Summary Basis for Regulatory Action

Date: April 14, 2016

From: CDR Mike Smith, Ph.D., Chair of the Review Committee

BLA/STN#: 125549/17

Applicant Name: Wyeth Pharmaceuticals, Inc.

Date of Submission: March 27, 2015

PDUFA Goal Date: April 25, 2016

Proprietary Name/Established Name: Trumenba®/Meningococcal Group B Vaccine

Indication: Trumenba® is indicated for active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroup B. Trumenba is approved for use in individuals 10 through 25 years of age.

Reason for the Submission: Initially to include a change in the dosing regimen from a three-dose series administered according to a 0, 2 and 6 month schedule to a two-dose series, with the doses administered at least 1 month apart, followed by an optional booster (3rd) dose that may be administered at least four months after the second dose. Subsequently during the review cycle the Applicant requested the addition of a two-dosing regimen administered according to a 0 and 6 month schedule.

Recommended Action:
We recommend approval of Wyeth's supplement to their biologics license application (sBLA) for Meningococcal Group B Vaccine (Trumenba) to include a two-dose schedule (a dose administered at 0 and 6 months) according to the regulations for accelerated approval, 21 CFR 601.40-46. We also recommend approval of a modification of the three-dose schedule (approved under the original BLA according to the regulations for accelerated approval) from administration at 0, 2, and 6 months to administration at 0, 1-2, and 6 months.

Signatory Authority's Action: Approval

Office's Signatory Authority: Wellington Sun, M.D., Director, Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research

X 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(s) Date
Clinical Review	Lucia Lee, M.D. – April 14, 2016
Statistical Review	Barbara Krasnicka, Ph.D. – November 20, 2015 Lihan Yan, Ph.D. – April 12, 2016
APLB Review	Michael Brony, Pharm.D. – July 28, 2015

Executive Summary

Trumenba is a bivalent meningococcal group B vaccine that contains two factor H binding protein (fHBP) antigens from *Neisseria meningitidis* serogroup B. fHBP is a conserved, outer membrane lipoprotein and a virulence factor that contributes to the ability of *N. meningitidis* to avoid host defenses. Trumenba was approved by the FDA on October 29, 2014, for use as a three-dose series (0, 2 and 6 month schedule), in accordance with the regulations for accelerated approval, 21 CFR 601.40-46.

The Applicant submitted this efficacy supplement (STN125549/17) to request changes to the Trumenba dosing regimen. The clinical data support approval of two dosing schedules according to the regulations for accelerated approval, 21 CFR 601.40-46:

- Three-dose schedule: a 0.5 mL dose administered at 0, 1-2, and 6 months
- Two-dose schedule: a 0.5 mL dose administered at 0 and 6 months.

The schedules enable flexibility in vaccination intervals depending on the risk of exposure over the course of the 6 month interval and the patient's susceptibility to *N. meningitidis* serogroup B disease.

1. Introduction

On March 27, 2015, Wyeth Pharmaceuticals Inc., (U.S. license 0003) submitted an sBLA for Trumenba® (Meningococcal Group B Vaccine) to revise the dosing regimen from a three-dose series administered at 0, 2 and 6 months, to a two-dose series, with the doses given at least one month apart, and an optional booster (3rd dose) that may be administered at least four months after the second dose. Also, on November 16, 2015, the Applicant submitted an amendment to the supplement requesting an additional dosing regimen of two doses administered according to a 0 and 6 month schedule. The review of this supplement focused on the *post-hoc* analyses of immunogenicity data from three phase 2 clinical trials (B1971011, B1971012 and B1971010) and frequencies of SAEs from 7 studies (in the original BLA) categorized by 4 time periods.

2. Background

On June 16, 2014, Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc., submitted a BLA for Trumenba. The FDA approved Trumenba on October 29, 2014, under the

accelerated approval regulations, 21 CFR 601.40-46, as a three-dose series (0, 2 and 6 months) for use in individuals 10 through 25 years of age to prevent invasive disease caused by *N. meningitidis* serogroup B.

In this sBLA, STN 125549/17, the Applicant proposed a revision of the three dose primary series to a two-dose series, with the doses administered at least one month apart, followed by what the Applicant designated as an optional booster (3rd) dose that may be administered at least four months after the second dose. The Applicant was informed on September 8, 2015, that their data did not support a schedule in which the third dose was considered optional following two doses administered at least 1 month apart; however, CBER noted that the data did support flexibility in the dosing interval. CBER indicated that the Dosage and Administration sections of the Package Insert (PI) would indicate the following language: "Administer two doses (0.5 mL each) of Trumenba at least one month apart, followed by a third dose at least 6 months after the first dose", providing flexibility in timing for the second dose. The Applicant then submitted an amendment to their sBLA on November 16, 2015, requesting approval according to the accelerated approval regulations of an additional dosing regimen of two doses administered according to a 0 and 6 month schedule. The Applicant also submitted an amendment on November 25, 2015, with additional information pertaining to the November 16, 2015, submission, including the proposed confirmatory trial for the two-dose schedule (i.e., 0 and 6 months) in healthy subjects 10 years to less than 26 years of age, a revised PI and their updated pediatric plans regarding the two-dose schedule (i.e., 0 and 6 months). The review team deemed the November 25, 2015, amendment as a major amendment because additional time was needed to review this additional information and the revised PI. In addition, the revised pediatric plan had to be reviewed by the Pediatric Review Committee (PeRC). Therefore, the review clock was revised from January 25, 2016, to April 25, 2016.

