children and adolescents 10-17 years of age 1 dose of **Prevnar 13** elicited immune responses to all 13 serotypes.

In children 5 to <10 years of age, serum IgG concentrations for the 7 common serotypes 1 month after administration of a single dose of **Prevnar 13** vaccination (Study 6096A1-3011) were non-inferior (i.e., the lower limit of the 2-sided 95% CI for the geometric mean ratio [GMR] of >0.5) to those elicited by the fourth dose of pneumococcal 7-valent conjugate vaccine at 12-15 months of age (Study 6096A1-3005). In addition, IgG concentrations elicited by a single dose of **Prevnar 13** for the 6 additional serotypes in children 5 to <10 years of age were non-inferior to those elicited by the fourth dose of **Prevnar 13** at 12-15 months of age (Study 6096A1-3005) as shown in Tables 6 and 7.

**Table 6: Comparison of Pneumococcal IgG GMCs (µg/mL) for the 7 Common Serotypes After a Single Dose of Prevnar 13 (Study 6096A1-3011) Relative to Pneumococcal 7-valent Conjugate Vaccine After the Fourth Dose (Study 6096A1-3005)[a]**

| | Vaccine Group (as Enrolled/Randomized) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Prevnar 13 5 to <10 Years of Age (Study 6096A1-3011) | | | Pneumococcal 7-valent Conjugate Vaccine 12-15 Months of Age (Study 6096A1-3005) | | | | |
| **Serotype** | **n[b]** | **GMC[c]** | **(95% CI[d])** | **n[b]** | **GMC[c]** | **(95% CI[d])** | **Ratio[e]** | **(95% CI[f])** |
| Common | | | | | | | | |
| 4 | 169 | 8.45 | (7.24, 9.87) | 173 | 2.79 | (2.45, 3.18) | 3.03 | (2.48, 3.71) |
| 6B | 171 | 53.56 | (45.48, 63.07) | 173 | 9.47 | (8.26, 10.86) | 5.66 | (4.57, 6.99) |
| 9V | 171 | 9.51 | (8.38, 10.78) | 172 | 1.97 | (1.77, 2.19) | 4.83 | (4.10, 5.70) |
| 14 | 169 | 29.36 | (24.78, 34.78) | 173 | 8.19 | (7.31, 9.18) | 3.58 | (2.93, 4.39) |
| 18C | 171 | 8.23 | (7.13, 9.51) | 173 | 2.33 | (2.05, 2.65) | 3.53 | (2.91, 4.29) |
| 19F | 171 | 17.58 | (14.95, 20.67) | 173 | 3.31 | (2.87, 3.81) | 5.31 | (4.29, 6.58) |
| 23F | 169 | 11.26 | (9.79, 12.95) | 173 | 4.49 | (3.86, 5.23) | 2.51 | (2.04, 3.08) |

[a] Evaluable immunogenicity population.

[b] n = Number of subjects with a determinate antibody concentration for the specified serotype.

[c] Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw. GMCs after the fourth dose for pneumococcal 7-valent conjugate vaccine (Study 6096A1-3005).

[d] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.

[e] Ratio of GMCs: **Prevnar 13** (Study 6096A1-3011) to pneumococcal 7-valent conjugate vaccine (Study 6096A1-3005).

[f] CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (**Prevnar 13** [Study 6096A1-3011] – pneumococcal 7-valent conjugate vaccine [Study 6096A1-3005]).

Note – ClinicalTrials.gov NCT numbers are as follows: (Study 6096A1-3011) NCT00761631, (Study 6096A1-3005) NCT00444457.

**Table 7: Comparison of Pneumococcal IgG GMCs (µg/mL) for Additional 6 Serotypes After A Single Dose of Prevnar 13 (Study 6096A1-3011) Relative to Prevnar 13 in Study 6096A1-3005 After Fourth Dose (in Study 6096A1-3005)[a]**

| | Vaccine Group (as Enrolled/Randomized) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Prevnar 13 (5 to <10 years) (Study 6096A1-3011) | | | Prevnar 13 (12-15 Months) (Study 6096A1-3005) | | | | |
| Serotype | n[b] | GMC[c] | (95% CI[d]) | n[b] | GMC[c] | (95% CI[d]) | Ratio[e] | (95% CI[f]) |
| Additional | | | | | | | | |
| 1 | 171 | 3.57 | (3.05, 4.18) | 1068 | 2.90 | (2.75, 3.05) | 1.23 | (1.07, 1.42) |
| 3 | 171 | 2.38 | (2.07, 2.74) | 1065 | 0.75 | (0.72, 0.79) | 3.17 | (2.78, 3.62) |
| 5 | 171 | 5.52 | (4.82, 6.32) | 1068 | 2.85 | (2.72, 2.98) | 1.94 | (1.71, 2.20) |
| 6A | 169 | 21.51 | (18.15, 25.51) | 1063 | 7.11 | (6.78, 7.46) | 3.03 | (2.64, 3.47) |
| 7F | 170 | 6.24 | (5.49, 7.08) | 1067 | 4.39 | (4.18, 4.61) | 1.42 | (1.24, 1.62) |
| 19A | 170 | 17.18 | (15.01, 19.67) | 1056 | 8.44 | (8.05, 8.86) | 2.03 | (1.78, 2.32) |

[a] Evaluable immunogenicity population.

[b] n = Number of subjects with a determinate antibody concentration for the specified serotype.

[c] Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw. GMCs after fourth dose for **Prevnar 13** (Study 6096A1-3005).

[d] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the concentrations.

[e] Ratio of GMCs: **Prevnar 13** (Study 6096A1-3011) to **Prevnar 13** (Study 6096A1-3005).

[f] CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures (**Prevnar 13** [Study 6096A1-3011] – **Prevnar 13** [Study 6096A1-3005]).

Note – ClinicalTrials.gov NCT numbers are as follows: (Study 6096A1-3011) NCT00761631, (Study 6096A1-3005) NCT00444457.

In children and adolescents 10-17 years of age opsonophagocytic activity (OPA) GMTs 1 month after vaccination were non-inferior (i.e., the lower limit of the 2-sided 95% CI for the GMR of >0.5) to OPA GMTs in the 5 to <10 year old group for 12 of the 13 serotypes (except for serotype 3), as shown in Table 8.

**Table 8: Comparison of Pneumococcal OPA GMTs After Vaccination, Prevnar 13 (10-17 years) Relative to Prevnar 13 (5 to <10 years) in Study 6096A1-3011[a]**

| | Vaccine Group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Prevnar 13 (10-17 years) | | | Prevnar 13 (5 to <10 years) | | | | |
| Serotype | n[b] | GMT[c] | (95% CI[d]) | n[b] | GMT[c] | (95% CI[d]) | Ratio[e] | (95% CI[f]) |
| Common | | | | | | | | |
| 4 | 188 | 6912 | (6101.2, 7831.4) | 181 | 4629 | (4017.2, 5334.3) | 1.5 | (1.24, 1.80) |
| 6B | 183 | 14224 | (12316.4, 16427.3) | 178 | 14996 | (13164.1, 17083.1) | 0.9 | (0.78, 1.15) |
| 9V | 186 | 4485 | (4001.1, 5027.5) | 180 | 4733 | (4203.3, 5328.4) | 0.9 | (0.80, 1.12) |
| 14 | 187 | 6894 | (6028.3, 7884.0) | 176 | 4759 | (4120.4, 5497.0) | 1.4 | (1.19, 1.76) |
| 18C | 182 | 6263 | (5436.4, 7215.1) | 175 | 8815 | (7738.2, 10041.0) | 0.7 | (0.59, 0.86) |
| 19F | 184 | 2280 | (1949.4, 2667.6) | 178 | 1559 | (1293.3, 1878.9) | 1.5 | (1.15, 1.86) |
| 23F | 187 | 3808 | (3354.7, 4322.6) | 176 | 3245 | (2818.8, 3735.5) | 1.2 | (0.97, 1.42) |
| | | | | | | | | |
| Additional | | | | | | | | |
| 1 | 189 | 319 | (271.2, 376.0) | 179 | 187 | (160.4, 218.6) | 1.7 | (1.36, 2.13) |
| 3 | 181 | 114 | (100.4, 129.4) | 178 | 202 | (180.9, 226.3) | 0.6 | (0.48, 0.67) |
| 5 | 183 | 336 | (270.3, 417.6) | 178 | 491 | (426.3, 565.3) | 0.7 | (0.53, 0.89) |
| 6A | 182 | 9928 | (8457.0, 11654.8) | 178 | 7514 | (6350.8, 8890.7) | 1.3 | (1.05, 1.67) |
| 7F | 185 | 6584 | (5829.4, 7435.5) | 178 | 10334 | (9099.0, 11736.8) | 0.6 | (0.53, 0.76) |
| 19A | 187 | 1276 | (1131.7, 1439.0) | 180 | 1180 | (1047.5, 1329.4) | 1.1 | (0.91, 1.28) |

[a] Evaluable immunogenicity population.

[b] n = Number of subjects with a determinate antibody titer for the specified serotype.

[c] Geometric mean titers (GMTs) were calculated using all subjects with available data for the specified blood draw.

[d] Confidence intervals (CIs) are back transformations of a confidence interval based on the Student t distribution for the mean logarithm of the titers.

[e] Ratio of GMTs: **Prevnar 13** (10-17 years) to **Prevnar 13** (5 to <10 years).

[f] CIs for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures [**Prevnar 13** (10-17 years) – **Prevnar 13** (5 to <10 years)].

