

Indications and Usage Memo - February 19, 2010 - Prevnar 13

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TO: Biologics License Application (BLA) 1253240/0

SUBJECT: Prevnar 13, Indications and Usage
1. Serotype 3
2. Otitis media

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Background

In BLA submission 1253240, the applicant (Pfizer, formerly Wyeth Vaccines) proposes that data in the application support approval of Prevnar 13 for the following indications: 1) prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes in the vaccine, and 2) prevention of otitis media caused by *S. pneumoniae* serotypes in the vaccine. Prevnar 13 is a 13-valent pneumococcal conjugate vaccine that includes 7 serotypes in common with the U.S. licensed 7-valent pneumococcal conjugate vaccine, Prevnar (4, 6B, 9V, 14, 18C, 19F, 23F), and 6 additional new serotypes (1, 3, 5, 6A, 7F, 19A). Polysaccharides from each of the 13 pneumococcal serotypes are individually conjugated to the same protein carrier (CRM197). Both Prevnar 13 and Prevnar are manufactured by the applicant.

The purpose of this memorandum is to clarify why the Office of Vaccines Research and Review recommends that Prevnar 13 include within the indications: 1) prevention of invasive disease caused by serotype 3, and 2) prevention of otitis media caused by serotypes in common with Prevnar (i.e., serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F).

1. Prevention of invasive pneumococcal disease due to serotype 3

Evidence supporting the safety and effectiveness of Prevnar 13 for the prevention of invasive disease is based primarily on the U.S. pivotal study 004 using a non-inferiority design comparing antibody responses following vaccination with Prevnar 13 to antibody responses after Prevnar for the common serotypes, and comparing the new serotypes in Prevnar 13 to the lowest of the responses among the 7 common serotypes.

Ten of the 13 serotypes in Prevnar 13 met the pre-specified non-inferiority criteria for both co-primary endpoints. For three vaccine serotypes (6B, 9V, 3), the non-inferiority criterion was not met for the proportion of subjects with an IgG antibody concentration ≥ 0.35 $\mu\text{g/mL}$ one month after the third dose. The lower limit of the 95% confidence interval (CI) for the difference in proportions achieving ≥ 0.35 $\mu\text{g/mL}$ (Prevnar13 – Prevnar) exceeded the pre-specified non-inferiority margin of -10%; the margins were -10.9%, -12.4%, and -36.2% for serotypes 6B, 9V, and 3 respectively. Although this study was not designed to demonstrate non-inferiority for secondary or exploratory endpoints, these additional immunogenicity endpoints were taken into account for serotypes 6B, 9V, and 3. Serotype 6B met the non-inferiority criteria for three out of four secondary endpoints. Serotype 9V met the non-inferiority criteria for two out of four secondary endpoints. Serotype 3 failed all four secondary endpoints. Exploratory analyses of pre-dose 4 Geometric Mean Concentrations (GMC) showed that with the exception of serotype 3, all responses in the Prevnar 13 group met the non-inferiority criteria. Based on these results, the clinical reviewer recommended approval of Prevnar 13 for the prevention of invasive pneumococcal disease caused by *S. pneumoniae* serotypes 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F in children 6 weeks through 5 years of age, but concluded that the available data were insufficient to support effectiveness for prevention of invasive pneumococcal disease caused by serotype 3.

While serotype 3 did not meet any of the pre-specified immunogenicity primary endpoints based on serotype-specific IgG, it is important to note that the protective level of IgG antibody is not established for any serotype. In Study 004, even though serotype 3 is clearly the least immunogenic of the 6 additional serotypes, with IgG GMC of 0.49 $\mu\text{g/mL}$ (95% CI: 0.43, 0.55) after Dose 3 and 0.94 $\mu\text{g/mL}$ (95% CI: 0.83, 1.05) after Dose 4, these mean titers are nonetheless above the 0.35 $\mu\text{g/mL}$ threshold; the proportion of subjects above 0.35 $\mu\text{g/mL}$ increased from 63.5% (95% CI: 57.1, 69.4) after dose 3 to 90.5% (95% CI: 86.0, 94.0) after dose 4.

Opsonophagocytic antibodies (OPA) are likely more important in mediating protection against invasive disease.^{1,2} At the end-of Phase 2 Meeting on 11 May, 2006, both CBER and Wyeth agreed that OPA is an important measure of functional immune response and CBER strongly recommended that it be evaluated as a secondary endpoint in the non-inferior evaluation of Prevnar 13 vaccine. CBER has continued to view use of OPA as an important endpoint in the pivotal immunogenicity study, even though CBER has referred to OPA as a secondary endpoint and Wyeth has referred to OPA as an exploratory endpoint. As with IgG, the OPA titer that correlates with protection has not been determined. Nevertheless, Prevnar 13 elicited OPA titers $\geq 1:8$ after 3 doses in 96% of infants, and a Geometric Mean Titer (GMT) of 121. After the toddler Dose 4, the OPA GMT increased to 380, a 3.1-fold increase, a fold-rise increase greater than that observed with serotypes 6A and 7F; this finding is consistent with a memory response. Thus, it is reasonable to include serotype 3 in the *Indications* for Prevnar 13 because the vaccine elicits functional antibodies that will likely protect against invasive pneumococcal disease.

Importantly, the applicant plans to monitor serotype-specific IPD rates post licensure. Such post-marketing surveillance studies will examine serotype 3-specific disease rates over time and other measures of vaccine effectiveness against serotype 3.

