

Summary Basis for Regulatory Action

Date: April 14, 2011

From: Lucia H. Lee, M.D., Review Committee Chair

BLA/ STN#: 125089.395

Applicant Name: Sanofi Pasteur, Inc.

Date of Submission: 24-Jul- 2010

Proprietary Name/ Established Name: Menactra[®] Meningococcal (Groups A,C,Y,W135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine

Subject: Supplemental biologics license application to extend Menactra use to children as young as 9 months of age. Indication: active immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroup A, C, Y and W-135.

Recommended Action: Approval

Signatory Authorities Action

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.**

Review Committee

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CMC (assay- diphtheria toxoid)

CMC (assay- meningococcal, pneumococcal)

CMC (assay- M,M,R,V)

BIMO

Pharmacovigilance

APLB

1. Introduction

Menactra is a tetravalent meningococcal (Group A,C,Y,W135) conjugate vaccine manufactured by Sanofi Pasteur Inc. Diphtheria toxoid is used as a carrier protein. Menactra is indicated for active immunization of individuals, 2 years through 55 years of age, to prevent invasive disease caused by *Neisseria meningitidis* vaccine serogroups.

Sanofi Pasteur Inc. submitted the current clinical supplemental biologics license application (sBLA) to extend Menactra use to children as young as 9 months of age. The highest rate of meningococcal disease in the U.S. occurs in children younger than one year of age. In 1999-2008, serogroup Y on average accounted for ~30% of annual meningococcal cases. In 2009, preliminary data indicated that the incidence of meningococcal disease in children <1 year old due to serogroups C, W-135/non-groupable, and Y was 0.19, 0.19, 0.58 cases/ 100,000 population, respectively.

2. Regulatory Background

An approach to demonstrating effectiveness of meningococcal conjugate vaccines in young children was a discussion topic at a Vaccines and Related Biological Products Advisory Committee meeting. The meeting was held April 6-7, 2011. In brief, the committee concurred that serum bactericidal activity with human complement (SBA-H) could be used as an immune measure to infer effectiveness of meningococcal conjugate vaccines for children <2 years old. For individuals 2 years of age and older, immunological non-inferiority to a U.S. licensed meningococcal vaccine was demonstrated in a randomized, controlled trial. At present, no meningococcal conjugate vaccine is licensed in the U.S. for children younger than 2 years old. Seroreponse above a pre-defined SBA-H titer would indicate that meningococcal-specific functional antibodies present at the time of exposure were protective against systemic infection.

3. Chemistry Manufacturing and Controls (CMC)- serological assay methods

Validation information was submitted for serological assays used to assess functional and/or IgG antibody responses to meningococcal, pneumococcal, measles, mumps, rubella, and varicella vaccine antigens and to the diphtheria toxoid carrier protein. CBER CMC reviewers concurred that the assays were validated for their intended use.

4. Non-clinical Pharmacology/Toxicology

Not applicable.

5. Clinical/Statistical

Clinical evaluation of Menactra included four studies. Studies MTA-48 and MTA-44 were pivotal trials for an evaluation of safety and immunogenicity, respectively. Menactra was administered as a 2-dose series at 9 months and 12 months old. The first Menactra dose was given alone. The second Menactra dose was administered alone or concomitantly with U.S. licensed childhood vaccine(s). In study MTA-26, dose selection included evaluations of other 2-dose regimens.

Table 1. Clinical Overview

Study	Description	First Dose of Menactra	Second Vaccination		
			Menactra only	Menactra + Concomitant Vaccine(s)*	Concomitant Vaccine(s)* only
Pivotal Studies					
MTA-44 USA	Phase III Safety and immunogenicity study (Pivotal immunogenicity)	1247	386	773	N/A
MTA-37 USA	Phase III, Safety and immunogenicity Com vx: MMRV (or MMR+V), PCV7	1191	246	850	1052
MTA-48 USA, Chile	Phase III Safety study Com vx (safety): MMRV, PCV7, HepA	1253	N/A	959	521
Total number of vaccine recipients in phase 3 trials		3691		2582	1573
Supportive study					
MTA-26 USA	Phase II Dose ranging study 1-dose: 15m, 18m; 2-dose: (9m,12m); (9m,15m); (12m,15m)	302	176	N/A	N/A

*Number of subjects who received concomitant PRP-T (MTA-44 n=128; MTA-37 n=24 (study group 2), n=601 (study group 4))

Study MTA-44 was a randomized, parallel group U.S. trial. The study was viewed by CBER as an open-label trial since the number of administered injections and routes of administration differed among study groups. Laboratory personnel were blinded to the treatment assignment.

