Summary Basis for Regulatory Action

Date: January 27, 2011

From: Cara R. Fiore, Ph D, Chair of the Review Committee

BLA/ STN#: 125300/95

Applicant Name: Novartis Vaccines and Diagnostics

Date of Submission: March 31, 2010

PDUFA Goal Date: January 29, 2011

Proprietary Name/ Established Name: MENVEO®

Additional Indication Sought Under This BLA Supplment: Active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135 when administered to individuals 2 through 10 years of age.

Recommended Action: Approval

Signatory Authorities Action: Approval

Offices Signatory Authority: Wellington Sun, M.D., Director, Division of Vaccines and Related Products Applications, Office of Vaccine 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.**

Table 1: Review documents used in compiling this SBRA:

Review Category	Reviewer--date of review
Clinical Review	Paulina Mariki, MD; Margaret Bash, MPH, MD
Statistical Review	Lihan Yan, Ph.D. 27 January 2010
Pharmacovigilance Review	Manette Nui, MD. 23 November 2010, addendum January 2, 2011
CMC Review	Mustafa Akkoyunlu MD, Ph.D., 10 November 2010
Bioresearch Monitoring	Janet White - 22 November 2010
Container and Labeling	Catherine Miller, Maryann Gallagher – 16 December 2010
Pharmacology/Toxicology	Nabil Al-Hamadi 28 June 2010

1. Introduction

MENVEO® (also referred to as MenACWY in this document), manufactured by Novartis Vaccines and Diagnostics S.r.L. Bellaria-Rosia, 53018 Sovicille, (b)(4), Italy (Novartis) is a Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine for prevention of invasive meningococcal disease caused by *Neisseria meningitidis*, serogroups A, C, W-135, and Y. The vaccine was approved by the FDA for use in subjects 11-55 years of age in the U. S. on February 19, 2010. On March 31, 2010, Novartis submitted sBLA 125300_95 to expand the indication of MENVEO® vaccine to include use in children 2 through 10 years of age for prevention of invasive meningococcal disease caused by *Neisseria meningitidis*, serogroups A, C, W-135 and Y.

2. Chemistry Manufacturing and Controls (CMC)

MENVEO consists of four drug substances, each composed of a Meningococcal capsular oligosaccharide covalently attached to the nontoxic genetically modified Diphtheria Toxin CRM197 protein. Each drug substance is prepared from materials purified from two starting products of bacterial fermentation origin: *Corynebacterium diphtheriae* Cross Reactive Material 197 (CRM197) and capsular polysaccharide (A, C, W-135 and Y obtained from *Neisseria meningitidis* serogroups A, C, W-135 and Y, respectively).

Full review of CMC information for MENVEO was completed at the time of original licensure on February 19, 2010. All lots of vaccine used in the clinical study of concomitantly administered vaccines were reviewed and released for distribution by CBER. The CMC review in this supplement concentrated on the human serum bactericidal assay (hSBA) and on an impurities report that contains updated toxicology specifications.

Serology Assay Review:

The hSBA (human Serum Bactericidal Assay) is used to measure specific antibody titers (Groups A, C, Y and W-135) in sera from the subjects from the clinical trials in order to evaluate the immune response before and after vaccination with the quadrivalent vaccine directed against the serogroups A,

C, W-135 and Y of *Neisseria meningitidis.* The antibody mediated hSBA titer following vaccination serves as a marker for the immunogenicity of the vaccine. Briefly, the serum bactericidal assay is based on the measurement of complement dependent killing of bacteria through the binding of serogroup specific antibodies to the polysaccharide capsule of the meningococcal strains. The C1q subunit of the complement system binds to the Fc portion of the bound antibodies, which activates the classical complement pathway, resulting in lysis of the meningococci. The hSBA titer is defined as the reciprocal value of the interpolated serum dilution that kills 50% of the bacteria used in the test.

In this supplement, the sponsor presented a document that reports on the performance of assay controls since the assay was originally validated. The SOP and the validation protocol of the hSBA were evaluated during the original application of Menveo and found to be satisfactory for the measurement of serum bactericidal activity using an exogenous source of human complement. The sponsor has not made any changes to the hSBA test method since licensure. Therefore, the hSBA results presented in this BLA are based on an assay reviewed and considered validated by CBER.

Review of the impurities:
This report concerning the "Impurities" contains updated toxicology specifications. The toxicology specifications were updated because the company has changed the specifications ----------(b)(4)---------- As a result of the change in active product concentrations, the residual chemical concentrations also change. The methods used to recalculate the final residual chemical amounts based on the toxicology specifications for each of the (b)(4) compounds were reviewed and determined to be adequate. The methods used to assess the toxicology specifications were identical as the ones used during the original submission and involve the use of available toxicology literature and/or allowable limits set by FDA-accepted guidelines.

CBER Lot Release
There are no ongoing or pending investigations or compliance actions with respect to the above facilities or their product(s). Therefore, the Office of Compliance and Biologics Quality, Division of Case Management does not object to the approval of this supplement.

3. Non-clinical/Toxicology

Two nonclinical studies that used the final formulation of the product (with no adjuvant) to support the nonclinical safety of the marketed formulation were included in this submission. The original application for MENVEO had non-clinical studies that used the ---(b)(4)--- product.

