HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

18 February 2009

PREVENAR 0.5 ml suspension for injection
Pneumococcal saccharide conjugated vaccine, adsorbed
Pack of 1 vial with 1 syringe (CIP: 356 818-4)
Pack of 1 prefilled syringe (CIP: 359 480-4)
Pack of 10 prefilled syringes (CIP: 359 481-0)

Applicant: WYETH PHARMACEUTICALS FRANCE

Pneumococcal saccharide serotype 4*
Pneumococcal saccharide serotype 6B*
Pneumococcal saccharide serotype 9V*
Pneumococcal saccharide serotype 14*
Pneumococcal saccharide serotype 18C*
Pneumococcal saccharide serotype 19F*
Pneumococcal saccharide serotype 23F*
*conjugated to the CRM_{197} carrier protein and adsorbed on aluminium phosphate (0.5 mg)

ATC Code 2008: J07AL02

List I

Date of initial MA (centralised procedure): February 2, 2001 – variations of March 9, 2007 (acute otitis media), April 2, 2007 (pneumonia without microbiological confirmation of diagnosis) and February 6, 2008 (alternative vaccination schedule for wide-scale vaccination).

Reasons for request:

- Inclusion on the list of medicines reimbursed by National Insurance (pack of 1 vial with syringe and pack of 1 prefilled syringe) and approved for use by hospital (pack of 1 vial with syringe, pack of 1 and pack of 10 prefilled syringes) in the “acute otitis media” and “pneumonia without microbiological confirmation of diagnosis” indication extension

- Validation of alternative vaccination schedule: 2 doses followed by a booster dose for infants, in the context of wide-scale vaccination

Documents enclosed:

Opinion of the High Council for Public Health:

- relating to the review of recommendations for the heptavalent pneumococcal conjugate vaccine subsequent to the extension of the MA to the prevention of acute otitis media and pneumococcal pneumonia (October 17, 2008).
- relating to the vaccination schedule for the heptavalent pneumococcal conjugate vaccine (October 17, 2008)

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Pneumococcal saccharide serotype 4*
Pneumococcal saccharide serotype 6B*
Pneumococcal saccharide serotype 9V*
Pneumococcal saccharide serotype 14*
Pneumococcal saccharide serotype 18C*
Pneumococcal saccharide serotype 19F*
Pneumococcal saccharide serotype 23F*

*conjugated to the carrier protein (CRM197) and adsorbed on aluminium phosphate (0.5 mg).

1.2. Indication

"Active immunisation against diseases caused by *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23F (including sepsis, meningitis, pneumonia[1], bacteraemia and acute otitis media) in infants and children from 2 months up to 5 years of age (see sections 4.2, 4.4 and 5.1).

For the number of doses to be administered according to age category, see section 4.2.

PREVENAR must be used on the basis of the official recommendations that taking into account the impact of invasive infections among the different age groups and variability of serotype epidemiology in different geographical areas."

1.3. Dosage

"The vaccine must be administered by intramuscular injection. Recommended sites are the anterolateral aspect of the thigh (vastus lateralis muscle) in infants, or the deltoid muscle of the upper arm in young children.

Vaccination schedules
The vaccination schedules for PREVENAR should be based on official recommendations.

Infants aged 2 to 6 months:
The primary infants vaccination series consists of three doses of 0.5ml; the first dose usually administered at 2 months of age and with an interval of at least one month between doses.
A fourth dose is recommended during the child's second year.
A two-dose schedule can be considered as an alternative to the administration of PREVENAR in the context of a wide-scale vaccination programme for infants. The first dose may be administered from the age of 2 months followed by a second dose, at least two months later, and a third dose (booster dose) at 11-15 months of age.

Previously unvaccinated older infants and children:
Infants aged 7 to 11 months: two doses each of 0.5 ml with an interval of at least one month between doses. A third dose is recommended during the child's second year of life.
Children aged 12 to 23 months: two doses each of 0.5 ml with an interval of at least 2 months between doses.

Children aged 24 months to 5 years of age: one single dose.

[1] The indication extension concerns "pneumonia without microbiological confirmation of diagnosis" as PREVENAR was already indicated for the prevention of bacterial pneumonia (vaccine serotypes).