**Prevnar 13 Effectiveness**

Invasive Pneumococcal Disease

Four years after the introduction of Prevnar as a two dose primary series plus booster dose in the second year of life and with a 94% vaccine uptake a 98% (95% CI 95; 99) reduction of disease caused by the 7 vaccine serotypes was reported in England and Wales. Subsequently, four years following the switch to **Prevnar 13**, the additional reduction in incidence of IPD due to the 7 serotypes in Prevnar ranged from 76% in children less than 2 years of age to 91% in children 5-14 years of age. The serotype specific reductions for each of the 5 additional serotypes in **Prevnar 13** (no cases of serotype 5 IPD were observed) by age group are shown in Table 9 and ranged from 68% (serotype 3) to 100% (serotype 6A) for children less than 5 years of age. Significant incidence reductions were also observed in older age groups who had not been vaccinated with **Prevnar 13** (indirect effect).

**Table 9: Serotype Specific Number of Cases and Incidence Reductions of IPD in 2013/14 Compared to 2008/09-2009/10 (2008/10) by Age in England and Wales**

| | **<5 years of age** | | | **5 to 64 years of age** | | | **≥65 years of age** | | |
|---|---|---|---|---|---|---|---|---|---|
| | 2008-10[§] | 2013/14[§] | % Incidence reduction (95% CI*) | 2008-10[§] | 2013/14[§] | % Incidence reduction (95% CI*) | 2008-10[§] | 2013/14[§] | % Incidence reduction (95% CI*) |
| **Additional serotypes covered by Prevnar 13** | | | | | | | | | |
| **1** | 59 (54) | 5 (5) | 91% (98%; 68%)** | 458 (382) | 77 (71) | 83% (88%; 74%)** | 102 (89) | 13 (13) | 87% (94%; 72%)** |
| **3** | 26 (24) | 8 (8) | 68% (89%; 6%) | 178 (148) | 73 (68) | 59% (72%; 38%)** | 256 (224) | 143 (146) | 44% (57%; 27%)** |
| **6A** | 10 (9) | 0 (0) | 100% (100%; 62%)** | 53 (44) | 5 (5) | 90% (97%; 56%)** | 94 (82) | 5 (5) | 95% (99%; 81%)** |
| **7F** | 90 (82) | 8 (8) | 91% (97%; 74%)** | 430 (361) | 160 (148) | 63% (71%; 50%)** | 173 (152) | 75 (77) | 56% (70%; 37%)** |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **19A** | 85 (77) | 7 (7) | 91% (97%; 75%)** | 225 (191) | 104 (97) | 54% (65%; 32%)** | 279 (246) | 97 (99) | 65% (75%; 53%)** |

[§]Corrected for proportion of samples serotyped, missing age, denominator compared with 2009/10, and for the trend in total invasive pneumococcal disease up to 2009/10 (after which no trend correction was applied).

*95% CI inflated from a Poisson interval based on over-dispersion of 2·1 seen from modelling of 2000-06 pre-Prevnar all IPD data.

**p<0·005 to cover 6A where p=0.002

Otitis Media (OM)

In a two-dose primary series plus booster dose in the second year of life the impact of **Prevnar 13** on OM was documented in a population based active surveillance system in Israel with tympanocentesis culturing of middle ear fluid in children less than 2 years of age with OM. Following the introduction of pneumococcal 7-valent conjugate vaccine and subsequently **Prevnar 13** there was a decline in incidence of 96% of OM for the pneumococcal 7-valent conjugate vaccine serotypes plus serotype 6A and a decline in incidence of 85% for the additional serotypes 1, 3, 5, 7F, and 19A in **Prevnar 13**.

In a prospective, population-based, long-term surveillance study conducted in Israel between 2004 and 2015 following the introduction of pneumococcal 7-valent conjugate vaccine and subsequently **Prevnar 13**, reductions of non-pneumococcal bacteria isolated from children <3 years of age with OM were 75% for all NTHi cases, and 81% and 62% for cases of OM due to *M. catarrhalis* and *S. pyogenes*, respectively.

Pneumonia

In a multicenter observational study in France comparing the periods before and after the switch from pneumococcal 7-valent conjugate vaccine to **Prevnar 13**, there was 16% reduction in all CAP cases in emergency departments in children 1 month to 15 years of age. Reductions were 53% (p<0.001) for CAP cases with pleural effusion and 63% (p<0.001) for microbiologically confirmed pneumococcal CAP cases. In the second year after the introduction of **Prevnar 13** the total number of CAP cases due to the 6 additional vaccine serotypes in **Prevnar 13** was reduced by 74% (27 to 7 isolates).

In an ongoing surveillance system (2004 to 2013) to document the impact of pneumococcal 7-valent conjugate vaccine and subsequently **Prevnar 13** on CAP in children less than 5 years in Southern

Israel using a 2 dose primary series with a booster dose in the second year of life, there was a reduction of 68% (95% CI 73; 61) in outpatient visits and 32% (95% CI 39; 22) in hospitalizations for alveolar CAP following the introduction of **Prevnar 13** when compared to the period before the introduction of pneumococcal 7-valent conjugate vaccine was introduced.

Reduction of Antimicrobial Resistance (AMR)

Following the introduction of pneumococcal 7-valent conjugate vaccine and subsequently **Prevnar 13**, a reduction in AMR has been shown as a result of direct reduction of serotypes and clones associated with AMR from the population (including 19A), reduction of transmission (herd effects), and reduction in the use of antimicrobial agents.

In a double-blind, randomized, controlled study in Israel comparing pneumococcal 7-valent conjugate vaccine and **Prevnar 13** that reported the acquisition of *S. pneumoniae*, reductions of serotypes 19A, 19F, and 6A not susceptible to either penicillin, erythromycin, clindamycin, penicillin plus erythromycin, or multiple drugs (≥3 antibiotics) ranged between 34% and 62% depending on serotype and antibiotic.

Analyses of data from the United States Centers for Disease Control and Prevention evaluated temporal trends for four antibiotic classes and showed that compared to 2009 (the last year of pneumococcal 7-valent conjugate vaccine use in the US, following which it was replaced with **Prevnar 13**), by 2013 the annual incidence of IPD due to pneumococci non-susceptible to macrolides, cephalosporins, penicillins, and tetracyclines had decreased by 63%, 81%, 83%, and 81% in children less than 5 years of age and 24%, 49%, 57%, and 53% in persons 65 years of age and older.

**Prevnar 13** Effect on Nasopharyngeal Carriage

In a surveillance study in France in children presenting with AOM, changes in nasopharyngeal (NP) carriage of pneumococcal serotypes were evaluated following the introduction of pneumococcal 7-valent conjugate vaccine and subsequently **Prevnar 13**. **Prevnar 13** significantly reduced NP carriage of the 6 additional serotypes (and serotype 6C) combined and individual serotypes 6C, 7F, 19A when compared with pneumococcal 7-valent conjugate vaccine. A reduction in carriage was also seen for serotype 3 (2.5% vs. 1.1%; p=0.1). There was no carriage of serotypes 1 or 5 observed.

The effect of pneumococcal conjugate vaccination on NP carriage was studied in a randomized double-blind study (6096A1-3006) in which infants received either **Prevnar 13** or pneumococcal 7-valent conjugate vaccine at 2, 4, 6 and 12 months of age in Israel. **Prevnar 13** significantly reduced newly identified NP acquisition of the 6 additional serotypes (and serotype 6C) combined and of individual serotypes 1, 6A, 6C, 7F, 19A when compared with pneumococcal 7-valent conjugate vaccine. There was no reduction seen in serotype 3 and for serotype 5 the colonization was too infrequent to assess impact. For 6 of the remaining 7 common serotypes, similar rates of NP acquisition were observed in both vaccine groups; for serotype 19F a significant reduction was observed.

**Efficacy Study in Adults 65 Years and Older**

Efficacy against vaccine type (VT) pneumococcal CAP and IPD was assessed in a large-scale randomized double-blind, placebo controlled study (Community-Acquired Pneumonia Immunization Trial in Adults–CAPiTA) in the Netherlands. 84,496 subjects, 65 years and older received a single vaccination of either **Prevnar 13** or placebo in a 1:1 randomization.

Efficacy of **Prevnar 13** in preventing a first episode of VT pneumococcal CAP (the primary endpoint of the study) and the two secondary endpoints was demonstrated as shown in Table 10.

**Table 10: Vaccine Efficacy (VE) in Primary and Secondary Endpoints of the CAPiTA Study (per protocol population)**

| Efficacy Endpoint | Cases | | | VE (%) (95.2% CI) | p-value |
|---|---|---|---|---|---|
| | Total | Prevnar 13 group | Placebo group | | |
| *Primary endpoint* | | | | | |
| **First episode of confirmed VT pneumococcal CAP** | 139 | 49 | 90 | 45.56 (21.82, 62.49) | 0.0006 |
| *Secondary endpoints* | | | | | |

**Table 10: Vaccine Efficacy (VE) in Primary and Secondary Endpoints of the CAPiTA Study (per protocol population)**

| Efficacy Endpoint | Cases | | | VE (%) (95.2% CI) | p-value |
|---|---|---|---|---|---|
| | Total | Prevnar 13 group | Placebo group | | |
| **First episode of confirmed NB/NI[1] vaccine type pneumococcal CAP** | 93 | 33 | 60 | 45.00 (14.21, 65.31) | 0.0067 |
| **First episode of VT-IPD[2]** | 35 | 7 | 28 | 75.00 (41.06, 90.87) | 0.0005 |

[1]NB/NI – non-bacteraemic/non-invasive.
[2]VT-IPD – vaccine-type invasive pneumococcal disease.

The protective efficacy of **Prevnar 13** against a first episode of VT pneumococcal CAP, VT NB/NI pneumococcal CAP, and VT-IPD was evident shortly after vaccination and was sustained throughout the duration of the study.