Study 1
In this repeated (25 µg/0.5 mL dose) dose toxicology study, ---------(b)(4)------- rabbits were treated with either control or test articles. Control or test article were administered via intramuscular injection in the left and right hind limbs on study days (SDs) 1 and 15, respectively. Terminal and recovery sacrifice necropsies were conducted on SD's 17 and 29, respectively. The delivery of an active dose of the product in the toxicology study was verified.
Study 2

In this repeated (25 µg/0.5 mL dose at two weeks interval) dose toxicology study, ---------(b)(4)------- rabbits were treated with either control or test articles. Control or test article were administered via intramuscular injection in the right and left hind limbs on study days (SD's) 0 and 14, respectively. Terminal and recovery sacrifice necropsies were conducted on SD's 16 and 28, respectively. The delivery of an active dose of the product in the toxicology study was verified.

Adequate nonclinical toxicology data to support the safety of the unadjuvanted product were included in this section of the supplement submission. Based on review of these nonclinical toxicology studies, there are no significant safety issues to preclude the sBLA from being approved.

4. Clinical

Background

BLA supplement 125300/95.0 contains safety and immunogenicity data intended to support an extension of the age indication for MENVEO from the current 11 through 55 years of age to include use of a single dose of MENVEO in children 2 through 10 years of age. Currently, two other U.S.-licensed meningococcal vaccines for prevention of disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135 in children 2 through 10 years of age. Menomune (Sanofi Pasteur Inc.) is a quadrivalent polysaccharide vaccine and Menactra (Sanofi Pasteur Inc,) is a quadrivalent polysaccharide-diphtheria toxoid conjugate vaccine. Novartis developed MENVEO by conjugation of meningococcal polysaccharides from serogroups A, C, W, and Y to a nontoxic mutated form of diphtheria toxin (CRM197).

Clinical Program

Neisseria meningitis is a leading cause of bacterial meningitis and sepsis worldwide. Invasive meningococcal disease has occured in the U.S at a rate of 0.9 to 1.5/100,000 persons over the past 4 decades. The relatively low prevalence of disease combined with the availability of currently licensed meningococcal vaccines precludes the conduct of studies to evaluate directly the efficacy of new meningococcal vaccines in prevention of clinical invasive disease. Licensure of serogroup A and serogroup C meningococcal polysaccharide vaccines were originally supported by demonstrated clinical efficacy in preventing invasive meningococcal disease. In addition to serogroups A and C, the quadrivalent polysaccharide vaccine also contains serogroup Y and W-135 polysaccharides which were evaluated on the basis of demonstrating four-fold rise in serum bactericidal activity (SBA) in an assay using exogenous rabbit complement (rSBA). Menactra was licensed in 2005 on the basis of immunologic (SBA) non-inferiority to Menomune using an exogenous complement source that was either human (hSBA) or, when correlated to hSBA, baby rabbit complement.

The safety and effectiveness of MENVEO in children 2 through 10 years of age were evaluated in comparison to currently licensed vaccines, Menactra or Menomune. Vaccine effectiveness was assessed by comparing the hSBA responses after immunization with MENVEO to those following immunization wth licensed meningococcal vaccines. The bactericidal activity of serum from vaccine recipients is considered an appropriate serologic measure for evaluating vaccine effectiveness of

meningococcal vaccines because complement mediated bacterial killing by bactericidal antibodies has been shown to be the primary mechanism of protection against meningococcal disease. Studies by Goldschneider et. al. 1969, showed that invasive disease did not occur in individuals whose sera (tested at a dilution of 1:4) killed the circulating strain.

Table 1: Description of Clinical Studies

Study	Geographic Location	Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration (*N*)	Subjects	Number of Menveo Injections
V59P7	Finland, Poland	Safety and Immune Response of Menveo ----------(b)(4)---------- vs Mencevax™	Observer-Blind, Randomized, Active Controlled Phase 2 Multi-Center Study	– MENVEO 10-5-5-5µg (b)(4) IM (*N=205*) – MENVEO 10-5-5-5µg (b)(4) IM (*N=224 safety data*) – Mencevax™ IM followed by MENVEO 10-5-5-5µg (b)(4) IM (*N=81*)	Toddlers 12-35 m Children 36-59 m	Two
V59P8	US	Safety and Immune Response of Menveo vs Menomune™	Single-Blind, Randomized, Active Controlled Phase 2 Single-Center Study	– MENVEO 10-5-5-5µg (b)(4) IM (*N=308 safety data*) – Menomune™ SC (*N=310*)	Children 2-10 y	One
V59P10	Argentina	Safety and Immune Response Menveo vs Menomune	Observer-Blind, Randomized, Active Controlled Phase 3 Multi-Center Study	– MENVEO 10-5-5-5µg (b)(4) IM (*N=949 safety data*) – Menomune™ SC (*N=551*)	Children 2-10 y	One
V59P20	US, Canada	Safety and Immune response to Menveo vs Menactra®	Observer-Blind, Randomized, Active Controlled Phase 3 Multi-Center Study	– MENVEO 10-5-5-5µg (b)(4) IM (*N=1626 safety data*) – MENVEO x 2 doses *(N=351)* – Menactra® (*N=1255 safety data*)	Children 2-10 y	One or Two