It has not been established whether a booster dose is useful subsequent to these vaccination schedules."

2. REMINDER OF THE COMMITTEE'S OPINION AND LISTING CONDITIONS

Transparency Committee's opinion of November 21, 2001

The committee concurs with the opinion of the Superior Council for Public Health (session of September 14, 2001), which was as follows:
"Wide-scale anti-pneumococcal vaccination with the heptavalent conjugate vaccine for all children under the age of 2 years cannot be recommended at present."

Transparency Committee's opinion of April 24, 2002

"Given
- the severity of invasive pneumococcal infections,
- the efficacy of PREVENAR in the prevention of bacteraemia, sepsis, bacterial meningitis and bacterial pneumonia caused by *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F and 23 F in infants and young children at 2 months to 2 years of age,
- the absence of any available alternative,
this vaccine is a major breakthrough in the prevention of these infections."

Transparency Committee's opinion of December 13, 2006

"PREVENAR preserves the major therapeutic benefit recognised by the Transparency Committee on April 24, 2002 in the prevention of invasive *Streptococcus pneumoniae* infections (serotypes 4, 6B, 9V, 14, 18C, 19F and 23 F) in the context of the extension of vaccination recommendations to all children at 2 months to 2 years of age, to children not previously vaccinated at 2 years to below 5 years old children identified as at a high risk of suffering from an invasive pneumococcal infection and children eligible for a cochlear implant or carrying cochlear implants."

3. SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2008)

J	:	Anti-infectives
J07	:	Vaccines
J07A	:	Bacterial vaccines
J07A L	:	Antipneumococcal vaccines
J07A L 02	:	Pneumococcus, purified polysaccharides antigen conjugated

3.2. Medicines in the same therapeutic category

There is no directly comparable vaccine.

3.3. Medicines with a similar therapeutic aim

PNEUMO 23 (polysaccharide pneumococcal vaccine), whose indication is not identical to PREVENAR's and whose recommendations[2] are limited to vaccination against invasive pneumococcal infections:
- at least two months after the second dose of PREVENAR in children aged 24 to 59 months presenting with a condition exposing them to an elevated risk of invasive pneumococcal infection and not previously vaccinated with PREVENAR,

[2] BEH No.16-17, Vaccination calendar 2008

- every five years, for adults and children aged 5 years and over, suffering from certain conditions.

4. ANALYSIS OF AVAILABLE DATA

4.1. Efficacy data in the acute otitis media (AOM) indication extension

The company submitted:
- two pivotal studies, FinOM and Kaiser (NCKP), that were evaluated when the initial MA was granted,
- long-term follow-up data for these studies,
- data from scientific literature,
- studies concerning a 9-valency pneumococcal vaccine (not described).

4.1.1. FinOM study[3]

The efficacy of PREVENAR in the prevention of acute otitis media (AOM) was evaluated during a randomised, double-blind clinical study on 1,662 Finnish infants immunised either with PREVENAR or with a control vaccine (hepatitis B vaccine) at the age of 2, 4, 6 months and 12-15 months (priming vaccination comprising 3 doses + a booster dose) and initially monitored up to the age of 2 years.

Primary endpoint: to reduce the incidence of episodes of pneumococcal and vaccine serotype AOM compared to the control group.

Results:
A sample was taken from the inner ear to perform the serological typing during 93% of visits.
During the follow-up of the children aged under 2 years, 2,596 episodes of AOM were observed (by per protocol). The overall incidence of AOM was 1.16 episodes per child per year in the PREVENAR group and 1.24 episodes per child per year in the control group.
In children vaccinated with PREVENAR, the following was observed compared to the control group:
- a decrease of 186 episodes of pneumococcal vaccine serotype AOM,
- an increase of 30 episodes due to non-vaccine serotype pneumococci,
- 30 additional cases due to H. influenzae and M. catarrhalis.

Therefore, the number of episodes avoided before the age of 2 years was 126, corresponding to a decrease of 118 episodes of AOM for every 1,000 children vaccinated with PREVENAR.