A post-hoc analysis was used to estimate the following public health outcomes against clinical CAP (as defined in the CAPiTA study, and based on clinical findings regardless of radiologic infiltrate or etiologic confirmation): vaccine efficacy, incidence rate reduction and number needed to vaccinate (see Table 11):

**Table 11: Public Health Outcomes Against Clinical CAP* (modified intent-to-treat population)**

| | Vaccine efficacy % (95% CI) | Incidence rate reduction[1] (95% CI) | Number needed to vaccinate[2] |
|---|---|---|---|
| **All episodes analysis** | 8.1 (-0.6, 16.1) | 72.2 (-5.3, 149.6) | 277 |
| **First episode analysis** | 7.3 (-0.4, 14.4) | 53.0 (-2.7, 108.7) | 378 |

* Patients with at least 2 of the following: Cough; purulent sputum, temperature >38°C or <36.1°C; pneumonia (auscultatory findings); leukocytosis; C-reactive protein value >3 times the upper limit of normal; hypoxemia with a partial oxygen pressure <60 mm Hg while breathing room air.
[1] per 100,000 person-years of follow-up.

[2] based on a 5-year duration of protection.

Although CAPiTA was not powered to demonstrate serotype specific VE, an evaluation of clinical CAP data was performed for serotypes with at least 10 outcomes in the placebo group. VE (95% CI) for the five evaluated serotypes against first clinical CAP episodes were: serotype 1, 20.0% (-83.1% to 65.8%); serotype 3, 61.5% (17.6% to 83.4%); serotype 6A, 33.3% (-58.6% to 73.2%); serotype 7F, 73.3% (40.5% to 89.4%); and serotype 19A, 45.2% (-2.2% to 71.5%).

**Prevnar 13 Immunogenicity Clinical Trials in Adults**

An antipolysaccharide binding antibody IgG level to predict protection against IPD or non-bacteremic pneumonia has not been defined for adults. However, non-clinical and clinical data support functional antibody, measured by OPA assay, as a contributor to protection against pneumococcal disease. OPA provides an *in vitro* measurement of the ability of serum antibodies to eliminate pneumococci by promoting complement-mediated phagocytosis and is believed to reflect relevant *in vivo* mechanisms of protection against pneumococcal disease. OPA titers are expressed as the reciprocal of the highest serum dilution that reduces survival of the pneumococci by at least 50%. Pivotal trials for **Prevnar 13** were designed to show that functional OPA antibody responses for the **Prevnar 13** serotypes are non-inferior and for some serotypes superior to the common serotypes in the currently licensed PPSV23.

Serotype-specific OPA geometric mean titers (GMTs) measured 1 month after each vaccination were calculated. Non-inferiority between vaccines was defined as the lower bound of the 2-sided, 95% confidence interval (CI) for the ratio of the GMTs (GMR) >0.5 (2-fold criterion); statistically significantly greater responses were defined as the lower bound of the 2-sided 95% CI for the GMR>1.

The response to the additional serotype 6A, which is unique to **Prevnar 13** but not in PPSV23 was assessed by demonstration of a 4-fold increase in the specific OPA titer above pre-immunization levels. Superiority of the response for **Prevnar 13** was defined as the lower bound of the 2-sided, 95% CI for the difference in percentages of adults achieving a 4-fold increase in OPA titer greater than zero. For comparison of OPA GMTs, a statistically greater response for serotype 6A was defined as the lower bound of the 2-sided 95% CI for the GMR>2.

Five (5) Phase 3 clinical trials (6115A1-004, 6115A1-3005, 6115A1-3010, 6115A1-3001, 6115A1-3008) were conducted in a number of European countries and in the US evaluating the immunogenicity of **Prevnar 13** in different age groups, and in individuals who were either not previously vaccinated (PPSV23 unvaccinated) with PPSV23 or had received 1 or more doses of PPSV23 (PPSV23 pre-vaccinated).

Each study included healthy adults and immunocompetent adults with stable underlying conditions including chronic cardiovascular disease, chronic pulmonary disease, renal disorders, diabetes mellitus, chronic liver disease including alcoholic liver disease, and alcoholism because it is known that these are common conditions in adults that increase risk of serious pneumococcal CAP and IPD.

Two (2) pivotal non-inferiority trials were conducted in which **Prevnar 13** response was compared to PPSV23 immune response, 1 in PPSV23 unvaccinated adults aged 50-64 years (6115A1-004), and 1 in PPSV23 pre-vaccinated adults aged ≥70 years (6115A1-3005). One (1) study (6115A1-3000) in PPSV23 pre-vaccinated adults collected safety data only. Two (2) studies (6115A1-3001 and 6115A1-3008) assessed the concomitant administration of **Prevnar 13** with seasonal Trivalent Inactivated Influenza Vaccine (TIV).

Clinical Trials Conducted in Adults Not Previously Vaccinated with PPSV23

In an active-controlled modified double-blind (the site staff dispensing and administering the vaccine were unblinded, but all other study personnel including the principal investigator and subject were blinded) clinical trial (6115A1-004) of **Prevnar 13** in the US, PPSV23-unvaccinated adults aged 60-64 years were randomly assigned (1:1) to receive **Prevnar 13** or PPSV23. In addition, adults aged 18-49 years (with age sub-groups 18-29 years, 30-39 years, 40-49 years) and 50-59 years were enrolled and received 1 dose of **Prevnar 13** (open-label).

The OPA antibody responses elicited by **Prevnar 13** were non-inferior to those elicited by PPSV23 for the 12 serotypes in common to both vaccines. In addition, 8 of the serotypes in common exhibited a statistically significantly greater immune response after **Prevnar 13** compared with after PPSV23.

For serotype 6A, which is unique to **Prevnar 13**, the proportions of adults with a 4-fold increase after **Prevnar 13** (88.5%) were significantly greater than after PPSV23 (39.2%) in PPSV23-unvaccinated adults aged 60-64 years. OPA GMTs for serotype 6A were statistically significantly greater after **Prevnar 13** compared with after PPSV23.

The OPA responses elicited by **Prevnar 13** in adults aged 50-59 years were non-inferior to the **Prevnar 13** responses in adults aged 60-64 years for all 13 serotypes. In addition, 9 of the 13 serotypes exhibited a statistically significantly greater immune response in adults aged 50-59 years compared with adults aged 60-64 years.

This clinical trial demonstrated that the immune responses elicited by **Prevnar 13** are non-inferior and for most serotypes statistically significantly greater than PPSV23. In addition, the immune responses in adults aged 50-59 years were non-inferior and for most serotypes statistically significantly greater than those observed in adults aged 60-64 years.

In adults aged 60-64 years, antibody levels 1 year after vaccination were greater after **Prevnar 13** compared to antibody levels after PPSV23 for 7 of 12 serotypes in common. In adults aged 50-59 years, antibody levels 1 year after vaccination with **Prevnar 13** were greater for 12 of 13 serotypes compared to vaccination with **Prevnar 13** in 60-64 year olds.

**Table 12: OPA GMTs in PPSV23 Unvaccinated Adults Aged 50-59 Years Given Prevnar 13; and in Adults Aged 60-64 Years Given Prevnar 13 or PPSV23 (in Study 6115A1-004)[a,b]**

| | Prevnar 13 50-59 Years N=350-384 | Prevnar 13 60-64 Years N=359-404 | PPSV23 60-64 Years N=367-402 | Prevnar 13, 50-59 Relative to 60-64 Years | | Prevnar 13 Relative to PPSV23, 60-64 Years | |
|---|---|---|---|---|---|---|---|
| **Serotype** | **GMT** | **GMT** | **GMT** | **GMR** | **(95% CI)** | **GMR** | **(95% CI)** |
| 1 | 200 | 146 | 104 | 1.4 | (1.08, 1.73) | 1.4 | (1.10, 1.78) |
| 3 | 91 | 93 | 85 | 1.0 | (0.81, 1.19) | 1.1 | (0.90, 1.32) |
| 4 | 2833 | 2062 | 1295 | 1.4 | (1.07, 1.77) | 1.6 | (1.19, 2.13) |
| 5 | 269 | 199 | 162 | 1.4 | (1.01, 1.80) | 1.2 | (0.93, 1.62) |
| 6A[†] | 4328 | 2593 | 213 | 1.7 | (1.30, 2.15) | 12.1 | (8.63, 17.08) |
| 6B | 3212 | 1984 | 788 | 1.6 | (1.24, 2.12) | 2.5 | (1.82, 3.48) |
| 7F | 1520 | 1120 | 405 | 1.4 | (1.03, 1.79) | 2.8 | (1.98, 3.87) |
| 9V | 1726 | 1164 | 407 | 1.5 | (1.11, 1.98) | 2.9 | (2.00, 4.08) |
| 14 | 957 | 612 | 692 | 1.6 | (1.16, 2.12) | 0.9 | (0.64, 1.21) |
| 18C | 1939 | 1726 | 925 | 1.1 | (0.86, 1.47) | 1.9 | (1.39, 2.51) |
| 19A | 956 | 682 | 352 | 1.4 | (1.16, 1.69) | 1.9 | (1.56, 2.41) |
| 19F | 599 | 517 | 539 | 1.2 | (0.87, 1.54) | 1.0 | (0.72, 1.28) |

**Table 12: OPA GMTs in PPSV23 Unvaccinated Adults Aged 50-59 Years Given Prevnar 13; and in Adults Aged 60-64 Years Given Prevnar 13 or PPSV23 (in Study 6115A1-004)[a,b]**

| | Prevnar 13 50-59 Years N=350-384 | Prevnar 13 60-64 Years N=359-404 | PPSV23 60-64 Years N=367-402 | Prevnar 13, 50-59 Relative to 60-64 Years | | Prevnar 13 Relative to PPSV23, 60-64 Years | |
|---|---|---|---|---|---|---|---|
| **Serotype** | **GMT** | **GMT** | **GMT** | **GMR** | **(95% CI)** | **GMR** | **(95% CI)** |
| 23F | 494 | 375 | 72 | 1.3 | (0.94, 1.84) | 5.2 | (3.67, 7.33) |

GMT, Geometric mean titer.

