HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

1 December 2010

MENVEO, powder and solution for injection
Meningococcal group A, C, W_{135} and Y conjugate vaccine
Box of 1 vial + 1 prefilled syringe (CIP: 360 379-1)

Applicant: NOVARTIS VACCINES AND DIAGNOSTICS SAS

Neisseira meningitidis group A oligosaccharide*
Neisseira meningitidis group C oligosaccharide*
Neisseira meningitidis group W_{135} oligosaccharide*
Neisseira meningitidis group Y oligosaccharide*
* conjugated to *Corynebacterium diphtheriae* CRM_{197} protein

ATC code: J07AH08

List I

Medicine for medical prescription only

Date of Marketing Authorisation (centralised procedure): 15 March 2010

Reason for request: Inclusion on the list of medicines approved for hospital use.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1 Active ingredient

Neisseira meningitidis group A oligosaccharide*
Neisseira meningitidis group C oligosaccharide*
Neisseira meningitidis group W_{135} oligosaccharide*
Neisseira meningitidis group Y oligosaccharide*

* conjugated to *Corynebacterium diphtheriae* CRM_{197} protein

1.2 Background

MENVEO is a tetravalent conjugate vaccine (serogroups A, C, W_{135}, Y) indicated in the prevention of invasive meningococcal infections in persons aged 11 years and over.

1.3 Indication

"MENVEO is indicated for active immunisation of adolescents (from 11 years of age) and adults at risk of exposure to *Neisseria meningitidis* serogroups A, C, W_{135} and Y, to prevent invasive disease.
The use of this vaccine should be in accordance with official recommendations."

1.4 Dosage

"Adults
MENVEO should be administered as a single 0.5 ml injection.

Paediatric population
MENVEO is indicated from the age of 11 years and above and should be administered as a single 0.5 ml injection.

Elderly
There are limited data in individuals aged 56-65 years and there are no data in individuals aged > 65 years.

The need for, and timing of, a booster dose of MENVEO has not yet been determined.

Method of administration
MENVEO is given as an intramuscular injection, preferably into the deltoid muscle.
It must not be administered intravenously, subcutaneously or intradermally.
Separate injection sites must be used if more than one vaccine is being administered at the same time."

1.5 Interactions with other vaccines

"MENVEO has been evaluated in two co-administration studies with the absorbed tetanus-diphtheria-acellular pertussis vaccine(Tdap) alone or Tdap and recombinant human papillomavirus quadrivalent (Types 6, 11, 16 and 18) vaccine (HPV).

There was no evidence of an increased rate of reactogenicity or change in the safety profile of the vaccines in either study. Antibody responses to MENVEO and to the diphtheria, tetanus or HPV vaccines were not negatively affected by co-administration.
The administration of MENVEO one month after Tdap resulted in statistically significantly lower serogroup W_{135} antibody responses. Since there was no impact on the seroprotection rate, the clinical consequences are presently unknown.

There was evidence of some suppression of antibody response to two of the three B pertussis antigens. The clinical relevance of this observation is unknown. After vaccination, over 97% of subjects had detectable pertussis titres to all three pertussis antigens.

Concomitant administration of MENVEO and vaccines other than those listed above has not been studied. It is advised that MENVEO should not be administered at the same time as other vaccines in particular live vaccines, unless absolutely necessary. Concomitant vaccines should always be administered at separate injection sites and preferably contralateral. It should be checked if the adverse reactions may be intensified by any co-administration.
If a vaccine recipient is undergoing immunosuppressant treatment, the immunological response may be diminished."

2. SIMILAR MEDICINAL PRODUCTS

2.1 ATC Classification (2010)

J: Antiinfectives for systemic use
J07: Vaccines
J07A: Bacterial vaccines
J07AH: Meningococcal vaccines
J07AH08: Meningococcus conjugated to purified tetravalent polysaccharide antigens

2.2 Medicines in the same therapeutic category

2.2.1 Strictly comparator medicines

There is no other tetravalent meningococcal conjugate vaccine with marketing authorisation.

