**NIMENRIX, powder and solvent for injectable solution.**
**Meningococcal Group A, C, W135 and Y conjugate vaccine.**
B/1 glass vial and 1 prefilled glass syringe with 2 needles (CIP code: 34009 222 539 3 0)

**APPLICANT:** GLAXOSMITHKLINE

| INN | Neisseira meningitidis group A polysaccharide*  
|     | Neisseira meningitidis group C polysaccharide*  
|     | Neisseira meningitidis group W135 polysaccharide*  
|     | Neisseira meningitidis group Y polysaccharide*  
|     | * conjugated to tetanus toxoid carrier protein. |
| ATC Code (2012) | J07AH08 (Meningococcal vaccine) |
| Reason for the review | Inclusion |
| List(s) concerned | Inclusion for hospital use (French Public Health Code L.5123-2) |
| Indication(s) concerned | “Active immunisation for individuals from the age of 12 months and above against invasive meningococcal diseases caused by *Neisseria meningitidis* group A, C, W135 and Y.” |
### Actual Benefit

Substantial in subjects aged 12 months and older, and only in those populations recommended by the Haut Conseil de santé publique (HCSP, or the French High Council for Public Health), i.e., people with risk factors for invasive meningococcal infections and people visiting an endemic area.

### Improvement in Actual Benefit

- In light of the available information and given the lack of alternative treatments with a Marketing Authorisation for serogroups A, W135 and Y in the 12-to-23-month age range, the Committee considers that NIMENRIX offers a substantial improvement in actual benefit (IAB I) in the prevention of invasive meningococcal infection caused by serogroups A, W135 and Y in children 12 to 23 months of age in the populations recommended by the HCSP.

- NIMENRIX does not offer an improvement in actual benefit (non-existent IAB) in the prevention of invasive meningococcal infection caused by serogroups A, C, W135 and Y in children aged 2 years and older, adolescents and adults.

### Therapeutic use

The HCSP recommends opting for tetravalent meningococcal conjugate vaccines:
- from the age mentioned in their respective Marketing Authorisations (1 year of age for NIMENRIX, 2 years of age for MENVEO)
- instead of non-conjugated meningococcal vaccines (meningococcal polysaccharide vaccine A+C and MENCEVAX).

The need for immunisation against meningococcal infections caused by serogroups A, W135 and Y is seen in specific populations: certain laboratory research staff, certain people with risk factors for invasive meningococcal infection and people visiting an endemic area, and particularly pilgrims visiting Mecca.
# 01 Administrative and Regulatory Information

<table>
<thead>
<tr>
<th><strong>Marketing Authorisation (centralised procedure)</strong></th>
<th>20 April 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prescribing and dispensing conditions/special status</strong></td>
<td>List I Medicinal products subject to medical prescription</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th><strong>ATC classification</strong></th>
<th>2012 Antiinfectives for systemic use</th>
<th></th>
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<tbody>
<tr>
<td>J:</td>
<td>Vaccines</td>
<td></td>
</tr>
<tr>
<td>J07:</td>
<td>Bacterial vaccines</td>
<td></td>
</tr>
<tr>
<td>J07A:</td>
<td>Meningococcal vaccines</td>
<td></td>
</tr>
<tr>
<td>J07AH:</td>
<td>Meningococcus, tetravalent purified polysaccharides antigen conjugated</td>
<td></td>
</tr>
</tbody>
</table>
02 BACKGROUND

- Request for initial registration of the proprietary medicinal product NIMENRIX.

- NIMENRIX is a new tetravalent meningococcal conjugate vaccine for active immunisation of individuals against invasive meningococcal infections caused by Neisseria meningitidis groups A, C, W_{135} and Y. The vaccine is indicated from the age of 12 months and above unlike MENVEO which is indicated from the age of 2 years and above.

03 THERAPEUTIC INDICATION

“Nimenrix is indicated for active immunisation of individuals from the age of 12 months and above against invasive meningococcal diseases caused by Neisseria meningitidis group A, C, W_{135} and Y”.

04 DOSAGE

Posology
NIMENRIX should be used in accordance with available official recommendations.

Primary vaccination:
A single dose of 0.5 ml of the reconstituted vaccine is used for immunisation.

Booster vaccination:
NIMENRIX may be given as a booster dose in subjects who have previously been vaccinated with a plain polysaccharide meningococcal vaccine.

The need for a booster dose in subjects primed with NIMENRIX has not yet been established.

Paediatric population
The safety and efficacy of NIMENRIX in children under 12 months of age has not yet been established. No data are available.

Elderly population
There are no data in individuals aged > 55 years.

Method of administration
Immunisation should be carried out by intramuscular injection only, preferably into the deltoid muscle.
In children 12 to 23 months of age, the vaccine may also be administered in the anterolateral part of the thigh.
**05 INTERACTIONS WITH OTHER VACCINES**

“NIMENRIX can be given concomitantly with any of the following vaccines: hepatitis A (HAV) and hepatitis B (HBV) vaccines, measles - mumps - rubella (MMR) vaccine, measles - mumps - rubella - varicella (MMRV) vaccine, 10-valent pneumococcal conjugate vaccine or unadjuvanted seasonal influenza vaccine.

NIMENRIX can also be given concomitantly with combined diphtheria - tetanus - acellular pertussis vaccines in the second year of life, including combination DTaP vaccines with hepatitis B, inactivated polio or *Haemophilus influenzae* type b, such as DTaP-HBV-IPV/Hib vaccine.

Whenever possible, NIMENRIX and a TT-containing vaccine, such as DTaP-HBV-IPV/Hib vaccine, should be co-administered or NIMENRIX should be administered at least one month before the TT-containing vaccine. The sequential administration of NIMENRIX one month after a DTaP-HBV-IPV/Hib vaccine resulted in lower MenA, MenC and MenW-135 GMTs. The clinical relevance of this observation is unknown, since at least 99.4% of subjects (N=178) had rSBA titres \( \geq 8 \) for each group (A, C, W-135, Y).

One month after co-administration with a 10-valent pneumococcal conjugate vaccine, lower Geometric Mean antibody Concentrations (GMCs) and opsonophagocytic assay (OPA) antibody GMTs were observed for one pneumococcal serotype (18C conjugated to tetanus toxoid carrier protein). Clinical relevance of this observation is unknown. There was no impact of co-administration on the other nine pneumococcal serotypes.

If NIMENRIX is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

It may be expected that in subjects receiving immunosuppressive treatment, an adequate response may not be elicited.”

**06 THERAPEUTIC NEED**

Invasive meningococcal infections (IMI) are serious transmissible diseases that mainly present as meningitis or meningococcal septicaemia, of which the most severe form is *purpura fulminans*.

According to the BEH,¹ 522 cases of IMI were reported in 2010, including 510 in mainland France, i.e., an incidence corrected for underreporting of 0.89 per 100,000 people. IMI cases in France are still mainly caused by meningococcal serogroup B (74% of cases): the highest meningococcal serogroup B IMI rate is seen in children under the age of 5 years (85% of cases, all serogroups combined). Forty-one of the reported cases involved serogroups A, W₁₃₅ and Y. The incidence of IMI C cases began to fall in 2003, and should continue to fall due to the 2010 introduction of the meningococcal C vaccine into the vaccination schedule. IMI mortality in 2010 was 10% (53 deaths). The proportion of reported cases with *purpura fulminans* was 26% (130 cases), with a mortality rate of 23% for these cases compared with 6% for the others.

---

The age groups most affected are under 1-year-olds, 1-4 year olds and 15-19 year olds. The IMI risk is far lower in adulthood, except for immunologically new strains (such as those seen in epidemics among pilgrims visiting Mecca).

