

Summary Basis for Regulatory Action

Date: May 22, 2015

From: Jon R. Daugherty, Ph.D., Chair of the Review Committee

Thru: Loris D. McVittie, Ph.D., Acting Chief, Regulatory Review Branch 1

BLA/ STN#: STN 125324/1196

Applicant Name: Wyeth Pharmaceuticals, Inc.

Date of Submission: July 22, 2014

PDUFA Goal Date: May 22, 2015

Proprietary Name/ Established Name: Prevnar 13/Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein)

Indication: In adults 50 years of age and older, Prevnar 13 is indicated for active immunization for the prevention of pneumonia and invasive disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F.

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: Wellington Sun, M.D., Director, Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review

I concur with the summary review.

I concur with the summary review and include a separate review to add further analysis.

I do not concur with the summary review and include a separate review.

Material Reviewed/ Consulted	Specific documentation used in developing the SBRA	
Reviewer Name – Document(s)	Date	
Clinical Review	Tina Khoie Mongeau, MD, MPH; Roshan Ramanathan, MD, MPH	5/22/2015
Serological Immune Response Assay Review	Mustafa Akkoyunlu, M.D., Ph.D.	2/25/2015
Statistical Review	Lihan Yan, Ph.D.	4/9/2015
Pharmacovigilance Review	Marthe G. Bryant-Genevier, M.D.	4/20/2015
Clinical Serology & Bioassay Review	Freyja Williams, B.S.	11/21/2014

Bioresearch Monitoring Review	Bhanu Kannan, M.S.	3/18/2015
Promotional Materials	Michael Brony, Pharm.D.	2/6/2015
Co-Regulatory Project Manager	Christina M. Houck, B.S.	
Co-Regulatory Project Manager	Holly Wieland, RN, MPH	

1. Introduction

Pevnar 13, Pneumococcal 13-valent conjugate vaccine (Diphtheria CRM197 Protein) is a sterile suspension 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 linked to non-toxic diphtheria CRM197 protein. On December 30, 2011, Pevnar 13 was approved in the United States (US) for active immunization for the prevention of pneumonia and invasive disease caused by *S. pneumoniae* serotypes contained in the vaccine in persons 50 years of age and older under accelerated approval of biological products (21 CFR 601.40 and 601.41). The demonstration of effectiveness of immunization with Pevnar 13 in adults ≥ 50 years of age was based on a serological endpoint (opsonophagocytic antibody) that was accepted as being reasonably likely to predict protection from pneumonia and invasive disease caused by *S. pneumoniae*. Prior to the licensure of Pevnar 13 in 2011, the safety of Pevnar 13 in adults was assessed in 6 clinical studies conducted in the US and Europe which included 6,198 adults ranging in age from 50 through 95 years. As a condition of accelerated approval, the December 30, 2011 approval letter stated that a postmarketing study was required to study Pevnar 13 in an adequate and well-controlled clinical trial to verify and describe its clinical benefit and to submit the final clinical study report.

On June 25, 2014, Wyeth submitted supplement 125324/1194 to fulfill the requirement to submit the final clinical study report of the CAPiTA confirmatory efficacy study to its Biologics License Application. On May 19, 2015, CBER issued a letter informing Wyeth that it had fulfilled this requirement.

With the current supplement to the Biologics License Application (sBLA 125324/1196), Wyeth Pharmaceuticals Inc. requests to update the Pevnar 13 package insert with efficacy and safety results from this postmarketing requirement (PMR) study, the Community Acquired Pneumonia Immunization Trial in Adults (CAPiTA).

In a Type B meeting on August 27, 2013, CBER agreed that the immunogenicity data (serotype OPA assays and serum IgG responses), exploratory efficacy data, health outcomes and nasopharyngeal carriage data and correlate of protection analyses from the CAPiTA study could be submitted separately from the safety and efficacy data for CBER's review. Therefore, these data from the CAPiTA study were not included in STN 125324/1196.

2. Background

Streptococcus pneumoniae remains a leading infectious cause of serious illness, including community acquired pneumonia (CAP) among older adults in the United States (US), which is an important cause of hospitalization and mortality in the older adult population (≥ 65 years of

age). Although precise estimates of the rates of pneumococcal pneumonia and serotype-specific etiology have historically been challenging to measure, recent data suggests that an estimated 4 million cases of CAP occur annually in the U.S., resulting in >1 million hospitalizations and substantial morbidity and mortality, particularly among older adults. A recent study conducted in the U.S. suggested that serotypes contained in Prevnar 13 (19A, 7F/A, 5, 3 and 6A) caused most cases of *S. pneumoniae*-positive CAP.