2.2.2 Not-strictly comparator medicines in the same therapeutic category

MENCEVAX, powder and solvent for solution for injection: tetravalent meningococcal polysaccharide (A, C, W_{135}, Y) non-conjugate vaccine indicated in a broader population (adults, adolescents and children over 2 years) than that of MENVEO (adults and adolescents aged over 11 years).
Recommended in individuals aged 2 years and over[1] and approved for use by hospitals[2].

2.3 Medicines with a similar therapeutic aim

- Monovalent meningococcal serogroup C conjugate vaccines:
  MENJUGATEKIT 10 micrograms, powder and solvent for suspension for injection.
  MENINGITEC, suspension for injection in prefilled syringe.
  NEISVAC, suspension for injection in prefilled syringe.
  The HCSP recommends, in its opinion of 24 April and 26 June 2009, the systematic vaccination of infants aged between 12 and 24 months with a single dose of meningococcal group C conjugate vaccine and the extension of this systematic vaccination up to the age of 24 years.
  They are included on the list of medicines reimbursed by National Insurance and approved for hospital use.

- Bivalent meningococcal serogroups A+C non-conjugate vaccine:
  MENINGOCOCCAL POLYSACCHARIDE A+C VACCINE, powder and solvent for suspension for injection in prefilled syringe. Indicated in individuals aged 2 years and over and approved for use by hospitals.

[1] Haut Conseil de la Santé Publique opinion of 5 September 2008 on the use of the vaccine MENCEVAX
[2] Transparency Committee opinion of 4 March 2009 on MENCEVAX

3. ANALYSIS OF AVAILABLE DATA

In support of its application, the company has submitted five clinical studies that evaluated the immunogenicity and safety of MENVEO (tetravalent meningococcal conjugate vaccine):

- Two non-inferiority studies:
  - V59P13, which was a phase III study in adolescents and adults aged between 11 and 55 years versus a tetravalent conjugate vaccine (MENACTRA);
  - V59P6, which was a phase II study in adolescents aged between 11 and 17 years versus a tetravalent non-conjugate vaccine (MENOMUNE).
- VP59P11 and V59P18, two phase III studies of coadministration with other vaccines, which are described previously under *Interactions with other vaccines*.
- V59P9, a phase II study in babies aged between 6 and 12 months versus a meningococcal serogroup C conjugate vaccine (MENJUGATE Kit), which is not described, as this age range is not covered by the marketing authorisation of MENVEO.

No studies have been carried out of the protective efficacy of MENVEO.

3.1 Immunogenicity data

3.1.1 Study V59P13[3]

Randomised, open-label phase III study in subjects aged between 11 and 55 years who had not previously been vaccinated against meningococcus.
One of the main objectives was to demonstrate the non-inferiority, in terms of immunogenicity, of the MENVEO tetravalent group A, C, Y, W_{135} conjugate vaccine compared with another tetravalent group A, C, Y, W_{135} conjugate vaccine (MENACTRA[4]) that does not have marketing authorisation in France (it was available under a temporary authorisation for use by a named patient [ATU nominative in French] up to June 2010).

Vaccination schedule: Randomisation was stratified by patient age (11 to 18 years, 19 to 34 years and 35 to 55 years) and by centre:
- MENVEO group: one 0.5 ml intramuscular injection (n = 2649);
- MENACTRA group: one 0.5 ml intramuscular injection (n = 875).

Primary endpoint: Percentage of subjects showing an antibody response for each serogroup (A, C, W_{135} and Y) at day 28 in adolescents (11 to 18 years) and adults (19 to 55 years).

Antibody response was defined as an hSBA antibody titre[5] ≥ 1:8 for subjects who were seronegative at inclusion (hSBA < 1:4) or multiplied by a factor of 4 in the case of subjects seropositive at inclusion (hSBA ≥ 1:4).

Non-inferiority was achieved if the lower limit of the $CI_{95\%}$ of the difference in the percentage of subjects showing an antibody response (MENVEO minus MENACTRA) was above -10% for each of the four serogroups.