Prevention by immunisation is recognised as being the most effective means for long-term control. Immunisation involves the use of a vaccine based on the cell wall polysaccharide, which is group-specific. Subsequently, polysaccharides are available for groups A, C, Y and W\textsubscript{135}, but not group B, which is insufficiently antigenic. After 5 to 7 days, these polysaccharides trigger the formation of group-specific, protective, bactericidal antibodies. The protection lasts at least 3 years.

There are two main types of anti-meningococcal vaccines:
- non-conjugated vaccines: either bivalent (A+C) or tetravalent (A/C/Y/W\textsubscript{135})
- conjugate vaccines: either monovalent (C) or tetravalent (A/C/Y/W\textsubscript{135})

The monovalent serogroup C conjugate vaccine can be used from the age of 2 months, and the non-conjugated bivalent A+C vaccine can be used from the age of 6 months (Marketing Authorisation from the age of 2 years).

The tetravalent vaccines currently on the market in France are MENVEO (a polysaccharide conjugate vaccine) and MENCEVAX (a plain polysaccharide vaccine). Both can be used from the age of 2 years.

Only immunisation against serogroup C is recommended for the general population (2012 vaccination schedule), with a single dose of meningococcal serogroup C conjugate vaccine in all infants aged 12 to 24 months and the extension of routine immunisation until the 25\textsuperscript{th} birthday, pending the impact of infant immunisation on group immunity\textsuperscript{2}.

The need for immunisation against meningococcal infections caused by serogroups A, W\textsubscript{135} and Y is seen in specific populations: certain laboratory research staff, certain people with risk factors for invasive meningococcal infection and people visiting an endemic area, particularly pilgrims visiting Mecca. This intermittent requirement is currently met with the MENCEVAX vaccine (non-conjugated tetravalent vaccine) and the MENVEO vaccine (tetravalent conjugate vaccine), which cover all of these serogroups and can be used from the age of 2 years, as well as with the non-conjugated A+C bivalent vaccine recommended from 6 months of age (Marketing Authorisation from the age of 2 years).

NIMENRIX is a new tetravalent meningococcal conjugate vaccine indicated for active immunisation of individuals aged 12 months and older against invasive meningococcal infections caused by \textit{Neisseria meningitidis} groups A, C, W\textsubscript{135} and Y.

NIMENRIX is also the only vaccine with a Marketing Authorisation for use in young children aged 12 to 23 months, extending meningococcal immunisation to serogroups other than group C (A, W\textsubscript{135} and Y).

\textsuperscript{2} 12 July 2012 opinion of the French Haut Conseil de Santé Publique (High Council for Public Health) on the use of the NIMENRIX tetravalent (A, C, Y, W\textsubscript{135}) meningococcal conjugate vaccine and the respective therapeutic uses of conjugated and non-conjugated tetravalent meningococcal vaccines.
07 CLINICALLY RELEVANT COMPARATORS

07.1 Medicinal products

❖ Tetravalent vaccines (A,C,Y,W_{135})

<table>
<thead>
<tr>
<th>NAME (INN) Company</th>
<th>Indication</th>
<th>Date of opinion</th>
<th>AB</th>
<th>IAB (Wording)</th>
<th>Reimbursement</th>
</tr>
</thead>
<tbody>
<tr>
<td>MENCEVAX (non-conjugated tetravalent vaccine A, C, Y, W135) GlaxoSmithKline</td>
<td>Children (aged 2 years and over), adolescents and adults at risk of exposure</td>
<td>4 March 2009</td>
<td>substantial</td>
<td>IAB I in the prevention of infections caused by serogroups Y and W135</td>
<td>YES (For hospital use)</td>
</tr>
<tr>
<td>MENVEO* (tetravalent A, C, Y, W135 conjugate vaccine) Novartis Vaccines and Diagnostics</td>
<td>Children (aged 11 years and over), adolescents and adults at risk of exposure*</td>
<td>1 December 2010</td>
<td>substantial</td>
<td>IAB V compared with MENCEVAX**</td>
<td>YES (For hospital use)</td>
</tr>
</tbody>
</table>

*MENCEVAX obtained an extension of indication in April 2012 (to include children aged 2 years and over) in its European Marketing Authorisation. This extension has not yet been assessed by the Committee.

**IAB for MENVEO (TC opinion of 1 Dec, 2010)

“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 French High Council for Public Health”.

❖ For information: the other vaccines used for meningococcal immunisation

- Monovalent (serogroup C) meningococcal conjugate vaccines, indicated from the age of 2 and approved for National Health Insurance reimbursement and hospital use:
  - MENJUGATEKIT 10 micrograms, powder and solution for injectable suspension
  - MENINGITEC, injectable suspension in a prefilled syringe
  - NEISVAC, injectable suspension in a prefilled syringe.

- Non-conjugated bivalent meningococcal vaccine (serogroups A and C), indicated from the age of 2 years and approved for hospital use:
  - MENINGOCOCCAL POLYSACCHARIDE A+C VACCINE, powder and solvent for injectable suspension in a prefilled syringe.

07.2 Other health technologies

Not applicable

❖ Conclusion

MENCEVAX and MENVEO (tetravalent vaccines) are the relevant comparators.
INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

This vaccine does not yet have a Marketing Authorisation in the United States (clinical development is ongoing). According to the applicant, the vaccine is marketed in Europe in Germany, Austria, the Netherlands, England, Malta, the Czech Republic, Slovakia and Hungary. An application for non-reimbursement (private markets) has been submitted to the Spanish authorities.

ANALYSIS OF AVAILABLE DATA

In support of its request, the applicant submitted immunogenicity and safety data on NIMENRIX from the following studies:

• Six controlled phase III studies:
  - three studies versus the MENCEVAX non-conjugated tetravalent meningococcal vaccine conducted in individuals aged 2 to 55 years (studies MenACWY-TT-035, -036 and -038)
  - three studies versus a monovalent serogroup C meningococcal conjugate vaccine, MENJUGATEKIT or MENINGITEC, conducted in children aged 12 months to 10 years (studies MenACWY-TT-039, -40 and -081)

• Nine studies whose objective was to evaluate the persistence of immune response. When the request was submitted, two studies had been completed (extensions of the MenACWY-TT-013 and -012 phase II studies) and seven studies were ongoing.

• One phase II study, which evaluated vaccine response to NIMENRIX in individuals aged 4.5 to 34 years who had previously received the MENCEVAX non-conjugated tetravalent meningococcal vaccine (MenACWY-TT-021 study).

• One phase II study, which evaluated immune memory response in young children aged 12 to 14 months (MenACWY-TT-014 study). The results of this study showing that NIMENRIX induces immune memory for the four serogroups are presented in the SPC (Paragraph 5.1) and will not be described in this document.

• Five phase III studies of coadministration with other vaccines conducted in individuals aged 12 months to 55 years (studies MenACWY-TT-035, -037, -039, -40 and -80). These studies are described in the “Interactions with other vaccines” section above.

No protective efficacy studies have been conducted on NIMENRIX.

No studies have compared the NIMENRIX vaccine with the MENVEO vaccine since the products were developed concomitantly.
09.1 Study methodology

9.1.1 Subject characteristics at inclusion

The subjects included in the phase III studies were aged 12 months to 55 years, depending on the study. The non-inclusion criteria included:
- Prior immunisation with a conjugated meningococcal vaccine
- Immunisation within the last 5 years with a non-conjugated vaccine
- Past history of meningococcal infection
- Immunodeficiency
- Subjects at risk for severe vaccine reactions.

9.1.2 Immune response endpoints

9.1.2.1 Primary endpoint
The primary endpoint in the phase III studies was vaccine response for each of the considered serogroups (A, C, W\textsubscript{135} and Y), 30 or 42 days after immunisation. Vaccine response was based on immunogenicity as determined through an assessment of the bactericidal activity of serum antibodies (SBA, Serum Bactericidal Assay) against serogroups A, C, W\textsubscript{135} and Y. Antibody titres were measured using rabbit complement (rSBA).