S. pneumoniae can also cause invasive pneumococcal disease (IPD), which is defined by isolation of *S. pneumoniae* from a normally sterile site (i.e., blood, cerebrospinal, pleural or peritoneal fluid). The most common types of IPD in older adults include invasive (bacteremic) pneumonia, bacteremia without a focus, and meningitis. Invasive (bacteremic) pneumococcal pneumonia affects approximately 5-10% of older adult patients hospitalized with community-acquired pneumonia (CAP). Another 13-34% of adults ≥ 65 years of age who are hospitalized with CAP are affected by non-invasive (non-bacteremic) pneumococcal pneumonia.

The introduction of the use of Prevnar 13 among children in the US in 2010 reduced the burden of invasive disease caused by serotypes unique to Prevnar 13 among adults ≥ 65 years of age by more than 50%. Despite this decline, the incidence of IPD in 2012 was 29.6 cases for every 100,000 adults aged ≥ 65 years. In 2013, an estimated 13,500 cases of all invasive pneumococcal disease occurred among adults ≥ 65 years of age.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

The product formulation used in the study of Prevnar 13 in persons ages 50 and older is identical to the formulation described in and approved with the original Prevnar 13 BLA. Therefore, no new data regarding product quality, facilities inspection or environmental assessment were provided by the applicant or reviewed in support of this supplement.

b) CBER Lot Release

No lots or issues are pending that would preclude approval of this supplement.

c) Facilities Review/Inspection

No ongoing or impending investigations or compliance actions with respect to Wyeth's facilities or products are in effect. Therefore, the Office of Compliance and Biologics Quality, Division of Case Management did not object to approval of this supplement.

4. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology data were submitted as part of this supplement.

5. Clinical Pharmacology

No new pharmacology data were submitted as part of this supplement.

6. Clinical/ Statistical

a) Clinical Program

CAPiTA, conducted in The Netherlands, was a randomized (1:1), parallel-group, placebo-controlled, double-blind, clinical endpoint trial of Prevnar 13 in 84,496 community-dwelling adults aged 65 years and older with no prior pneumococcal vaccination history. Approximately 2000 of these subjects were also enrolled in an immunogenicity subset; enrollment in this subset was stratified by age: 65-69, 70-79 and ≥ 80 years of age. A placebo-controlled study was an acceptable study design because Pneumovax 23 was not routinely recommended for adults ≥ 65 years of age in the Netherlands; rather, it was only recommended for a small number of very high risk individuals. Subjects were enrolled in the study at 101 community-based sites (or by home visits organized by Spaarne Hospital for the immunogenicity subset) throughout the Netherlands. A single investigative site (Julius Center) managed enrollment sites, sentinel centers and data collection, coordinated laboratories, and performed safety surveillance. The blinded and unblinded data were reviewed on an ongoing basis by three blinded oversight committees (radiology adjudication committee, immune status committee and mortality assessment committee) as well as an independent data monitoring committee (DMC).

The primary objective of CAPiTA was to evaluate the efficacy of Prevnar 13 in the prevention of a first episode of vaccine type (VT) pneumococcal CAP, defined as an episode of CAP in which VT *S. pneumoniae* was cultivated from blood, pleural fluid, and/or other sterile site or a positive result for the presence of VT *S. pneumoniae* was obtained by the Applicant's serotype-specific urinary antigen detection assay (SSUAD, see section on Clinical Serology Assays below). An episode of CAP was defined as a positive chest radiograph and the presence of at least 2 of the following clinical criteria: cough, purulent sputum production or a change in the character of the sputum, temperature $> 38.0^{\circ}\text{C}$, auscultatory findings consistent with pneumonia, leukocytosis, C-reactive protein > 3 times the upper limit of normal, hypoxemia with a partial oxygen pressure < 60 mm Hg while the patient is breathing room air.

The study's secondary objectives included demonstrating efficacy of Prevnar 13 in the prevention of a first episode of VT IPD and the first episode of VT non-bacteremic/non-invasive pneumococcal (NB/NI) CAP. A first episode of VT IPD was defined as the presence of VT *S. pneumoniae* in a sterile site (i.e., blood cerebrospinal, pleural, peritoneal, or pericardial fluid, surgical aspirate, or bone or joint fluid); if no serotype was determined from the *S. pneumoniae* culture isolate but a serotype was determined by a positive VT SSUAD assay result, then the SSUAD serotype was assigned to the episode. A first episode of NB/NI VT pneumococcal CAP was defined as a first episode of VT pneumococcal CAP for which the blood culture results and any other available sterile site culture results were negative for *S. pneumoniae*.

