NEISVAC suspension for injection in prefilled syringes
Meningococcal group C polysaccharide conjugate vaccine
prefilled syringe 2 needles, pack of 1 (CIP: 362 773-9)

Applicant: BAXTER SAS

group C Neisseria meningitidis polysaccharide (de-O-acetylated) (strain C11)
conjugated to tetanus toxoid, adsorbed on aluminium hydroxide

ATC Code: J07AH07

List I


Product included on the list of medicines approved for use by hospitals and various public services.

Reason for request: inclusion on the list of products reimbursed by National Insurance for the new population recommended by the HCSP¹:

- systematic vaccination for all infants aged 12 to 24 months
- systematic catch-up vaccination up to and including the age of 24 years during the introduction of this new strategy and pending its optimal impact through group immunity.

Additional document:
Opinion of the HCPH regarding vaccination with meningococcal serogroup C conjugate vaccine (sessions of April 24 and June 26, 2006)
http://www.hcsp.fr/docspdf/avisrapports/hcspa20090424_meningC.pdf

¹ Haut conseil pour la Santé Publique (HCSP) / High Council for Public Health
1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Group C Neisseria meningitidis polysaccharide (de-O-acetylated) (strain C11) conjugated to tetanus toxoid adsorbed on aluminium hydroxide

1.2. Indication
“Active immunisation of children from the age of 2 months, adolescents and adults for the prevention of invasive diseases caused by serogroup C Neisseria meningitidis. NEISVAC must be used according to official guidelines.”

1.3. Dosage (in the newly recommended population)
“Children over one year of age, adolescents and adults: one single dose of 0.5 ml. The need for booster doses for subjects vaccinated with a single dose has not yet been established.”

2 SIMILAR MEDICINAL PRODUCTS

2.1 ATC Classification (2009)

J : Antiinfectives for systemic use
J07 : Vaccines
J07A : Bacterial vaccines
J07AH : Meningococcal vaccines
J07AH07 : Conjugate vaccines

2.2. Medicines in the same therapeutic category

Comparator medicines
There are no comparable vaccines reimbursed by National Insurance under the new vaccine recommendations

2.3. Medicines with a similar therapeutic aim
Vaccines not recommended by the HCSP among the newly designated population:

Meningococcal A + C polysaccharide vaccine (PASTEUR VACCINS)
Indicated from the age of 18 months (approved for use by hospitals)

MENCEVAX meningococcal A + C+ Y+ W_{135} vaccine (GSK)
Indicated from the age of 24 months (approved for use by hospitals)

3 UPDATE WITH DATA AVAILABLE SINCE PREVIOUS OPINION

3.1. Efficacy

3.1.1 Reminder (Transparency Committee’s opinion of March 24, 2004) in the new population recommended by the HCSP/administration schedule of 1 dose without booster recommended)
Study on infants aged 12 to 17 months (study MCT 9701)

Aims:
- To assess the immunogenicity of NEISVAC after injection of a single dose in infants aged 12 to 17 months.
- To assess immune memory by administering a single dose of non-conjugated A/C meningococcal vaccine 6 months after vaccination.

1- Comparative study on 226 infants aged 12 to 17 months in 3 groups:
   Group I (N=75): MENJUGATE
   Group II (N=75): MENINGITEC
   Group III (N=76): NEISVAC

Primary endpoints measured 4 to 6 weeks after vaccination:
- Increase in SBA (serum bactericidal antibody) level at least fourfold compared to baseline
- Specific IgG titre of group C ≥ 2 µg/ml
- Increase in specific IgG titre of group C at least fourfold

Results:

<table>
<thead>
<tr>
<th></th>
<th>MENJUGATE n/N (%)</th>
<th>MENINGITEC n/N (%)</th>
<th>NEISVAC n/N (%)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific IgG titre ≥ 2µg/ml</td>
<td>64/64 (100)</td>
<td>57/57 (100)</td>
<td>62/62 (100)</td>
<td>ns</td>
</tr>
<tr>
<td>Increase in specific IgG (fourfold increase)</td>
<td>64/64 (100)</td>
<td>57/57 (100)</td>
<td>62/62 (100)</td>
<td>ns</td>
</tr>
<tr>
<td>SBA titre ≥ 1/8</td>
<td>66/72 (92)</td>
<td>64/70 (91)</td>
<td>72/72 (100)</td>
<td>0.022</td>
</tr>
<tr>
<td>SBA titre ≥ 1/32</td>
<td>59/72 (82)</td>
<td>58/70 (83)</td>
<td>70/72 (97)</td>
<td>0.004</td>
</tr>
<tr>
<td>Increase in SBA (fourfold increase)</td>
<td>61/67 (91)</td>
<td>58/65 (89)</td>
<td>72/72 (100)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

* compared to group with closest value. ns = not significant

This study demonstrated NEISVAC’s immunogenicity in children aged 12 to 17 months after administering one single dose. The percentage of infants aged 12 to 17 months with SBA titres of > 1/8 in the group vaccinated with NEISVAC is greater than that of the MENINGITEC and MENJUGATE groups after injecting one single dose.

Study of children aged 3½ to 6 (study MCPSB 9701)

Objective: to evaluate whether a prior, later or simultaneous injection of a tetanus and diphtheria booster vaccine dose interferes with the immunogenicity of NEISVAC.

This study demonstrated:
- the immunogenicity of administering one single dose of NEISVAC to children aged 3 ½ to 6 years old.
- the absence of interference between NEISVAC and the tetanus and diphtheria booster vaccination, regardless of when NEISVAC is administered (before, at the same time or after the booster).

Study of adolescents aged 13 to 17 years (study MCPSB 9701)

Objective: to evaluate whether a prior, later or simultaneous injection of a tetanus and diphtheria booster vaccine dose interferes with the immunogenicity of NEISVAC.
This study demonstrated:
- the immunogenicity of administering one single dose of NEISVAC to adolescents aged 13 to 17 years old.
- the absence of interference between NEISVAC and the tetanus and diphtheria booster vaccination, regardless of when NEISVAC is administered (before, at the same time or after the booster).

- **Study on adults** (study NAVA 94C001)
  Objective: to evaluate the immunisation achieved by the vaccine after injecting one single dose by identifying specific antibody levels in healthy adults.
  Primary endpoints evaluated 28 days after vaccination:
  - increase in SBA level at least fourfold compared to baseline
  - SBA titre greater than 1/32
  - increase in specific IgG titre of group C at least fourfold
  Results:

<p>| | |</p>
<table>
<thead>
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<tbody>
<tr>
<td>SBA titre ≥ 1/32</td>
<td>30/30 (100%)</td>
</tr>
<tr>
<td>SBA level increased fourfold</td>
<td>29/30 (96.7%)</td>
</tr>
<tr>
<td>Specific IgG titre increased fourfold</td>
<td>27/30 (90%)</td>
</tr>
</tbody>
</table>

This study demonstrated the immunogenicity of administering one single dose of the vaccine to adults. There is no data for adults aged 65 and over.

**Postmarketing surveillance following a vaccination campaign in the UK** The Public Health services in the UK conducted a postmarketing surveillance programme and analysed the efficacy of three meningococcal serogroup C conjugate vaccines introduced in stages on young children and 15 to 17 year in the UK:

- November 1, 1999  WYETH vaccine  15 to 17 year
- November 29, 1999 WYETH vaccine  Children
- January 10, 2000 WYETH vaccine  Children under the age of 2 years
- March 6, 2000 - May 8, 2000 CHIRON vaccine  9 to 14 years
- April 10, 2000 WYETH vaccine  2 to 5 years
- August 2000 BAXTER vaccine  5 to 8 years

Eighteen months after the start of the meningococcal serogroup C conjugate vaccination programme, the preliminary estimates suggested short-term efficacy as:

<table>
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<tr>
<th>Age group</th>
<th>doses</th>
<th>Protection efficacy (95%CI)</th>
</tr>
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<tbody>
<tr>
<td>Under 1 year</td>
<td>3</td>
<td>89% (69-96)</td>
</tr>
<tr>
<td>1-2 years</td>
<td>1</td>
<td>87% (69-94)</td>
</tr>
<tr>
<td>3-4 years</td>
<td>1</td>
<td>100% (93-100)</td>
</tr>
<tr>
<td>5-14</td>
<td>1</td>
<td>95% (87-97)</td>
</tr>
<tr>
<td>15-17</td>
<td>1</td>
<td>94% (79-99)</td>
</tr>
</tbody>
</table>