GMR, Geometric mean ratio.

[†] 6A is a serotype unique to **Prevnar 13** but not contained in PPSV23.

[a] Non-inferiority was defined as the lower limit of the 2-sided 95% CI for GMR greater than 0.5. Statistically significantly greater responses were defined as the lower bound of the 2-sided 95% CI for the GMR greater than 1.

[b] For serotype 6A, which is unique to **Prevnar 13**, a statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GMR greater than 2.

Table 13 shows OPA GMTs 1 month after vaccination in subjects 18-29 years of age, 30-39 years of age, and 40-49 years of age given a single dose of **Prevnar 13**. It also shows a comparison of OPA GMTs in subjects 18-49 years of age and 60-64 years of age.

**Table 13: OPA GMTs in Adults Aged 18-49 Years and Adults Aged 60-64 Years (in Study 6115A1-004) Given Prevnar 13[a,b]**

| | 18-29 Years N=276-290 | 30-39 Years N=276-288 | 40-49 Years N=279-290 | 18-49 Years N=836-866 | 60-64 Years N=359-404 | 18-49 Years Relative to 60-64 Years | |
|---|---|---|---|---|---|---|---|
| **Serotype** | **GMT[b]** | **GMT[b]** | **GMT[b]** | **GMT[b]** | **GMT[b]** | **GMR** | **(95% CI[c])** |
| 1 | 409 | 353 | 305 | 353 | 146 | 2.4 | (2.03, 2.87) |
| 3 | 112 | 93 | 72 | 91 | 93 | 1.0 | (0.84, 1.13) |
| 4 | 7152 | 4589 | 3229 | 4747 | 2062 | 2.3 | (1.92, 2.76) |
| 5 | 567 | 375 | 271 | 386 | 199 | 1.9 | (1.55, 2.42) |
| 6A | 8476 | 6131 | 3626 | 5746 | 2593 | 2.2 | (1.84, 2.67) |
| 6B | 14134 | 10180 | 6571 | 9813 | 1984 | 4.9 | (4.13, 5.93) |
| 7F | 3741 | 3276 | 2792 | 3249 | 1120 | 2.9 | (2.41, 3.49) |
| 9V | 5086 | 3208 | 2292 | 3339 | 1164 | 2.9 | (2.34, 3.52) |
| 14 | 4452 | 2919 | 2049 | 2983 | 612 | 4.9 | (4.01, 5.93) |
| 18C | 5240 | 3841 | 3171 | 3989 | 1726 | 2.3 | (1.91, 2.79) |
| 19A | 2162 | 1504 | 1209 | 1580 | 682 | 2.3 | (2.02, 2.66) |
| 19F | 2251 | 1507 | 1076 | 1533 | 517 | 3.0 | (2.44, 3.60) |
| 23F | 2954 | 1606 | 814 | 1570 | 375 | 4.2 | (3.31, 5.31) |

[a] Non-inferiority was defined as the lower limit of the 2-sided 95% CI for GMR greater than 0.5.

[b] Statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GMR greater than 1.

[c] Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student t distribution for the mean difference of the logarithms of the measures.

In adults aged 18-29 years, OPA GMTs to all 13 serotypes in **Prevnar 13** were non-inferior to the **Prevnar 13** responses in adults aged 60-64 years. For 12 serotypes, immune responses were related to age, with adults aged 18-49 years showing statistically significantly greater responses than adults aged 60-64 years. Similarly, statistically significantly greater responses for 12 serotypes were observed for adults in age subgroups 18-29 years, 30-39 years and 40-49 years compared with adults aged 60-64 years. OPA GMTs were highest in adults aged 18-29 years and lowest in adults aged 60-64 years.

One (1) year after vaccination with **Prevnar 13** OPA titers had declined compared to titers measured 1 month after vaccination ranging from 23 to 2,948; however, OPA titers for all serotypes remained higher than levels measured at baseline ranging from 5 to 186.

**Immune Responses in Special Populations**

Individuals with the conditions described below have an increased risk of pneumococcal disease.

Sickle Cell Disease

An open-label single-arm study (6096A1-3014 [B1851013]) with 2 doses of **Prevnar 13** given 6 months apart was conducted in 158 children and adolescents ≥6 to <18 years of age with sickle cell disease who were previously vaccinated with 1 or more doses of PPSV23 at least 6 months prior to enrollment. After the first vaccination, **Prevnar 13** elicited antibody levels measured by both IgG GMCs and OPA GMTs that were statistically significant higher when compared to levels prior to vaccination. After the second dose immune responses were comparable to the ones after the first dose. One (1) year after the second dose, antibody levels measured by both IgG GMCs and OPA GMTs were higher than levels prior to the first dose of **Prevnar 13**, except the IgG GMC for serotype 3 that was similar.

Additional Pneumococcal 7-valent Conjugate Vaccine Immunogenicity Data: Children with Sickle Cell Disease

The immunogenicity of pneumococcal 7-valent conjugate vaccine has been investigated in an open-label, multicenter study (0887X1-100722) in 49 infants with sickle cell disease. Children were vaccinated with pneumococcal 7-valent conjugate vaccine (3 doses 1 month apart from the age of 2 months), and 46 of these children also received a PPSV23 at the age of 15-18 months. After primary immunization, 95.6% of the subjects had antibody levels of >0.35 µg/mL for all 7 serotypes found in pneumococcal 7-valent conjugate vaccine. A significant increase was seen in the concentrations of antibodies against the 7 serotypes after PPSV23, suggesting that immunological memory was well established.

Adults with HIV infection

*Children and adults not previously vaccinated with a pneumococcal vaccine*

In study 6115A1-3002 (B1851021), HIV-infected children and adults (CD4 ≥200 cells/µL, viral load <50,000 copies/mL and free of active AIDS-related illness) not previously vaccinated with a pneumococcal vaccine received 3 doses of **Prevnar 13**. As per general recommendations, a single dose of PPSV23 was subsequently administered. Vaccines were administered at 1 month intervals.

Immune responses were assessed in 259-270 evaluable subjects approximately 1 month after each dose of vaccine. After the first dose, **Prevnar 13** elicited antibody levels, measured by both IgG GMCs and OPA GMTs that were statistically significantly higher when compared to levels prior to vaccination. After the second and third dose of **Prevnar 13**, immune responses were similar or higher than those after the first dose.

*Adults previously vaccinated with 23-valent pneumococcal polysaccharide vaccine*

In study 6115A1-3017 (B1851028), immune responses were assessed in 329 HIV-infected adults ≥18 years of age (CD4+ T-cell count >200 cells/μL and viral load <50,000 copies/mL) previously vaccinated with PPSV23 administered at least 6 months prior to enrollment. Subjects received 3 doses of **Prevnar 13**, at enrollment, 6 months and 12 months after the first dose of **Prevnar 13**. After the first vaccination, **Prevnar 13** elicited antibody levels measured by both IgG GMCs and OPA GMTs that were statistically significant higher when compared to levels prior to vaccination. After the second and third dose of **Prevnar 13**, immune responses were comparable or higher than those after the first dose. Subjects who received 2 or more previous doses of PPSV23 showed a similar immune response compared with subjects who received a single previous dose.

Hematopoietic Stem Cell Transplant

In study 6115A1-3003 (B1851022), children and adults with an allogeneic HSCT at ≥2 years of age received 3 doses of **Prevnar 13** with an interval of at least 1 month between doses. The first dose was administered at 3 to 6 months after HSCT. A fourth (booster) dose of **Prevnar 13** was administered 6 months after the third dose. As per general recommendations, a single dose of PPSV23 was administered 1 month after the fourth dose of **Prevnar 13**. Immune responses as measured by IgG GMCs were assessed in 168-211 evaluable subjects approximately 1 month after vaccination. **Prevnar 13** elicited increased antibody levels after each dose of **Prevnar 13**. Immune responses after the fourth dose of **Prevnar 13** were significantly increased for all serotypes compared with after the third dose.

This study demonstrated that 4 doses of **Prevnar 13** elicited serum IgG concentrations similar to those induced by a single dose in healthy individuals of the same age group.

Clinical Trials Conducted in Adults Previously Vaccinated with PPSV23 (Pre-vaccinated)

In a Phase 3 active-controlled, modified double-blind (the site staff dispensing and administering the vaccine were unblinded, but all other study personnel including the principal investigator and subject were blinded) clinical trial (6115A1-3005) of **Prevnar 13** in the US and Sweden

PPSV23-prevaccinated adults aged ≥70 years who had received 1 dose of PPSV23 ≥5 years prior were randomly assigned (1:1) to receive either **Prevnar 13** or PPSV23.

The OPA antibody responses elicited by **Prevnar 13** were non-inferior for the 12 serotypes in common to those elicited by PPSV23 when the vaccines were administered at a minimum of 5 years after PPSV23. In addition, 10 of the serotypes in common exhibited a statistically significantly greater immune response after **Prevnar 13** compared with after PPSV23.

For serotype 6A, which is unique to **Prevnar 13**, proportions of adults with a 4-fold increase after **Prevnar 13** (71.1%) was significantly greater than after PPSV23 (27.3%) in PPSV23-pre-vaccinated adults aged ≥70 years. OPA GMTs for serotype 6A were statistically significantly greater after **Prevnar 13** compared with after PPSV23.

This clinical trial demonstrated that in adults aged ≥70 years and pre-vaccinated with PPSV23 ≥5 years prior, vaccination with **Prevnar 13** shows an improved immune response as compared to re-vaccination with PPSV23.

