Summary Basis for Regulatory Action

Date: August 31, 2016

From: Christina Houck, Review Committee Chair

Through: Jon R. Daugherty, Ph.D., Chief, Regulatory Review Branch 1

BLA/ STN#: 125324/1371

Applicant Name: Wyeth Pharmaceuticals, Inc.

Date of Submission: November 4, 2015

PDUFA Goal Date: September 3, 2016

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

Reason for the Submission:

To revise the Prevnar 13 package insert based on safety and immunogenicity data from Prevnar 13 clinical studies in HIV-infected subjects 6 years of age and older, a population at increased risk of infection with \textit{Streptococcus pneumoniae}.

Recommended Action: Approval

Signatory Authorities Action: Approval

Office 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.

<table>
<thead>
<tr>
<th>Material Reviewed/ Consulted Reviewer Name – Document(s)</th>
<th>Specific documentation used in developing the SBRA</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistical Review</td>
<td>Lihan Yan, Ph.D.</td>
<td>7/27/2016</td>
</tr>
<tr>
<td>Serological Immune Response Assay Review</td>
<td>Mustafa Akkoyunlu, M.D., Ph.D.</td>
<td>6/1/2016</td>
</tr>
</tbody>
</table>
1. Introduction

Prevnar 13, a Pneumococcal 13-valent conjugate vaccine, was licensed in the United States (US) on February 24, 2010, for the active immunization of children 6 weeks through 5 years of age for the prevention of invasive pneumococcal disease (IPD) caused by the 13 serotypes contained in the vaccine and for the prevention of otitis media caused by the seven original serotypes contained in Prevnar (4, 6B, 9V, 14, 18C, 19F and 23F). On December 30, 2011, Prevnar 13 was approved for active immunization for prevention of pneumococcal disease (pneumonia and invasive disease) in adults 50 years of age and older caused by the 13 serotypes contained in the vaccine, based on an immunological surrogate endpoint through the Accelerated Approval regulation [21CFR 601.41]. On January 25, 2013, Prevnar 13 was approved for the active immunization of children 6 through 17 years of age for the prevention of IPD caused by the 13 serotypes contained in the vaccine. As a necessary condition of the accelerated approval Wyeth agreed to a post marketing study confirmatory trial, entitled, “A Phase 4, Randomized, Placebo-Controlled Clinical Trial of 13-Valent Pneumococcal Conjugate Vaccine Efficacy in Prevention of Vaccine-Serotype Pneumococcal Community-Acquired Pneumonia and Invasive Pneumococcal Disease” to verify and describe clinical benefit. Upon successful verification that the vaccine is safe and effective against community-acquired pneumonia, on May 19, 2015, Wyeth had fulfilled this post-marketing requirement and Prevnar 13 was given traditional approval for the prevention of IPD and pneumonia in adults over 50 years of age. On June 11, 2016, Prevnar 13 was approved for active immunization for prevention of pneumococcal disease in adults 18 through 49 years of age.

In this submission, the Applicant proposes to update the Prevnar 13 package insert with safety and immunogenicity data from a Prevnar 13 clinical study in human immunodeficiency virus (HIV) infected subjects six years of age and older.

2. Background

*Streptococcus pneumoniae* causes serious illness, including bacteremia, meningitis and pneumonia among children and adults in the United States. Invasive pneumococcal disease (IPD) disproportionally affects the very young, the elderly, certain ethnic groups, and those with underlying conditions. Invasive pneumococcal disease occurs when *S. pneumoniae* invades normally sterile body sites such as blood, cerebrospinal, pleural or peritoneal cavities. The Advisory Committee on Immunization Practices (ACIP) has identified HIV infection as a disease that places individuals at especially increased risk for complications due to *S. pneumoniae* infection. Since the licensure of Prevnar 13 in adults in the United States, a single dose of pneumococcal conjugate vaccine (PnC) has been added to the recommendations for immunocompromised populations. The ACIP recommends that immunocompromised adults
aged ≥19 years, who have not previously received Prevnar 13 or the 23-valent pneumococcal polysaccharide vaccine (PPSV23) should receive a dose of Prevnar 13 first, followed by a dose of PPSV23 at least 8 weeks later.