Safety

The total safety database for MENVEO in children 2 through 10 years of age consists of 3107 children from 1 pivotal study (V59P20) and 3 supportive (V59P7, P8 and P10) studies in which children were exposed to at least one dose of MENVEO. The comparator safety populations in the 2 through 10 year age group were 1255 and 861 enrolled subjects who received Menactra and Menomune, respectively. The comparator vaccine in the supportive study V59P7, Mencevax, is not licensed in the U.S., hence the safety and immunogenicity data from this study were not considered comparative for this clinical review. However, recipients of MENVEO in this study contributed to the overall safety database.

In the safety evaluation of MENVEO in the pivotal trial (V59P20), the following were observed:

- Demographics and other baseline characteristics were similar across the vaccine groups.
- No major differences were observed in the percentages of subjects who withdrew prematurely, or withdrew consent. The most common reason for withdrawal was lost to follow up.
- No major differences in the percentages of subjects reporting any solicited local or systemic reactions after MENVEO vs Menactra were observed.

Solicited adverse events in the pivotal U.S. safety study:

Adverse events (AE) were recorded on study specific diary cards daily for 7 days post-vaccination by subject's parents/legal guardians. The percentages of subjects reporting any solicited AE in the MENVEO group and in the Menactra group were similar at 55% vs 56% respectively; 49% reported local reactions for both vaccines, and 17% vs 16% reported systemic adverse reactions respectively. The solicited events "use of analgesic/antipyretic medication" and "stayed at home due to vaccination" occurred in 12% of both vaccine groups.

Injection site pain was the most frequently reported local solicited AE (33% in MENVEO recipients vs 35% in Menactra recipients). While local AEs were reported in slightly fewer MENVEO than Menactra recipients, rates of severe local reactions were similar in both vaccine groups (overall, <1% to 1% vs 0% to 2% respectively). For both vaccine groups, almost all solicited local AEs were experienced during the first three days immediately following vaccination. The most commonly reported systemic solicited AEs in the 2 through 5 year age group for MENVEO and Menactra were irritability (21% vs 22%, respectively) and sleepiness (16% and 18%, respectively). In the 6 through 10 year age group the most common solicted AEs for MENVEO and Menactra were headache (18% vs 13%, respectively), malaise (14% vs 11%,, respectively) and myalgia (10% in both vaccine groups). Rates of severe systemic reactions were also similar in the 2 through 5 year age group, severe irritability or severe sleepiness occurred in 1% of participants in both vaccine groups, and in the 6 through 10 year age group, severe headache, myalgia and malaise, were each reported by 1% of study participants in both vaccine groups.

Serious adverse events in the pivotal U.S. safety study:

Serious adverse events (SAE) were reported by 8/1626 subjects (0.5%) in the MENVEO 1 dose group, 2/351 subjects (0.6%) in the MENVEO 2 dose group and 7/1255 subjects (0.6%) in the Menactra group. None of the SAEs were assessed by the study investigators as related to the vaccine

administered. No deaths occurred and no AE led to subject withdrawal. Most of the SAEs started > 6 weeks post vaccination with the exception of 4 SAEs in MENVEO recipients: streptococcal infection, bronchopneumonia, dehydration and a case of worsening of an inguinal hernia. The majority of SAEs lasted for six days or less and resolved completely.

Adverse events in the two-dose group:
When a two-dose regimen was explored in the 2 through 5 years age stratum, the percentage of subjects reporting solicited local reactions after any vaccination was higher in the MENVEO 2-dose group vs. MENVEO single dose group (43% and 33% respectively). However, the percentages of subjects reporting solicited local reactions after 1st vaccination and 2nd vaccination in the MENVEO 2 dose group were similar (32% and 28% respectively). Overall, among subjects who received two doses, there was a general tendency towards decreased reports of local reactions following the second vaccination. This tendency was more evident for erythema and induration than for injection site pain. Additionally, the percentages of subjects reporting SAEs were similar ($\leq$1%) regardless of whether one or two doses of MENVEO were administered.

Solicited and Serious Adverse Events in the Supportive Studies V59P7, V59P8, and V59P10:
Across the three studies, the most commonly reported local reaction following vaccination with MENVEO was injection site pain (any: 19% to 33%, severe: 0 to 1%). The most commonly reported systemic reaction in children 2 through 5 years old who received MENVEO was irritability (11% to 22%), followed by sleepiness (9% to 18%) and change in eating habits (9% to 11%), and in children 6 through 10 years old, the most frequently reported systemic reaction was headache (11% to 19%), followed by malaise (6% to 14%) and myalgia (3% to 10%). Within each comparative study, rates of adverse events were similar between vaccine groups. Overall, reports of severe local or systemic reactions were low and similar across the vaccine groups at $\leq$1%.The exception was the higher percentages of unsolicited SAEs observed in study V59P7 (8%) which was attributed to a high incidence of varicella infection in this unvaccinated population during the study. In this study, all varicella cases, regardless of severity and hospitalization status, were categorized by the investigator as SAEs. Although the comparator vaccine, Mencevax, is not a U.S. licensed vaccine, it is of note that there were no observed differences in varicella severity by vaccine group.