The evaluation was performed on day 30 for all studies except for study-039, when it was performed on day 42 because of the assessment of co-administration with the PRIORIX TETRA vaccine.

In infants aged 12 to 23 months, vaccine response was defined as the percentage of subjects with a post-immunisation rSBA antibody titre $\geq 8$.

In subjects aged 2 to 55 years old, vaccine response was defined as the percentage of subjects with:
- an rSBA antibody titre $\geq 32$ for subjects who were seronegative at inclusion (rSBA titre $< 8$)
- an rSBA antibody titre that increased fourfold between the pre- and post-immunisation periods for subjects who were seropositive at inclusion (rSBA titre $\geq 8$).

9.1.2.2 Secondary endpoints
The secondary immunogenicity endpoints included, for each of the serogroups A, C, W\textsubscript{135} and Y:
- the percentage of subjects with an rSBA titre of $\geq 8$ on D30 or D42
- the geometric mean antibody titre (GMT).

The immune response was also evaluated in some studies using the bactericidal activity of antibodies measured with human complement (hSBA). This was a secondary endpoint or post-hoc analysis, depending on the study.
9.1.3 Statistical analysis

In all of the studies, the population used for the main analysis was the “according-to-protocol” (ATP) population, defined as all evaluable subjects\(^3\) for whom immunogenicity results were available for at least one of the vaccine antigens after immunisation. If more than 5% of subjects of any of the vaccine groups did not fulfil the ATP population definition criteria, a second analysis was carried out on the entire immunised population (TVC: Total Vaccinated Cohort).

The primary non-inferiority endpoint for NIMENRIX versus the comparator vaccine in each study was achieved if the lower limit of the 95% confidence interval (95% CI) of the difference in the percentage of subjects with an rSBA vaccine response (NIMENRIX - Comparator) was ≥ -10% for each of the four serogroups A, C, \(W_{135}\) and Y, or only for serogroup C, depending on the comparator.

09.2 Immunogenicity

9.2.1 Immunogenicity in young children aged 12 to 23 months

The applicant presented two open, randomised, controlled phase III studies versus the MENINGITEC conjugated monovalent C meningococcal vaccine in this age group:\(^4\)

- Study-039,\(^5\) whose primary objective was to demonstrate the non-inferiority (delta threshold = 10%) of NIMENRIX versus MENINGITEC for serogroup C in terms of vaccine response (rSBA ≥ 8). For the other three serogroups (A, \(W_{135}\) and Y), NIMENRIX was deemed to be immunogenic if the lower limit of the CI of vaccine response (rSBA ≥ 8) was ≥ 90% (co-primary endpoint).

- Study-040,\(^6\) whose primary objective was to evaluate the immune response of NIMENRIX when co-administered with INFANRIX HEXA. The vaccine response induced by NIMENRIX was compared with the vaccine response induced by MENINGITEC as a secondary objective.

**Results:** the results of these two studies are shown in tables 1 and 2.

In study-039, NIMENRIX was shown to be non-inferior to MENINGITEC in terms of percentage of young children with an rSBA antibody titre of ≥ 8 on D42 post-immunisation (the lower limit of the 95% CI of the difference in the percentage of subjects whose rSBA vaccine response was ≥ -10%).

The co-primary endpoint for this study, which was to demonstrate the immunogenicity of NIMENRIX in terms of vaccine response for the other three serogroups A, \(W_{135}\) and Y, was also achieved (the lower limit of the 95% CI was > 90% for the three serogroups).

In study-040, the vaccine response (rSBA ≥ 8) compared with serogroup C at D30 post-immunisation was similar in the NIMENRIX and MENINGITEC groups (97.3% versus 98.2%).

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\(^3\) Subjects who met the inclusion and non-inclusion criteria for the study and complied with the procedures defined in the protocol.

\(^4\) Because of the difference in appearance and route of administration for NIMENRIX compared with the comparator vaccines.


Table 1. Studies MenACWY-TT-039 and -040 - Vaccine response (rSBA ≥ 8) in young children aged 12 to 23 months - ATP population.

| Serogroup | Study-039 | | | Study-040 | | |
|-----------|-----------|-----------|-----------|-----------|-----------|
|           | NIMENRIX  | MEINGITEC | NIMENRIX  | MEINGITEC |
|           | rSBA ≥ 8  | [95% CI]  | rSBA ≥ 8  | [95% CI]  |
|           | N         |           | N         |           |
| A         | 354       | 99.7% [98.4; 100] | 51       | 45.1% [31.1; 59.7] |
| C         | 354       | 99.7% [98.4; 100] | 121      | 97.5% [92.9; 99.5] |
| W135      | 354       | 100% [99.0; 100] | 58       | 50.0% [36.6; 63.4] |
| Y         | 354       | 100% [99.0; 100] | 59       | 54.2% [40.8; 67.3] |
| Difference| NIMENRIX – MEINGITEC | for the C serogroup | * | 2.2% [0.29; 6.78] |

* primary endpoint of study-039.
** secondary endpoint of study-040.

In study-039, evaluation of the immune response was combined with post-hoc analyses using a human complement serology test (hSBA) (see table 2).

Table 2. Study MenACWY-TT-039 – Vaccine response (hSBA ≥ 8), on D42 in young children aged 12 to 23 months - ATP population.

| Serogroup | NIMENRIX | | | MENINGITEC | | |
|-----------|----------|-----------|-----------|-----------|-----------|
|           | N        | hSBA ≥ 8  | [95% CI]  | N         | hSBA ≥ 8  | [95% CI]  |
| A         | 338      | 77.2% [72.4; 81.6] | 117 | 0.9% [0.0; 4.7] |
| C         | 341      | 98.5% [96.6; 99.5] | 116 | 81.9% [73.7; 88.4] |
| W135      | 336      | 87.5% [83.5; 90.8] | 114 | 0.9% [0.0; 4.8] |
| Y         | 329      | 79.3% [74.5; 83.6] | 117 | 1.7% [0.2; 6.0] |

9.2.2 Immunogenicity in children aged 2 to 10 years

The applicant submitted two open, randomised, controlled phase III studies in this age group.
- Study-038, which was controlled versus the MENCEVAX non-conjugated tetravalent meningococcal vaccine and included 1,501 children aged 2 to 10 years
- Study-081, which was controlled versus the MENJUGATEKIT conjugated monovalent C meningococcal vaccine and included 414 children aged 2 to 10 years

The primary objective of these studies was to demonstrate the non-inferiority (delta threshold = 10%) of NIMENRIX versus the comparator vaccine in terms of vaccine response.

Results: the results of these studies are shown in tables 3 to 5.

NIMENRIX was shown to be non-inferior in these studies with respect to vaccine response at D30 post immunisation compared with MENCEVAX for each of the four serogroups and compared with MENJUGATEKIT for serogroup C (the lower limit of the 95% CI of the difference in the percentage of subjects who achieved an rSBA vaccine response ≥ 10%).

Table 3. Study MenACWY-TT-038 – Vaccine response (rSBA) on D30 in children aged 2 to 10 years, ATP population.

<table>
<thead>
<tr>
<th>Serogroup</th>
<th>Vaccine response (rSBA)</th>
<th>Difference NIMENRIX - MENCEVAX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NIMENRIX</td>
<td>MENCEVAX</td>
</tr>
<tr>
<td>A</td>
<td>638</td>
<td>88.6 [85.8; 90.9]</td>
</tr>
<tr>
<td>C</td>
<td>732</td>
<td>95.9 [94.2; 97.2]</td>
</tr>
<tr>
<td>W, Y</td>
<td>738</td>
<td>97.4 [96.0; 98.4]</td>
</tr>
</tbody>
</table>

N: number of subjects with pre- and post-immunisation serologies available.