Data updated to March 2004 (SPC of October 6, 2008)

"The efficacy estimates based on a limited number of cases, more than one year after the end of priming vaccination, indicate that protection can decrease in young children given a single priming vaccination dose.
In all other age categories (up to 18 years) vaccinated with a single dose, efficacy was maintained at around 90% or more during the year following vaccination and beyond."
3.1.2. Update of data available:
- No new immunogenicity data has been provided for the population concerned by the new HCSP recommendations.

- Data relating to the vaccination programme in the Netherlands with the NEISVAC vaccine since 2002 for 14 months old children with a catch-up programme for adolescents (3 million people vaccinated)
  The data published showed a substantial decrease in the incidence of invasive meningococcal serogroup C infections (>90%) including a direct and indirect effect of the vaccination beyond the target populations through group immunity from the first year of surveillance.
  In the Netherlands, 14 month old children were vaccinated with a catch-up programme for those up to the age of 18 (single dose). This substantial efficacy is related to the high vaccination coverage achieved for children (94%) and targeted catch-up subjects, including adolescents, who constitute a major focus for carriage and transmission.
  It should be noted, however, that there has been moderate follow-up time in the Netherlands to evaluate the middle-term efficacy of this strategy.

- French data on vaccination campaigns conducted with the NEISVAC vaccine as an exceptional measure related to a hyperendemic or unusual occurrence of group cases:
  "... in 2006 in Migennes (Yonne) (2,500 vaccinations)
  ... in 2007 in Barcelonnette (Alpes de Haute Provence) (3,000 vaccinations – 67% vaccination coverage)
  ... in 2007 in the Haute Vienne department (72,000 vaccinations – 86% vaccination coverage)."

- The SPC was updated with the following additions:
  - potential risk of apnoea to be taken into account in the priming vaccination of very premature infants in the “warnings” section
  - relapse of nephrotic syndrome reported in association with meningococcal serogroup C vaccines and dizziness, syncope (reported spontaneously) in the “adverse effects” section.

3.2. Safety

3.2.1. Reminder (Committee’s opinion of March 24, 2004)
  “The adverse effects (referred to in the SPC) most frequently reported in the studies were:
  Very common (>10%)
  - Injection area reactions: redness, sensitivity/pain and oedema
  - Pain in the limbs in older children
  - Headaches
  - Crying and irritability among infants and young children
  - Drowsiness and sleep disorders in infants and young children
  - Vomiting, nausea, diarrhoea in infants
  - Anorexia in infants”

3.2.2. Update of data available
  One SPC update since the last MA referred to by the Committee on March 24, 2004 concerning adverse effects; the following was added:
  - potential risk of apnoea to be taken into consideration for priming vaccination of very premature infants
  - relapse of nephrotic syndrome reported in association with meningococcal group C vaccines
  - dizziness, syncope (reported spontaneously)

3.3. Conclusion
  This conjugate vaccine is immunogenic in infants, children, adolescents and young adults.
In infants aged 12 to 17 months, the immunogenicity observed after injecting a dose of NEISVAC was greater than that observed after injecting a dose of MENINGITEC and MENJUGATE. However, the difference in immunogenicity does not confirm that this vaccine offers greater protection (antibody avidity test and vaccine failure surveillance not conducted).

The duration of longer term protection has not been determined. The need for a late booster dose has not been established in subjects over the age of 12 months.

Data published concerning the impact of prevention strategies in the four countries (UK, Spain, Quebec and the Netherlands) introducing a targeted vaccination strategy with a catch-up campaign demonstrated a substantial decrease in the incidence of invasive meningococcal serogroup C infections from the first year of surveillance (>90%) with a vaccination coverage of around 90% in the targeted populations and those concerned by the catch-up programme.

