

PHARMACOVIGILANCE PLAN REVIEW, NOVEMBER 10, 2010 -- MENACTRA®

IN INFANTS AND TODDLERS
OBE/DE/VSB MEMO

Date: November 10, 2010

FDA STN: 125089_395

Serial No.: 001

Sponsor: Sanofi Pasteur

Product: Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria Toxoid Conjugate Vaccine (MENACTRA®)

Subject: Pharmacovigilance Plan review for the supplemental biologic license application in support of a two dose series of MENACTRA® at 9 and 12 months of age

To: Lucia Lee
Chair, BLA Committee

From: Manette Niu, MD (HFM-222)
Medical Officer, Vaccine Safety Branch (VSB)

Through: David Martin, MD, MPH (HFM-222)
Acting Branch Chief, VSB

Richey Wilson, MD, JD, MS (HFM-220)
Director, Division of Epidemiology

CC: HFM-99/DCC
HFM-220/Robert Ball, MD, MPH
HFM-220/Rickey Wilson, MD, JD, MS
HFM-222/David Martin, MD, MPH
HFM-220/Chronological File

1. Background:

The sponsor is seeking an extension of the indication for use of Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria Toxoid Conjugate Vaccine (MENACTRA®) in children aged 9 and 12 months. This BLA supplement seeks licensure for active immunization by two intramuscular administrations of individuals at ages 9 and 12 months to prevent invasive meningococcal disease caused by *Neisseria meningitides* serogroups A, C, Y, and W-135.

ages 9 and 12 months to prevent invasive meningococcal disease caused by
The efficacy supplement reports data derived from one Phase II (MTA26), and three Phase III clinical studies conducted between 2006 and 2009 in the intended indication age range of infants and toddlers aged 9 months and 12 months. In the one Phase II study (MTA26), 55 subjects received 2 doses of MENACTRA® at age 9 and 12 months. In the three Phase III studies the first injection of MENACTRA® was administered alone to subjects at 9 months, and the second injection of MENACTRA® was administered either alone at 12 months (Group 1, Studies MTA44 and MTA37) or concomitantly with another pediatric vaccine: PROQUAD® [MMRV](Group 2), PREVNAR-7® [PCV](Group3), PROQUAD®, PREVNAR-7®, VAQTA® (HAV)(MTA48), or MMRV, PCV (Group 4, MTA37), or MMRV, PCV, HAV (Group 2, MTA48).

2. Safety data review:

2.1 Clinical Studies

2.1.1 Adverse Events

The primary safety population (Phase III studies alone) includes 3,267 subjects who received one dose of MENACTRA® at 9 months of age, 632 subjects who received a second dose of MENACTRA® alone at 12 months, 2,384 subjects who received a second dose of MENACTRA® with concomitant vaccine(s) at 12 months of age, and 797 subjects who received only a concomitant vaccine at 12 months of age, without MENACTRA®. Duration of follow up for each of the three Phase III studies was 180 days.

The most frequently reported SAE was febrile convulsion (26) most of which occurred more than 30 days after vaccination (i.e., two subjects experienced convulsions within 7 days of vaccination, 3 subjects between 8-30 days, and 21 subjects >30 days after vaccination). The next most common SAE was infection (i.e., bronchiolitis, gastroenteritis, pneumonia). Two subjects had febrile convulsion within 7 days of vaccination: 1) 5 days after vaccination preceded by fever and vomiting, 2) 1 day after MENACTRA® and PCV in a patient with suppurative otitis media--this patient also had a febrile seizure after receipt of Daptacel vaccination. Three subjects had febrile convulsion between 8 and 30 days after vaccination: 1) 23 days after vaccination in a patient with recent history of otitis media and mycoplasma infection, 2) 19 days after MENACTRA® and MMRV, this patient had two other febrile convulsions approximately 90 and 145 days after vaccination, 3) 26 days after MENACTRA® and MMRV in a patient with a recent history of pneumonia. Four SAEs were considered related to the vaccine by the clinical investigator: 1) IDDM, 2) 2 febrile convulsions (occurring 5 days after MENACTRA® vaccination in a patient with fever and vomiting, and 19 days after vaccination in a patient with suppurative otitis media with a history of 2 other febrile convulsions occurring approximately 90, and 145 days after vaccination), and, 3) respiratory distress occurring 7.5 hours after receiving 9 month vaccination—no

subsequent SAE or AE occurred in this patient after 12 month vaccination with MENACTRA® and concomitant vaccine. Four events of potential autoimmune conditions occurred more than 10 weeks after vaccination with MENACTRA® (juvenile arthritis, Kawasaki's disease, autoimmune neutropenia, diabetes mellitus).

In the three Phase III studies, nine subjects were discontinued from study due to a SAE (4 febrile convulsions or convulsions [days 45, 58, 65, 88], 1 asphyxia [accidental suffocation], 1 epilepsy [day 34], 1 Kawasaki's disease [day 77], 1 staphylococcal infection, 1 closed head trauma). In the MENACTRA® alone group, no patient did not complete vaccination of the study vaccine due to a SAE. Three SAE had an outcome of death (accidental suffocation, head trauma, and a fatality that occurred 125 days after vaccination presumably due to a convulsive disorder of undetermined etiology—the first episode of this subject's convulsion occurred 58 days after vaccination).