* Vaccine response: rSBA ≥ 32 for subjects who were seronegative at inclusion (rSBA titre < 8) or an rSBA increase of at least fourfold between the pre- and post-immunisation periods for subjects who were seropositive at inclusion (rSBA titre ≥ 8).

Table 4. Study MenACWY-TT-081 – Vaccine response (rSBA) on D30 in children aged 2 to 10 years, ATP population.

<table>
<thead>
<tr>
<th>Serogroup</th>
<th>Vaccine response (rSBA)</th>
<th>Difference NIMENRIX - MENJUGATEKIT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NIMENRIX</td>
<td>MENJUGATEKIT</td>
</tr>
<tr>
<td>A</td>
<td>226</td>
<td>94.7 [90.9; 97.2]</td>
</tr>
<tr>
<td>C</td>
<td>268</td>
<td>94.8 [91.4; 97.1]</td>
</tr>
<tr>
<td>W, Y</td>
<td>282</td>
<td>98.6 [96.4; 99.6]</td>
</tr>
</tbody>
</table>

N: number of subjects with available pre- and post-immunisation serologies.

* Vaccine response: rSBA ≥ 32 for subjects who were seronegative at inclusion (rSBA titre < 8) or an rSBA increase of at least fourfold between the pre- and post-immunisation periods for subjects who were seropositive at inclusion (rSBA titre ≥ 8).

In study-038, the geometric mean antibody titres (GMT) were higher in subjects given NIMENRIX than in those given MENCEVAX for each of the four serogroups. In study-081, however, the GMTs for serogroup C were lower in the NIMENRIX group compared with the group given the MENJUGATEKIT conjugated monovalent C vaccine (see table 5).

Table 5. Studies MenACWY-TT-038 and -081. Geometric mean titres (GMT) on D30 post-immunisation in children aged 2 to 10 years - ATP population.

<table>
<thead>
<tr>
<th>Study</th>
<th>NIMENRIX</th>
<th>Comparator vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GMT [95% CI]</td>
<td>GMT [95% CI]</td>
</tr>
<tr>
<td>Study-038</td>
<td>MENCEVAX</td>
<td>MENJUGATEKIT</td>
</tr>
<tr>
<td>A</td>
<td>788 6309.7 [5979.0; 6658.8]</td>
<td>265 2309.4 [2055.8; 2594.3]</td>
</tr>
<tr>
<td>C</td>
<td>791 4983.6 [4514.1; 5502.0]</td>
<td>265 1386.8 [1108.9; 1734.4]</td>
</tr>
<tr>
<td>W, Y</td>
<td>791 11569.8 [10910.7; 12268.7]</td>
<td>267 2150.6 [1823.9; 2535.8]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>MENCEVAX</th>
<th>MENJUGATEKIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>294 6236.1 [5574.5; 6976.3]</td>
<td>82 32.9 [15.6; 47.4]</td>
</tr>
<tr>
<td>C</td>
<td>293 2794.8 [2393.5; 3263.3]</td>
<td>97 5291.6 [3814.6; 7340.5]</td>
</tr>
<tr>
<td>W, Y</td>
<td>296 8549.5 [7618.5; 9594.3]</td>
<td>95 87.3 [58.5; 130.4]</td>
</tr>
</tbody>
</table>

HAS - Medical, Economic and Public Health Assessment Division
9.2.3 Immunogenicity in adolescents aged 11 to 17 years

The applicant submitted a controlled phase III study (study-036)\(^8\) \textit{versus} the MENCEVAX non-conjugated tetravalent meningococcal vaccine. This study included 1,025 adolescents aged 11 to 17 years. The average age of the subjects at inclusion was 14.3 years.

The primary objective of this study was to demonstrate the non-inferiority (delta threshold = 10\%) of NIMENRIX compared with MENCEVAX in terms of vaccine response.

\textbf{Results:} The results of this study are shown in tables 6 and 7.

NIMENRIX was shown to be non-inferior to MENCEVAX in terms of vaccine response on D30 post-immunisation for each of the four serogroups (the lower limit of the 95\% CI of the difference in the percentage of subjects with an rSBA vaccine response $\geq -10\%)$.

The GMTs were higher in subjects given NIMENRIX than in those given MENCEVAX for each of the four serogroups.

\textbf{Table 6.} Study MenACWY-TT-036 – Vaccine response on D30 post-immunisation in adolescents aged 11 to 17 years, ATP population.

<table>
<thead>
<tr>
<th>Serogroup</th>
<th>Vaccine response* (rSBA)</th>
<th>NIMENRIX</th>
<th>MENCEVAX</th>
<th>Difference NIMENRIX - MENCEVAX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>% [95% CI]</td>
<td>N</td>
<td>% [95% CI]</td>
</tr>
<tr>
<td>A</td>
<td>615</td>
<td>85.4 [82.3; 88.1]</td>
<td>215</td>
<td>79.5 [73.5; 84.7]</td>
</tr>
<tr>
<td>C</td>
<td>719</td>
<td>97.1 [95.6; 98.2]</td>
<td>237</td>
<td>96.6 [93.5; 98.5]</td>
</tr>
<tr>
<td>W(_{135})</td>
<td>717</td>
<td>96.5 [94.9; 97.7]</td>
<td>242</td>
<td>88.0 [83.2; 91.8]</td>
</tr>
<tr>
<td>Y</td>
<td>737</td>
<td>93.1 [91.0; 94.8]</td>
<td>246</td>
<td>78.0 [72.3; 83.1]</td>
</tr>
</tbody>
</table>

* primary endpoint. Vaccine response: rSBA $\geq 32$ in subjects who were seronegative at inclusion (rSBA < 8) or an rSBA increase of at least fourfold between the pre- and post-immunisation periods in subjects who were seropositive at inclusion (rSBA titre $\geq 8$).

N: number of subjects with available pre- and post-immunisation serologies.

\textbf{Table 7.} Study MenACWY-TT-036 – Geometric mean antibody titres (GMT) on D30 in adolescents aged 11 to 17 years, ATP population.

<table>
<thead>
<tr>
<th>Serogroup</th>
<th>N</th>
<th>GMT $^*$ [95% CI]</th>
<th>N</th>
<th>GMT [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>752</td>
<td>6106.8 [5739.5; 6497.6]</td>
<td>252</td>
<td>3203.0 [2854.1; 3594.6]</td>
</tr>
<tr>
<td>C</td>
<td>754</td>
<td>12645.5 [11531.8; 13866.7]</td>
<td>252</td>
<td>8271.6 [6937.3; 9862.4]</td>
</tr>
<tr>
<td>W(_{135})</td>
<td>759</td>
<td>8390.1 [7777.8; 9050.7]</td>
<td>252</td>
<td>2679.3 [2363.7; 3037.2]</td>
</tr>
<tr>
<td>Y</td>
<td>758</td>
<td>13865.2 [12968.1; 14824.4]</td>
<td>252</td>
<td>5245.3 [4644.2; 5924.1]</td>
</tr>
</tbody>
</table>

* secondary endpoint

N: number of subjects with available pre- and post-immunisation serologies.

9.2.4 Immunogenicity in adults between 18 and 55 years old

The applicant submitted a controlled phase III study (study-035) against the MENCEVAX non-conjugated tetravalent meningococcal vaccine. This study included 1,352 adults aged 18 to 55 years. The average age of subjects at inclusion was 35.5 years old.

The primary objective of this study was to demonstrate non-inferiority (delta threshold = 10%) of NIMENRIX versus MENCEVAX in terms of vaccine response.

**Results:** The results of this study are shown in tables 8 and 9. NIMENRIX was shown to be non-inferior to MENCEVAX in terms of vaccine response on D30 post-immunisation for each of the four serogroups (the lower limit of the 95% CI of the difference in the percentage of subjects with an rSBA vaccine response ≥ -10%). GMTs were higher in subjects given NIMENRIX than in those given MENCEVAX for serogroups A, W<sub>135</sub> and Y.