**Table 14: OPA GMTs in PPSV23-Previously Vaccinated Adults Aged ≥70 Years (in Study 6115A1-3005) Given Prevnar 13 or PPSV23[a,b]**

| Serotype | Prevnar 13 N=400-426 GMT | PPSV23 N=395-445 GMT | Prevnar 13 Relative to PPSV23 | |
|---|---|---|---|---|
| | | | Ratio | (95% CI) |
| 1 | 81 | 55 | 1.5 | (1.17, 1.88) |
| 3 | 55 | 49 | 1.1 | (0.91, 1.35) |
| 4 | 545 | 203 | 2.7 | (1.93, 3.74) |
| 5 | 72 | 36 | 2.0 | (1.55, 2.63) |
| 6A[†] | 903 | 94 | 9.6 | (7.00, 13.26) |
| 6B | 1261 | 417 | 3.0 | (2.21, 4.13) |
| 7F | 245 | 160 | 1.5 | (1.07, 2.18) |
| 9V | 181 | 90 | 2.0 | (1.36, 2.97) |
| 14 | 280 | 285 | 1.0 | (0.73, 1.33) |
| 18C | 907 | 481 | 1.9 | (1.42, 2.50) |
| 19A | 354 | 200 | 1.8 | (1.43, 2.20) |
| 19F | 333 | 214 | 1.6 | (1.17, 2.06) |
| 23F | 158 | 43 | 3.7 | (2.69, 5.09) |

GMT, Geometric mean titer.

[†] 6A is a serotype unique to **Prevnar 13** but not contained in PPSV23.

[a] Non-inferiority was defined as the lower limit of the 2-sided 95% CI for GMR greater than 0.5. Statistically significantly greater responses defined as the lower bound of the 2-sided 95% CI for the GMR greater than 1.

[b] For serotype 6A, which is unique to **Prevnar 13**, a statistically significantly greater response was defined as the lower bound of the 2-sided 95% CI for the GMR greater than 2.

Clinical Trials to Assess **Prevnar 13** Given With Seasonal TIV in Adults

Two (2) randomized, double-blind clinical trials (6115A1-3001 and 6115A1-3008) evaluated the immunogenicity of **Prevnar 13** given with TIV (A/H1N1, A/H3N2, and B strains) in adults who were PPSV23 unvaccinated aged 50-59 years and in adults ≥65 years.

Each clinical trial compared concomitant administration of **Prevnar 13** and TIV (administered in opposite arms) with [1] TIV given with placebo and [2] with **Prevnar 13** given alone. Group 1

received **Prevnar 13** given with TIV, followed 1 month later by placebo; Group 2 received TIV given with placebo, followed 1 month later by **Prevnar 13**.

A Phase 3 randomized, double-blind clinical trial (6115A1-3001) of **Prevnar 13** given with TIV in adults aged 50-59 years who were PPSV23 unvaccinated in the US assessed the immune responses of TIV when TIV was given with **Prevnar 13** compared with TIV given with placebo (in the following called TIV alone).

A Phase 3 randomized, double-blind clinical trial (6115A1-3008) of **Prevnar 13** given with TIV in adults aged ≥65 years who were PPSV23 unvaccinated in Europe assessed the immune responses of TIV when TIV was given with **Prevnar 13** compared with TIV given with placebo.

Immune responses elicited by TIV were measured by hemagglutination inhibition (HAI) assays 1 month after TIV vaccination. The immune responses were measured as the proportion of adults achieving a ≥4-fold increase in HAI titer (responder) for each TIV strain 1 month after vaccination. The non-inferiority criterion was achieved for each vaccine antigen if the lower limit of the 95% CI for the difference in proportions of responders was ≥10%.

The studies also assessed the immune responses of **Prevnar 13** when **Prevnar 13** was given with TIV compared with **Prevnar 13** given alone. The immune responses elicited by **Prevnar 13** were measured by ELISA IgG GMC 1 month after **Prevnar 13** vaccination. The non-inferiority criterion was achieved if the lower limit of the 2-sided, 95% CI for the IgG GMC ratios (**Prevnar 13** and TIV relative to **Prevnar 13** alone) was >0.5 (2-fold criterion).

TIV immune responses 50-59 years of age: The immune responses were similar after **Prevnar 13** given concomitantly with TIV compared to TIV alone. Non-inferiority was met for all 3 TIV strains after **Prevnar 13** given concomitantly with TIV compared to TIV alone (Table 15).

TIV immune responses in ≥65 years of age: The immune responses were similar after **Prevnar 13** given concomitantly with TIV compared to TIV alone. Non-inferiority was met for A/H1N1, and B-strains but not for A/H3N2 with a lower limit of the 95% CI of -10.4% (Table 16).

**Table 15: Proportion of Participants Aged 50–59 Years With a ≥4-Fold Increase in HAI Titer After TIV With Prevnar 13 and TIV With Placebo (in Study 6115A1-3001)**

| TIV | TIV + Prevnar 13 | | TIV + Placebo | | Difference |
|---|---|---|---|---|---|
| HAI | n/N | % (95% CI) | n/N | % (95% CI) | % (95% CI) |
| A/H1N1 | 445/530 | 84.0 (80.6, 87.0) | 431/531 | 81.2 (77.6, 84.4) | 2.8 (-1.8, 7.4) |
| A/H3N2 | 377/530 | 71.1 (67.1, 75.0) | 369/531 | 69.5 (65.4, 73.4) | 1.6 (-3.9, 7.2) |
| B | 321/530 | 60.6 (56.3, 64.8) | 320/531 | 60.3 (56.0, 64.5) | 0.3 (-5.6, 6.2) |

**Table 16: Proportion of Participants Aged ≥65 Years With a ≥4-Fold Increase in HAI Titer After TIV With Prevnar 13 and TIV With Placebo (in Study 6115A1-3008)**

| TIV | TIV + Prevnar 13 | | TIV + Placebo | | Difference |
|---|---|---|---|---|---|
| HAI | n/N | % (95% CI) | n/N | % (95% CI) | % (95% CI) |
| A/H1N1 | 440/548 | 80.3 (76.7, 83.5) | 429/546 | 78.6 (74.9, 81.9) | 1.7 (-3.1, 6.5) |
| A/H3N2 | 316/545 | 58.0 (53.7, 62.2) | 341/545 | 62.6 (58.4, 66.6) | -4.6 (-10.4, 1.3) |
| B | 286/548 | 52.2 (47.9, 56.4) | 295/546 | 54.0 (49.7, 58.3) | -1.8 (-7.8, 4.1) |

**Prevnar 13** immune responses in 50-59 year olds: Non-inferiority was met for all serotypes (Table 17).

**Prevnar 13** immune responses in ≥65 year olds: Non-inferiority was met for all serotypes except serotype 19F. The lower limit of the 95% CI of the GMR for 19F was 0.49 [criterion 0.5] (Table 18).

**Table 17: Pneumococcal IgG GMC 1 Month After Prevnar 13 and TIV; and 1 Month After Prevnar 13 (Given 1 Month After Placebo and TIV) for Participants 50-59 Years (in Study 6115A1-3001)[a,b]**

| | Post-dose 1 | Post-dose 2 | |
|---|---|---|---|
| | Prevnar 13 + TIV (N=247-294) | Prevnar 13* (N=247-289) | Vaccine Comparison |
| Serotype | GMC, µg/mL | GMC, µg/mL | Ratio (95% CI) |
| 1 | 4.05 | 5.45 | 0.74 (0.58, 0.95) |
| 3 | 1.15 | 1.46 | 0.79 (0.66, 0.93) |
| 4 | 2.35 | 3.41 | 0.69 (0.55, 0.87) |
| 5 | 6.03 | 7.18 | 0.84 (0.67, 1.05) |
| 6A | 5.78 | 6.70 | 0.86 (0.70, 1.06) |
| 6B | 7.58 | 10.09 | 0.75 (0.60, 0.93) |
| 7F | 8.14 | 10.57 | 0.77 (0.63, 0.95) |
| 9V | 4.96 | 6.97 | 0.71 (0.59, 0.86) |
| 14 | 10.77 | 14.05 | 0.77 (0.60, 0.98) |
| 18C | 9.65 | 13.49 | 0.72 (0.58, 0.88) |
| 19A | 16.80 | 18.84 | 0.89 (0.74, 1.08) |
| 19F | 6.13 | 7.13 | 0.86 (0.67, 1.10) |
| 23F | 7.17 | 8.54 | 0.84 (0.66, 1.08) |

GMC, Geometric mean concentration.

* Given 4 weeks after placebo and TIV.

[a] Antibody measured by a standardized ELISA.

[b] The non-inferiority criterion was achieved if the lower limit of the 2-sided, 95% CI for the IgG GMC ratios (**Prevnar 13** and TIV relative to **Prevnar 13** alone) was >0.5 (2-fold criterion).

**Table 18: Pneumococcal IgG GMC 1 Month After Prevnar 13 and TIV; and 1 Month After Prevnar 13 (Given 1 Month After Placebo and TIV) for Participants ≥65 Years (in Study 6115A1-3008)[a,b]**

| | Post-dose 1 | Post-dose 2 | |
|---|---|---|---|
| | Prevnar 13 + TIV (N=247-294) | Prevnar 13* (N=247-289) | Vaccine Comparison |
| Serotype | GMC, µg/mL | GMC, µg/mL | Ratio (95% CI) |
| 1 | 2.52 | 3.20 | 0.79 (0.60, 1.04) |
| 3 | 1.08 | 1.15 | 0.94 (0.78, 1.13) |
| 4 | 2.15 | 3.24 | 0.66 (0.51, 0.87) |
| 5 | 4.74 | 6.90 | 0.69 (0.55, 0.86) |
| 6A | 4.61 | 6.10 | 0.76 (0.61, 0.94) |
| 6B | 6.24 | 6.43 | 0.97 (0.75, 1.25) |
| 7F | 7.63 | 9.04 | 0.84 (0.67, 1.07) |
| 9V | 4.97 | 6.21 | 0.80 (0.63, 1.02) |
| 14 | 8.95 | 12.44 | 0.72 (0.53, 0.97) |
| 18C | 8.88 | 11.07 | 0.80 (0.64, 1.01) |
| 19A | 11.93 | 17.10 | 0.70 (0.56, 0.87) |
| 19F | 4.78 | 7.39 | 0.65 (0.49, 0.85) |
| 23F | 5.82 | 6.11 | 0.95 (0.71, 1.27) |

GMC, Geometric mean concentration.

