

Summary Basis for Regulatory Action

Date: December 1, 2011

From: LCDR Mike Smith, Chair of the Review Committee

BLA/ STN: 125089/424

Applicant Name: Sanofi Pasteur Inc.

Date of Submission: January 31, 2011

Proprietary Name/Established Name: Menactra[®]/Meningococcal (Groups A, C, Y, & W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine

Indication: Menactra is indicated for active immunization to prevent invasive meningococcal disease caused by *N meningitidis* serogroups A, C, Y and W-135. Menactra is approved for use in individuals 9 months through 55 years of age.

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: Wellington Sun, M.D., Director, DVRPA

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.

Specific Documentation used in Developing the SBRA	Reviewer Name – Document Date
Clinical (Labeling) Review	Lucia Lee, M.D., 11/30/2011
Epidemiology Review	Manette Niu, M.D., 10/17/2011
Lot Release Clearance	Jacqueline Glen, 11/3/11
Labeling Reviews	Pete Arambula, J.D., 9/29/2011 Mike Smith, Ph.D., 11/30/2011

1. INTRODUCTION

On January 31, 2011, Sanofi Pasteur Inc. (US License 1725) submitted a supplement to their Biological License Application (BLA) for Menactra[®] to update the package insert with results from a retrospective study to assess the risk of Guillain-Barre Syndrome (GBS) following administration of Menactra.

2. BACKGROUND

Menactra[®] is a tetravalent meningococcal (Group A, C, Y, W-135) polysaccharide Diphtheria toxoid conjugate vaccine manufactured by Sanofi Pasteur Inc. Menactra is indicated for active immunization of individuals, 9 months through 55 years of age, to prevent invasive disease caused by *Neisseria meningitidis* vaccine serogroups A, C, Y, & W-135.

Menactra was licensed in January 2005 and shortly thereafter the Advisory Committee for Immunization Practices recommended the vaccine for routine adolescent use. From March 2005 to September 2006, 17 cases of GBS were reported to the Vaccine Adverse Event Reporting System within six weeks after vaccination of adolescents/young adults with Menactra.

The sponsor is seeking to revise the GBS statement in the warnings and precautions and post-marketing experience sections of the package insert based on a recent retrospective cohort study of the relationship between Menactra[®] and GBS in adolescents, titled “Risk of Guillain-Barre Syndrome following Meningococcal Conjugate (MCV4) Vaccination.”

The study is a multi-site retrospective cohort study that evaluated the relationship between immunization with Menactra[®] and GBS in adolescents over the period of March 1, 2005 to August 31, 2008. Identification of potential GBS cases was based on first time ICD-9 code 357.0 during an inpatient/outpatient service visit within the study period. Validation was done by medical chart abstraction, and determined by a panel of neurologists using a clinical case definition from the Brighton Collaboration.

3. CHEMISTRY, MANUFACTURING, AND CONTROL INFORMATION

No Chemistry, Manufacturing, and Control Information was provided in the supplement.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

No nonclinical pharmacology/toxicology data were provided in the supplement.

5. CLINICAL PHARMACOLOGY

No clinical pharmacology data were provided in the supplement.

6. CLINICAL/STATISTICAL

The supplement contained a revised final study report for a recent retrospective cohort study, titled “Risk of Guillain-Barre Syndrome following Meningococcal Conjugate (MCV4) Vaccination,” which was reviewed by the epidemiology reviewer, Dr. Manette Niu. Additionally, Dr. Niu reviewed the May 26, 2011, amendment in response to CBER’s request for more information about the 129/429 (30%) individuals whose medical records were unavailable or had insufficient information for classification as well as any updates to the sensitivity analysis for the primary analysis.