The efficacy of PREVENAR, expressed as a relative decrease in the incidence of vaccine serotype AOM episodes was 54% (95% CI: [41%; 64%]) analysed on an intention to treat basis and 57% (95% CI: [44%; 67%]) analysed per protocol.
In parallel, a relative increase of 33% (IC 95%: [-1%; 80%]) of AOM due to serotypes not included in the vaccine was observed in children vaccinated compared to the control group.
Consequently, the overall benefit was a relative decrease of 34% (95% CI [21%; 45%]) in the incidence of all pneumococcal AOM.

The impact of the vaccine on the total number of otitis media episodes, regardless of cause, was a non-statistically significant decrease of 6% (95% CI: [-4%; 16%]).

[3] Eskola J, Kilpi T et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med. 2001 Feb 8;344(6):403-9

According to scientific literature[4], the 7 serotypes contained in the vaccine correspond to 60 to 80% of pneumococcal acute otitis media. It is therefore estimated that PREVENAR could prevent 6-13% of all clinical AOM episodes.

Long-term results:
One subgroup of children in this study (n=756) was monitored up to the age of 4 to 5 years. In this follow-up, the efficacy of the vaccine on severe AOM, expressed as a relative decrease in the incidence of vaccine serotype AOM episodes, was:

- 18% (95% CI: [1%; 32%]) for frequent AOM (defined as at least 3 episodes within 6 months),
- 50% (95% CI: [15%; 71%]) for chronic otitis media with effusion,
- 39% (95% CI: [4%; 61%]) concerning the fitting of tympanostomy tubes.

4.1.2. Kaiser study (NCKP)[5]

The efficacy of PREVENAR in the prevention of AOM was evaluated as a secondary endpoint in a wide-scale randomised, double-blind clinical study carried out between October 1995 and August 1998 on a multiethnic Northern Californian population (Kaiser Permanente trial) of 37,868 children.
The infants were vaccinated either with PREVENAR or with a control vaccine (meningococcal group C vaccine) at the ages of 2, 4, 6 months and 12-15 months (priming vaccination of 3 doses + one booster dose).
This study was extended by an open-label phase up to April 1999 on 27,754 children of which 4,646 were over 3 years of age at the end of the follow-up period.

Primary endpoint: to reduce the incidence of bacteriologically documented invasive infections.

Secondary endpoint: to reduce the incidence of episodes of AOM without microbiological confirmation compared to the control group.

Results:
The overall incidence of AOM was 1.60 episodes per child per year in the PREVENAR group and 1.72 episodes per child per year in the control group, giving a decrease of 12 AOM episodes for every 100 children vaccinated with PREVENAR.
The impact of the vaccine on the total number of AOM episodes, regardless of cause, was a statistically significant relative decrease of 7% (95% CI: [4%; 10%]).
- Analysed on an intention to treat basis, the number of tympanostomy tubes fitted was reduced by 23.2% (95% CI: [11.3%; 33.5%]) and 24.2% (95% CI: [11.7%; 35%]) analysed per protocol.
- Analysed per protocol, the following was observed:

- a relative decrease of 9% (95% CI: [3%; 15%]) of recurrent AOM (defined as 3 episodes in 6 months or 4 episodes in 1 year) or,
- a relative decrease of 23% (95% CI: [7%; 36%]) of recurrent AOM (defined as 5 episodes in 6 months or 6 episodes in 1 year).

[4] Fletcher MA, Fritzell B. Brief review of the clinical effectiveness of PREVENAR against otitis media Vaccine 25 (2007) 2507-2512
[5] Fireman B, Black SB et al. Impact of the pneumococcal conjugate vaccine on otitis media. Pediatr Infect Dis J. 2003 ;22(1):10-6. Links Erratum in: Pediatr Infect Dis J. 2003 Feb;22(2):163

4.2. Efficacy data in the indication extension to pneumoniae without microbiological confirmation of diagnosis

The company submitted:
- one pivotal Kaiser study (NCKP), which was evaluated when the initial MA was granted,
- further data from this study,
- surveillance data from the United States,
- two studies concerning a 9-valency pneumococcal vaccine.

The only study described is the pivotal Kaiser study (NCKP), accompanied by further data.