* Given 4 weeks after placebo and TIV.

[a] Antibody measured by a standardized ELISA.

[b] The non-inferiority criterion was achieved if the lower limit of the 2-sided, 95% CI for the IgG GMC ratios (**Prevnar 13** and TIV relative to **Prevnar 13** alone) was >0.5 (2-fold criterion).

**Prevnar 13** may be administered concomitantly with seasonal TIV.

When **Prevnar 13** was given concomitantly with TIV, the immune responses to TIV were similar to the responses when TIV was given alone.

When **Prevnar 13** was given concomitantly with TIV, the immune responses to **Prevnar 13** were lower compared to when **Prevnar 13** was given alone. The clinical significance of this is unknown.

**Clinical Trial to Assess Prevnar 13 Given With Seasonal QIV in Adults**

A randomized, double-blind post-marketing study evaluated the immunogenicity of **Prevnar 13** given with inactivated QIV (Fall 2014/Spring 2015 Fluzone, A/H1N1, A/H3N2, B/Brisbane, and B/Massachusetts strains) in PPSV23 previously vaccinated adults aged ≥50 years conducted in the US. One group received **Prevnar 13** and QIV concurrently, followed approximately 1 month later by placebo. The other group received QIV and placebo concurrently, followed approximately 1 month later by **Prevnar 13**.

The antibody responses elicited by **Prevnar 13** were measured as OPA GMTs 1 month after **Prevnar 13** vaccination. Noninferiority was demonstrated if the lower limit of the 2-sided 95% CI for the OPA GMT ratios (**Prevnar 13** + QIV relative to **Prevnar 13** alone) was >0.5. **Prevnar 13** mcOPA antibody responses met noninferiority for all 13 serotypes after **Prevnar 13** was given concomitantly with QIV compared to **Prevnar 13** given alone (Table 19).

**Table 19. Pneumococcal OPA GMTs 1 Month After Prevnar 13 and QIV and 1 Month After Prevnar 13 (Given 1 Month After Placebo and QIV)**

| | **Prevnar 13 + QIV** ($n^a$=412-425) | **Prevnar 13** ($n^a$=405-419) | **Vaccine Comparison** |
|---|---|---|---|
| **Serotype** | **GMT[b]** | **GMT[b]** | **Ratio[c] (95% CI[d])** |
| 1 | 75 | 83 | 0.9 (0.74, 1.12) |
| 3 | 41 | 49 | 0.8 (0.70, 0.98) |
| 4 | 587 | 824 | 0.7 (0.55, 0.91) |
| 5 | 97 | 101 | 1.0 (0.78, 1.18) |
| 6A | 953 | 1413 | 0.7 (0.53, 0.85) |
| 6B | 867 | 1041 | 0.8 (0.64, 1.08) |
| 7F | 651 | 670 | 1.0 (0.83, 1.14) |
| 9V | 699 | 838 | 0.8 (0.69, 1.00) |
| 14 | 574 | 760 | 0.8 (0.62, 0.92) |
| 18C | 713 | 865 | 0.8 (0.64, 1.06) |
| 19A | 337 | 390 | 0.9 (0.72, 1.04) |
| 19F | 324 | 360 | 0.9 (0.71, 1.14) |
| 23F | 278 | 364 | 0.8 (0.56, 1.03) |

Abbreviations: GMT = geometric mean titer; OPA = opsonophagocytic activity.

a. n = Number of subjects with a determinate OPA titer to the given serotype.

b. GMTs were calculated using all subjects with available data for the specified blood draw.

c. Ratio of GMTs (**Prevnar 13**+QIV/placebo to placebo+QIV/**Prevnar 13**) was calculated by back transforming the mean difference between vaccine sequences on the logarithmic scale.

d. CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (**Prevnar 13**+QIV/placebo – placebo+QIV/**Prevnar 13**).

Antibody responses elicited by QIV were measured by HAI 1 month after QIV vaccination. The immune responses were measured as HAI GMTs for each QIV strain 1 month after vaccination. Noninferiority was demonstrated for each vaccine antigen if the lower limit of the 2-sided 95% CI for the GMT ratio of the HAI titer was >0.5. Noninferiority was demonstrated for each of the 4 QIV strains after **Prevnar 13** was given concomitantly with QIV compared with QIV given alone (Table 20).

**Table 20. HAI GMTs 1 Month After Prevnar 13 With QIV and Placebo With QIV**

| Strain | Prevnar 13+QIV n[a]=427 GMT[b] | Placebo+QIV n[a]=430 GMT[b] | Vaccine Comparison Ratio[c] | (95% CI[d]) |
|---|---|---|---|---|
| A/H1N1 | 115 | 113 | 1.0 | (0.88, 1.18) |
| A/H3N2 | 226 | 196 | 1.2 | (1.01, 1.32) |
| B/Brisbane | 28 | 26 | 1.1 | (0.95, 1.24) |
| B/Massachusetts | 45 | 43 | 1.0 | (0.90, 1.21) |

Abbreviations: GMT = geometric mean titer; HAI = hemagglutination inhibition assay.

a. n = Number of subjects with a determinate HAI titer to the given strain.

b. GMTs were calculated using all subjects with available data for the specified blood draw.

c. Ratio of GMTs (**Prevnar 13**+QIV/placebo to placebo+QIV/**Prevnar 13**) was calculated by back transforming the mean difference between vaccine sequences on the logarithmic scale.

d. CIs for the ratio are back transformations of a CI based on the Student t distribution for the mean difference of the logarithms of the measures (**Prevnar 13**+QIV/placebo – placebo+QIV/**Prevnar 13**).

### 4.2 Pharmacokinetic Properties

Evaluation of pharmacokinetic properties is not available for vaccines.

### 4.3 Preclinical Safety Data

A repeated-dose intramuscular (5 IM doses) rabbit toxicity study of **Prevnar 13** resulted in the generation of serotype-specific antibody responses and did not demonstrate any significant local or systemic adverse effects. In addition, there were no significant adverse findings in a single-dose IM local tolerance study in rabbits.

In single-dose subcutaneous (SC) safety pharmacology studies of **Prevnar 13** in rats or monkeys, there were no effects on central nervous, respiratory, or cardiovascular systems. In repeated-dose (7 SC doses) toxicity studies in rats and monkeys, no significant adverse effects were observed. In addition, in a repeated-dose (5 SC doses) toxicity study in juvenile rats, no significant adverse effects were observed.

A reproductive toxicity study in female rabbits showed that IM administration of **Prevnar 13** prior to mating and during gestation did not affect fertility, embryo/fetal development, or post-natal development.

## 5. INDICATION

**Infants and Children Aged 6 Weeks to 17 Years**

Active immunization for the prevention of invasive disease, pneumonia and AOM caused by *S. pneumoniae* in infants, children and adolescents from 6 weeks to 17 years of age.

**Adults Aged 18 Years and Older**

Active immunization for the prevention of pneumococcal disease (including pneumonia and invasive disease) in adults 18 years of age and older caused by *S. pneumoniae*.

See sections 4.1 and 9 for information on protection against specific pneumococcal serotypes.

The use of **Prevnar 13** should be determined on the basis of official recommendations taking into consideration the impact of invasive disease in different age groups as well as the variability of serotype epidemiology in different geographical areas.

## 6. RECOMMENDED DOSE

The immunization schedules for **Prevnar 13** should be based on official recommendations.

Data on the interchangeability of pneumococcal 7-valent conjugate vaccine or **Prevnar 13** with other pneumococcal conjugate vaccines containing a protein carrier different from $CRM_{197}$ are not available.

**Infants and Children Aged 6 Weeks to 17 Years (Prior to the 18$^{th}$ Birthday)**

It is recommended that infants who receive a first dose of **Prevnar 13** complete the vaccination course with **Prevnar 13**.

<u>Infants Aged 6 Weeks-6 Months</u>

*Three-dose primary series*

The recommended immunization series consists of 4 doses, each of 0.5 mL. The primary infant series consists of 3 doses, each of 0.5 mL, with the first dose usually given at 2 months of age and with an interval of at least 1 month between doses. The first dose may be given as early as 6 weeks of age. A fourth dose is recommended in the second year of life.

| Prevnar 13 Routine Vaccine Schedule for Infants and Toddlers | | | | |
|---|---|---|---|---|
| Dose | Dose 1*† | Dose 2† | Dose 3† | Dose 4‡ |
| Age at Dose | 2 months | 4 months | 6 months | 12-15 months |
| * Dose 1 may be given as early as 6 weeks of age.<br>† The recommended dosing interval is 4-8 weeks.<br>‡ The fourth dose should be administered at approximately 12-15 months of age, and at least 2 months after the third dose. | | | | |

Alternatively, when **Prevnar 13** is given as part of a routine infant immunization program, a 3-dose schedule may be considered. The first dose may be given from the age of 2 months, with a second dose 2 months later, and a third (booster) dose is recommended between 11-15 months of age (see section 4.1).