The sponsor was seeking to revise the GBS statement in the warnings and precautions and post-marketing experience sections of the package insert based on this retrospective cohort study, which is described below:

Study Design:

Briefly, the study was conducted from March 2005 to August 2008. The risk of GBS following receipt of Menactra vaccine was evaluated in a US retrospective cohort study using healthcare claims data from 9,578,688 individuals 11 through 18 years of age, of whom 1,431,906 (15%) received Menactra. The incidence rate of GBS was 0.45 (0.24, 0.75) per 100,000 among individuals in the primary study population, who had received Menactra (MenACWY-D) at any time prior to the onset of GBS symptoms, compared with 0.55 (0.41, 0.69) per 100,000 among those who had never received MenACWY-D. Of 72 medical chart-confirmed GBS cases, none had received Menactra vaccine within 42 days prior to symptom onset. Of 18 potential cases of GBS, 9 cases could not be confirmed or excluded due to absent or insufficient medical chart information. A sensitivity analysis, using the “rule of three” was performed by the sponsor to estimate the upper 95% confidence limit of the attributable risk estimate. Accordingly, imputation of 1 or 2 missing cases would result in 2.4 and 3.9 excess cases per million doses, respectively. The full range of possible cases was evaluated in a CBER-generated sensitivity analysis. Imputation of the maximum number of cases (n=9) resulted in an attributable risk of 10.6 excess cases per million doses; however, since the observed case confirmation rate was consistent with experiences with similar healthcare databases, CBER concluded that an excess of 4.9 cases of GBS per million doses was likely a more reasonable estimate.

7. SAFETY

No additional safety data were provided in the supplement.

8. ADVISORY COMMITTEE MEETING

This supplement did not go before the Vaccines and Related Biological Products Advisory Committee (VRBPAC).

9. OTHER RELEVANT REGULATORY ISSUES

There are no other relevant regulatory issues of note.

10. LABELING

After numerous labeling negotiations, the revisions to the package insert were reviewed by Dr. Lucia Lee and other review committee members were consulted as necessary. The acceptable package insert was revised to update the Guillain-Barre Syndrome (GBS) statements in the Warnings and Precautions sections and Post-Marketing Experience sections. Itemized below are four of the more important revisions to the package insert.

- a. The statement “Known history of Guillain Barre Syndrome” was deleted from the contraindications sections in both the Highlights and the Full Prescribing Information.
- b. The Warnings and Precautions section in both the Highlights and the Full Prescribing Information was revised to include the following language: “Persons previously diagnosed with Guillain-Barré syndrome (GBS) may be at increased risk of GBS following receipt of Menactra vaccine. The decision to give Menactra vaccine should take into account the potential benefits and risks.”
- c. The Warnings and Precautions section of the Full Prescribing Information was revised to include the following language: “GBS has been reported in temporal relationship following administration of Menactra vaccine. (1) (2) The risk of GBS following Menactra vaccination was evaluated in a post-marketing retrospective cohort study [*Post-Marketing Experience* (6.2)].
- d. A recommendation was made with input from the Office of Epidemiology and DVRPA clinical reviewers to add the paragraph below to describe the post-marketing safety study information:

Post-marketing Safety Study

The risk of GBS following receipt of Menactra vaccine was evaluated in a US retrospective cohort study using healthcare claims data from 9,578,688 individuals 11 through 18 years of age, of whom 1,431,906 (15%) received Menactra vaccine. Of 72 medical chart-confirmed GBS cases, none had received Menactra vaccine within 42 days prior to symptom onset. An additional 129 potential cases of GBS could not be confirmed or excluded due to absent or insufficient medical chart information. In an analysis that took into account the missing data, estimates of the attributable risk of GBS ranged from 0 to 5 additional cases of GBS per 1,000,000 vaccinees within the 6 week period following vaccination.

OVRP received from the APLB reviewer numerous comments/recommendations for revisions to the package insert, which were considered by the clinical/labeling reviewer, Dr. Lucia Lee. Several of these comments were addressed in the revised labeling and/or discussed in Dr. Lee’s review.

11. RECOMMENDATIONS AND RISK/BENEFIT ASSESSMENT

There were no post-marketing commitments related to the approval of this supplement.

The committee recommends approval of this sBLA.