4.2.1. Kaiser study (NCKP)[6]

(see paragraph 4.1.2 for description of method)

Secondary endpoints: to reduce the incidence of episodes of:
- clinical pneumonia,
- X-ray documented clinical pneumonia (regardless of results),
- clinical pneumonia with abnormal pulmonary X-ray (presence of infiltrate beyond the perihilar region, alveolar focus, or pleuropulmonary disease).

In the prevention of pneumonia without microbiological confirmation of diagnosis, the decrease in the risk of a first episode of clinical pneumonia with an abnormal pulmonary X-ray was estimated as 17.7% (95% CI: [4.8%; 28.9%]) compared to the non-vaccinated group, analysed on an ITT basis (see table).

The decrease in the incidence of episodes of pneumonia with an abnormal pulmonary X-ray was the highest in the first year of life (24.3%; 95% CI: [4.1%; 40.2%]) and during the first 2 years of life (22.7%, (95% CI: [8.7%; 34.5%]) analysed on an ITT basis.
In children over the age of 2, the decrease in the incidence of episodes of pneumonia with an abnormal pulmonary X-ray was not significant (-6.1%; (95% CI: [-43.7%; 21.7%] on an ITT basis).

Table: efficacy concerning the first episode of pneumonia in children vaccinated with PREVENAR compared to the control group

	Intention to treat			Per protocol		
	Cases/1,000 person-years		Decrease in incidence (95% CI)	Cases/1,000 person-years		Decrease in incidence (95% CI)
	PREVENAR	CONTROL		PREVENAR	CONTROL	
Any clinical pneumonia	43.5	45.8	6.0 [-1.5; 11.0] p=0.13	53.4	55.9	4.3 [-3.5; 11.5] p=0.27
X-ray documented clinical pneumonia	26.3	28.9	8.9 [0.9; 16.3] p=0.03	30.9	34.2	9.8 [0.1; 18.5] p=0.05
X-ray-confirmed clinical pneumonia	8.3	10.1	17.7 [4.8; 28.9] p=0.01	8.7	11.0	20.5 [4.4; 34.0] p=0.02

A reminder that the efficacy was 87.5% (95% CI: [7%; 99%]) in the prevention of bacterial pneumonia due to a *S. pneumoniae* vaccine serotype.

[6] Black SB, Shinefield HR et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia. Pediatr Infect Dis J. 2002 Sep;21(9):810-5.

The Committee stresses that, in the context of the studies carried out with a vaccination schedule of 3 doses followed by one booster dose, the way in which the results are expressed, in terms of a relative decrease in the number of AOM episodes and pneumonias without microbiological confirmation of diagnosis, makes it difficult to ascertain the extent of the effect.

4.3. Data relating to alternative vaccination schedule of two-dose priming vaccination followed by a booster dose

4.3.1. Immunogenicity data (extracted from SPC)

Of the nine studies contributing to the evaluation of the immunogenicity of the 2 doses + one booster vaccination schedule, 2 randomised studies compared the schedules comprising 2 or 3 doses followed by one booster. These immunogenicity studies were carried out on infants carrying no risk of an invasive pneumococcal infection.

"The immunogenicity of a two-dose priming vaccination in infants, followed by one booster dose around the age of 1 year, has been documented in several studies.

Most of the data has indicated that a small proportion of infants reached antibody concentrations ≥ 0.35 µg/mL (WHO-recommended reference antibody concentration) for serotypes 6B and 23F after a two-dose priming vaccination, directly or indirectly compared to three-dose priming vaccination."

"The clinical consequences of lower antibody concentrations for serotypes 6B and 23F after two-dose priming vaccination in infants are unknown."

"Furthermore, the average geometric antibody concentrations in infants were lower for most serotypes after two-dose priming vaccination than after three-dose priming vaccination.

However, the responses in terms of antibodies after a booster dose in young children given a priming vaccination in two or three doses were comparable for each of the 7 vaccine serotypes and demonstrated that a satisfactory immune memory was induced with both priming vaccination schedules."

4.3.2. Efficacy data

No clinical study has been conducted on the efficacy of two-dose priming vaccination followed by a booster, be it in pneumonia or acute otitis media.
However, the clinical impact of using the simplified vaccination schedule (2 + 1) has been documented in wide-scale national vaccination programmes by the Americans, Canadians, British and Norwegians (see results given in appendix 2).