The pre-specified primary efficacy endpoints in the study were met and support the approval of the application. Vaccine efficacy (VE) was demonstrated for Prevnar 13 for

both the primary endpoint, the prevention of first episode of confirmed VT pneumococcal CAP (46% (95.2% CI 22, 63), and secondary endpoints: confirmed NB/NI VT pneumococcal CAP (45% (95.2% CI 14, 65), and VT-IPD (75% (95.2% CI 41, 91), in the primary per-protocol and the modified intent-to-treat (mITT) population analyses. For each of these endpoints, the lower limit of the 95.2% CI was > 0%, which was the protocol-defined criterion for demonstrating vaccine efficacy. The most common serotypes of VT pneumococcal CAP in the placebo group were 1(12.2%), 3(17.8%),7F(24.4%) and 19A(20.0%). Primary and key secondary results were confirmed by the reviewer's independent analyses.

Regarding exploratory endpoints, in the per-protocol population prevention of all episodes of confirmed VT pneumococcal CAP showed statistically significant VE (42.4%) when adjusted for multiple comparisons accounting for the interim analysis. Prevention of a first episode of confirmed pneumococcal CAP and a first episode of IPD (endpoints that contain VT and also NVT pneumococcal disease episodes, for which there is no expectation of effect from this vaccine) also showed statistically significant VE (30.6% (95% CI 9.8, 46.7) and 51.8% (95% CI 22.4, 70.7), respectively). VE against a first episode of NB/NI pneumococcal CAP, which contains episodes of both VT and NVT disease, did not reach statistical significance (24.1% (95% CI -5.7, 45.8); P=0.1056).

In the mITT population, which includes subjects who are immune-deficient/suppressed, the same pattern was observed. No statistically significant VE was observed for the first episode of CAP, an endpoint that is predominantly composed of non-pneumococcal CAP. The 5.08% VE against all-cause CAP observed in this study was consistent with a 46% reduction in VT pneumococcal CAP, as approximately 13% of the first CAP episodes observed in subjects in the placebo group (787 episodes) were episodes of confirmed VT pneumococcal CAP (106 episodes).

Statistically significant VE against the prevention of death from all causes or from pneumococcal-related causes was not demonstrated; the number of deaths associated with pneumococcal disease during this study was very small, less than 0.1% in each of both Prevnar 13 (8/42,237 subjects) and placebo groups (9/42,255 subjects). The study was not powered to demonstrate serotype-specific VE against prevention of VT-CAP and NB/NI VT CAP endpoints.

No issues were identified with the data used to determine cases. The percentage of missing SSUAD data was low (approximately 7%), and sensitivity analyses of the effect of missed SSUAD urine samples on the primary and secondary endpoints showed that the statistical findings for VE were robust relative to missing SSUAD data in both the per-protocol and mITT populations.

Bioresearch Monitoring Review

Bioresearch monitoring site inspections were performed for one clinical investigator and two sentinel centers. The inspections did not reveal substantive problems that impact the

data submitted in the sBLA. The inspections were performed for data verification for 200 subjects who participated in the Phase 4 study.

Clinical Assays

(b)(4) is a commercial kit that was used to qualitatively detect pneumococcal antigen in urine. assay was performed at each study sentinel center as well as at Pfizer Vaccine Research, Pearl River, NY, USA. The assay is based on the detection of C-PS antigen present in all pneumococcal strains and as a result, it does not specify serotype. CBER accepted performance of the kit based on manufacturer's data and did not require additional validation.

The Serotype Specific Urinary Antigen Detection (SSUAD or UAD) Assay was validated with regard to accuracy, precision, linearity and clinical specificity. Clinical validation of the assay was performed by comparing SSUAD results to blood culture results from patients with radiologically confirmed CAP in a pilot study conducted by the Julius Center for Health Sciences and Primary Care. Analysis showed 97.1% sensitivity and 100% specificity and also demonstrated the ability of the assay to detect serotype-specific antigen in pneumococcal CAP in the absence of pneumococcal bacteremia. The SSUAD data generated during the CAPiTA study were evaluated and no aberrant or unusual data were identified. The SSUAD was considered appropriate for the intended use as a diagnostic test in this study.

b) Pediatrics

Under the Pediatric Research Equity Act (PREA) (section 505B of the Food, Drug, and Cosmetic Act [21 U.S.C. 355B]), PREA requirements do not apply to this application. The CAPiTA study was not designed to support approval of a formulation with a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration.

7. Safety

As the purpose of CAPiTA was to provide confirmatory efficacy data to support traditional approval for licensed Prevnar 13, safety was not the primary objective of this study. For the majority of enrolled subjects (N=84,492), data were collected on serious adverse events (SAEs) (for 28 days post-vaccination) and deaths (until the end of the case acquisition period). For a subset of the study population (n=2,011), safety data were collected on local and systemic adverse reactions (7 days), unsolicited AEs (28 days), newly diagnosed chronic medical conditions and SAEs (6 months).

