

## Summary Basis for Regulatory Action

**Date:** January 9, 2015

**From:** Kelsy Hoffman, Ph.D., Review Committee Chair

**Through:** Paul G. Richman, Ph.D., Chief, CMC Branch 1

**BLA/ STN#:** 125324/1174

**Applicant Name:** Wyeth Pharmaceuticals, Inc.

**Date of Submission:** March 12, 2014

**PDUFA Goal Date:** January 10, 2015

**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 (PCV13) clinical study to assess the effect of prophylactic antipyretic medication on the immunogenicity of PCV13 in healthy infants.

**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	Lucia Lee, M.D.	1/9/2015
Statistical Review	Lihan Yan, Ph.D.	11/12/2014
Statistical Review	Tielin Qin, Ph.D.	11/12/2014
Prescribing Information	Michael Brony	6/25/2014
Regulatory Project Manager	Katie Rivers, M.S.	

## **1. Introduction**

Prevnar 13, a pneumococcal conjugate vaccine (PCV13), 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).

In this submission, the Applicant proposes to update the PCV13 package insert with safety and immunogenicity data from a PCV13 clinical study to assess the impact of prophylactic antipyretic medication on the immunogenicity of 13-valent Pneumococcal Conjugate Vaccine when given with a routine pediatric vaccine in healthy infants.

## **2. Background**

Antipyretic medication has been administered to children prophylactically or as a treatment for local and systemic reactions following vaccination. Fever after vaccination is generally self-limiting, but is frequently a concern for parents and health-care professionals.

Reduced pneumococcal antibody responses have been observed in clinical studies in which infants were immunized with a 10-valent pneumococcal conjugate vaccine (PCV) and received antipyretics prophylactically.

## **3. Chemistry Manufacturing and Controls (CMC)**

### **a) Product Quality**

The product formulation used in the study of PCV13 in healthy infants administered with prophylactic antipyretics is identical to the formulation described in and approved with the original PCV13 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.

Of note, the lot used in the study to support this supplement (i.e., lot number ---(b)(4)---) was not released by CBER.

### **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 applicant submitted data from a Phase 4, randomized, open-label study (B1851047 or 6096A1-4027-PL) to assess the impact of prophylactic antipyretic medication, namely, paracetamol (acetaminophen) or ibuprofen, on the immunogenicity and safety of PCV13 when given with a routine vaccine to healthy infants. This study was conducted per request by the European Medicines Agency. The study was conducted in Poland from August 5, 2011 to January 16, 2013. The primary objective was to assess the immunogenicity of PCV13 following administration of prophylactic acetaminophen (paracetamol) or ibuprofen after the third PCV13 dose, as measured by geometric mean concentration (GMCs) to each vaccine serotype. The proportion of participants with serotype-specific IgG concentrations  $\geq 0.35 \mu\text{g}/\text{mL}$  and opsonophagocytic activity (OPA) evaluations after the third PCV13 dose and GMCs after the fourth PCV13 dose were included as secondary objectives. All subjects received PCV13 and INFANRIX hexa at approximately 2, 3, 4 (infant series), and 12 months (toddler dose) of age. Subjects were randomized to one of the following treatment regimens on the day of vaccination: two doses of paracetamol (Group 1), two doses of ibuprofen (Group 2), three doses of paracetamol (Group 3), three doses of ibuprofen (Group 4), or none (Group 5). Antipyretic medication (other than the regimen described above), given during the four day post-vaccination period for reasons such as treatment of fever or other symptoms, were recorded as a non-study medication.

A significant proportion of subjects, including Group 5 (control group), received non-study antipyretic medications (33% for the infant series and 45% for the toddler dose) during the post-vaccination period, and therefore, were excluded from per-protocol population. However, the following observations could be made from analyses based on the modified intent-to-treat (mITT) population, which included participants who received non-study medications:

- Among participants who received three doses of acetaminophen, trends toward reduced antibody responses to serotypes 3, 4, 5, 6B, and 23F were observed following the third dose of PCV13, compared with responses among infants who received antipyretics only as needed for treatment. The lower bounds of the 95% CIs for the GMC ratios for all serotypes were above 0.5, a criterion often used for non-inferiority comparisons of

GMC. The proportions of subjects with an IgG concentration of  $\geq 0.35 \mu\text{g/mL}$  were also lower in subjects receiving paracetamol compared to the control group. The interpretation of the OPA data was limited, because the number of subjects available in the subset population was small.