A total of 1257 children enrolled in the study and were randomized into three study groups (1:1:1 ratio) as follows: For each study group, Menactra was administered alone at 9 months of age. At 12 months of age, a second Menactra dose was given alone (study group 1), with MMRV (study group 2; ProQuad, Merck & Co, Inc.) or with PCV7 (study group 3; Prevnar, Pfizer, Inc.). Blood samples were obtained 30 days after the second vaccination visit.

The primary outcome measure was the percentage of subjects (study group 1) with an SBA-H titer $\geq 1:8$, for each serogroup. Table 2 includes the primary analysis based on the per-protocol population. Results from the intent to treat analysis were consistent with the per-protocol analysis. Except for serogroup W135, the lower 95% CI limit for the percentage of infants achieving an SBA-H titer $\geq 1:8$ was $\geq 90\%$.

Among study groups 1 and 2, SBA-H GMTs and percentages of participants who achieved SBA-H titers $\geq 1:8$ were similar for each serogroup. The 95% CIs for each immune parameter overlapped. A trend towards a lower percentage of participants who achieved serogroup-specific SBA-H titer $\geq 1:8$ was observed in the study group who received Menactra (2nd dose) concomitantly with PCV7 (4th dose), compared to the study group who received Menactra alone or with MMRV. The difference between serogroup-specific SBA-H GMTs among participants who received Menactra + PCV7 or Menactra alone were within 2-fold, and 95% CIs were largely non-overlapping. The reverse cumulative distribution curves among the study groups 1-3 were similar for each serogroup.

Table 2. MTA-44. Serum Bactericidal Antibody Responses^a Following a Second Dose of Menactra Vaccine Administered Alone or Concomitantly with MMRV or PCV7 Vaccines, Per-protocol population

Serogroup	Immune Parameter ^c	Vaccine(s) administered at 12 months of age					
		Menactra (study group 1)		Menactra+MMRV (study group 2)		Menactra+PCV7 (study group 3)	
		(N=272-277) ^b (95% CI)		(N=177-180) ^b (95% CI)		(N=264-267) (95% CI)	
A	% $\geq 1:8$	95.6%	(92.4, 97.7)	92.7%	(87.8, 96.0)	90.5%	(86.3, 93.8)
	GMT	55	(47, 65)	52	(42, 65)	41	(35, 49)
C	% $\geq 1:8$	100%	(98.7, 100)	98.9%	(96.0, 99.9)	97.8%	(95.2, 99.2)
	GMT	142	(124, 163)	162	(136, 192)	110	(94, 128)
Y	% $\geq 1:8$	96.4%	(93.4, 98.2)	96.6%	(92.8, 98.8)	95.1%	(91.8, 97.4)
	GMT	52	(45, 61)	60	(50, 72)	40	(34, 46)
W-135	% $\geq 1:8$	86.4%	(81.8, 90.3)	88.2%	(82.5, 92.5)	81.2%	(76.0, 85.7)
	GMT	24	(21, 28)	28	(23, 34)	18	(15, 21)

^a Serum bactericidal assay with an exogenous human complement (SBA-H) source.

^b N=Number of participants with at least one valid serology result at Day 30.

^c Timepoint: 30 days after the second Menactra dose. Menactra was administered at 9 months and 12 months of age.

Source: adapted from 125089.395.0, m5.3.5.1, MTA44 report.pdf, pages 104-105, Tables 5.4 and 5.5

6. Safety

Safety data was available for 3993 children received the 1st dose of Menactra, 2582 received a 2nd Menactra dose concomitantly with ≥ 1 U.S. licensed childhood vaccine, and 1573 children received only U.S. licensed vaccines. No new safety signals were identified in the review of this BLA supplement.

Safety assessment: Study participants in the 4 trials were monitored for immediate reactions 30 minutes after each vaccination. Pre-specified adverse events included injection site reactions (erythema, swelling, tenderness) and systemic adverse events (fever, vomiting, inconsolable crying, drowsiness, loss of appetite and irritability). The events were recorded daily on a diary card during the 7 days after each vaccination, and by telephone interview eight days after vaccination. Other non-serious, unexpected adverse events, including rash, were obtained by telephone interview eight and twenty-eight days after each vaccination. Medically significant

AEs were defined as events that prompted medical advice/attention from a physician's office or emergency room between Day 30 and 6 months after the last vaccination. Information was obtained by scripted telephone interview. Serious adverse events (SAEs) reported were recorded through the 6-month study period following the last vaccination.