**Prevnar 13** Schedule for Preterm Infants (<37 Weeks Gestation)

In preterm infants, the recommended immunization series consists of 4 doses, each of 0.5 mL. The primary infant series consists of 3 doses, with the first dose given at 2 months of age and with an interval of at least 1 month between doses. The first dose may be given as early as 6 weeks of age. The fourth (booster) dose is recommended at approximately 12 months of age.

For children who are beyond the age of routine infant schedule, the following **Prevnar 13** schedule applies.

| Prevnar 13 Vaccine Schedule for Previously Unvaccinated Children ≥7 Months to 5 Years of Age (Prior to the 6th Birthday) | |
|---|---|
| Age at First Dose | Total Number of 0.5 mL Doses |
| 7-11 months of age | 3* |
| 12-23 months of age | 2† |
| ≥24 months to 5 years of age | 1 |
| * 2 doses at least 4 weeks apart; third dose after the 1-year birthday, separated from the second dose by at least 2 months. | |

| **Prevnar 13 Vaccine Schedule for Previously Unvaccinated Children ≥7 Months to 5 Years of Age (Prior to the 6th Birthday)** |
|---|
| † 2 doses at least 2 months apart. |

**Prevnar 13** Schedule for Infants and Children Previously Vaccinated with Pneumococcal 7-valent Conjugate Vaccine (*Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F):

**Prevnar 13** contains the same 7 serotypes contained in pneumococcal 7-valent conjugate vaccine and is manufactured based on the same conjugate technology using the same carrier protein $CRM_{197}$. Children who have begun immunization with pneumococcal 7-valent conjugate vaccine may complete immunization by switching to **Prevnar 13** at any point in the schedule. In clinical trials, immunogenicity and safety profiles were comparable. Children 15 months to 5 years of age who are considered completely immunized, or with any incomplete pneumococcal 7-valent conjugate vaccine schedule may receive 1 dose of **Prevnar 13** to elicit immune responses to the 6 additional serotypes. The catch-up (supplemental) dose of **Prevnar 13** should be administered with an interval of at least 8 weeks after the final dose of pneumococcal 7-valent conjugate vaccine. To ensure adequate protection against all 13 serotypes, children 15-23 months of age that received only a single dose of pneumococcal 7-valent conjugate vaccine before the age of 12 months, should receive 2 doses of **Prevnar 13** at least 2 months apart and separated from the first dose by at least 2 months.

**Prevnar 13** Schedule for Children 12 Months to 5 Years of Age Incompletely Vaccinated with **Prevnar 13**:

For children 7 months to 5 years of age that have not received any prior doses of **Prevnar 13,** see the Vaccine Schedule for Previously Unvaccinated Children ≥7 Months to 5 Years of Age (Prior to the 6th Birthday).

Children who are considered incompletely vaccinated with **Prevnar 13** are children who have received 3 or fewer doses of **Prevnar 13** before 12 months of age and no **Prevnar 13** dose after 12 months of age or children who did not complete the recommended age-appropriate vaccine schedule for previously unvaccinated children [see the Vaccine Schedule for Previously Unvaccinated Children ≥7 Months of Age].

For children 12 months to 5 years of age with any incomplete **Prevnar 13** schedule, the following schedule applies to complete the **Prevnar 13** immunization schedule:

| **Vaccine Schedule for Children 12 Months to 5 Years of Age Incompletely Vaccinated With Prevnar 13** | | |
|---|---|---|
| Current Age (months) | Previous **Prevnar 13** Vaccination History | Total Number of 0.5 mL Doses |
| 12-23 months | 1 dose <12 months | 2* |
| | 2 or 3 doses <12 months | 1† |
| 24-71 months | Any incomplete schedule | 1† |
| * Two doses at least 2 months apart and separated from the first dose by at least 2 months.<br>† Separated from the previous dose by at least 2 months. | | |

The immune responses induced by this **Prevnar 13** schedule may result in lower antibody concentrations compared to antibody concentrations following 4 doses of **Prevnar 13** (given at 2, 4, 6 and 12-15 months).

Protective immunity to the 6 new serotypes in **Prevnar 13** requires age-appropriate dosing as described above.

**Prevnar 13** Schedule for Children 24 Months to 17 Years of Age:

Children 24 months to 5 years of age and children 6 years to 17 years of age may receive a single dose of **Prevnar 13** whether or not they have been previously vaccinated with 1 or more doses of pneumococcal 7-valent conjugate vaccine. If pneumococcal 7-valent conjugate vaccine was previously administered, then at least 8 weeks should elapse before receiving **Prevnar 13**.

In children 5 to <10 years of age who received a single dose of **Prevnar 13**, there were no differences in the antibody concentrations compared to antibody concentrations following the fourth dose of either pneumococcal 7-valent conjugate vaccine or **Prevnar 13**. In children 10-17 years of age, functional antibody responses were comparable to those in the 5 to <10 year age group after each group received a single dose of **Prevnar 13**.

**Adults Aged 18 Years and Older**

**Prevnar 13** is to be administered as a single dose to adults 18 years and older including those previously vaccinated with a pneumococcal polysaccharide vaccine.

The need for re-vaccination with a subsequent dose of **Prevnar 13** has not been established. For specific guidelines, please refer to local recommendations.

**Special Populations**

Individuals who may be 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 23-valent pneumococcal polysaccharide vaccine (PPSV23) may receive at least 1 dose of **Prevnar 13**.

In individuals with a hematopoietic stem cell transplant (HSCT), the recommended immunization series consists of 4 doses of **Prevnar 13**, each of 0.5 mL. The primary series consists 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 is recommended 6 months after the third dose (see section 4.1).

**Pediatric Use**

The safety and effectiveness of **Prevnar 13** in children below the age of 6 weeks have not been established.

**Geriatric Use**

**Prevnar 13** has been shown to be safe and immunogenic in the geriatric population (see section 4.1).

Of the 48,806 adults in the 7 studies (6115A1-004, 6115A1-3005, 6115A1-3010, 6115A1-3000, 6115A1-3001, 6115A1-3008, 6115A1-3006) of the clinical development program who received **Prevnar 13**, 30,793 (63.1%) were 65-74 years of age, and 14,498 (29.7%) were 75 years of age and over. No clinically significant differences in safety or immunogenicity were observed between 65-74 year-old individuals and greater than 75 year-old individuals.

## 7. MODE OF ADMINISTRATION

For intramuscular use only.

The dose is 0.5 mL given intramuscularly, with care to avoid injection into or near nerves and blood vessels. The preferred sites are the anterolateral aspect of the thigh (vastus lateralis muscle) in infants and young children or the deltoid muscle of the upper arm in older children and adults. The vaccine should not be injected in the gluteal area. Do not administer **Prevnar 13** intravascularly.

## 8. CONTRAINDICATION

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

## 9. WARNING AND PRECAUTION

As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in case of a rare anaphylactic event following the administration of the vaccine (see section 12).

The administration of **Prevnar 13** should be postponed in subjects suffering from acute severe febrile illness.

As with any intramuscular injection, **Prevnar 13** should be given with caution to infants, children or adults with thrombocytopenia or any coagulation disorder, or to those receiving anticoagulant therapy.

**Prevnar 13** will only protect against *S. pneumoniae* serotypes included in the vaccine, and will not protect against other microorganisms that cause invasive disease, pneumonia, or otitis media.

As with any vaccine, **Prevnar 13** may not protect all individuals receiving the vaccine from pneumococcal disease.

Children with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunization.

Safety and immunogenicity data on **Prevnar 13** are not available for individuals in immunocompromised groups (e.g., individuals with malignancy or nephrotic syndrome) and vaccination should be considered on an individual basis.

**Infants and Children Aged 6 Weeks to 5 Years**

Limited data have demonstrated that pneumococcal 7-valent conjugate vaccine (3-dose primary series) induces an acceptable immune response in infants with sickle cell disease with a safety profile similar to that observed in non-high-risk groups (see section 4.1).

The use of pneumococcal conjugate vaccine does not replace the use of PPSV23 in children ≥24 months of age with sickle cell disease, asplenia, HIV infection, chronic illness, or who are otherwise immunocompromised. Data on sequential vaccination with **Prevnar 13** followed by PPSV23 are not available; data on sequential vaccination with pneumococcal 7-valent conjugate vaccine followed by PPSV23 are limited.

As with all injectable pediatric vaccines, the potential risk of apnea should be considered when administering the primary immunization series to premature infants. The need for monitoring for at least 48 hours after vaccination should be considered for very premature infants (born ≤30 weeks of gestation) who remain hospitalized at the time of the recommended administration.

As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

When **Prevnar 13** is administered concomitantly with Infanrix hexa (DTaP-HBV-IPV/Hib), the rates of febrile reactions are similar to those seen with concomitant administration of pneumococcal 7-valent conjugate vaccine and Infanrix hexa (see section 12).

**Effects on Ability to Drive and Use Machines**

**Prevnar 13** has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 12 “Undesirable Effects” may temporarily affect the ability to drive or use machines.

## 10. INTERACTIONS WITH OTHER MEDICAMENTS

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

**Infants and Children Aged 6 Weeks to 5 Years**

**Prevnar 13** can be given with any of the following vaccine antigens, either as monovalent or combination vaccines: diphtheria, tetanus, acellular or whole cell pertussis, *Haemophilus influenzae* type b, inactivated poliomyelitis, hepatitis A, hepatitis B, meningococcal serogroup C, measles, mumps, rubella, varicella, and rotavirus.

**Prevnar 13** can also be given concomitantly between 12-23 months of age with the tetanus toxoid conjugated meningococcal polysaccharide serogroups A, C, W and Y vaccine.

Data from a post-marketing clinical study evaluating the impact of prophylactic use of antipyretics on the immune response to **Prevnar 13** suggest that concomitant administration of paracetamol may reduce the immune response to **Prevnar 13** after the infant series. Responses to the booster dose administered at 12 months were unaffected. The clinical significance of this observation is unknown.