- Reduced pneumococcal antibody responses were not observed after the fourth dose of PCV13 when acetaminophen was administered prophylactically.
- No reduction in IgG antibody responses to vaccine serotypes were observed with prophylactic administration of ibuprofen.

The safety evaluation was based on assessments of fever (solicited adverse events (AE)) and unsolicited AEs. The percentage of participants who received antipyretic medications only as specified in the protocol was limited (for reasons described above). For PCV13 doses administered during infancy, the frequencies of fever reported on the day of vaccination were significantly reduced among participants who received three doses of acetaminophen prophylactically, with the first dose administered at the time of (just prior to) vaccination, compared to participants who received antipyretic medication only as needed for fever or other symptoms. Although the pathophysiology of fever in the first and second years of life does not differ, no distinct changes in the reported fever rates could be attributed to antipyretics administered prophylactically with the fourth PCV13 dose given at 12 months of age. The AEs reported in this study were consistent with the AEs commonly observed in infants and toddlers. No febrile seizures were noted in any of the study participants. No deaths occurred during the study. No new safety concerns were identified from review of the data contained in the study report.

In conclusion, the data suggest that acetaminophen used prophylactically, but not for treatment of fever in infants, may result in reduced antibody responses to certain vaccine serotypes following PCV13 immunization. No reduction in pneumococcal IgG antibody responses to vaccine serotypes were observed with prophylactic administration of ibuprofen. The adverse events were consistent with the expected safety profile of PCV13 in the population studied.

## **b) Pediatrics**

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**

The safety profile of PCV13 was evaluated based on the incidence of fever and on the incidence of AEs. The majority of reported fever was mild ( $\geq 38^\circ\text{C}$  but  $\leq 39^\circ\text{C}$ ) and no subjects reported a fever  $>40^\circ\text{C}$  in any group at any dose. Among controls, fever rates in the four days after each of the infant series vaccinations were approximately 30% to 40%, which is within the ranges of expected rates for PCV13 administered at 2, 3, 4 and 12 months of age. There were no deaths during the study. There were few severe AEs, SAEs, or related AEs reported, and the incidences were generally similar among the five antipyretic regimen groups during the infant series, after the infant series, and at the toddler dose. No SAEs were

considered by the investigator to be related to vaccine. In general, no new safety signals were observed during the course of this study. Fever was consistent with previous experience, generally mild, and of short duration, and no subjects reported a fever  $\geq 40^{\circ}\text{C}$  in any group at any dose.

## **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 immunogenicity of PCV13 in healthy infants administered prophylactic antipyretics.

### **b) Risk/Benefit Assessment**

The PCV13 immunogenicity data suggest that acetaminophen used prophylactically, but not for treatment of fever, in infants, may result in reduced antibody responses to certain vaccine serotypes following PCV13 immunization. Ibuprofen is an effective antipyretic, but has adverse drug reactions that include thrombocytopenia. In medical practice, administration of three doses of antipyretic medication for all vaccinations in the 4-dose series is an uncommon scenario.

The adverse events reported in infants and toddlers, who received antipyretic medications, were consistent with the expected safety profile of PCV13 in the population studied.

### **c) Recommendation for Postmarketing Risk Management Activities**

No Postmarketing Risk Management Activities are recommended.

### **d) Recommendation for Postmarketing Activities**

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

Based on a review of the submitted clinical data, the Committee concurs with continued routine safety surveillance for PCV13, i.e., monitoring for any unanticipated risks in ongoing clinical trials, surveillance systems of various countries, and post-marketing adverse reaction reports.