

Summary Basis for Regulatory Action

Date: July 11, 2016

From: Christina Houck, Review Committee Chair

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

BLA/ STN#: 125324/1358

Applicant Name: Wyeth Pharmaceuticals, Inc.

Date of Submission: September 11, 2015

PDUFA Goal Date: July 11, 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 a Prevnar 13 clinical study to include adults 18 through 49 years of age.

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.

Material Reviewed/ Consulted	Specific documentation used in developing the SBRA
Reviewer Name – Document(s)	Date
Clinical Review	Gueorgui Dubrocq, M.D. 7/11/2016
Statistical Review	Lihan Yan, Ph.D. 4/18/2016
Serological Immune Response Assay Review Serological Immune Response	Mustafa Akkoyunlu, M.D., Ph.D. 6/1/2016

Assay Review	Freyja Lynn	6/1/2016
Pharmacovigilance Review	Marthe G. Bryant-Genevier, M.D., MPH, MHS	6/17/2016
Prescribing Information	Loan Nguyen	4/12/2016
Regulatory Project Manager	Katie River, M.S.	

1. Introduction

Pprevnar 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 Pprevnar (4, 6B, 9V, 14, 18C, 19F and 23F). On January 25, 2013, Pprevnar 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. On January 1, 2012, Pprevnar 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]. 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 was informed that they had fulfilled this post-marketing requirement and on May 22, 2015 Pprevnar 13 was approved for the prevention of IPD and pneumonia in adults over 50.

In this submission, the Applicant proposes to update the Pprevnar 13 package insert with safety and immunogenicity data from a Pprevnar 13 clinical study in adults 18 through 49 years of age.

2. Background

Streptococcus pneumoniae (*S. pneumoniae*) causes serious illness, including bacteremia, meningitis and pneumonia among adults in the United States. Invasive pneumococcal disease (IPD) disproportionately 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) recognizes several groups at increased risk for pneumococcal disease. The risk for IPD is greatest among adults who have congenital or acquired immunodeficiency, abnormal immune response, or functional or anatomic asplenia. Since the introduction of Pprevnar 13 among children in the U.S., there has been a significant reduction of pneumococcal disease in children and interestingly in elderly

even before licensure of the vaccine in that age group. Adults 18 through 49 years of age, especially subjects with an underlying medical condition are at an increased risk of IPD.

Prior to the approval of Prevnar 13 for IPD and pneumonia in adults 50 years and older, the only other pneumococcal vaccine available for use in this age group was the 23-valent pneumococcal polysaccharide vaccine (PPSV23) which contains 23 serotype polysaccharides.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

The product formulation used in the study of Prevnar 13 in adults 18 through 49 years of age is identical to the formulation described and approved within 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 clinical study submitted to this supplement, Study 6115A1-004, was a randomized, active-controlled, modified double blind trial designed to compare the immunogenicity, tolerability, and safety of Prevnar13 between adults 18 to 49 years of age (cohort 3) and 60 to 64 years old (cohort 1) who were naïve to 23vPS. The primary objective of the study was to demonstrate that the immune response to the 13 serotypes in Prevnar 13 in the 18 to 49 year old age group was non-inferior to the immune response to Prevnar 13 in the 60 to 64 year old group as

measured by serotype-specific opsonophagocytic assay (OPA) titers 1 month after vaccination. The study's secondary objectives were to demonstrate that the proportion of subjects achieving an OPA titer \geq lower limit of quantitation (LLOQ) in cohort 3 is non-inferior to cohort 1, measured one month after vaccination; to evaluate the immune responses 1 month after vaccination with Prevnar 13 in cohort 3 and 1, as measured by serotype-specific fold rise OPA geometric mean titers (GMTs); and to evaluate the immune responses 1 month after vaccination with Prevnar 13 between each subgroup (18 to 29, 30 to 39 and 40 to 49 year old age groups) and cohort 1 as measured by serotype-specific fold rise OPA GMTs.

