

Summary Basis for Regulatory Action

Date: October 25, 2011

From: Rosemary Tiernan, MD, MPH
Chair of the Review Committee

BLA/STN#: 101094.5324

Applicant Name: Merck Sharp & Dohme Corporation

Date of Submission: March 5, 2009

PDUFA Goal Date: October 27, 2011

Proprietary Name: PNEUMOVAX®23

Established Name: Pneumococcal Vaccine Polyvalent

Application Type: Efficacy Supplement

Reason for Submission: To add information to the label regarding concomitant administration of PNEUMOVAX®23 with ZOSTAVAX®.

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority: Wellington Sun, MD
Director, Division of Vaccines and Related Product Applications/Office of Vaccines Research and Review/CBER/FDA

- 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.

STN 101094.5324	
Clinical Review	Rosemary Tiernan, MD, MPH
Statistical Review	Ghideon Ghebregiorgis , PhD
Statistical Review	Lev Sirota, PhD
Bioassay Review	Margaret Bash, MD, MPH
Biomonitoring Review	Janet White, PhD
Regulatory Project Manager	Holly Wieland, RN, MPH

1. Introduction

This efficacy supplement included data from a concomitant vaccine administration study utilizing two FDA approved vaccines, ZOSTAVAX and PNEUMOVAX23. In addition, the PNEUMOVAX 23 label was revised to comply with the Physician Labeling Rule (PLR) (21 CFR 201.56 and 21 CFR 201.57).

This study did not confirm its pre-specified primary hypothesis that the concomitant administration of PNEUMOVAX 23 and ZOSTAVAX vaccines would result in similar (non-inferior) immune response as compared to the administration of PNEUMOVAX 23 and ZOSTAVAX individually. Interference with the immune response to ZOSTAVAX was demonstrated using a geometric mean titer (GMT) immunogenicity endpoint with a validated varicella zoster virus (VZV) gpELISA assay. The information regarding immune response interference with concomitant administration of PNEUMOVAX23 and ZOSTAVAX was added to the ZOSTAVAX Package insert (PI) and Patient Package Insert (PPI) with approval of STN 125123.430 on December 18, 2009.

To assess antibody response induced by PNEUMOVAX23, serotypes (3, 14, 19A, 22F) that are included in the PNEUMOVAX23 vaccine, were selected by the Applicant to serve as a representative assessment of the immune response to the vaccine. The Applicant states these 4 serotypes were chosen from an epidemiological perspective as they are some of the most common serotypes causing invasive pneumococcal disease in adults in the Australia, Europe and the U.S., and because they include a broad array of structural characteristics associated with the pneumococcal polysaccharides, which are important components of polysaccharide immunogenicity. The GMTs of the specific pneumococcal polysaccharide antibody responses for four of the twenty three serotypes, 3, 14, 19A, and 23F, at 4 weeks post-vaccination in subjects who received ZOSTAVAX concomitantly with PNEUMOVAX 23 were similar to those in subjects who received ZOSTAVAX and PNEUMOVAX 23 given one month apart.

The immune response to the other 19 pneumococcal serotypes were not evaluated in this concomitant administration study of ZOSTAVAX and PNEUMOVAX 23.

The following information regarding concomitant vaccination will now be added to the PNEUMOVAX 23 U.S. package insert (PI) in Physician's Labeling Rule (PLR) format:

In a randomized clinical study, a reduced immune response to ZOSTAVAX as measured by gpELISA was observed in individuals who received concurrent administration of PNEUMOVAX 23 and ZOSTAVAX compared with individuals who received these vaccines 4 weeks apart. Consider administration of the two vaccines separated by at least 4 weeks.

2. Background

This summary will focus on serological assay, statistical and clinical review issues. There were no new chemistry and manufacturing or non-clinical pharmacology toxicology issues relevant to this application.

3. Chemistry, Manufacturing and Controls (CMC)

No data concerning product quality, facilities review/inspection or environmental assessment were provided by the applicant or reviewed in support of this supplement. Approval of this supplement is not dependent on any lot release testing.