**Children and Adolescents 6 to 17 Years of Age**

In children and adolescents, there are no data on the concomitant administration of **Prevnar 13** with human papillomavirus vaccine (HPV), meningococcal protein conjugate vaccine (MCV4), or tetanus, diphtheria and acellular pertussis vaccine (Tdap).

**Adults 18 to 49 Years of Age**

No data are currently available regarding concomitant use with other vaccines.

**Adults 50 Years and Older**

**Prevnar 13** can be administered concomitantly with trivalent or quadrivalent inactivated influenza vaccine (TIV or QIV) (see section 4.1).

**Interference with Laboratory and other Diagnostic Tests**

Not applicable.

## 11. PREGNANCY AND LACTATION

Information on the safety of **Prevnar 13** when used during pregnancy and lactation is not available.

It is not known whether vaccine antigens or antibodies are excreted in human milk.

## 12. UNDESIRABLE EFFECTS

**Infants and Children Aged 6 Weeks to 5 Years**

In a clinical study (0887X-100811) with pneumococcal 7-valent conjugate vaccine in infants vaccinated at 2, 3, and 4 months of age, fever ≥38°C was reported at higher rates among infants who received pneumococcal 7-valent conjugate vaccine concomitantly with Infanrix hexa (28.3% to 42.3%) than in infants receiving Infanrix hexa alone (15.6% to 23.1%). After a booster dose at 12-15 months of age, the rate of fever ≥38°C was 50.0% in infants who received pneumococcal 7-valent conjugate vaccine and Infanrix hexa at the same time as compared to 33.6% in infants receiving Infanrix hexa alone. These reactions were mostly moderate (less than or equal to 39°C)

and transient.

**Additional Information in Special Populations**

Children and adolescents with sickle cell disease, HIV infection or an hematopoietic stem cell transplant had similar frequencies of adverse reactions as children and adolescents 2-17 years of age, except that headaches, vomiting, diarrhea, pyrexia, fatigue, arthralgia and myalgia were very common.

**Adults Aged 18 Years and Older**

A trend to lower frequency of adverse reactions was associated with increasing age; adults >65 years of age (regardless of prior pneumococcal vaccination status) reported fewer adverse reactions than younger adults, with adverse reactions generally most common in adults, 18-29 years of age.

Overall, the frequency categories were similar in adults 18-49 years of age compared to adults >50 years of age, with the exception of vomiting which was very common (≥1/10) in adults aged 18-49 years and common (≥1/100 to <1/10) in adults >50 years of age.

**Additional Information in Special Populations**

Adults with HIV infection had similar frequencies of adverse reactions as adults 50 years of age and older, except that fever and vomiting were very common and nausea was common.

Adults with an hematopoietic stem cell transplant have similar frequencies of adverse reactions as adults 18 years and older, except that fever and vomiting were very common.

**Adverse Reactions from Clinical Trials with Prevnar 13**

Infants and children aged 6 weeks to 5 years

These data are from clinical trials in which **Prevnar 13** was administered simultaneously with other routine childhood vaccines.

| **Adverse Reactions Table** | | | | |
|---|---|---|---|---|
| **System Organ Class** | **Very Common ≥1/10** | **Common ≥1/100 to <1/10** | **Uncommon ≥1/1,000 to <1/100** | **Rare ≥1/10,000 to <1/1,000** |
| Immune System Disorders | | | | Hypersensitivity reaction including face edema, dyspnea, bronchospasm |
| Metabolism and Nutrition Disorders | Decreased appetite | | | |
| Psychiatric Disorders | Irritability | | Crying | |
| Nervous System Disorders | Drowsiness/increased sleep; restless sleep/decreased sleep | | Seizures (including febrile seizures) | Hypotonic-hyporesponsive episode |
| Gastrointestinal Disorders | | Diarrhea; vomiting | | |
| Skin and Subcutaneous Tissue Disorders | | Rash | Urticaria or urticaria-like rash | |
| General Disorders and Administration Site Conditions | Fever; any vaccination-site erythema, induration/swelling or pain/tenderness; Vaccination-site erythema or induration/swelling 2.5 cm - 7.0 cm (after toddler dose and in older children [age 2 to 5 years]) | Fever greater than 39°C; vaccination-site erythema or induration/ swelling 2.5 cm - 7.0 cm (after infant series); vaccination-site pain/tenderness interfering with movement | Vaccination-site induration/swelling or erythema greater than 7.0 cm | |

Children and adolescents aged 5-17 years

The most common adverse reactions in children and adolescents 5-17 years of age were:

| **Adverse Reactions Table** | | |
|---|---|---|
| **System Organ Class** | **Very Common**<br>**≥1/10** | **Common**<br>**≥1/100 to <1/10** |
| Metabolism and Nutrition Disorders | Decreased appetite | |
| Psychiatric Disorders | Irritability | |
| Nervous System Disorders | Drowsiness/increased sleep, restless sleep/decreased sleep | Headache |
| Gastrointestinal Disorders | | Diarrhea; vomiting |
| Skin and Subcutaneous Tissue Disorders | | Rash; urticaria or urticaria-like rash |
| General Disorders and Administration Site Conditions | Any vaccination-site erythema, induration/swelling, or pain/tenderness, vaccination-site tenderness (including impaired movement) | Fever |

Other adverse reactions observed in other age groups may also be applicable in this age group but due to the small sample size in this study (6096A1-3011) were not seen.

Adults aged 18 years and older

| **Adverse Reactions Table** | | | |
|---|---|---|---|
| **System Organ Class** | **Very Common**<br>**≥1/10** | **Common**<br>**≥1/100 to <1/10** | **Uncommon**<br>**≥1/1,000 to <1/100** |
| Immune System Disorders | | | Hypersensitivity reaction including face edema, dyspnea, bronchospasm |
| Metabolism and Nutrition Disorders | Decreased appetite | | |

| **Adverse Reactions Table** | | | |
|---|---|---|---|
| **System Organ Class** | **Very Common ≥1/10** | **Common ≥1/100 to <1/10** | **Uncommon ≥1/1,000 to <1/100** |
| Nervous System Disorders | Headache | | |
| Gastrointestinal Disorders | Diarrhea; vomiting (in adults aged 18-49 years) | Vomiting (in adults aged 50 years and over) | Nausea |
| Skin and Subcutaneous Tissue Disorders | Rash | | |
| Musculoskeletal, Connective Tissue and Bone Disorders | Generalized new/aggravated joint pain; generalized new/aggravated muscle pain | | |
| General Disorders and Administration Site Conditions | Chills; fatigue; vaccination-site erythema, vaccination-site induration/swelling; vaccination-site pain/tenderness; limitation of arm movement | Fever | Lymphadenopathy localized to the region of the vaccination site |

Overall, no significant differences in frequencies of adverse reactions were noted if **Prevnar 13** was given to adults pre-vaccinated with PPSV23 or adults PPSV23 unvaccinated. Frequency categories for all adverse reactions of adults aged 50-64 years and adults ≥65 years of age were similar.

**Solicited Adverse Reactions in Adult Studies with Prevnar 13 and TIV**

Frequencies of local reactions in adults aged 50-59 years and in adults aged ≥65 years were similar after **Prevnar 13** was administered with TIV compared to **Prevnar 13** administered alone.

Higher frequency of some solicited systemic reactions was observed when **Prevnar 13** was administered concomitantly with TIV compared to TIV given alone (headache, chills, rash, decreased

appetite, muscle and joint pain) or **Prevnar 13** given alone (headache, fatigue, chills, decreased appetite, and joint pain).

**Adverse Reactions from Prevnar 13 Post-marketing Experience**

Although the following adverse drug reactions were not observed in the clinical trials, they are considered adverse drug reactions for **Prevnar 13** as they were reported in the post-marketing experience.

Because these reactions were derived from spontaneous reports, the frequencies could not be determined and are thus considered as not known.

| **Adverse Reactions Table** | |
|---|---|
| **System Organ Class** | **Frequency not known (cannot be estimated from available data)*** |
| Blood and Lymphatic System Disorders | Lymphadenopathy localized to the region of the vaccination site |
| Immune System Disorders | Anaphylactic/anaphylactoid reaction including shock |
| Skin and Subcutaneous Tissue Disorders | Angioedema; erythema multiforme |
| General Disorders and Administration Site Conditions | Vaccination-site dermatitis; vaccination-site urticaria; vaccination-site pruritus |
| * ADR identified post-marketing. | |

## 13. OVERDOSE AND TREATMENT

Overdose with **Prevnar 13** is unlikely due to its presentation as a single dose vial. However, in infants and children there have been reports of overdose with **Prevnar 13** defined as subsequent doses administered closer than recommended to the previous dose. In general, adverse reactions reported with overdose are consistent with those that have been reported with doses given in the recommended pediatric schedules of **Prevnar 13**.

## 14. STORAGE CONDITION

Store in a refrigerator (2°C – 8°C).

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

## 15. DOSAGE FORMS AND PACKAGING AVAILABLE

**Prevnar 13 suspension for injection** is available in 2 mL clear, Type I borosilicate glass vial – pack size of 5, 10, 25 and 50.

Not all pack sizes may be marketed.

**Prevnar 13** is a suspension containing an adjuvant. The vaccine should be shaken well to obtain a homogeneous white suspension prior to expelling air from the syringe, and should be inspected visually for any particulate matter and/or variation of physical aspect prior to administration. Do not use if the content appears otherwise.

The vaccine is to be administered immediately after being drawn up into a syringe.

See also sections 6 Recommended dose and 7 Mode of administration.

## 16. NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER

Pfizer (Thailand) Limited
Bangkok, Thailand

## 17. DATE OF REVISION OF PACKAGE INSERT

02 August 2022