Solicited adverse events (AEs): In the primary safety study, MTA-48, children were enrolled into two study groups. One study group received the 1st dose of Menactra alone at 9 months old. At 12 months of age, they received a 2nd Menactra dose, which was given concomitantly with MMRV, PCV7 and hepatitis A (HepA) vaccines. A control group of children received only childhood vaccines (MMRV, PCV7 and HepA) at 12 months of age. Administration of measles, mumps, rubella (MMR) and varicella (V) vaccines was an acceptable alternative to a MMRV combination vaccine.

The most common adverse events were after either Menactra dose were injection site tenderness (49%, 1st dose; 52% 2nd dose + concomitant vaccines) and irritability (57%, 1st dose; 62% 2nd dose + concomitant vaccines). Injection site tenderness at the Menactra site was more frequent than at any of the concomitant vaccine sites (41%-46%). The frequency of systemic reactions was similar between the Menactra and the control group.

Serious adverse events (SAEs): The percentage of participants in the three main studies (MTA-44, MTA-37 and MTA-48) with at least one SAE after Menactra vaccination (alone or with concomitant vaccines) was 2.0-2.5%. Events were mainly due to common childhood illnesses, such as broncholitis and gastroenteritis. Two participants experienced a febrile seizure <5 days after vaccination, a 12-month old who received Menactra+PCV7 and a 10-month old who received Menactra+MMRV+PCV7+HepA who developed a febrile seizure 1 and 2 days after vaccination, respectively. One of the two participants had a concurrent acute otitis media. Febrile seizures were not viewed by the review team as a safety signal.

Deaths: A total of three deaths occurred in the four trials. Two deaths were due to closed head injury and asphyxia, respectively. The third participant was a boy who experienced a seizure 58 days after (EEG) findings were consistent with a diagnosis of epilepsy. He died 125 days later from complications of his medical condition. None of the deaths were considered by the review team to be related to vaccination.

7. Clinical Pharmacology

Study MTA-37 was a trial with primary objectives to evaluate the safety and immunogenicity of measles, mumps, rubella, varicella vaccine [MMRV] and a 7-valent pneumococcal CRM₁₉₇ conjugate vaccine [PCV7] concomitantly administered with Menactra. Menactra was administered alone at 9 months of age. At 12 months of age, a second dose was given alone (study group 1), with MMRV (study group 2) or with PCV7 (study group 3). A fourth study group received MMRV + PCV7. Also, MMR+V could be given as an alternative to MMRV. Blood samples were obtained 30-44 days after the second vaccination visit.

Study MTA-37 cont.

Primary immunogenicity analyses were based on the per-protocol population who received the vaccines described above. Primary endpoints for each vaccine component were as follows

Study groups 2 and 4

- Measles: ≥ 300 mIU/mL (ELISA) or ≥ 120 mIU/mL (neutralization assay)*
- Mumps: ≥ 500 U/mL (ELISA) or ≥ 60 (1/dil (neutralization assay)*
- Rubella: ≥ 10 IU/mL
- Varicella: ≥ 300 mIU/mL or ≥ 4 (1/dil) (FAMA assay)*

* The second assay (neutralization or FAMA was performed when the measured antibody concentration was less than the concentration specified for the first assay (ELISA).

Study groups 3 and 4

- Pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F and 23F (ELISA)

Non-inferiority criteria would be met if the upper limit of the 2-sided 95% CI of $p_{\text{Group4}} - p_{\text{Group 2}}$ is less than 0.05 for measles, mumps, and rubella antigens, and less than 0.10 for varicella and pneumococcal antigens.

MMRV (or MMR + V)

Non-inferiority criteria were met for antibody responses antigens contained in MMRV. The primary intent to treat analysis for immunogenicity was consistent with the per-protocol analysis. Forty-eight study group 2 subjects received separate injection of MMR and V. Except for the measles seroresponse rate (91.3; 95% CI (79.2; 97.6)), antibody responses in the study group who received MMR + V were higher than responses in the group who received MMRV.

PCV7

Pneumococcal IgG antibody responses

For serotypes 4, 6B and 18C, the upper limit of the 95% CI for the IgG GMC ratio exceeded the 2.0-fold criterion for non-inferiority.