[3] Jackson LA, Baxter R, Reisinger K et al. V59P13 Study Group. Phase III comparison of an investigational quadrivalent meningococcal conjugate vaccine with the licensed meningococcal ACWY conjugate vaccine in adolescents. Clin Infect Dis 2009; 49 (1): e1-10
[4] MENACTRA has been granted marketing authorisation in the United States, having demonstrated its equivalence to the vaccine MENOMUNE, for which the marketing authorisation was rescinded on 6 April 2008.
[5] The serogroup-specific subcapsular serum bactericidal antibody (hSBA) titre was determined using human serum as the exogenous complement source.

Results:
A total of 3539 subjects underwent randomisation (2180 aged between 11 and 18 years, 413 aged between 19 and 34 years and 946 between 35 and 55 years).

The percentage of adolescents who showed an antibody response was between 68% and 75% in the MENVEO group and between 41% and 73% in the MENACTRA group, i.e. a difference of 2% to 27% depending on serogroup.
The percentage of adults aged between 19 and 55 years who showed an antibody response was between 50% and 67% in the MENVEO group and between 40% and 68% in the MENACTRA group, i.e. a difference of -1% to 16% depending on serogroup.
The lower limit of the confidence interval of the difference in the percentages of adults and adolescents who showed an antibody response was above the predefined threshold of -10% in the PP population for each of the four serogroups (see Table 1).

Table 1: Study V59P13: Percentage of subjects showing an antibody response by serogroup and age range in the per-protocol analysis (n = 3393)

Serogroup			11-18 years			19-55 years		
			MENVEO	**MENACTRA**	**Difference (95% CI)**	**MENVEO**	**MENACTRA**	**Difference (95% CI)**
A	Initial titre	<1;4	75% 780/1039	66% 230/347	9% (3%,15%)	67% 582/875	67% 191/283	-1% (-7%,5%)
		≥1:4	58% 21/36	67% 8/12	-8% (-35%,24%)	70% 62/88	71% 27/38	-1% (-17%,18%)
	Total		75% 801/1075	66% 238/359	**8%** **(3%,14%)**	67% 780/1039	68% 218/321	**-1%** **(-7%,5%)**
C	Initial titre	<1;4	79% 771/977	79% 260/331	0% (-5%,6%)	71% 425/596	62% 133/214	9% (2%,17%)
		≥1:4	68% 345/506	62% 105/170	6% (-2%,15%)	61% 223/365	51% 53/104	10% (-1%,21%)
	Total		75% 1116/1483	73% 365/501	**2%** **(-2%,7%)**	67% 648/961	58% 186/318	**9%** **(3%,15%)**
W	Initial titre	<1;4	94% 570/609	83% 150/180	10% (5%,17%)	82% 131/160	71% 67/94	11% (0%,22%)
		≥1:4	47% 193/415	28% 30/108	19% (9%,28%)	35% 112/324	26% 52/198	8% (0%,16%)
	Total		75% 763/1024	63% 180/288	**12%** **(6%,18%)**	50% 243/484	41% 119/292	**9%** **(2%,17%)**
Y	Initial titre	<1;4	81% 510/630	54% 95/176	27% (19%,35%)	66% 173/263	52% 83/160	14% (4%,23%)
		≥1:4	47% 192/406	22% 26/118	25% (16%,34%)	45% 108/240	27% 39/146	18% (9%,28%)
	Total		68% 702/1036	41% 121/294	**27%** **(20%,33%)**	56% 281/503	40% 123/306	**16%** **(9%,23%)**

The non-inferiority of MENVEO to MENACTRA was therefore demonstrated at day 28 in terms of the percentage of adolescents and adults who showed an antibody response for each serogroup (A, C, W_{135} and Y).

For three of the four serogroups (A, W_{135} and Y), the results also suggest that MENVEO is superior to MENACTRA, assuming this is replicated in the different analysis populations of the study (data not supplied).

3.1.2 Study V59P6[6]

Randomised, open-label phase II study in 524 adolescents aged between 11 and 17 years who had not previously been vaccinated against meningococcus.
One of the main objectives was to demonstrate the non-inferiority, in terms of immunogenicity, of the MENVEO tetravalent group A, C, Y, W_{135} conjugate vaccine (single injection) compared with a tetravalent group A, C, Y, W_{135} non-conjugate vaccine (single injection of MENOMUNE).