4.4. Further immunogenicity data on children with sickle-cell anaemia[7]
(extracted from SPC)

"The immunogenicity of PREVENAR was studied during an open-label, multicentre study on 49 infants with sickle-cell anaemia. The children were vaccinated with PREVENAR (3 doses 1 month apart from the age of 2 months) and 46 of these children were also given the 23-valency polysaccharide pneumococcal vaccine (PNEUMO 23) at the age of 15-18 months. After the priming vaccination, 95.6% of the infants had antibody levels of at least 0.35 µg/ml for the 7 serotypes contained in PREVENAR. A significant increase in the concentrations of

[7] Reinert P et al. Immunogenicity and safety of a pneumococcal conjugate 7-valent vaccine in infants with Sickle cell disease. Pediatr Infect Dis J 2007

antibodies against the 7 serotypes was observed after vaccination with the polysaccharide vaccine, suggesting a satisfactory immune memory."

"This limited data demonstrated that PREVENAR (with a three-dose priming vaccination) brought about a suitable immune response in infants with sickle-cell anaemia, with a similar safety profile to the one observed in non-high risk groups."

4.5. Safety

No new safety data has been provided for the indication extension requests.
The most common adverse effects reported (≥ 1/10) included an injection site reaction and a fever.
Since the previous opinion, a warning has been added to the SPC (MA of 11/12/2007) concerning a potential risk of apnoea in very premature infants (born at or under 28 weeks) and especially in infants with a history of respiratory immaturity.

4.6. Conclusion

The indication extension to acute otitis media and pneumonia without microbiological confirmation of diagnosis was evaluated during 2 pivotal studies.
The additional protection provided by PREVENAR in this indication extension was minor.
This indication extension concerns the same target population as the one currently vaccinated with PREVENAR for the prevention of invasive pneumococcal vaccine serotype diseases.

The alternative two-dose vaccination schedule + booster dose in the context of wide-scale vaccination was evaluated in terms of immunogenicity in infants without risk factors.
The responses in terms of antibodies after a booster dose in young children given a priming vaccination in two or three doses were comparable for each of the 7 vaccine serotypes.

It will be necessary to continue monitoring the emergence of non-vaccine serotypes, the sensitivity of the strains to antibiotics, nasopharyngeal carrier data and the epidemiology of pneumococcal infections to collect long-term data in France.

5. TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Actual benefit

In the context of vaccination with PREVENAR, the extended prevention to acute otitis media and pneumonia without microbiological confirmation of diagnosis does not modify the actual benefit.

The actual benefit of this vaccine in the population recommended by the High Council for Public Health remains substantial.

5.2. Improvement in actual benefit

In the indication extension (acute otitis media and pneumonia without microbiological confirmation of diagnosis), PREVENAR does not improve actual benefit (IAB V) in the care of children recommended for vaccination by the High Council for Public Health.

The Committee stresses that it will reevaluate this vaccine based on any new data concerning inclusion conditions.

5.3. Therapeutic use

The indication extension does not change the therapeutic use recommended by the High Council for Public Health.
Only the vaccination schedule is simplified for the majority of the target population corresponding to children under 2 years of age not at risk of an invasive pneumococcal infection[8] and not premature, in the context of wide-scale vaccination.

In accordance with the opinions of the High Council for Public Health of October 17, 2008 (enclosed in the appendices), vaccination with PREVENAR is currently recommended:

- for children aged 2 months to 2 years, with a simplified vaccination schedule of 2 doses at the age of 2 and 4 months followed by a booster at 12 months and excluding premature infants and those with a high risk of invasive pneumococcal infection[8] for which the 3-dose vaccination schedule is maintained at 2, 3 and 4 months followed by a booster between 12 and 15 months;
- for children not previously vaccinated aged between 2 and 5 and identified as at a high risk of an invasive pneumococcal infection[8], with a vaccination schedule maintained at 2 doses 2 months apart followed by one dose of PNEUMO 23 at least 2 months later.

5.4. Target population

The indication extension and the alternative vaccination schedule do not modify the vaccine's target population, as PREVENAR is already recommended for children under 2 and children not previously vaccinated between the age of 2 and 5 and identified as being at a high risk of invasive pneumococcal infection.