3. Chemistry Manufacturing and Controls (CMC)

No manufacturing changes were proposed for this supplement; thus, no manufacturing information was submitted in this supplement.

4. Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology or toxicology information was submitted in this supplement.

5. Clinical Pharmacology

No clinical pharmacology or pharmacokinetic data were submitted in this supplement.

6. Clinical/Statistical

a. Clinical Program

Immunogenicity of Trumenba

For both schedules, bactericidal antibodies to fHBP were measured using serum bactericidal activity with human complement (hSBA) assays. Five endpoints were assessed one month after a two-dose series (i.e., 0 and 6 months), and in a subset of subjects, after a third dose:

- The percentage of subjects with a ≥4-fold increase in hSBA titer compared to pre-dose #1 (each of four primary strains) and

- The percentage of subjects with a composite response (defined as the % of subjects with hSBA titer ≥LLOQ for all four meningococcal primary strains).

The Meningococcal serogroup B (MenB) primary strains (PMB80, PMB2001, PMB2948, and PMB2707) express fHBP variants A22, A56, B24 and B44, respectively, which are among the prevalent fHBP variants in the US. The endpoints were analogous to the primary endpoints that were previously agreed upon by CBER for the confirmatory studies supporting the three-dose schedule as required under accelerated approval regulations.

Three-dose schedule (0, 1-2, and 6 months)

Post-hoc analyses of data for the three-dose schedule were provided from three studies (B1971012, B1971011 and B1971010) previously submitted to the BLA (STN 125549/0). Overall, the studies included individuals 11 to <19 years of age from Europe and the US. The analyses of the 5 endpoints were descriptive; nonetheless, hSBA responses, an accepted immune marker of protection, were evaluated in a substantial number of evaluable participants (2,300 Trumenba participants received doses at 0, 1 and 6 months or 0, 2 and 6 months, and an additional ~200 received 2 doses at 0 and 2 months).

- Dosing interval: The proportions of subjects with a >4-fold increase in hSBA titer from baseline (pre-dose #1), compared by individual strain, were similar when two doses of Trumenba were administered at 0 and 1 month or 0 and 2 months, and variations in baseline titer were accounted for.

- Dosing regimen: hSBA responses after a third Trumenba dose were notably higher, especially for the subfamily B variant-expressing strains, than corresponding hSBA responses after two doses. The composite response was approximately 50% after the second dose (administered at 0 and 1-2 months) and approximately 80% after a third dose administered at 6 months, indicating that a third dose was necessary if the interval between the first two doses was separated by 1 month.

Two-dose schedule (0 and 6 months)

Study B1971012 was already completed at the time of the Applicant's proposal to add the two-dose schedule administered at 0 and 6 months. Therefore, hSBA responses following the two-dose schedule [Group #3] were evaluated descriptively along with hSBA responses after the three-dose schedule described in the preceding bullet point in the context of the proposed changes to the Dosage and Administration sections of the PI. The longer interval between administration of the first and second dose (i.e., 1-2 months compared with 6 months between 1st and 2nd doses) resulted in higher percentages of participants with a ≥4-fold increase in post-vaccination hSBA titer (64.5% to 90.1%, depending on the individual MenB strain) compared to corresponding titers reported prior to dose #1. The composite response after the second dose given at 6 months was 72.9%.

b. Pediatrics

The three-dose schedule (0, 1-2 and 6 months) was viewed by PeRC as a change in the dosing interval, not a change in the dosing regimen, and therefore not subject to PREA. The pediatric study plan remains unchanged from the plan outlined in STN 125549/0.

The two-dose schedule (0 and 6 months) was viewed by PeRC as a change in the dosing regimen, and therefore was subject to PREA:

- 0 to <12 months of age: The requirement for studies in this age group was waived due to adverse safety outcomes observed in infants (same data as for the three-dose schedule).

- 1 year to <10 years of age: The Applicant plans to conduct a safety and immunogenicity study in children 1 year to <10 years of age; the requirement for studies in this age group was deferred because Trumenba is ready for approval for use in individuals 10 to <26 years of age before the pediatric study is completed.

- 10 years of age: Extrapolation of safety and immunogenicity to children age 10 years is supported by the safety and immunogenicity profile observed in children ages 11 to <18 years.

- 11 to <18 years of age: This age range is supported by safety and immunogenicity data from studies included in this sBLA.