Note: Following the withdrawal, on 6 April 2008, of the marketing authorisation of MENOMUNE, the Haut Conseil de la Santé Publique (HCSP) recommends, in its opinion of 5 September 2008 on the use of the vaccine MENCEVAX, that the vaccines MENOMUNE and MENCEVAX should be considered equivalent and that the previous recommendations concerning the vaccine MENOMUNE should apply to the latter.

One month after vaccination, the percentage of adolescents in the MENVEO group (no distinction made between seronegative or seropositive[7] at inclusion) who showed an antibody response defined as an hSBA titre ≥ 1:4 was shown to be non-inferior to that of the MENOMUNE group for each of the four serogroups (primary endpoint).
Non-inferiority was assumed if the lower limit of the $CI_{95\%}$ of the difference in the percentage of subjects showing an antibody response (MENVEO minus MENOMUNE) was above -10% for each of the serogroups.

An exploratory analysis to evaluate the percentage of adolescents showing an antibody response defined as an hSBA titre ≥ 1:8 (i.e. a stricter threshold than the ≥ 1:4 employed for the analysis of the primary endpoint) was carried out after exclusion of adolescents who were seropositive at inclusion. In this analysis, the percentage of adolescents showing an antibody response one month after vaccination was higher in the MENVEO group than in the MENOMUNE group for each of the serogroups (A, C, W and Y).

3.1.3 Other data

In the absence of a direct comparison of the immune response induced for serogroup C between the MENVEO tetravalent conjugate vaccine and a monovalent serogroup C conjugate vaccine, the company refers in its dossier to a comparison of immunogenicity results for serogroup C obtained in four studies.
This comparison has not been subjected to a statistical analysis and cannot be taken into account by the Committee.

3.3 Adverse effects

In the studies that compared MENVEO with other tetravalent meningococcal vaccines, the incidence and severity of local, systemic or other reactions was, according to the SPC, generally comparable in adolescents and adults.

The most frequently reported adverse events were as follows:

- very common (frequency ≥ 1/10): headache; nausea; pain, erythema (≤ 50 mm), induration (≤ 50 mm) and pruritus at the injection site; malaise
- common (≥ 1/100 and < 1/10): erythema; erythema at the injection site (> 50 mm); induration at the injection site (> 50 mm); fever ≥ 38 °C; chills

These non-serious events generally lasted one or two days.

[6] Jackson LA, Jacobson RM, Dull PM et al. A randomized trial to determine the tolerability and immunogenicity of a quadrivalent meningococcal glyconjugate vaccine in healthy adolescents. Pediatr Infect Dis J 2009; 28:86-91
[7] Subjects were considered seropositive at inclusion if their hSBA titre was ≥ 1:4 (and seronegative if it was < 1:4).

In adolescents the safety of the vaccine MENVEO was better than that of the adsorbed tetanus-diphtheria-acellular pertussis vaccine, and was similar when given concomitantly or sequentially.

Moreover, the number of adverse events in a limited number of subjects aged between 56 and 65 years who were administered MENVEO (N = 216) was similar to that observed in subjects aged between 11 and 55 years.

3.4 Conclusion

The immunogenicity data for MENVEO in individuals aged between 11 and 55 years not previously vaccinated against meningococcus are based primarily on one non-inferiority study versus another tetravalent (A, C, W_{135} and Y) conjugate vaccine, MENACTRA, which does not have marketing authorisation in France.
The non-inferiority of MENVEO to MENACTRA was demonstrated one month after vaccination in terms of the percentage of adolescents and adults who showed an antibody response for each of the four serogroups (A, C, W_{135} and Y).

The need for a booster dose and the duration of protection conferred by this vaccine are unknown.
The comparison of the immune response against serogroup C of the MENVEO tetravalent conjugate vaccine with that of a monovalent group C conjugate vaccine was not carried out in accordance with vaccine evaluation standards.
No data are available in individuals aged over 65 years or with immunodeficiency and in adolescents and adults for evaluation of the immunogenicity of MENVEO when administered after another meningococcal vaccine (bivalent A+C or tetravalent non-conjugate).