The target population for PREVENAR is therefore:
- all children between 2 months and 2 years of age,
- children not previously vaccinated, aged 2 years to 5 years, identified as being at a high risk of suffering from an invasive pneumococcal infection.

The number of births is around 834,000 per year (estimated according to the cohort of children born in 2008[9]).
The number of children not previously vaccinated, aged 2 years to 5 years, identified as being at a high risk of suffering from an invasive pneumococcal infection[8] is thought to be very limited.
The target population for PREVENAR is therefore estimated as 834,000 children.

5.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indication extension, with the alternative vaccination schedule and for the populations recommended by the High Council for Public Health in the opinions of October 17, 2008 (enclosed in the appendices).

5.5.1 Packaging: Appropriate for the prescription requirements.

5.5.2 Reimbursement rate: 65%

[8] In other words, presenting with any of the following: functional asplenia or splenectomy, homozygous sickle cell anaemia, HIV, immunodeficiency that is congenital (or induced by chronic renal failure or nephrotic syndrome, immunosuppressants or radiotherapy for neoplasia, lymphoma or Hodgkin's disease, leukaemia, organ transplant), cyanogenic congenital heart disease, heart failure, chronic pneumopathy (excluding asthma, except when on long-term corticosteroid treatment), osteomeningeal lesion, diabetes, patients eligible for cochlear implants or wearing a cochlear implant.
[9] INSEE data http://www.insee.fr/fr/themes/document.

APPENDIX 1:

Opinion of the High Council for Public Health
relating to the reevaluation of vaccine recommendations for the heptavalent pneumococcal conjugate vaccine
subsequent to the extension of the MA[10] to the prevention of acute otitis media and pneumococcal pneumonia

(October 17, 2008)

This opinion complements the opinion of the Superior Council for Public Health in France, transmissible diseases section, of May 19, 2006, relating to the vaccination with the heptavalent pneumococcal conjugate vaccine of children under the age of 2 and children aged 2 to 5,

And after taking into account the report of the technical vaccinations committee work group on vaccination with the heptavalent pneumococcal conjugate vaccine.

The heptavalent pneumococcal conjugate vaccine (PCV_7) Prevenar® has been granted an extension to its European MA to acute otitis media (AOM) and pneumococcal pneumonia (PP). This MA extension is the reason for which the technical vaccinations committee was called upon. Its conclusions are as follows:

- In AOM, PCV_7 has a moderate impact on the total number of cases in children under the age of 2. Its impact appears to be greater in the prevention of recurrent, lingering otitis, cases justifying the fitting of a tympanostomy tube and otitis refractory to treatment.

- In pneumonia, data from controlled studies and the impact observed in the United States since wide-scale vaccination show that the vaccine decreases the incidence of pneumonia in children under the age of 2, complementary to its primary benefit, i.e. its efficacy on invasive pneumococcal infections in infants and young children.

Indeed, according to:

- **Efficacy data on the vaccine in the prevention of AOM**

The impact of vaccination with the PCV_7 was a decrease:

- of 6 to 7% in the total number of episodes of AOM, regardless of cause, according to two vaccine trials in the United States([i]) and Finland([ii]). In the bacteriologically documented study ([ii]), the vaccine's efficacy was 57% (95% CI: 44-67) against AOM due to a vaccine serotype pneumococcus, but with a 33% increase (95% CI: - 1 to 80) in the number of episodes related to non-vaccine serogroups, the overall benefit being a 34% decrease (95% CI: 21-45) in the incidence of all pneumococcal AOM;

- in AOM seen in consultations of 6 to 20% in children under the age of 2 ([iii, iv]);

- of 9 to 18% of recurrent AOM (or even 23%[11]) and a decrease of 24% (95% CI: 12-35) to 39% (95% CI: 4-61) in the number of tympanostomy tubes fitted ([i, ii, v]);

[10] Marketing Authorisation
[11] Depending on whether defined as 3 episodes in 6 months (or 4 episodes in 1 year) or as 5 episodes in 6 months (or 6 episodes in 1 year).