2. Otitis Media

No clinical studies evaluating the effect of Prevnar 13 on otitis media were included in the BLA. Noting this, the clinical reviewer concluded that insufficient information was provided in the BLA to support an indication for prevention of otitis media due to serotypes in Prevnar 13. Additionally, the clinical reviewer cites two main reasons why the available serologic data are not supportive: (a) No consensus exists regarding the serologic criteria for assessing effectiveness of pneumococcal conjugate vaccines against otitis media. The 0.35 µg/mL IgG antibody reference value used for non-inferiority primary endpoint comparisons in the U.S. pivotal immunogenicity trial applies only to IPD, and not to otitis media or other non-invasive disease endpoints; and (b) The proportions of infants achieving the higher secondary IgG reference level of 1.0 µg/mL were generally lower in the Prevnar 13 recipients compared to the Prevnar recipients. Relative to IgG antibody concentrations needed to prevent IPD, higher IgG antibody concentrations might be needed to prevent otitis media.

Data supporting approval of Prevnar (7-valent) for prevention of otitis media were provided by the applicant in cross-referenced BLA supplement STN 103905/1003. Prevnar is indicated for the prevention of otitis media caused by serotypes contained in the vaccine. The indication was supported by (1) Northern California Kaiser Permanente (NCKP) trial data showing the effect of Prevnar on all-cause otitis media; and (2) Finnish Otitis Media (FinOM) efficacy trial results. Finnish infant acute otitis media (AOM) episodes were confirmed by culture and identification of pneumococcal serotypes in middle ear fluid. In the Finnish study, Prevnar efficacy was 57% (95% CI 44, 67) for vaccine serotype AOM and 34% (95% CI 21, 45) for all pneumococcal AOM, regardless of serotype.³ In the NCKP study, infant AOM cases were identified from automated database searches of visits within NCKP health care system. AOM was diagnosed during the course of routine U.S. medical practices. In this setting, Prevnar efficacy was 7% (95% CI 4.1, 9.7) for all-cause AOM.¹ Recurrent AOM, defined as 3 episodes in 6 months or 4 episodes in 12 months, was reduced by 9% (95% CI: 3%-15%). Tympanostomy tubes placement decreased by 20% (95% CI: 2, 35).³

As discussed in the clinical review, comparisons of IgG antibody responses at a higher reference value were useful as an additional immune response measures to evaluate pneumococcal vaccine immunogenicity. However, this reference value was not chosen for evaluating the vaccine effect in preventing otitis media. Of note, otitis media effectiveness for individual serotypes was not associated with ELISA IgG antibody levels measured from FinOM trial participant sera.

Functional antibody activity, as measured by serum antibody that exhibits OPA is the primary mechanism of protection against pneumococcal disease. In the U.S. pivotal immunogenicity trial, IgG and OPA responses after Prevnar 13 vaccinations were compared to corresponding Prevnar responses. After the 3rd and 4th Prevnar 13 vaccinations, OPA titers to each of the 7 common serotypes were within 1 dilution of corresponding Prevnar OPA antibody responses. Measurable OPA antibody responses provided evidence that vaccine-induced IgG antibody capsular antibodies were functional, and therefore likely to

have a preventive effect on otitis media due to pneumococcal serotypes in the vaccine, as was observed for Prevnar in pre-licensure trials.

The proposed Prevnar 13 indication for prevention of otitis media was addressed by committee members at the November 18, 2009 Vaccines and Related Biologic Products Advisory Committee (VRBPAC) meeting.⁴ Based primarily on the cross-referenced Prevnar otitis media data, the majority of VRBPAC committee members supported the effectiveness of Prevnar 13 to prevent OM caused by serotypes shared with Prevnar although no official vote was taken.

Post-Licensure Studies

Controlled clinical studies to evaluate the effect of Prevnar 13 on OM post- licensure will not be possible within the U.S. because nearly all infants and children will receive a pneumococcal conjugate vaccine, consistent with recommendations of CDC's Advisory Committee on Immunization Practices. However, observational studies examining the effectiveness of Prevnar were conducted after its licensure and introduction in February 2000. For example, in studies published after approval of Prevnar, the percentage of pressure-equalizing (PE) tube insertions was compared among Tennessee and New York children born in 1998-1999 and 2000-2001. PE tube insertions declined by 16% for Tennessee and 23% for New York children, respectively.⁵ Rates of ambulatory visits and antibiotic prescriptions for acute OM in 2004 were compared to corresponding rates in 1997-1999. Acute OM-related healthcare utilization decreased from 2173 to 1244 office visits per 1000 person-years (42.7% reduction). Antibiotic prescriptions for acute OM were reduced by 41.9%; concurrent guidelines for judicious antibiotic use may have also contributed to the observed trend.⁶ Observational studies such as those cited above, though limited by possible randomization and controls biases, may provide the best opportunity to obtain confirmatory evidence of Prevnar 13 vaccine otitis media effectiveness in a post-licensure setting. The applicant has proposed observational post-marketing studies to evaluate Prevnar 13 effectiveness against OM.

Given the demonstrated effectiveness of Prevnar in well-controlled clinical trials, the similarities between Prevnar and Prevnar 13 with respect to product manufacture, and serum IgG antibody and OPA responses for serotypes common to both vaccines, it is reasonable to conclude that similar effectiveness against otitis media would be observed for the serotypes shared with Prevnar.

While the applicant has proposed that the indication include prevention of otitis media due to serotypes in the vaccine, the available data, and advice from VRBPAC, support the more limited indication of prevention of OM due to serotypes common with Prevnar (i.e., serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F).

References

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