The frequency and severity of adverse events were generally comparable between MENVEO and other tetravalent meningococcal vaccines. The adverse events most frequently reported with MENVEO were primarily headache and pain at the injection site.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1 Actual benefit

Invasive meningococcal infections are serious transmissible infections which manifest primarily as forms of meningitis or meningococcaemia, the most severe form being *purpura fulminans*.

This proprietary medicinal product is a preventive therapy.

The efficacy (immunogenicity)/adverse effects ratio is high.

There is an alternative vaccine against serogroups A, C, W_{135}, Y (MENCEVAX, non-conjugate vaccine, recommended by the HCSP for the past 24 months).

Public health benefit

The burden, in France, of invasive meningococcal infection (IMI) caused by serogroups W_{135} and Y can be considered low.
Only vaccination against serogroup C is recommended for the general population (2010 vaccination schedule), for which a monovalent group C conjugate vaccine is used.
The need for vaccination against meningococcal infection due to serogroups A, C, W_{135} and Y is confined to particular populations (primarily certain research laboratory workers, persons travelling to endemic areas or pilgrims travelling to Mecca). This is most often an acute preventive need, as opposed to a long-term need (such as for vaccination against serogroup C).
This acute need is already covered by the vaccine MENCEVAX, a non-conjugate vaccine covering all these serogroups.

The data presented for MENVEO (studies of the non-inferiority of the immune response and safety) do not allow us to quantify its potential impact on morbidity/mortality due to IMI, an impact which may be linked in particular with an immune response that could be stronger and more long-lasting, and with a booster effect, than that of the non-conjugate vaccine.
However, MENVEO only partly meets an identified need, due in particular to the absence of data in children under 11 years.

Consequently, MENVEO does not benefit public health at the present time.

The actual benefit of MENVEO is substantial in populations aged over 11 years and recommended by the Haut Conseil de la Santé Publique.

4.2 Improvement in actual benefit (IAB)

In view of the demonstration, in individuals aged between 11 and 55 years, of the non-inferiority of the short-term immunogenicity of MENVEO versus conjugate and non-conjugate meningococcal vaccines and comparable safety, but taking into account:

- the absence of comparative immunogenicity data on the duration of protection,
- the absence of immunogenicity data in individuals undergoing revaccination after a different meningococcal vaccine (monovalent group C conjugate, bivalent group A+C or tetravalent non-conjugate),

the Committee considers that MENVEO does not offer any improvement in actual benefit (IAB V) over MENCEVAX in the prevention of invasive meningococcal infections caused by serogroups A, C, W_{135} and Y, in adolescents over 11 years and adults, in the populations recommended by the Haut Conseil de la Santé Publique.

4.3 Therapeutic use

According to the opinion of the Haut Conseil de la Santé Publique[8], vaccination with the MENVEO tetravalent meningococcal group A, C, Y, W_{135} conjugate vaccine is preferentially recommended in situations where expansion of meningococcal vaccination to the other serogroups A, Y and W_{135} is necessary for the following populations:

- research laboratory staff working specifically on meningococcus,
- individuals aged 11 years and over temporarily exposed to meningococcus A, Y or W_{135}
  - as a result of contact with a person with invasive meningococcal infection of serogroup A, Y or W_{135}. The vaccination must then be carried out no later than 10 days after hospitalisation of the index case,
  - persons travelling:
    - to a region where meningococcus A, Y or W_{135} is endemic, in particular the meningitis belt in sub-Saharan Africa during the dry season or to any other region in the grip of an epidemic, staying under conditions of prolonged close contact with the local population. Vaccination must be carried out at least 10 days before departure,
    - on pilgrimage to Mecca (Hajj or Umrah). Vaccination must be carried out at least 10 days before departure.