Prior to the approval of Prevnar 13 for IPD and pneumonia in adults 18 years and older, the only other pneumococcal vaccine available for use in this age group was PPSV23.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

The product formulation used in the study of Prevnar 13 in HIV-infected subjects is identical to the formulation described in and approved with the original Prevnar 13 Biologics License Application (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

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

c) Facilities Review/inspection

There are no ongoing or impending investigations or compliance actions with respect to Wyeth’s facilities or products. 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

The two clinical studies submitted to this supplement were Study 6115A1-3002 and Study 6115A1-3017. Study 6115A1-3002 was an open-label, single-arm trial to evaluate the safety, tolerability, and immunogenicity of 1, 2, and 3 doses of Prevnar 13 in HIV-infected subjects ≥6 years of age that had not been previously immunized with a pneumococcal vaccine.
Primary objective for Study 6115A1-3002:
• To evaluate the immune responses 1 month after 3 doses of Prevnar 13 compared with the immune responses 1 month after 2 doses of Prevnar 13 as measured by serotype-specific immunoglobulin G (IgG) geometric mean fold rises (GMFRs) in subjects ≥6 years of age.

Secondary objectives for Study 6115A1-3002:
• To evaluate the immune response 1 month after 3 doses of Prevnar 13 compared with the immune responses 1 month after 2 doses of Prevnar 13, as measured by serotype-specific IgG geometric mean concentrations (GMCs), in subjects ≥6 years of age.
• To evaluate the immune responses 1 month after 3 doses of Prevnar 13 compared with the immune responses 1 month after 2 doses of Prevnar 13 as measured by serotype-specific OPA GMTs and fold rise OPA GMTs in subjects ≥6 years of age.
• To evaluate the immune responses 1 month after 3 doses of Prevnar 13 compared with the immune responses 1 month after 2 doses of Prevnar 13 as measured by serotype-specific IgG GMCs, IgG GMFRs, OPA GMTs, and OPA GMFRs in the pediatric subgroup (6 to <18 years of age), and in the adult subgroup (≥18 years of age).

Study 6115A1-3017 was an open-label, single-arm, descriptive study in which 3 doses of Prevnar 13 were administered 6 months apart to 330 HIV-infected adults with CD4 counts ≥ 200 cells/μL and serum HIV RNA titer < 50,000 copies/mL. For this study the review focused on data from adults ≥18 to <50 years of age, as the data for adults ≥ 50 years of age was previously reviewed under supplement STN 125324/950. All subjects in the study had been previously vaccinated with PPSV23 at least 6 months prior to enrollment.

Primary objective for Study 6115A1-3017:
• To evaluate the immune responses 1 month after 3 doses of Prevnar 13, given 6 months apart, compared to 1 month after 2 doses of Prevnar 13, given 6 months apart, as measured by the fold rise in serotypes-specific IgG GMCs in HIV-infected subjects who had previously been vaccinated with at least 1 dose of PPSV23.

Secondary objectives for Study 6115A1-3017:
• To evaluate the immune response 1 month after 3 doses of Prevnar 13 given 6 months apart, compared to 1 month after 2 doses of Prevnar 13, as measured by the serotype-specific IgG GMCs in HIV-infected subjects who had previously been vaccinated with at least 1 dose of PPSV23.
• Evaluate the immune response 1 month after 3 doses of Prevnar 13, given 6 months apart, compared to 1 month after 2 doses of Prevnar 13, as measured by serotype-specific opsonophagocytic assay (OPA) geometric mean titers (GMTs) and the fold rise in OPA GMTs in HIV-infected subjects who had previously been vaccinated with at least 1 dose of PPSV23.
• Evaluate the immune response 1 month after 2 doses of PCV13, given 6 months apart, compared to 1 month after 1 dose of Prevnar 13, as measured by the serotype-specific IgG GMCs and the fold rise in IgG GMCs in HIV-infected subjects who had previously been vaccinated with at least 1 dose of PPSV23.
• Evaluate the immune response 1 month after 2 doses of Prevnar 13, given 6 months apart, compared to 1 month after 1 dose of Prevnar 13, as measured by the serotype-specific OPA GMTs and the fold rise in OPA GMTs in HIV-infected subjects who had previously been vaccinated with at least 1 dose of PPSV23.