4. Nonclinical Pharmacology/Toxicology

Not applicable; two U.S.-licensed vaccines were used in the clinical study.

5. Clinical Pharmacology

This study demonstrated interference with the immune response to ZOSTAVAX when PNEUMOVAX 23 and ZOSTAVAX were administered concomitantly (see Clinical and Statistical section below). Although the study did not demonstrate interference of ZOSTAVAX with the immune response to PNEUMOVAX 23 when these two vaccines were administered concomitantly; the immunologic assessment was limited to 4 of 23 pneumococcal serotypes contained in PNEUMOVAX 23.

The immune responses measured in this study were similar across genders. Caucasian subjects were predominantly enrolled in this study and thus no analyses were performed based on race. Subjects were >60 years of age with a median age of 64 years in each treatment arm.

6. Clinical/ Statistical

In 2007, Merck conducted a clinical trial in 471 adults entitled: "A Phase III Double-Blind, Randomized Multicenter Study to Evaluate the Safety, Tolerability, and Immunogenicity of ZOSTAVAX Administered Concomitantly Versus Non-concomitantly with PNEUMOVAX 23 in Subjects 60 Years of Age and Older" in Canada, Australia and Europe.

The study design included the following treatment arms:

ZOSTAVAX administered concomitantly with PNEUMOVAX 23
or
PNEUMOVAX 23 followed by ZOSTAVAX 4 weeks later.

The information submitted supported the use of the ELISA assays for the four serotypes tested in this study for the limited purpose of comparing the anti-

polysaccharide antibody responses to 4 of 23 serotypes of PNEUMOVAX 23 when administered concomitantly with ZOSTAVAX versus when administered separately.

The Applicant stated that these 4 pneumococcal serotypes (3, 14, 19A, 22F) were chosen to serve as a representative assessment of the immune response to PNEUMOVAX23 from an epidemiological perspective as they are some of the most common serotypes causing invasive pneumococcal disease in adults in Australia, Europe and the U.S., and because they include a broad array of structural characteristics associated with the pneumococcal polysaccharides which are important components of polysaccharide immunogenicity. One of the primary hypotheses of the study was that the GMTs of the serotype- specific pneumococcal polysaccharide antibody responses to serotypes 3, 14, 19A, and 22F at 4 weeks post-vaccination in subjects who receive ZOSTAVAX concomitantly with PNEUMOVAX 23 will be non-inferior to those in subjects who receive ZOSTAVAX and PNEUMOVAX23 non-concomitantly. The statistical criteria correspond to the lower bound of the two-sided 95% confidence interval (CI) on the GMT ratio [concomitant/ non-concomitant] being >0.5, thus ruling out a 2 fold decrease or more between the study arms for each of the four pneumococcal serotypes. Since the lower bounds of the 2-sided 95% CIs were > 0.5 for all the four serotypes and the 1-sided p-values for the testing of these non-inferiority hypotheses were ≤ 0.025 for all 4 serotypes, the findings (see tables below from the Applicant's submission) provide evidence that the 4 serotype-specific pneumococcal polysaccharide antibody responses induced by PNEUMOVAX 23 vaccine when given concomitantly with ZOSTAVAX, were similar (non-inferior) to those induced by PNEUMOVAX 23 vaccine when administered non-concomitantly.

Statistical Analysis (Non-inferiority) of Pneumococcal Polysaccharide Serotype Antibody Responses at Week 4 Post-vaccination with PNEUMOVAX 23 (Per-Protocol Population)

Serotype 3

Endpoint	Concomitant Group (N=235) (n, Estimated GMT)	Non-concomitant Group (N=236) (n, Estimated GMT)	Estimated GMT Ratio (95% CI)	p-Value	Conclusion
GMT	234, 1.1	235, 1.2	0.91 (0.80, 1.03)	<0.001	Similar

Serotype 14

Endpoint	Concomitant Group (N=235) (n, Estimated GMT)	Non-concomitant Group (N=236) (n, Estimated GMT)	Estimated GMT Ratio (95% CI)	p-Value	Conclusion
GMT	234, 25.3	235, 26.9	0.94 (0.77, 1.14)	<0.001	Similar