**Table 8.** Study MenACWY-TT-035 – rSBA vaccine response on D30 in adults aged 18 to 55 years, ATP population.

<table>
<thead>
<tr>
<th>Serogroup</th>
<th>Vaccine response* (rSBA)</th>
<th>Difference NIMENRIX - MENCEVAX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NIMENRIX</td>
<td>MENCEVAX</td>
</tr>
<tr>
<td>A</td>
<td>N</td>
<td>% [95% CI]</td>
</tr>
<tr>
<td></td>
<td>743</td>
<td>80.1 [77.0; 82.9]</td>
</tr>
<tr>
<td>C</td>
<td>849</td>
<td>91.5 [89.4; 93.3]</td>
</tr>
<tr>
<td>W&lt;sub&gt;135&lt;/sub&gt;</td>
<td>860</td>
<td>90.2 [88.1; 92.1]</td>
</tr>
<tr>
<td>Y</td>
<td>862</td>
<td>87.0 [84.6; 89.2]</td>
</tr>
</tbody>
</table>

*primary endpoint. Vaccine response: rSBA ≥ 32 in subjects who were seronegative at inclusion (rSBA < 8) or an rSBA increase of at least fourfold between the pre- and post-immunisation periods in subjects who were seropositive at inclusion (rSBA titre ≥ 8).

N: number of subjects with available pre- and post-immunisation serologies.

**Table 9.** Study MenACWY-TT-035 – Geometric mean antibody titres (GMT) on D30 in adults aged 18 to 55 years, ATP population.

<table>
<thead>
<tr>
<th>Serogroup</th>
<th>NIMENRIX</th>
<th>MENCEVAX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>GMT* [95% CI]</td>
</tr>
<tr>
<td>A</td>
<td>869</td>
<td>3624.7 [3371.7; 3896.8]</td>
</tr>
<tr>
<td>C</td>
<td>882</td>
<td>8865.9 [8011.0; 9812.0]</td>
</tr>
<tr>
<td>W&lt;sub&gt;135&lt;/sub&gt;</td>
<td>885</td>
<td>5136.2 [4698.8; 5614.3]</td>
</tr>
<tr>
<td>Y</td>
<td>884</td>
<td>7710.7 [7100.1; 8373.8]</td>
</tr>
</tbody>
</table>

*secondary endpoint

N: number of subjects with available pre- and post-immunisation serologies.
09.3 Persistence of immune response

The persistence of a NIMENRIX-induced immune response was evaluated in subjects aged 12 months to 55 years by measuring serum bactericidal antibody titres with a test using either rabbit complement (rSBA) or human complement (hSBA).

The NIMENRIX vaccine response rate percentages were at least as high as those of the comparator vaccines for up to 24 months after primary immunisation with NIMENRIX.

- **Children aged 12 to 23 months:** in the MenACWY-TT-048 study, the immune response rate percentages (rSBA ≥ 8) remained high for two years after immunisation in children who were given primary immunisation in the MenACWY-TT-039 study: average values were 98 to 99% for serogroups A, W135, Y and 88.2% for serogroup C. However, in contrast to the persistence of rSBA antibodies, hSBA antibodies decreased rapidly for serogroup A (23% after two years versus 81.0% after 42 days).

- **Children aged 6 to 10 years:** immune response persistence in children aged 6 to 10 years was evaluated in study MenACWY-TT-028 using the hSBA test one year after primary immunisation of these children in the MenACWY-TT-027 study. The response rate percentages (hSBA ≥ 8) remained high (average 95 to 100%) except for serogroup A (16.3% after one year versus 80% at one month).

- **Adolescents aged 11 to 17 year:** immune response persistence was evaluated in study MenACWY-TT-043 two years after immunisation in adolescents who received primary immunisation in study MenACWY-TT-036. The response rate percentages (rSBA ≥ 8) remained high for the four serogroups (average values > 99%) and were similar to those of the MENCEVAX vaccine.

- **Adolescents and adults aged 11 to 25 years:** immune response persistence was evaluated in study MenACWY-TT-059 using the hSBA test one year after primary immunisation of these adolescents and adults in the MenACWY-TT-052 study. The response rate percentages (hSBA ≥8) remained high (average 95 to 98%), except for serogroup A (29% at 1 year compared with 82% at 1 month).

09.4 Immune response to NIMENRIX after immunisation with a plain polysaccharide meningococcal vaccine

In the phase II MenACWY-TT-021 study, the immune response to the NIMENRIX vaccine administered 30 to 42 months after administration of the MENCEVAX non-conjugated tetravalent vaccine was compared with the immune response to NIMENRIX administered to subjects who had not been given a meningococcal vaccine in the last 10 years.

This study was conducted on 244 subjects aged 4.5 to 34 years. The average age at inclusion was 14.3 years old and the geometric mean titres were higher in the group that had previously been given the MENCEVAX vaccine than in the group that had not been given a meningococcal vaccine in the last ten years.

**Results:** the results are shown in table 10.

Immune response (rSBA ≥ 8) was observed versus the four serogroups (A, C, W135 and Y) one month after NIMENRIX immunisation in all subjects regardless of their meningococcal immunisation history.

GMTs were lower in subjects who had been given a MENCEVAX dose 30 to 42 months before NIMENRIX administration than in subjects who had not been given a meningococcal vaccine in the last ten years.
Table 10. Study MenACWY-TT-021 – Immune response after a dose of NIMENRIX depending on the past history of meningococcal immunisation – ATP population.

<table>
<thead>
<tr>
<th>Group</th>
<th>Subjects immunised 30 to 42 months previously with MENCEVAX</th>
<th>Subjects who had not been given a meningococcal vaccine in the previous 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N rSBA ≥ 8 [95% CI] GMT [95% CI]</td>
<td>N rSBA ≥ 8 [95% CI] GMT [95% CI]</td>
</tr>
<tr>
<td>A</td>
<td>146 100% [97.5; 100] 6888.8 [6044.9; 7805.0]</td>
<td>69 100% [94.8; 100] 13014.9 [10722.2; 15798.0]</td>
</tr>
<tr>
<td>C</td>
<td>169 100% [97.8; 100] 1945.8 [1583.3; 2391.1]</td>
<td>75 100% [95.2; 100] 5494.6 [4266.3; 7076.5]</td>
</tr>
<tr>
<td>W_{135}</td>
<td>169 100% [97.8; 100] 4635.7 [3942.5; 5450.7]</td>
<td>75 100% [95.2; 100] 9078.0 [7087.7; 11627.1]</td>
</tr>
<tr>
<td>Y</td>
<td>169 100% [97.8; 100] 7799.9 [6682.8; 9103.6]</td>
<td>75 100% [95.2; 100] 13895.5 [11186.2; 17260.9]</td>
</tr>
</tbody>
</table>

09.5 Safety/adverse effects

The NIMENRIX safety profile is based on data from clinical studies involving 8,108 subjects immunised with NIMENRIX. These included 2,237 young children (aged 12 months to 23 months), 1,809 children (aged 2 to 10 years), 2,011 adolescents (aged 11 to 17 years) and 2,051 adults (≥ 18 years).

NIMENRIX versus MENINGITEC (12–to-23-month-olds)
Analysis of the data shows a higher incidence of local adverse events (AE) reported between D0 and D3 with NIMENRIX than with the MENINGITEC conjugated monovalent C vaccine: pain at the injection site (27.4% versus 20.3%), redness at the injection site (39.6% versus 31.4%) and swelling at the injection site (19.3 % versus 14.6%). In contrast, no difference was found for systemic adverse events (drowsiness, irritability and loss of appetite), except for fever ≥ 37.5°C (17.6% in the NIMENRIX group versus 13.5% in the MENINGITEC group). The incidence of grade 3 AEs was low and similar in both treatment groups, except for redness (3.7% versus 1.1%) and swelling at the injection site (3.0% versus 0.3%).