Individuals aged 2 years and over,
- with a terminal complement component deficiency or undergoing anti-C5A treatment,
- with properdin deficiency,
- or who have anatomic or functional asplenia,

must be provided with sustained, long-lasting protection against all meningococcus serogroups. In order to avoid immunological hyporeactivity phenomena during successive administrations of meningococcal non-conjugate vaccines, the MENVEO tetravalent conjugate vaccine should be preferred.

Note: A clarification by AFSSAPS on the vaccination of children aged 2 to 11 years with risk factors for invasive meningococcal infection was issued on 25 November 2010[9].
Pending the application for extension of the indication to children aged 2 to 11 years, AFSSAPS recommends use of this vaccine in children aged 2 to 11 years with risk factors for invasive meningococcal infection, i.e. with terminal complement component deficiency (hereditary or acquired), properdin deficiency or anatomic or functional asplenia.

According to the Haut Conseil de la Santé Publique, if vaccination with MENVEO is planned in an individual who has previously received a meningococcal vaccine:
- there is no recommended gap between injections after vaccination with a monovalent group C conjugate vaccine;
- a gap of three years is recommended after vaccination with a tetravalent non-conjugate vaccine (estimated duration of protection of the non-conjugate vaccine);
- where there is an absolute and pressing need to extend protection to serogroups Y and W_{135} of individuals vaccinated less than three years previously with the group A+C non-conjugate vaccine, and in the absence of specific data, there is no recommended minimum gap between vaccinations.

[8] Haut Conseil de la Santé Publique opinion of 25 June 2010 on the use of the MENVEO tetravalent meningococcal group A, C, Y, W135 conjugate vaccine
[9] Clarification: Vaccination of children aged 2 to 11 years with risk factors for invasive meningococcal infection, November 2010

4.4 Target population

The target population of MENVEO is represented by the following subgroups:

1. Research laboratory staff working specifically on meningococcus;

There are no available data that allow estimation of this subgroup.

2. Individuals aged 11 years and over temporarily exposed to meningococcus A, Y or W_{135}

- as a result of contact with a person with invasive meningococcal infection of serogroup A, Y or W_{135}[10]:

  In 2009, of the 628 notified cases of invasive meningococcal infection in France, 35 concerned serotypes A, W_{135} and Y. Among people living in close proximity with a vaccine serogroup (A, C, W_{135}, Y) case, the mean number of vaccinated persons was 10 (i.e. 350 persons). In hospitals, this figure was 17.6 (i.e. 616 persons).
  On the basis of these data, the number of patients who would benefit from vaccination with MENVEO can be estimated at 970 persons.

- travelling to areas where meningococcus A, Y or W_{135} is endemic:

  There are no available epidemiological data that allow estimation of the number of travellers aged 11 years and over, particularly to the meningitis belt in sub-Saharan Africa during the dry season or to any other region in the grip of an epidemic, staying under conditions of prolonged close contact with the local population.

- travelling on pilgrimage to Mecca:

  In 2007, there were 30,120 pilgrims travelling from France[11].

3. Persons aged 11 years and over with a terminal complement component deficiency or undergoing anti-C5A treatment, properdin deficiency or with anatomic or functional asplenia.

The number of individuals with these immune deficiencies is very small and there are few data available. The target population of eculizumab, a monoclonal antibody that binds specifically to complement protein C5 and inhibits the terminal complement component, has been estimated at between 270 and 340 patients[12].

In these subgroups there are no available epidemiological data that allow estimation specifically of the number of individuals aged 11 years and over.

On this basis, the target population of MENVEO is estimated at about 31,500 persons.

4.5 Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the indications and at the dosages in the Marketing Authorisation and in the populations aged 11 years and over recommended by the Haut Conseil de Santé Publique.

Packaging: Appropriate for the prescription conditions.

[10] Parent du Châtelet I, Taha M-K, Lévy-Bruhl D et al. Les infections invasives à méningocoques en France, en 2009 [Invasive meningococcal infections in France in 2009]. Bull épidémiol Hebd 2010;31-32:339-43
[11] Transparency Committee opinion of 28 May 2008 on the proprietary medicinal product SOLIRIS
[12] Transparency Committee opinion of 28 May 2008 on the proprietary medicinal product SOLIRIS