The safety evaluation of Prevnar 13 in the study population for the CAPiTA study was supportive. No significant imbalances in deaths or SAEs were detected in participants who received Prevnar 13 when compared to placebo. During the follow up period for case accumulation, there were 3006 deaths (7.1%) in the Prevnar 13 group and 3005 deaths (7.1%) in the placebo group. There were 10 deaths (<0.1%) in the Prevnar 13 group and 10 deaths (<0.1%)

in the placebo group within 28 days of vaccination. SAEs within 1 month of vaccination were reported in 327 of 42,237 (0.8%) Prevnar 13 recipients and in 314 of 42,225 (0.7%) placebo recipients. In the subset of subjects where SAEs were monitored for 6 months, 70 of 1006 (7%) Prevnar 13 vaccinated subjects and 60 of 1005 (6%) placebo vaccinated subjects reported SAEs. These data do not provide evidence for a causal relationship between deaths and vaccination with Prevnar 13. No safety concerns were identified following the assessment of local and systemic adverse reactions, unsolicited AEs and newly diagnosed chronic medical conditions occurring post-vaccination with Prevnar 13 compared to placebo.

Frequencies of predefined local reactions and systemic events reported by subjects in the immunogenicity subset were higher in the Prevnar 13 group than in the placebo group. The most common local adverse reactions associated with Prevnar 13 within 7 days were pain (36.1%) and limitation of arm movement (14.1%). The most common systemic adverse reactions associated with Prevnar 13 within 7 days were fatigue, generalized muscle pain and headache (all \leq 1.4% each). The local reactions and systemic events were mild or moderate in severity.

A post-hoc analysis of safety of Prevnar 13 by age subgroup showed that more subjects <75 years of age reported local adverse reactions (pain and limitation of arm movement) occurring within 7 days post-vaccination than did subjects \geq 75 years of age (41% vs 32%). By contrast, systemic adverse reactions were reported more frequently by subjects \geq 75 years of age (44%) than by subjects <75 years of age within 7 days post-vaccination with Prevnar 13.

8. Advisory Committee Meeting

There were no issues pertaining to this supplement that required input from the Vaccines and Related Biological Products Advisory Committee.

9. Labeling

The package insert (PI) was reviewed by the review committee, including the reviewer from the Advertising and Promotional Labeling Branch. All issues were acceptably resolved after exchange of information and discussions with the Applicant.

10. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The data submitted in this supplement confirm clinical benefit and provide evidence for safety and efficacy of a single dose of Prevnar 13 in adults. Therefore, the Committee recommends approval of this supplement to update the Prevnar 13 package insert with results from the CAPiTA study.

b) Risk/ Benefit Assessment

Data submitted to this sBLA establish a substantial likelihood of benefit with respect to two clinically important outcomes in adults 65 years of age and older: prevention of community-acquired pneumonia and of invasive disease caused by the thirteen *S. pneumoniae* serotypes contained in the vaccine. These efficacy data can be extrapolated to adults ≥ 50 and ≤ 65 years of age who, in prior studies, had higher or similar serotype-specific opsonophagocytic activity (OPA) antibody levels following Prevnar 13 compared to adults ≥ 65 years of age. As the risks of vaccination with Prevnar 13 in adults 65 years of age and older have been found to be minimal (based on data submitted to this supplement, STN 125324/1196), in association with a substantial likelihood of benefit in the prevention of pneumococcal disease caused by pneumococcal serotypes contained in the vaccine, the overall risk-benefit profile of this product continues to be favorable.

c) Recommendation for Postmarketing Risk Management Activities

The reviewed safety data in the revised Pharmacovigilance Plan (PVP) do not suggest a need for a post-marketing requirement (PMR) study or a Risk Evaluation and Mitigation Strategy (REM). Therefore, no Postmarketing Risk Management Activities are recommended.

d) Recommendation for Postmarketing Activities

The updated version 5.0 of the PVP included results of three studies: the CAPiTA study involving adults aged 65 and older, study 6115A1-3003 involving individuals aged ≥ 2 years who had received allogeneic hematopoietic stem cell transplantation (HSCT) and study 6115A1-3002 involving HIV-infected subjects aged 6 years and older who had not been previously immunized with a pneumococcal vaccine. No new safety concerns were identified in any of these studies that would warrant post-marketing safety requirements other than routine pharmacovigilance.

The Office of Biostatistics and Epidemiology, Division of Epidemiology (OBE/DE) will also use standard surveillance tools and processes including VAERS and the Sentinel program to conduct post-marketing safety surveillance on a routine basis to identify and evaluate new or potential safety concerns. FDA may recommend modification of the sponsor's pharmacovigilance activities if any safety concerns are identified.