Summary of Safety Results:
Overall study participants who received MENVEO or U.S.-licensed comparator vaccines had similar rates of solicited and unsolicited local and systemic events. Additionally, the reports of severe local or systemic reactions were low and occurred at similar rates across the vaccine groups at $\leq$1%. An exception was supportive study V59P7, in which 8% SAEs were reported (primarily due to an outbreak of varicella). No AEs were reported to have led to subject withdrawal in any of the four studies within the 2 through 10 years age group. No death occurred in any of the four studies used to support this application.

Immunogenicity

The immunogenicity data presented in this sBLA are intended to provide evidence of vaccine effectiveness by establishing the immunologic non-inferiority of MENVEO compared to currently licensed vaccines.

An hSBA seroresponse (Table 2), was used as the primary immunogenicity outcome. Other outcomes of interest are also shown.

Table 2: Clinical Endpoints

Endpoint	**Endpoint Definitions**
Seroresponse	For subjects with prevaccination hSBA <1:4 (seronegatives), seroresponse was defined as postvaccination titer ≥1:8. For subjects with prevaccination hSBA ≥1:4 (seropositives), seroresponse was defined as postvaccination titer ≥ 4 times the prevaccination titer.
hSBA ≥ 1:4	Percentage of subjects achieving this hSBA ≥1:4
hSBA ≥ 1:8	Percentage of subjects achieving this hSBA ≥1:8
GMT	Geometric mean hSBA titer

Immunogenicity in the Pivotal Study, V59P20:

Primary Objective

- To demonstrate that the hSBA seroresponses to MENVEO were non-inferior to the hSBA seroresponses to Menactra. Non-inferiority was demonstrated if, for all four serogroups, the lower limit of the two-sided 95% CI around the difference in the percentage of subjects with seroresponse for that serogroup (MENVEO minus Menactra) was greater than -10%, i.e., if the CI for the difference is entirely to the right of -10%, then non-inferiority was declared for that serogroup.

Secondary Objectives

Secondary immunogenicity objectives included the following:

- To evaluate the difference of the percentage of subjects with hSBA $\geq$ 1:8 (or hSBA $\geq$1:4) for that serogroup (MENVEO minus Menactra) in children 2 through 5 years and 6 through 10 years of age.
- To evaluate hSBA Geometric Mean Titers (GMT), after administration of MENVEO compared to the Menactra, in the 2 to 10 years group, and in each age stratum separately.
- To evaluate hSBA $\geq$ 1:8 (or hSBA $\geq$ 1:4 or hSBA GMT) for each serogroup after administration of 2 doses of MENVEO given 2 months apart, compared to 1 dose of MENVEO in the 2 to 5 years age group.

The success criteria for the pivotal study V59P20 was based upon only the primary objective for the per protocol population. This study is considered a success if, for both age strata, all four serogroup analyses met the non-inferiority criteria identified for the primary endpoint noted above.

Summary of Immunogenicity Results, pivotal study V59P20

Results from analyses of primary and secondary immunogenicity endpoints evaluated in the pivotal study are shown in Table 3 below.

Table 3: Comparison of bactericidal antibody responses to MENVEO and Menactra 28 days after vaccination of subjects aged 2 through 5 years and 6 through 10 years of age

	2 through 5 years			6 through 10 years		
Endpoint by Serogroup	**MENVEO (95% CI)**	**Menactra (95%CI)**	**% difference (MENVEO – Menactra) or GMT ratio (MENVEO/ Menactra) (95%CI)**	**MENVEO (95%CI)**	**Menactra (95%CI)**	**% difference (MENVEO - Menactra) or GMT ratio (MENVEO/ Menactra) (95%CI)**
A	**N=606**	**N=611**		**N=551**	**N=541**	
% Seroresponse[α]	72 (68, 75)	77 (73, 80)	-5 (-10, -0)	77 (74, 81)	83 (80, 86)	-6 (-11, -1)
% $\geq$ 1:8	72 (68, 75)	78 (74, 81)	-6 (-11, -1)	77 (74, 81)	83 (80, 86)	-6 (-11, -1)
GMT	26 (22, 30)	25 (21, 29)	1.04 (0.86, 1.27)	35 (29, 42)	35 (29, 41)	1.01 (0.83, 1.24)
C	**N=607**	**N=615**		**N=554**	**N=539**	
% Seroresponse[α]	60 (56, 64)	56 (52, 60)	4[μ] (-2, 9)	63 (59, 67)	57 (53, 62)	6[μ] (0, 11)
% $\geq$ 1:8	68 (64, 72)	64 (60, 68)	4 (-1, 10)	77 (73, 80)	74 (70, 77)	3 (-2, 8)
GMT	18 (15, 20)	13 (11, 15)	1.33 (1.11, 1.6)	36 (29, 45)	27 (21, 33)	1.36 (1.06, 1.73)
W-135	**N=593**	**N=605**		**N=542**	**N=533**	
% Seroresponse[α]	72 (68, 75)	58 (54, 62)	14[μ] (9, 19)	57 (53, 61)	44 (40, 49)	13[μ] (7, 18)