For both studies the subjects were followed for six months after the last dose of study vaccine. In both studies the post-vaccination point estimates and 95% confidence intervals for the OPA GMTs and IgG GMCs were comparable for each vaccine serotype one month following the first, second, and third dose of Prevnar 13. Similarly, although GMFRs post dose one were numerically higher, GMFRs after subsequent doses did not demonstrate an additional booster response. This indicates that a second or third dose did not result in substantially higher post-dose titers compared with one dose. In both studies, a measurable increase in OPA GMTs was demonstrated one month following one dose of Prevnar 13 compared to pre-vaccination titers for all serotypes contained in the vaccine (based on point estimate and 95% CI). The GMFR before and after dose one was greater than 2.0 for all serotypes (GMFR ranges 1.74 to 5.07 and 1.15 to 15.79 for studies 6115A1-3017 and 6115A1-3002, respectively). Immune responses to vaccination with Prevnar 13 may be lower in HIV infected adults than in healthy controls. The data provided from these studies support an update to the Prevnar 13 package insert related to HIV infected children and adults ≥ 6 years of age.

Clinical Serology Assays

The microcolony opsonophagocytic assays (mcOPAs) and the enzyme-linked immunosorbent assays (ELISAs) were both used in Study 6115A1-3002 and Study 6115A1-3017. The mcOPAs developed by Wyeth were used in both studies and other than serotype 3, were performed at Pfizer Pearl River, NY. The mcOPA validation reports were reviewed under supplement STN 125324/950. The ELISAs used in these studies are the ELISAs, which were first reviewed by CBER in the original Prevnar 13 application submitted on October 24, 2008 and supplement STN 125324/950. For the ELISAs for study 6115A1-3017 the validation tests were performed at Wyeth facilities. The assay performance was deemed adequate for the intended use in this supplement.

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, as this 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
Limited safety data are available on Prevnar 13 administered to HIV infected subjects greater than 6 years of age. For both study 6115A1-3017 and study 6115A1-3002, an e-dairy was used to collect data on solicited local and systemic adverse events for 14 days following the first dose of Prevnar 13. For the subjects (N=331) enrolled in study 6115A1-3017 the most common solicited local adverse reaction reported was injection site pain (84.7%), although these reactions were not severe. The most commonly reported solicited systemic adverse events (SAEs) reported in this age group were muscle pain (69.9%), headache (72.9%), fatigue (66.2%), diarrhea (44.0%), and joint pain (35.2%). Severe systemic reactions were uncommon (<5%). For unsolicited adverse events (AE), approximately 66% of subjects in the ≥ 18 to <50 year old age subset reported an unsolicited AE after any vaccine dose. The frequency and types of unsolicited AEs reported appeared to be consistent with the underlying diagnosis and age of the study population. Within 6 months after the first dose of Prevnar 13, 5.8% of subjects reported a nonfatal serious adverse event (SAE), none of which were considered related to vaccination. There were no deaths during this study.

For the subjects (N=303) enrolled in study 6115A1-3002 the most common solicited local adverse reaction reported was injection site pain (65.5%), although these reactions were not severe. The most commonly reported solicited systemic AEs reported in this age group were muscle pain (55.8%), fatigue (53.5%), headache (50.5%), and joint pain (38.5%). The most common severe reaction was fatigue (≤9.0%). Fever over 40°C, which was not vaccine related, was noted in 14/181 subjects and may have been due to background rates of infection in an HIV infected largely South African population, particularly since the collection window for events was 14 days. Within 6 months after the first dose of Prevnar 13, 4% of subjects reported a nonfatal SAE, none of which were considered related to vaccination. One subject died due to a traffic accident. No other deaths were reported.

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. Other Relevant Regulatory Issues

No additional relevant regulatory issues were identified during the review of this supplement.

10. 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.

11. Recommendations and Risk/Benefit Assessment

a) Recommended Regulatory Action
The Committee recommends approval of the Applicant’s BLA supplement, which contains data supporting a labeling change to describe the safety and immunogenicity of Prevnar 13 in HIV-infected subjects 6 years of age and older.

b) Risk/Benefit Assessment

The Prevnar 13 data submitted for both studies demonstrate that the vaccines were immunogenic in HIV infected individuals with CD4 counts ≥ 200 cells/μL and serum HIV RNA titer < 50,000 copies/mL. The risks associated with the use of Prevnar 13 in HIV infected children and adults were minimal based on the limited safety data provided in two small single-arm descriptive studies. The overall risk benefit of Prevnar 13 is favorable in the HIV population.

c) Recommendation for Postmarketing Risk Management Activities

No Postmarketing Risk Management Activities are recommended.

d) Recommendation for Postmarketing Activities

No new safety signals have been identified to date that would justify a new post-marketing requirement.

Based on a review of the submitted clinical data, the review committee concurs with continued routine safety surveillance for Prevnar 13, i.e., monitoring for any unanticipated risks in ongoing clinical trials, surveillance systems of various countries, and post-marketing adverse reaction reports.