2.1.2 Limitations

Information regarding the safety of MENACTRA® in children aged 9-12 months is based on 3,899 subjects. With a background rate of zero (where all observed events are considered associated with receipt of vaccine), this study of 3,899 subjects has 80% power of observing at least one event with an incidence rate of 4.1 in 10,000 (0.000413). Events with incidence rates lower than 4.1 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.

2.2 Passive Surveillance (14 January 2005 through 13 January 2010)

Since licensure on 14 January 2005, a total of ---(b)(4)----- doses were distributed through the end of December 2009: ----(b)(4)---- (98.5%) in US, --(b)(4)- doses in Canada, --(b)(4)-- doses in Saudi Arabia, (b)(4) doses in Lebanon, and (b)(4) doses in France. The majority (95%) of doses were administered to adolescents 11 through 18 years of age. The most commonly reported AEs regardless of seriousness include: pyrexia, injection site reaction, headache, vomiting/nausea, GBS, fatigue, paresthesia, syncope, myalgia, dizziness/vertigo. The most commonly SAEs include: GBS, syncope, convulsion, acute disseminated encephalomyelitis, meningococcal disease, paresthesia, facial palsy, vaccination failure, headache, hypersensitivity/anaphylactic reaction. There were no cases of anaphylaxis, GBS, ADEM of transverse myelitis in the pre-licensure clinical trials submitted to the FDA in support of the original Biologics License Application. One case of facial palsy occurred in a subject with an ear infection 59 days after vaccination of the second dose of MENACTRA® and PCV.

2.3 Postmarketing Studies

In response to reports of GBS in MENACTRA® recipients, an epidemiologic study entitled "Risk of GBS following MCV4 vaccination," was completed. The study did not observe any cases of GBS within the 42 day risk window after MENACTRA® administration. Because of incomplete chart retrieval (67.5%), the incidence rates

produced from this study may be closer to a rate of 0.78 per 100,000 person-years, based on a 29% case validation rate for available charts. For a cohort of 1.4 million, it is unlikely that any potential excess risk would exceed 1.5 cases per million vaccinated.

3. Review of Proposed Pharmacovigilance Plan

The sponsor proposes to use routine and enhanced pharmacovigilance.

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 for one year following licensure of MENACTRA® in ages 9 and 12 months: all neurological events.
3. Routine signal detection and evaluation based on clinical review of individual case reports and case series, complemented by periodic disproportionality analysis of VAERS data (EBGM at least 2.5 or EB05 at least 1.8).
4. A large post-licensure descriptive, safety surveillance study of routine use of MENACTRA® in infants and toddlers (MTA57). The study will have 2 phases: Phase I started with first administration of MENACTRA® to 9 to 12 month old children in KPMCP following FDA approval and will continue until the effective date of a recommendation issued by the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics Committee on Infectious Diseases (COID) or both, for universal use of MENACTRA® by at least one birth cohort within the 9-12 month age range, or until 3 years have elapsed, whichever occurs first. Phase II will commence with the effective date of said universal recommendation, and will continue until 20,000 children have come under surveillance, or until 1 year has elapsed, whichever occurs last.
5. A clinical trial to determine the immunogenicity and safety profile of MENACTRA® in toddlers 13 through 23 months of age (MTA55).

4. Conclusions

ANALYSIS:

Information regarding the safety of MENACTRA® in children aged 9-12 months is based on 3,899 subjects. With a background rate of zero (where all observed events are considered associated with receipt of vaccine), this study of 3,899 subjects has 80% power of observing at least one event with an incidence rate of 4.1 10,000 (0.000413). Events with incidence rates lower than 4.1 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.

Questions and comments to the Sponsor:

COMMENT 1

At the time of this review, no safety issue has been identified that would warrant a Risk Evaluation and Mitigation Strategy (REMS) or Post Marketing Requirement. CBER OBE recommends that the list of adverse events included in enhanced pharmacovigilance reporting section is consistent with requirements for 30-day adverse event reporting as specified in the approval letter for MENACTRA® (ages 2-10 years)(October 18, 2007). Please include these events under requirements for 30-day adverse event reporting: all allergic events, including anaphylaxis and urticaria, not reported as a 15 day report; new-onset autoimmune disease, including idiopathic thrombocytopenia purpura, diabetes, arthritis, hemolytic anemia, myositis, Kawasaki's disease, Henoch-Schonlein purpura, and collagen-vascular disease not reported as a 15 day report.

QUESTION 1

What is the exclusion criterion regarding HMO membership status in MTA59 for evaluation of new onset autoimmune disease? (In Study MTA30/MTA38 analysis for new onset autoimmune disease was restricted to persons who have been continuously enrolled as plan members for at least 2 years).