Table 3. MTA- 37. Geometric Mean Concentrations of Pneumococcal IgG Antibodies ($\mu\text{g/mL}$), (Per-Protocol Population)

Serotype	PCV7 + MMRV	PCV7 + Menactra	Group 4 GMC /Group 3 GMC	
	Group 4	Group 3		
	N=399	N=191		
	GMC	GMC	IgG GMC Ratio	(95% CI)
4	3.33	1.82	1.83	(1.58, 2.11)
6B	10.8	5.40	1.99	(1.72, 2.31)
9V	3.57	2.06	1.74	(1.51, 2.00)
14	10.5	6.73	1.56	(1.35, 1.80)
18C	2.91	1.58	1.84	(1.59, 2.12)
19F	4.03	2.50	1.61	(1.42, 1.84)
23F	7.03	4.62	1.52	(1.29, 1.79)

Source: 125089.395.0, m5.3.5.1, MTA37 report.pdf, page 116

Pneumococcal OPA antibody responses

Pneumococcal OPA antibody responses were evaluated in subset of participants who had sera available after serological testing for the primary objectives was completed. The study group who received Menactra concomitantly with PCV7 had lower OPA GMTs compared to corresponding antibody responses in the study group receiving PCV7 without Menactra. The 95% CI for the OPA GMTs for each serotype were non-overlapping.

8. Advisory Committee Meeting

There were no product-specific concerns that would have benefited from an advisory committee discussion.

An approach to demonstrating effectiveness of meningococcal conjugate vaccines in young children was a discussion topic at a VRBPAC meeting held April 6-7, 2011.

9. Other Relevant Regulatory Issues

Safety and immunogenicity data from studies included in this supplement satisfactorily fulfill STN 125089.0 post-marketing commitment #2 and Pediatric Research Equity Act (PREA) requirements.

Pediatric Review Committee (PeRC) review outcomes

For children <9 months old, safety and immunogenicity of a 3-dose Menactra series (2, 4 and 6 months of age) was evaluated in 19 children. After the third dose, 47% (95% CI 43.5, 87.2), 47% (95% CI 24.5, 71.1), 53% (95% CI 28.9, 75.6), and 68% (95% CI 24.5, 71.1) of children achieved an SBA-H titer $\geq 1:8$ to serogroups C, W-135, Y and A, respectively. In pivotal study MTA-44, of participants who received a 2-dose Menactra series given at 9 and 12 months of age, 86-100% achieved an SBA-H titer $\geq 1:8$ for any serogroup. Immunogenicity data in study MTA-26 children who received a 2-dose Menactra regimen given at 12 months and 15 months of age supported bridging of immunogenicity data from children 9 and 12 months of age to children 13 months through 23 months of age.

The committee concluded that the assessment of Menactra safety and effectiveness for the claimed indication satisfied PREA requirements.

10. Bioresearch monitoring (BiMo) inspections

-----Removed Per the Privacy Act-----

11. Labeling

The package insert was revised to comply with the Physicians Labeling Rule. The Indication, Adverse Reactions, Drug Interactions, and Clinical Studies sections were updated to include safety, immunogenicity and concomitant use data from pivotal studies MTA-44, MTA-37 and MTA-48.

12. Recommendations and Risk/Benefit Assessment

Recommended Regulatory Action

Based on the safety and immunogenicity data provided, the committee recommends approval of Menactra for use in children 9 months through 23 months of age. The indication is the same as for individuals 2 years through 55 years of age: active immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroup A, C, Y and W-135.

Risk Management Plans

The applicant's pharmacovigilance plan includes routine post-marketing surveillance, biweekly reporting of serious expected or unexpected adverse events, monthly reporting of neurological events that were not previously identified through the venues described above, and a post-approval safety surveillance study (see post-marketing commitments below).

Post-marketing commitments (PMC)

The applicant commits to conduct the following studies:

1. Safety and immunogenicity study of Menactra when co-administered with DTaP-IPV/PRP-T at 15 to 18 months of age. This study was included as a PMC for two reasons: a) to evaluate the safety and immunogenicity of childhood vaccines given in the U.S. at 15 months to 18 months old; b) observed immunological interference between Menactra vaccine and a pneumococcal conjugate vaccine containing a similar carrier protein.
2. Post-marketing descriptive safety surveillance study. The study is being conducted to a) to obtain additional safety data in children 13 months through 23 months of age, an age group for whom cumulative pre-licensure data was limited; b) as a continued assessment of Menactra safety in children 9 months to 23 months old overall.