	2 through 5 years			6 through 10 years		
Endpoint by Serogroup	**MENVEO (95% CI)**	**Menactra (95%CI)**	**% difference (MENVEO – Menactra) or GMT ratio (MENVEO/ Menactra) (95%CI)**	**MENVEO (95%CI)**	**Menactra (95%CI)**	**% difference (MENVEO - Menactra) or GMT ratio (MENVEO/ Menactra) (95%CI)**
A	**N=606**	**N=611**		**N=551**	**N=541**	
% ≥ 1:8	90 (87, 92)	75 (71, 78)	15 (11, 19)	91 (88, 93)	84 (81, 87)	7 (3, 11)
GMT	43 (38, 50)	21 (19, 25)	2.02 (1.71, 2.39)	61 (52, 72)	35 (30, 42)	1.72 (1.44, 2.06)
Y	**N=593**	**N=600**		**N=545**	**N=539**	
% Seroresponse[α]	66 (62, 70)	45 (41, 49)	21 [μ] (16, 27)	58 (54, 62)	39 (35, 44)	19 [μ] (13, 24)
% ≥ 1:8	76 (72, 79)	57 (53, 61)	19 (14, 24)	79 (76, 83)	63 (59, 67)	16 (11, 21)
GMT	24 (20, 28)	10 (8.68, 12)	2.36 (1.95, 2.85)	34 (28, 41)	14 (12, 17)	2.41 (1.95, 2.97)

δ Serum bactericidal assay with exogenous human complement source (hSBA)

α Seroresponse was defined as: subjects with a pre-vaccination hSBA titer of <1:4, a post-vaccination titer of ≥1:8 and among subjects with a pre-vaccination hSBA titer of ≥ 1:4, a post-vaccination titer at least 4-fold higher than baseline.

μ Non-inferiority criterion for the primary endpoint met (the lower limit of the two sided 95%CI > -10% for vaccine group differences [MENVEO minus Menactra])

In Study V59P20, non-inferiority was demonstrated in both age strata for serogroups C, W-135 and Y. The non-inferiority end-point was narrowly missed for serogroup A in each age strata. The observed differences in seroresponse rates between the two vaccines were considered unlikely to represent clinically meaningful differences. In addition, non-inferiority was demonstrated for the secondary analysis of the combined age group (i.e., subjects 2 through 10 years of age) for all 4 serogroups.

The data presented in this application were intended to support a single dose schedule; however, as a secondary objective, the hSBA responses to a second dose were analyzed in study V59P20, and in the earlier supportive study V59P7. In the pivotal study, V59P20, children 2 through 5 years of age were randomized to receive a second dose 2 months following the first dose. Higher seroresponse rates, proportions with titers ≥ 1:8, and GMTs were observed for each serogroup at 28 days following the second dose compared to the group that received a single dose (see Table 4 below). In supportive study V59P7, the percentages of seroresponders were also notably higher in the MENVEO 2-dose group than in the MENVEO single dose group for all four serogroups (A 91% vs. 72%, C: 98% vs. 60%, W: 89% vs. 72%, and Y: 95% vs. 66%), and higher when the doses were spaced 12 months apart compared to a 6 month interval.

Table 4: V59P20 Immunogenicity of 2 doses vs 1 dose: % of Subjects with hSBA titer

1:8, seroresponse, and GMTs of Subjects One Month Post-Vaccination, in 2 through 5 year old, PP population

	hSBA Titer ≥ 1:8 (95% CI)		Seroresponse (95% CI)		GMTs (95% CI)	
	MENVEO 2 Doses	**MENVEO 1 Dose**	**MENVEO 2 Doses**	**MENVEO 1 Dose**	**MENVEO 2 Doses**	**MENVEO 1 Dose**
A[a]	91% (88-94)	72% (68-75)	91% (87-94)	72% (68-75)	64 (51-81)	27 (23-32)
C[b]	99% (97-100)	68% (64-72)	98% (95-99)	60% (56-64)	144 (118-177)	18 (15-21)
W[c]	99% (98-100)	90% (87-92)	89% (85-92)	72% (68-75)	132 (111-157)	41 (36-47)
Y[d]	98% (95-99)	76% (72-79)	95% (91-97)	66% (62-70)	102 (82-126)	23 (20-27)

a serogroup A: MENVEO 2 Doses N=291, MENVEO 1 Dose N=606
b serogroup C: MENVEO 2 Doses N=293, MENVEO 1 Dose N=607
c serogroup W: MENVEO 2 Doses N=288, MENVEO 1 Dose N=594
d serogroup Y: MENVEO 2 Doses N=286, MENVEO 1 Dose N=593