NIMENRIX versus MENJUGATEKIT (2-to-10-year-olds)
The frequency of AEs was similar overall in the two treatment groups. Among the AEs deemed to be related to the treatment, only headaches were reported at a higher incidence in the NIMENRIX group than in the MENJUGATEKIT group (16.2% versus 4.0% in the 6-to-10-year age group). No difference was seen in the incidence of grade 3 AEs.

NIMENRIX versus MENCEVAX (2-to-10-year-olds, 11-to-17-year-olds and adult ≥ 18 years of age)
The data analysis showed a similar frequency of AEs in children aged 2-to-10 years, except for grade 3 redness (in children aged 2–to-5 years: 2.3% versus 0.0%; aged 6–to-10 years: 3.2% versus 0.0%) and grade 3 swelling (in children aged 2-to-5 years: 1.9% versus 0.0%; aged 6–to-10 years: 2.3% versus 0.0%) at the injection site.
The data analysis in adolescents (11-to-17 years) showed a similar incidence of AEs, except for redness (12.4% versus 7.0%) and swelling (9.3% versus 5.6%) at the injection site, although there was no difference in grade 3 AEs.
The data analysis in adults showed a higher incidence of local AEs: pain (36.6% versus 27.8%), redness (15.4% versus 10.1%) and swelling (11.6% versus 6.9%) at the injection site. The incidence of grade 3 local AEs was also higher for redness and swelling at the injection site (0.8% versus 0.0%). The incidence of systemic AEs was similar in both groups, except for grade 3 fatigue (0.7% versus 0.0%).
No study has compared the safety of the NIMENRIX vaccine to that of the MENVEO vaccine.

Overall, the safety profile of NIMENRIX was satisfactory and similar to that of the meningococcal vaccines already on the market, apart from local AEs, which occurred more commonly with the NIMENRIX vaccine.

The most commonly reported post-immunisation local adverse effects in all age groups were pain (24.1% to 39.9%), redness (14.3% to 33.0%) and swelling (11.2% to 17.9%).

The most commonly reported post-immunisation systemic adverse effects in the 12-23 month and 2-5 year age groups were irritability, drowsiness, loss of appetite and fever.

The most commonly reported post-immunisation systemic adverse effects in the 6-10, 11-17 and ≥ 18 year age groups were headaches, fatigue, gastrointestinal symptoms and fever.

**09.6 Summary & discussion**

NIMENRIX is a tetravalent meningococcal conjugate vaccine with a Marketing Authorisation for active immunisation against invasive meningococcal infections caused by serogroups A, C, W<sub>135</sub> and Y in subjects 12 months or older.

No other vaccine against invasive meningococcal infections caused by groups A, W<sub>135</sub> and Y has a Marketing Authorisation for subjects aged 12-23 months. The MENVEO tetravalent meningococcal conjugate vaccine (A, C, W<sub>135</sub>, Y) has a Marketing Authorisation for subjects aged 2 years and older (European extension of indication obtained in April 2012, not yet evaluated by the Committee). The MENCEVAX non-conjugated tetravalent meningococcal vaccine (A, C, W<sub>135</sub>, Y) has a Marketing Authorisation for subjects aged 2 years and old.

The conjugated monovalent C meningococcal vaccines (MENJUGATEKIT and MENINGITEC, NEISVAC) can be used from the age of 2 months and the non-conjugated bivalent A+C vaccine from the age of 6 months (Marketing Authorisation indicates from the age of 2 years).

Comparative studies with other meningococcal vaccines have shown that NIMENRIX induces at least as great an immunogenicity as:

- the monovalent serogroup C conjugate vaccines (MENJUGATEKIT and MENINGITEC) in subjects aged 12 months to 10 years. The mean vaccine response in subjects aged 12-23 months (NIMENRIX) was at least 97.3% for the four serogroups and was similar to that of MENINGITEC for serogroup C.

- the non-conjugated tetravalent vaccine (MENCEVAX) in subjects aged 2 to 55 years with a vaccine response to NIMENRIX ranging on average from 80 to 97% depending on the four serogroups A, C, W<sub>135</sub> and Y.

There are no comparative studies versus the MENVEO tetravalent conjugate vaccine or the non-conjugated bivalent A+C meningococcal vaccine.

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<sup>9</sup> 12 July 2012 opinion of the French Haut Conseil de Santé Publique (High Council for Public Health) on the use of the NIMENRIX conjugated tetravalent (A, C, Y, W<sub>135</sub>) meningococcal vaccine and the respective role therapeutic uses of conjugated and non-conjugated tetravalent meningococcal vaccines.
The main results are summarised in the table below:

<table>
<thead>
<tr>
<th>Study</th>
<th>Age Band</th>
<th>Vaccine response</th>
<th>Comparator vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NIMENRIX</td>
<td>Comparator vaccine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% [95% CI]</td>
<td>% [95% CI]</td>
</tr>
<tr>
<td>MenACWY-TT-039</td>
<td>12-23 months</td>
<td>MenA: 99.7 [98.4; 100]</td>
<td>MenA: 45.1 [31.1; 59.7]</td>
</tr>
<tr>
<td>NIMENRIX versus</td>
<td></td>
<td>MenC: 99.7 [98.4; 100]</td>
<td>MenC: 97.5 [92.9; 99.5]</td>
</tr>
<tr>
<td>MENINGITEC for serogroup C</td>
<td></td>
<td>MenW135: 100 [99.0; 100]</td>
<td>MenW135: 50.0 [36.6; 63.4]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MenY: 100 [99.0; 100]</td>
<td>MenY: 54.2 [40.8; 67.3]</td>
</tr>
<tr>
<td>MenACWY-TT-040</td>
<td>12-23 months</td>
<td>MenA: 98.4 [95.3; 99.7]</td>
<td>MenA: 43.0 [33.1; 53.3]</td>
</tr>
<tr>
<td>NIMENRIX versus</td>
<td></td>
<td>MenC: 97.3 [93.7; 99.1]</td>
<td>MenC: 96.2 [93.8; 99.8]</td>
</tr>
<tr>
<td>MENINGITEC for serogroup C</td>
<td></td>
<td>MenW135: 98.4 [95.4; 99.7]</td>
<td>MenW135: 36.6 [27.7; 46.2]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MenY: 97.3 [93.8; 99.1]</td>
<td>MenY: 64.5 [54.9; 73.4]</td>
</tr>
<tr>
<td>MenACWY-TT-081</td>
<td>2-10 years</td>
<td>MenA: 94.7 [90.9; 97.2]</td>
<td>MenA: 11.9 [5.3; 22.2]</td>
</tr>
<tr>
<td>NIMENRIX versus</td>
<td></td>
<td>MenC: 94.8 [91.4; 97.1]</td>
<td>MenC: 95.7 [89.2; 98.8]</td>
</tr>
<tr>
<td>MENJUGATEKIT for serogroup C</td>
<td></td>
<td>MenW135: 98.6 [96.4; 99.6]</td>
<td>Men W135: 12.2 [6.3; 20.8]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MenY: 96.5 [93.6; 98.3]</td>
<td>MenY: 8.0 [3.3; 15.7]</td>
</tr>
<tr>
<td>MenACWY-TT-038</td>
<td>2-10 years</td>
<td>MenA: 88.6 [85.8; 90.9]</td>
<td>MenA: 65.5 [58.6; 72.0]</td>
</tr>
<tr>
<td>NIMENRIX versus</td>
<td></td>
<td>MenC: 95.9 [94.2; 97.2]</td>
<td>MenC: 89.6 [85.2; 93.1]</td>
</tr>
<tr>
<td>MENCEVAX</td>
<td></td>
<td>MenW135: 97.4 [96.0; 98.4]</td>
<td>MenW135: 82.5 [77.3; 87.0]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MenY: 92.5 [90.4; 94.2]</td>
<td>MenY: 68.6 [62.6; 74.2]</td>
</tr>
<tr>
<td>MenACWY-TT-036</td>
<td>11-17 years</td>
<td>MenA: 85.4 [82.3; 88.1]</td>
<td>MenA: 79.5 [73.5; 84.7]</td>
</tr>
<tr>
<td>NIMENRIX versus</td>
<td></td>
<td>MenC: 97.1 [95.6; 98.2]</td>
<td>MenC: 96.6 [93.5; 98.5]</td>
</tr>
<tr>
<td>MENCEVAX</td>
<td></td>
<td>MenW135: 96.5 [94.9; 97.7]</td>
<td>MenW135: 88.0 [83.2; 91.8]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MenY: 93.1 [91.0; 94.8]</td>
<td>MenY: 78.0 [72.3; 83.1]</td>
</tr>
<tr>
<td>MenACWY-TT-035</td>
<td>18-55 years</td>
<td>MenA: 80.1 [77.0; 82.9]</td>
<td>MenA: 69.8 [63.8; 75.4]</td>
</tr>
<tr>
<td>NIMENRIX versus</td>
<td></td>
<td>MenC: 91.5 [89.4; 93.3]</td>
<td>MenC: 92.0 [88.3; 94.9]</td>
</tr>
<tr>
<td>MENCEVAX</td>
<td></td>
<td>MenW135: 90.2 [88.1; 92.1]</td>
<td>MenW135: 85.5 [80.9; 89.4]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MenY: 87.0 [84.6; 89.2]</td>
<td>MenY: 78.8 [73.6; 83.4]</td>
</tr>
</tbody>
</table>