The safety of this vaccine is good and comparable to that of other conjugate vaccines currently marketed.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit
This vaccine prevents against serious infections that can be fatal.

This product is intended for preventive treatment.

The product’s efficacy (immunogenicity and protective efficacy) / adverse effects ratio is high.

There is no reimbursed alternative vaccine in this newly recommended population.

Public health benefit
Due to the severity of prognosis and contagiousness, the burden of infectious meningitis can be considered moderate. In France, Neisseria Meningitidis is thought to be responsible for 30% of all bacterial meningitis cases and 25 to 30% of Neisseria Meningitidis meningitis cases are thought to be attributable to serogroup C. Hence, given the limited number of cases observed in France (175 cases reported every year on average through mandatory declarations from 2003 to 2008*), the burden of invasive meningococcal serogroup C infections is therefore low.

Given recent epidemiological data available in France (increase in the incidence of invasive C meningococcal infections, episodes of grouped cases resulting in the creation of a vaccination programme), the prevention of these infections is now an established public health need (HCSP recommendations in 2009).

The efficacy data for NEISVAC is based on the immune response and the reported impact of prevention strategies promoted in other European countries. The implementation of vaccination programmes in certain European countries has demonstrated a significant decrease in the incidence of IMI (around 90%).

Subject to a high vaccination coverage, a substantial impact is expected in France in terms of morbidity and mortality in both vaccinated and unvaccinated populations. Indeed, an indirect impact, mainly due to the

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* In the Netherlands: 200 cases/year (2000 to 2002) to 42 cases in 2003 and 17 cases in 2004
vaccine’s ability to reduce nasopharyngeal carriage in adolescents and young adults, is also expected.

NEISVAC is therefore likely to provide a solution to the identified public health need. Consequently, a low public health benefit is expected for NEISVAC in this indication, as for the other meningococcal C vaccines. This benefit will depend on the vaccination coverage achieved.

*opinion of the High Council for Public Health regarding vaccination with the meningococcal serogroup C conjugate vaccine - sessions of April 24 and June 26, 2009

The actual benefit of this vaccine is substantial.

4.2. Improvement in actual benefit

Taking into account,
- the severity of Neisseria meningitidis serogroup C infections,
- the immunogenicity of this vaccine,
- the impact of the prevention strategies conducted in other European countries (infants, children, adolescents, young adults),
- the absence of any available alternative recommended by the HCSP for infants from the age of 12 months, children, adolescents and adults up to and including the age of 24 years,

This vaccine maintains a major improvement in actual benefit (IAB I) in the prevention of these invasive serogroup C Neisseria meningitidis diseases in children from the age of 12 months, adolescents and young adults up to and including the age of 24 years.

The Committee stresses that the efficacy of this prevention strategy is subject to a high vaccination coverage being achieved rapidly and that this strategy and the possible need for a booster during adolescence (not currently established) will be re-assessed according to surveillance data.

4.3. Therapeutic use

According to the HCSP, vaccination is recommended systematically to infants aged 12 to 24 months with a single meningococcal C conjugate vaccine dose. This systematic vaccination is extended up to and including the age of 24 years using the same single dose vaccination schedule during the introduction of this new strategy and pending its optimal impact through group immunity.

4.4. Target population

The target population of the NEISVAC vaccine includes:
- all infants aged 12 to 24 months
- children, adolescents and adults up to and including the age of 24 during the introduction of the strategy.

According to INSEE data, approximately 834,000 children are aged 12 to 24 months and around 17.6 million children, adolescents and young adults over 24 months are likely to be

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3 Opinion of the HCSP regarding vaccination with meningococcal serogroup C conjugate vaccine (sessions of April 24 and June 26, 2006) http://www.hcsp.fr/docspdf/avisrapports/hcspa20090424_meningC.pdf
included in the catch-up programme. The vaccination coverage concerning the catch-up programme is difficult to estimate.

4.5. Transparency Committee recommendations
The Transparency Committee recommends inclusion on the list of products reimbursed by National Insurance in the indications and dosages of the MA for the new population recommended by the HCSP.

4.5.1. Packaging: the packaging is appropriate for prescription requirements

4.5.2. Reimbursement rate: 65%