Additionally, persistence of serum bactericidal activity over a period of up to 12 months post-vaccination was investigated within the 2 years through 10 years age group in supportive studies V59P7, V59P8, and V59P10. The hSBA responses were assessed at 6 or 12 months post-vaccination in children 2 through 5 years of age in V59P7, 12 months after vaccination in children 2 through 10 years of age in V59P8, and 6 months after vaccination in children 2 through 10 years of age in study V59P10. In study V59P8 the percentage of subjects with hSBA ≥ 1:8 at 12 months compared to 1 month post-vaccination remained close for serogroup W (92% and 90% at 1 month and 12 months, respectively) and Y (88% and 77%, respectively). However the percentage of subjects with hSBA >1:8 at 12 months compared to 1 month post-vaccination was significantly lower for serogroup A (80% and 23% at 1 month and 12 months respectively) and C (73% and 53%, respectively). In study V59P10 the percentage of subjects with hSBA ≥ 1:8 at 6 months compared to 1 month post-vaccination decreased for all serogroups except for serogroup Y in the MENVEO group. In study V59P7 the percentage of subjects with hSBA ≥ 1:8 at 6 or 12 months compared to 1 month post-vaccination decreased by ~ 50 % for serogroup A with only 7-17% decrease for serogroup C, W-135 and Y.

Overall, the immunogenicity data from the pivotal and supportive studies indicate that MENVEO is immunogenic and stimulates functional antibody responses in children 2 through 10 years of age. The hSBA responses of MENVEO were non-inferior to those of the currently licensed quadrivalent vaccine Menactra, although in the pivotal study marginally lower responses were observed for serogroup A. The comparator vaccine is indicated for use in the 2 through 10 year age group as a single dose vaccine. This supplement contained immunogenicity data that showed an immunologic benefit to receipt of a second dose in the 2 through 5 year age group. Although the indication sought was for a single dose in children 2 though 10 years of age, the two dose data were considered clinically relevant. Therefore, the safety and immunogenicity of two doses administered to children 2

through 5 years of age was included in the package insert with permissive use of a second dose stated in the "Dosage and Administration" section.

Recommendations:

- The clinical data provided in this supplement demonstrate that MENVEO has a similar safety profile and similar immunogenicity to the licensed meningococcal conjugate vaccine Menactra in children 2 through 10 years of age. The data support a recommendation for approval of this vaccine administered as a single dose to individuals 2 through 10 years of age for prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroup A, C, Y and W-135.
- The hSBA responses following a two-dose regimen in children 2 through 5 years of age are substantially higher for each serologic end-point: proportion above the threshold of 1:8 hSBA, seroresponse and GMT, for all 4 serogroups. The difference in hSBA responses between a single dose regimen and a two-dose regimen is considered clinically relevant. Although the two-dose regimen was evaluated in an unblinded manner in the clinic, it was a randomized group and the comparison was a pre-defined secondary objective of the pivotal study. The safety data and the immunogenicity data should be presented in the label with permissive language for administration of a second dose 2 months after the first dose in children 2 through 5 years of age who are at continued high risk of meningococcal disease.
- Further evaluation of a 2-dose regimen of MENVEO is needed. The available data do not address: 1) whether older children (6 through 10 years of age) can benefit from a 2-dose regimen; 2) the need for revaccination (antibody persistence) of children 2 through 10 years of age; 3) safety of two dose regimens in the pediatric population. To address these limitations of the available data, a post marketing study is recommended.
- No safety signals were identified that should be specifically examined in post-marketing studies. However, because the total safety experience in the 2 through 10 year age group is insufficient to detect and characterize uncommon and rare adverse events of medical significance, a post marketing study to extend the safety experience is recommended.
- Please refer to the Postmarketing section for the agreed upon post marketing commitments.

5. Statistical

The statistical reviewer reached the following conclusions:

Results of the primary immunogenicity analyses performed in the per-protocol population show that non-inferiority was demonstrated for the primary immunogenicity endpoint, seroresponse at one month after a single vaccination, for serogroups C, W-135, and Y. However, for serogroup A, the non-inferiority criterion was narrowly missed, i.e., the lower bounds of the 95% confidence interval for the difference in seroresponse for Serogroup A between the MENVEO and the Menactra® groups (MENVEO-Menactra) were slightly below the pre-specified non-inferiority margin of -10% for both of the age groups (-10.1% and -10.8% for the 2-5 years and 6-10 years age groups, respectively. The pivotal study (Study V59P20) conducted in U.S. and Canada was designed to evaluate and ideally

demonstrate the non-inferiority of MENVEO® to Menactra®, an approved comparator in both the 2-5 years and 6-10 years age groups for serogroups A, C, W-135, and Y. It is important to note that the non-inferiority margin of -10% for seroresponse was nearly met when examining the 2-5 and 6-10 year old individuals, with observed lower confidence limits of -10.1% and -10.8%, respectively.

Three secondary objectives concerning various endpoints were examined in Study V59P20. When the endpoints were proportions of subjects achieving a post-vaccination titer of ≥1:4 or ≥1:8 in age groups 2-5 years and 6-10 years, the conclusions were similar to those based on the seroresponses (primary objective) described above, i.e. non-inferiority was not strictly met. However, the secondary objective of non-inferiority measured by geometric mean titers (GMTs) was met in both age groups for all the serogroups. In addition, two other secondary objectives were met. Specifically, when the seroresponse data were compared among children 2 through 10 years of age, i.e., the 2-5 years and 6-10 years were combined, the non-inferiority criteria measured by seroresponse was met. The combination of both age groups likely met the non-inferiority criterion because of the larger sample size which narrowed the confidence interval. Finally, another secondary objective in which the seroresponse rates were compared was between the two-dose and one-dose MENVEO® groups. The seroresponse rates were notably higher after two doses of MENVEO® (91%-98%) than those after a single dose of MENVEO® (60%-72%). The secondary objective of establishing the non-inferiority of the two-dose group to the single dose group was met.