**Persistence of response:**
The percentage of subjects with a protective bactericidal serum antibody titre for the four serogroups A, C, Y and W135 remained high 24 months after immunisation in the different age groups and was at least as high as the comparator vaccines. However, bactericidal serum antibody titres against the A serogroup fell rapidly (12 months post-immunisation) when the test used human complement (hSBA). Warnings have been incorporated into the SPC to state the need to administer a second dose to subjects who are particularly at risk of exposure to *Meningococcus A* and who had been given a first dose of NIMENRIX more than a year previously; the same applies for MENVEO. The clinical relevance of the drop in serogroup A hSBA antibody titres is unknown.

**Immune response to the NIMENRIX vaccine after immunisation with a polysaccharide vaccine:**
The immune response to a NIMENRIX vaccine given 30 to 42 months after immunisation with the MENCEVAX non-conjugated tetravalent vaccine was compared with the immune response to NIMENRIX given to subjects who had not been given a meningococcal vaccine in the previous 10 years. An immune response (rSBA antibody titre ≥ 8) was observed versus the four serotypes in all subjects one month after NIMENRIX, regardless of their past meningococcal immunisation history. However, the geometric mean antibody titres were lower in subjects who had been given MENCEVAX before NIMENRIX than in subjects who had not previously received a meningococcal vaccine. The relevance of this observation is still unknown and the SPC states that “NIMENRIX can be given as a booster dose in subjects who have previously been vaccinated with a plain polysaccharide meningococcal vaccine”.

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Safety:
The overall safety profile with NIMENRIX was satisfactory and similar to that of the meningococcal vaccines already on the market apart from local AEs, which are more common than with the comparators.
The most commonly reported local, post-immunisation adverse effects in all age groups were pain, redness and swelling.
The most commonly reported systemic, post-immunisation adverse effects in the 12-to-23 month and 2-to-5 year age groups were irritability, drowsiness, loss of appetite and fever.
The most commonly reported systemic post-immunisation adverse effects in the 6-10, 11-17 and ≥ 18 year age groups were headaches, fatigue, gastrointestinal symptoms and fever.
No study has compared the safety of the NIMENRIX vaccine to that of the MENVEO vaccine.

Missing data:
Safety and immunogenicity have not been evaluated in people at an increased risk of meningococcal infection such as those with terminal complement fraction deficiency or anatomical or functional asplenism. An adequate immune response may not be achieved in these people (see Warnings and precautions for use in the SPC).
Data are also lacking for children under one year of age and adults over 55 years of age.

Risk management plan:
Based on the data available at present, no significant risk was identified during the non-clinical and clinical development of a NIMENRIX vaccine.
A review of the safety data for meningococcal vaccines already on the market identified Guillain-Barré Syndrome (GBS) and purpura as potentially significant risks.
A risk management plan stipulates monitoring and evaluating for GBS, purpura and other significant risks (e.g., vasculitis, acute disseminated encephalomyelitis, brachial neuritis, anaphylaxis, lack of efficacy) through the pharmacovigilance plan.
It has been deemed that a risk minimisation plan is not necessary at this time.

09.7 Study programme
The study programme includes many studies, some of which have started, including two at the request of the registration authorities (CHMP):
- One study (MenACYW-TT-55) intends to evaluate the persistence of antibodies after administering a dose of NIMENRIX to 12-month-old subjects or two doses to 9- and 12-month-old subjects followed by a safety and immunogenicity evaluation of a booster dose administered 5 years after immunisation. The final report is expected in December 2014.
- One study (MenACWY-TT-104) intends to evaluate short- and longer-term antibody titres induced by one or two doses of NIMENRIX given to children aged 12-to-23 months in accordance with the CHMP-approved protocol. The final study report is expected in June 2015.
According to the opinion of the French High Council for Public Health (HCSP), immunisation with the NIMENRIX tetravalent A, C, Y, W\textsubscript{135} meningococcal conjugate vaccine is recommended in situations where the extension of the meningococcal vaccine to non-C serogroups (A, Y and W\textsubscript{135}) is necessary in the following populations:

- research laboratory staff working specifically on *Meningococcus*
- people exposed temporarily to *Meningococcus* A, Y or W\textsubscript{135}:
  - caused by contact with a case of invasive A, Y, or W\textsubscript{135} serogroup meningococcal infection (immunisation must then be given no more than 10 days after the index case has been hospitalised)
  - due to being on a pilgrimage to Mecca (Hadj or Umrah) or in the area where *Meningococcus* A, Y or W\textsubscript{135} is endemic, particularly in the Sub-Saharan African meningitis belt in the following conditions: during the dry season or in any other area in which an epidemic occurs, and in close prolonged contact with the local population. Immunisation must be given at least 10 days before departure.
- people who require extensive long-term protection against a large number of meningococcal serogroups:
  - people with terminal complement fraction deficiency or who are being treated with anti-C5A
  - people with properdin deficiency
  - people with anatomical or functional asplenism
  - people who have received a haematopoietic stem cell transplant.

The HCSP recommends that more immunogenic, conjugated vaccines be used than non-conjugated meningococcal vaccines (polysaccharide meningococcal A+C vaccine and MENCEVAX) (Grade B).

However, since the tetravalent meningococcal conjugate vaccines do not have a Marketing Authorisation for use in subjects under 1 year of age, currently only the non-conjugated bivalent A+C vaccine can be used in subjects aged 6 months to 1 year with the single objective of protecting against invasive group A meningococcal infections. In this situation, the advantage of early immunisation must be balanced against the theoretical risks of causing a reduced response following subsequent immunisations, particularly against *Meningococcus* C.