Serotype 19A

Endpoint	Concomitant Group (N=235) (n, Estimated GMT)	Non-concomitant Group (N=236) (n, Estimated GMT)	Estimated GMT Ratio (95% CI)	p-Value	Conclusion
GMT	234, 10.8	235, 10.5	1.03 (0.83, 1.26)	<0.001	Similar

Serotype 22F

Endpoint	Concomitant Group (N=235) (n, Estimated GMT)	Non-concomitant Group (N=236) (n, Estimated GMT)	Estimated GMT Ratio (95% CI)	p-Value	Conclusion
GMT	234, 2.4	235, 2.9	0.82 (0.66, 1.01)	<0.001	Similar

Based on the observed interference of the immunogenicity endpoint data for ZOSTAVAX provided within BLA 125123 amendment 430 and because of the incomplete information regarding antibody responses for 19 of the 23 pneumococcal serotypes, the review team recommends that the PNEUMOVAX 23 label also be revised to indicate that health care providers should consider administering ZOSTAVAX and PNEUMOVAX 23 separated by at least 4 weeks (28 days).

7. Safety

In this study, no new safety concerns were identified.

8. Advisory Committee Meeting

There were no issues in this supplement that required input from an Advisory Committee.

9. Other Relevant Regulatory Issues

This study contained in this sBLA was neither a post-marketing commitment nor a requirement. The timing of the submission of this efficacy supplement coincided with implementation of the PLR; therefore, the sponsor was advised that the labeling should be revised and submitted in PLR format. There were no additional relevant regulatory issues.

10. Labeling

Label revisions for PNEUMOVAX23 will include the following (new language is bolded):

In the HIGHLIGHTS OF PRESCRIBING INFORMATION:
DRUG INTERACTIONS

In a randomized clinical study, a reduced immune response to ZOSTAVAX as measured by gpELISA was observed in individuals who received concurrent administration of PNEUMOVAX 23 and ZOSTAVAX compared with individuals who received these vaccines 4 weeks apart. Consider administration of the two vaccines separated by at least 4 weeks (7.1, 14.3)

In Section 7 of DRUG INTERACTIONS:

7.1 Concomitant Administration with Other Vaccines

In a randomized clinical study, a reduced immune response to ZOSTAVAX as measured by gpELISA was observed in individuals who received concurrent administration of PNEUMOVAX 23 and ZOSTAVAX compared with individuals who received these vaccines 4 weeks apart. Consider administration of the two vaccines separated by at least 4 weeks (7.1, 14.3).

In section 14 Clinical Studies:

In a double-blind, controlled clinical trial, 473 adults, 60 years of age or older, were randomized to receive ZOSTAVAX and PNEUMOVAX23 concomitantly (N= 237), or PNEUMOVAX 23 alone followed 4 weeks later by ZOSTAVAX alone (N= 236). At four weeks postvaccination, the varicella zoster (VZV) antibody levels following concomitant use were significantly lower than the VZV antibody levels following nonconcomitant administration (GMTs of 338 vs. 484 gpELISA units/ mL, respectively; GMT ratio = 0.70 (95% CI: [0.61, 0.80]).

PNEUMOVAX23 will now have a Patient Package Insert which will include the following language regarding concomitant administration:

Can I get PNEUMOVAX23 with other vaccines?

Talk to your health care provider if you plan to get PNEUMOVAX23 at the same time as ZOSTAVAX because it may be better to get these vaccines at least 4 weeks apart.

11. Recommendations and Risk/ Benefit Assessment

Recommend: Approval of this supplement.

All members of the review team agreed to add this language to the PNEUMOVAX23 label:

In a randomized clinical study, a reduced immune response to ZOSTAVAX as measured by gpELISA was observed in individuals who received concurrent administration of PNEUMOVAX23 and ZOSTAVAX compared with individuals who received these vaccines 4 weeks apart. Consider administration of the two vaccines separated by at least 4 weeks (7.1, 14.3).