The study results indicated that the primary endpoints were met. For each of the 13 serotypes in Prevnar 13, the primary analysis compared the serotype-specific OPA GMTs measured 1 month after vaccination in cohort 3 (18 through 49 year-old age group) with those in subjects vaccinated with Prevnar 13 in cohort 1. The lower limit of the two-sided, 95% CI for the ratio of GMTs (GMT for cohort 3/GMT for cohort 1) was greater than 0.5 (2-fold criterion) for each of the 13 serotypes, indicating that non-inferiority criteria were met. The serotype-specific ratios of GMTs ranged from 1.0 for serotype 3 to 4.9 for serotypes 6B and 14. Non-inferiority criteria of subjects in cohort 3 and cohort 1 achieving an OPA titer \geq LLOQ after 1 month of vaccination was met for all 13 serotypes as the lower bound of the 95% CI of the difference was above -10%. For the analysis of the secondary endpoints, which included the three age subgroups of cohort 3, the immune response was non-inferior to that for cohort 1 for all 13 serotypes. There was a trend of decreasing magnitude of the immune responses as the subject's age increased. The data provided from this study supports an update to the Prevnar 13 package insert related to the immunogenicity of Prevnar 13 in adults 18 through 49 years of age.

Bioresearch Monitoring Review

Bioresearch monitoring site inspections were performed for four clinical sites. The inspections of these sites did not reveal significant problems that impact data submitted to this sBLA.

Clinical Serology Assays

The microcolony opsonophagocytic assay (mcOPA) and the enzyme-linked immunosorbent assay (ELISA) were both used in Study 6115A1-004 and were performed at Pfizer Vaccine Research & Early Development – High Throughput Clinical Testing Laboratory, Pearl River, NY. The mcOPA developed by Wyeth was used in this study to generate the data to support the clinical endpoints in the study. The ELISA used in this study is the [REDACTED] ELISA, which was first reviewed by CBER in the original Prevnar 13® application submitted on October 24, 2008, as well as part of subsequent supplements. The validation data for both assays were previously reviewed under the original BLA STN 125324/0, supplement STN 125324/262 to include adults 50 years of age and older and supplement STN 125324/933 titled 'Efficacy Evaluation of Prevnar 13® in Sickle Cell Disease patients'. The data were deemed adequate for their 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

An acceptable safety profile was demonstrated for the administration of Prevnar 13 to subjects 18 through 49 years old. For the subjects enrolled (N=899), an e-diary was used to collect data on solicited local and systemic adverse events for 14 days post vaccination. For solicited local reactions, the most common for Cohort 3 was injection site pain, followed by limitation of arm movement, and swelling. Nearly all subjects (96%) experienced injection site pain. Severe redness and severe swelling (>10cm in diameter) were each reported in 1-3% of subjects in Cohort 3. 15.6% of subjects in cohort 3 experienced severe limitation of arm movement from the injection. The mean duration of local reactions for cohort 3 ranged from 1 to 2 days. For solicited systemic adverse events, new generalized muscle pain followed by headaches and fatigue were the most common for cohort 3. The mean duration of systemic adverse events for subjects in cohort 3 ranged from 2-4 days. Unsolicited adverse events (AEs) were reported 1 month post-vaccination for 14.3% of subjects in Cohort 3. The most frequently reported individual AEs were nausea (12 subjects, 1.3%), upper respiratory tract infection (11 subjects, 1.2%), nasopharyngitis (7 subjects, 0.8%), and diarrhea (6 subjects, 0.7%). Nonfatal serious adverse events (SAEs) occurring within approximately 1 month after vaccination with Prevnar 13 were reported for 2 subjects (0.2%) in Cohort 3. One subject experienced migraines and the other basal cell carcinoma. SAEs occurring 1 to 6 months post-vaccination were reported for 2 subjects (0.2%) in cohort 3. One subject experienced a hip fracture and the other an ovarian cyst rupture. None of the SAEs reported during the study were considered to be related to the study vaccine, except for the SAE of migraine reported by one subject within one month of vaccination. No subjects died during this study and there were no life threatening AEs at 1 month post vaccination and at the 6 month follow up.

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 safety and effectiveness of Prevnar 13 in adults 18 through 49 years of age.

b) Risk/Benefit Assessment

The Prevnar 13 immunogenicity data suggest that one dose of Prevnar 13 in adults 18 through 49 years of age induces OPA titer one month post-vaccination that is non-inferior to that in individuals 60-64 years old in whom vaccine efficacy was previously demonstrated. The risks associated with use of Prevnar 13 in the study population appeared to be acceptable.

c) Recommendation for Postmarketing Risk Management Activities

No Postmarketing Risk Management Activities are recommended.

d) Recommendation for Postmarketing Activities

The updated version 6.0 of the Pharmacovigilance Plan (PVP) included data from Study 6115A1-004 comprised of subjects age 18 through 49 years of age, who received open-labeled Prevnar 13. No new safety signals have been identified to date that would justify a post-marketing requirement

Based on a review of the submitted clinical data and the proposed PVP, 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.