When immunisation with a tetravalent meningococcal conjugate vaccine is being considered in a person who has previously been given a meningococcal vaccine:
- there is no recommended time interval to wait after vaccinating with a conjugated monovalent C vaccine
- a time interval of three years is recommended after immunisation with an non-conjugated tetravalent vaccine (i.e., the estimated length of protection from the non-conjugated vaccine)
- if it is urgent and essential to extend protection to serogroups Y and W\textsubscript{135} in people who were immunised less than three years previously with the non-conjugated A+C vaccine, there is no minimum recommended time interval in the absence of specific data.
In view of all of the above data and information, and following the debate and vote, the Committee’s opinion is as follows:

**011.1 Actual benefit**

- Invasive meningococcal infections (IMI) are serious transmissible diseases that mainly present as meningitis or meningococcal septicaemia, of which the most severe form is *purpura fulminans*.
- This proprietary medicinal product is a preventative treatment.
- The efficacy (immunogenicity)/adverse effects ratio is high.
- Alternative vaccines are available against serogroups A, C, W<sub>135</sub> and Y for adults and children over 2 years of age (MENCEVAX non-conjugated tetravalent vaccine recommended by the HCSP for subjects 24 months of age and older, and MENVEO tetravalent conjugate vaccine).

There is no alternative treatment with a Marketing Authorisation to immunise children 12 to 23 months of age against serogroups A, W<sub>135</sub> and Y.

**Expected Public Health Benefit**

The burden of invasive meningococcal infections (IMI) caused by serogroups W<sub>135</sub> and Y in France is low.

Only immunisation against serogroup C is recommended for the general population (2012 vaccine schedule), and monovalent serogroup C conjugate vaccines are used for this purpose. The need for immunisation against meningococcal infections caused by serogroups A, C, W<sub>135</sub> and Y only affects specific populations (mostly certain people with risk factors for IMI, certain research laboratory staff and people entering endemic areas or pilgrims to Mecca). This need is already covered by currently-available vaccines, which cover all of the aforementioned serogroups for the population over two years of age. NIMENRIX only covers the paediatric population aged 12 to 23 months old.

The data presented for NIMENRIX (particularly non-inferiority studies on immune response) do not quantify its additional potential impact on IMI morbidity and mortality. At most, this impact on the population in question would be low.

The proprietary medicinal product NIMENRIX is not therefore expected to offer a public health benefit.

**As a result, the Committee considers that:**

The actual benefit of NIMENRIX for subjects aged 12 months and older is substantial only in those populations recommended by the Haut Conseil de la santé publique (HCSP, or the French High Council for Public Health), i.e., people with risk factors for invasive meningococcal infections and people entering an endemic area.

**011.2 Improvement in actual benefit (IAB)**

In view of the available data and in the absence of an alternative treatment with a Marketing Authorisation for serogroups A, W<sub>135</sub> and Y in the 12-to-23-month age group, the Committee considers that NIMENRIX provides an improvement in actual benefit in preventing invasive meningococcal infections caused by serogroups A, W<sub>135</sub> and Y, and that this IAB is:

- substantial (IAB I) in children aged 12-to-23 months in the populations recommended by the HCSP
- non-existent (IAB V) in children aged 2 years and over, adolescents and adults, in the populations recommended by the HCSP.
011.3 Target population

The target population for NIMENRIX consists of the following subgroups:

1. Research laboratory staff working specifically on the *Meningococcus*,

Data are not available to estimate the size of the subgroup.

2. Subjects aged 12 months and older transiently exposed to *Meningococcus* A, Y or W135
   - as a result of contact with a person who has invasive meningococcal infection caused by serogroup A, Y, or W135
   
   Of the 522 invasive meningococcal infections reported in France in 2010, 41 involved serogroups A, W135 and Y (BEH 2011). The mean number of people immunised among the close contacts of a person infected with serogroup (A, C, W135, Y) is estimated to be 8.2 (i.e., 336 people) plus 17.8 people in hospitals (i.e., 730 people).
   
   From these data, the estimated number of people who can be immunised with NIMENRIX is 1,100 people.

   - entering an area endemic for *Meningococcus* A, Y or W135:
     
     There are no epidemiological data available to estimate the number of travellers aged 12 months and over entering the sub-Saharan African meningitis belt in the dry season or any other area experiencing an epidemic, and who comes into close prolonged contact with the local population.

   - on a pilgrimage to Mecca:
     
     Approximately 30,000 pilgrims depart from France each year.

3. Subjects aged 12 months and older with terminal complement fraction deficiency, being treated with anti-C5A, with properdin deficiency or with anatomical or functional asplenism.

   A genetic (or acquired) terminal complement fraction or properdine deficiency or asplenism predispose subjects to a high risk of meningococcal septicemia caused by the five serogroups A, B, C, Y and W135 of *Neisseria meningitidis* principally involved in invasive infections as well as those caused by rarer serogroups. Since these situations are long-term or even permanent, they require regular re-immunisation in order to maintain protective antibody levels. The generally accepted time interval is 3 years. Immunisation with a meningococcal conjugate vaccine that does not carry a risk of a reduced response and induces a “booster” effect is therefore desirable for such subjects11.

   There are few people with these immunodeficiencies and the available data are limited:

   - People treated with anti-C5A: the target population for eculizumab, a monoclonal antibody, which specifically binds to complement protein C5, thereby inhibiting the terminal complement fraction, is estimated to be between 270 and 340 patients suffering from paroxysmal nocturnal haemoglobinuria (PNH) with a haemolytic form of the disease12 and 650 patients suffering from atypical haemolytic uraemic syndrome (atypical HUS)13.

   - People with terminal complement fraction or properdin deficiency: inherited deficiencies are rare (0.03% of the general population).14 Between 2005 and 2009 in France, CEREDIH (the French National Reference Centre for Primary Immunodeficiencies)15 identified 16 patients...

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11 Review: vaccination of children between 2 and 11 years old with risk factors for invasive meningococcal infections, November 2010.
12 Transparency Commission opinion of 28 May 2008 on the proprietary medicinal product SOLIRIS.
13 Transparency Commission opinion of 19 September 2012 on the proprietary medicinal product SOLIRIS.
who were alive in 2009, and suffering from primary complement system deficiency, all types of deficiency combined.

- People with anatomical or functional asplenism.
  The reported estimates of splenectomies refer to an incidence of 6,000 to 9,000 cases/year and a prevalence of 250,000 cases in France.\textsuperscript{14,16,17,18}
  We do not have sufficient epidemiological data to estimate the prevalence of functional asplenism.

  Current total number of people with anatomical or functional asplenism in France is believed to be \textbf{at least 250,000}.

- Population of people who have received a haemopoietic stem cell transplant.
  According to the Biomedicines Agency, 1,769 haemopoietic stem cell allotransplants were performed in 2011.\textsuperscript{19}

On these bases, the target population of NIMENRIX is estimated to be between 280,000 and 300,000 people. However, the majority of this population has probably already been immunised and a possible booster immunisation is only recommended every 3 years after primary immunisation with a non-conjugated tetravalent vaccine (MENCEVAX). The need for re-immunisation has not been established after primary immunisation with a tetravalent conjugate vaccine (MENVEO and NIMENRIX); these populations have not been included in the studies.

The population liable to be given a tetravalent vaccine for prevention of IMI in practice therefore is probably far smaller.

As a guide, 2011 sales data (GERS Hospital and Primary Care) for tetravalent meningococcal vaccines (MENCEVAX and MENVEO) show 91,800 units sold.

**NIMENRIX** is the only tetravalent meningococcal vaccine which can be used in the 12-23 month age group. However, we do not have data to quantify the proportion of people between 12 and 23 months old in this target population, although it is probably extremely small (expert opinion).

### 012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion on the list of medicines approved for hospital use in the indication and dosages in the Marketing Authorisation in the populations recommended by the French High Council for Public Health in its opinion on 12 July 2012.


\textsuperscript{19} http://www.agence-biomedecine.fr/IMG/pdf/2012_plan_greffe_vdef2.pdf