The fact that this secondary objective of the non-inferiority of the two-dose group to the single dose group was met merits further attention. This was a pre-specified secondary objective, and immunogenicity data comparisons were made between subjects receiving one dose of MenACWY (N=593 to 607 varying by serogroup) to subjects receiving two doses of MenACWY (N=288 to 293 varying by serogroup). The baseline (Day 1) hSBA data were similar between the two groups. At Day 29, the percentages of seroresponders were consistently higher in the MenACWY 2-dose group than in the MenACWY single dose group for all four serogroups (A: 91% vs. 72%, C: 98% vs. 60%, W: 89% vs. 72%, and Y: 95% vs. 66%). Similarly, the percentages of subjects with hSBA ≥ 1:8 showed a large increase for all four serogroups in both vaccine groups, but were consistently higher for all four serogroups in the MenACWY 2-dose group (A: 91% vs. 72%, C: 99% vs. 68%, W: 99% vs. 90%, and Y: 98% vs. 76%). The GMTs showed a large increase for all four serogroups in both vaccine groups, but were significantly higher ($p<0.001$) for all four serogroups in the MenACWY 2-dose group (A: 64 vs. 27, C: 144 vs. 18, W: 132 vs. 41, and Y: 102 vs. 23). Therefore, not only were the non-inferiority objectives met, the two-dose group exhibited significant improvement in serological response vs. the one-dose group. Additional studies on dosing interval, persistence of antibody response, and further safety monitoring might be desirable if an indication for two doses may be requested in the future.

The safety profile of MENVEO® was evaluated in all four studies. A total of 3,181 children aged 2-10 years were exposed to MENVEO®. The overall serious adverse event rates were approximately 0.6% (excluding the events related to the varicella among the unvaccinated subjects in Study V59P7). Only one of the SAEs (a subject in Study V59P10 who experienced febrile convulsion two days after vaccination) was considered to be possibly related to vaccine. All other SAEs were considered not

related to vaccine. For local and systemic reactogenicity, pain was the most reported local reaction (20% to 45%). The event rates for MENVEO® varied by study but the majority of them were comparable with the reference groups (the rate differences were within 3%). In Study V59P20, it appears that there was an increase in event rates for erythema (>50mm) and headache in the children 6-10 years of age in the MENVEO® group when compared to the Menactra™ group. Please refer to the clinical review for more safety details and assessment of clinical significance of some of the observed differences.

Reports of Potential Vaccination Failures

There were no reports of serious adverse events interpretable as potential vaccine failures.

6. Bioresearch Monitoring

----------Information withheld per the Privacy Act----------.

---------- Information withheld per the Privacy Act ----------

---------- Information withheld per the Privacy Act ----------

7. Labeling

The package insert (PI) was evaluated by the entire review committee of the supplement. Each committee member contributed to internal discussions. An important issue for labeling was the inclusion of safety and immunogenicity information for children 2 through 5 years of age who received a second dose of MENVEO administered 2 months after the first dose. The consensus of the review committee was that these data were clinically meaningful and should be included in labeling. Therefore, Section 2.3, Dosage and Schedule was revised as follows: "For children 2 through 5 years of age at continued high risk of meningococcal disease a second dose may be administered 2 months after the first dose." The clinical safety data supporting a second dose were included under Adverse Events, Section 6.1 Clinical Trials Experience, and immunogenicity data were included in Section 14

Clinical Studies, where the hSBA seroresponse rates, proportion with hSBA titers ≥1:8 and GMTs for each serogroup following a second dose were described. The sponsor updated Section 6.2 - Post Marketing Experience Section with data available through the last quarterly report of 2010. After several other less substantial revisions to the PI were agreed to in a series of discussions with the applicant, the committee determined that the prescribing information is acceptable.

8. Postmarketing

The sponsor proposed to use routine and enhanced pharmocovigilance, but did not propose a Post Marketing Commitment to study the safety of MENVEO further. In addition to complying with requirements for adverse experience reporting for licensed biological products (21 CFR 600.80), Novartis will use expanded adverse experience reporting, to the Vaccine Adverse Event Reporting System (VAERS) for one year following product licensure to ensure rapid review of all medically important allergic and neurologic adverse events that occur after receipt of MENVEO® in children 2 through 10 years of age.

1. As 15 day reports: All serious adverse events whether expected/labeled or unexpected/unlabeled.
2. As 30 day (monthly) reports if not already submitted as 15 day reports: all allergic events, including anaphylaxis; urticaria; neurological events including Bell's palsy, Guillain-Barré Syndrome (GBS), encephalitis, encephalopathy, brachial neuritis, optic neuritis, other neuropathy, myelitis including transverse myelitis, ptosis, ataxis, multiple sclerosis, acute disseminated encephalomyelitis, cerebrovascular accidents or transient ischemic attacks; and all cases of intentional or non-intentional injury.
3. AEs of specific interest, such as GBS, Kawasaki's disease, vasculitis, and thrombocytopenia will be closely monitored and cases followed up to maximize data quality for case assessment (2.5.5).