7. Safety

A total of 4,282 subjects 11 to <26 years of age received at least one dose of Trumenba overall, of which 2,557 subjects were enrolled in controlled trials. For the three-dose schedule, *post-hoc* analyses of serious adverse events (SAEs), that were defined by the following time intervals: 1) after completion of a two-dose series (0 and 1-2 months), 2)

after the third dose and 3) safety follow-up post-dose #3, indicated that SAE rates from studies B1971011, B1971012 and B1971010 combined were similar to SAE rates reported in the 7 studies overall. Analyses of safety data for the two-dose schedule (0 and 6 months) were the same as the analyses included in the individual study report (B1971012). There were no new concerns identified from a review of the SAEs after either the three-dose (0, 1-2 and 6 months) or the two-dose schedule (0 and 6 months).

8. Advisory Committee Meeting

This supplement did not require input from the Vaccines and Related Biological Products Advisory Committee.

9. Other Relevant Regulatory Issues

There were no additional relevant issues.

10. Labeling

All issues regarding the product labeling were resolved after exchange of information and discussions with the Applicant. The PI submitted by the Applicant was in the format required by FDA's Final Rule titled "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" published in January 2006. The Dosage and Administration, Adverse Reactions and Clinical Studies sections of the PI were revised; however, the carton and container labeling were not revised. Itemized below are the main revisions to the PI.

- The Dosage and Administration sections were revised from the following:

    - "Three doses (0.5 mL each) by intramuscular injection according to a 0-, 2-, and 6-month schedule."
      to
    - "Three-dose schedule: Administer a dose (0.5 mL) at 0, 1-2, and 6 months.
      and
    - Two-dose schedule: Administer a dose (0.5 mL) at 0 and 6 months."

- The Adverse Reactions and Clinical Studies sections were updated with information from study B1971012 (general description, local and systemic reactions for the two-dose schedule, and hSBA responses for the three-dose and two-dose schedules).

11. Recommendations and Risk/Benefit Assessment

a. Recommended Regulatory Action

Flexibility in the intervals between the first two doses (i.e., 0 and 1 months vs. 0 and 2 months) in the three-dose series (0, 1-2 and 6 months) may be beneficial in certain

situations when a person is at significantly high risk of exposure to circulating *N. meningitidis* serogroup B, e.g., during an outbreak of invasive MenB disease. Control of MenB disease might be facilitated by vaccination with Trumenba when the first two doses can be administered at a shorter interval (0 and 1 months) vs. waiting for a 2 month time period before being able to administer the second dose.

Completion of a two-dose vaccination series given at 0 and 6 months may be beneficial if: 1) compliance can be improved with a schedule consisting of a fewer number of doses (two doses at 0 and 6 months) and 2) a longer interval between vaccinations is possible without the imminent risk of exposure to *N. meningitidis* serogroup B during the 6 month interval.

Regulatory considerations for approval of the proposed schedules according to the accelerated approval regulations took into consideration the potential public health urgency for control during MenB outbreaks. The endpoints were analogous to the primary endpoints agreed upon by CBER for the confirmatory studies supporting the three-dose schedule. While the immunogenicity of the two-dose schedule at 0 and 6 months likely predicts clinical benefit, the applicant is required to confirm clinical benefit through demonstration of breadth of coverage as proposed for the three-dose schedule.

The immunogenicity and safety data submitted in this application support accelerated approval of the following Trumenba vaccination schedules:

- Three-dose schedule: a dose (0.5 mL) administered at 0, 1-2, and 6 months.

- Two-dose schedule: a dose (0.5 mL) administered at 0 and 6 months.

The review committee recommends approval of this supplement to revise the PI, including the following revisions that were made to the Dosage and Administration sections:

From

- "Three doses (0.5 mL each) by intramuscular injection according to a 0-, 2-, and 6-month schedule."

to

- "Three-dose schedule: Administer a dose (0.5 mL) at 0, 1-2, and 6 months. and
- Two-dose schedule: Administer a dose (0.5 mL) at 0 and 6 months."

The Adverse Reactions and Clinical Studies sections were updated with information from study B1971012 (general description, local and systemic reactions for the two-dose schedule, and hSBA responses for the three-dose and two-dose schedules).

b. Risk/Benefit Assessment

The assessment of risks and benefits of the revised dosing schedule is overall favorable (the Risk Management Plan was not revised).

c. Recommendation for Postmarketing Activities

For the three-dose schedule, the postmarketing studies are unchanged from the studies included in the approval letter for STN 125549/0.

For the two-dose schedule, postmarketing requirements are as follows:

- In accordance with the accelerated approval regulations, a confirmatory study in the post-marketing period will be conducted to verify and describe the clinical benefit of a two-dose schedule (0 and 6 months) for Trumenba in healthy subjects 10 years to less than 26 years of age. Clinical benefit will be confirmed by demonstration of effectiveness against diverse meningococcal group B strains.
- In accordance with PREA requirements, a study will be conducted to assess the safety and immunogenicity of administering Trumenba on a two-dose schedule (0 and 6 months) in children 1 year to less than 10 years of age.