In addition to complying with the requirements under 21 CFR 600.80, Novartis agreed to submit as 30 day (monthly) reports for one year following licensure of MENVEO in subjects 2-10 years of age: all allergic events, including anaphylaxis and urticaria, not reported as 15 day reports; neurological events not reported as 15 day reports, including Bell's palsy, Guillain-Barre syndrome, encephalitis, encephalopathy, brachial neuritis, optic neuritis, other neuropathy, myelitis including transverse myelitis, ptosis, ataxia, multiple sclerosis, acute disseminated encephalomyelitis, cerebrovascular accidents or transient ischemic attacks; all cases of intentional and non-intentional injury; and all cases of new-onset autoimmune disease, including ITP, Kawasaki's disease, myasthenia gravis, vasculitis, thrombocytopenia, arthritis, hemolytic anemia, and collagen-vascular disease not reported as a 15 day report.

As cited in the manufacturer's label, information regarding the safety of MENVEO® in children 2 through 10 years of age is based on 2,883 subjects. With a background rate of zero (where all observed events are considered associated with receipt of vaccine), this study of 2,883 subjects has 80% power of observing at least one event with an incidence rate of 5 or 6 in 10,000 (0.000559).

Events with incidence rates lower than 5 or 6 in 10,000 or with existing background rates, will be less likely to be observed. The size of the safety database is insufficient to exclude the possibility of very rare side effects. To better quantify and characterize observed adverse events, it was recommended that a larger post-marketing study be considered.

No safety issue has been identified that would warrant a Risk Evaluation and Mitigation Strategy (REMS) at this time.

As stated in the Labeling section, the sponsor updated Section 6.2 - Post Marketing Experience Section with data available through the end the last quarter of 2010 (the most recent data submitted to CBER).

Agreed upon Post Marketing Commitments

1. To conduct a comparative trial to further evaluate the safety, immunogenicity and antibody persistence of two doses of MENVEO versus one dose of MENVEO in children 2 through 10 years of age.

    - Concept Protocol Submission Date: May 2011
    - Final Protocol Submission Date: September 2011
    - Study Initiation Date: March 2012
    - Interim Study Report Submission Date: June 2013
    - Study/Trial Completion Date: February 2013
    - Final Report Submission Date: December 2013

2. To conduct an open label, descriptive, epidemiological safety surveillance study of MENVEO vaccine in subjects 2 through 10 years of age following licensure in this age range. The study will include two parts. Part I of the study will begin with the first administration of MENVEO vaccine to a child 2 through 10 years of age (inclusive) who receives medical care at the site where the study is being conducted. Part I will continue for 3 years, or until commencement of Part II, whichever occurs first. Part II of the study will be initiated if there is a recommendation by the Advisory Committee on Immunization Practices (ACIP) for routine use of MENVEO vaccine in at least one birth cohort within the 2-10 year age range.

    Part II will commence with the effective date of the ACIP recommendation, and will continue until 20,000 children are enrolled, or until 1 year has elapsed, whichever occurs last. The final study report for Part I will be submitted 1 year after the last subject has completed study Part I. If initiated, a final study report for Part II will be submitted 1 year after the last subject has completed study Part II. In the event there is no recommendation for routine use of meningococcal conjugate vaccine in this age group, Part II will be considered fulfilled when Part I is completed.

Study Milestones for PART 1

- Concept Protocol Submission Date: May 2011
- Final Protocol Submission Date: September 2011
- Study/Trial Completion Date: December 2014
- Final Report Submission Date: December 2015

9. Pediatrics

This supplement did not trigger PREA because the primary evaluation of effectiveness of MENVEO in children 2 through 10 years of age was a demonstration of non-inferiority of a single dose of MENVEO compared to a single dose of Menactra. The available data on 2 doses of MENVEO in children 2 through 5 years of age do not support a 2 dose primary series in the population.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

MENVEO was approved by the FDA for use in adolescents and adults 11-55 years of age in the U. S. on February 19, 2010. Under review of the original BLA for MENVEO, the FDA's Pediatric Review Committee agreed with Novartis' request to waive the pediatric study requirement for ages birth to 2 months because the necessary studies in this age group are impossible or highly impracticable and the product does not represent a meaningful therapeutic benefit in this age group. Pediatric studies for ages 2 months to 2 years are deferred for this application because this product is ready for approval for use in 2 years through 55 years and the pediatric studies for younger age groups are ongoing.

10. Advisory Committee Meeting

It was determined that review of the vaccine by the Vaccines and Related Biological Products Advisory Committee (VRBPAC) was not required because this product was not considered substantially different from other conjugated meningococcal vaccines licensed for a similar age-group, and there were no significant issues that required input from the VRBPAC.

11. Recommendation

The committee recommends approval of the BLA supplement.