- of 24% in the number of paracenteses for persistent otitis or refractory otitis in primary care in one US study([vi]) and a decrease in the rate of isolated pneumococci from 48% to 31% (p=0.009) ([i,vii]);

- in vaccine serotype AOM (correlated to the number of doses received), in particular for serotype 6B, and an increase in non-vaccine serotype AOM([viii]),

- in nasopharyngeal carriage of the pneumococcus in the children vaccinated (57% versus 71%), a decrease that was even greater after a booster dose ([ix]);

- in the carriage of strains with reduced sensitivity or refractory to penicillin in the population vaccinated ([ix]) but contemporary with a national campaign enabling a decrease in the use of antibiotics.

➢ **Efficacy data on the vaccine in the prevention of pneumonia**

- In a randomised, double-blind US study ([i]), the decrease in the incidence of pneumonia with infiltrate on the pulmonary X-ray beyond the hilar region was 20.5% (95% CI = 4.4 to 34; p=0.02) compared to the non-vaccinated group. In this study, the efficacy in children under the age of 2, reevaluated using WHO-recommended standardised interpretation criteria, was 30.3% (95% CI = 10.7-45.7; p=0.04) analysed per protocol ([x]).

- In the United States, in children under the age of 2 between 2001 and 2004, the rate of hospital admissions for pneumonia, regardless of cause, was reduced by 39% (95% CI = 22 to 52) compared to the rate expected, calculated based on the pre-vaccination period of 1997-1999 (xi) and admission rates for pneumococcal pneumonia decreased by 65% (p<0.0001). Other studies have shown, among children aged under 2, a comparable decrease in community-acquired pneumonia requiring admission ([xii, xiii]), a decrease in the number of hospital admissions, visits to A&E and consultations for pneumonia of 16% to 18% compared to the pre-vaccination period in Tennessee (xiv), and even as much as 35% for consultations in New York.

- **The High Council for Public Health notes the impact of vaccination with the heptavalent pneumococcal conjugate vaccine on the incidence of pneumonia** and, to a lesser extent, on acute otitis media, in children under the age of 2.

- **Nevertheless, the High Council for Public Health repeats that:**

- **vaccination** with the heptavalent pneumococcal conjugate vaccine **is already recommended[12] for all children under the age of 2;**
- **this recommendation serves for the prevention of invasive pneumococcal infections**.

- **The High Council for Public Health therefore declares that there is no need to modify current recommendations.**

[12] Opinion of the Superior Council for Public Health in France, transmissible diseases section, of May 19, 2006, relating to the vaccination with the heptavalent pneumococcal conjugate vaccine of children under the age of 2 and children aged 2 to 5.

References

[i] Black S, Shinefield H et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J 2000, 19, 187-195.

[ii] Eskola J, Kilpi T, Palmu AA et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med 2001, 344, 403-9.

[iii] Poehling KA, Lafleur BJ, Szilagyi PG et al. Population-based impact of pneumococcal conjugate vaccine in young children. Pediatrics 2004, 114, 755-61.

[iv] Grijalva CG, Poehling KA, Norti JP et al. National impact of universal childhood immunization with pneumococcal conjugate vaccine on outpatient medical care visits in the United States. Pediatr 2006, 118, 865-73.

[v] Palmu AA, Verho J, Jokinen J, Karma P, Kilpi TM. The seven-valent pneumococcal conjugate vaccine reduces tympanostomy tube placement in children. Pediatr Infect Dis J 2004, 23, 732-8.

[vi] Casey JR, Pichicero ME. Changes in frequency and pathogens causing acute otitis media in 1995-2003. Pediatr Infect Dis J 2004, 23, 824-8.

[vii] Block SL, Hedrick J, Harrison C et al. Community-wide vaccination with the heptavalent pneumococcal conjugate significantly alters the microbiology of acute otitis media. Pediatr Infect Dis J 2004, 23, 829-33.

[viii] Mc Ellistrem C et al. Acute otitis media due to Penicillin-nonsusceptible Streptococcus pneumoniae before and after the introduction of the pneumococcal conjugate vaccine. Clin Infect Dis 2005, 40, 1738-44.

[ix] Cohen R, Levy C, De La Rocque F et al. Impact of pneumococcal conjugate vaccine and of reduction of antibiotic use in nasopharyngeal carriage of non susceptible pneumococci in children with acute otitis media. Pediatr Infect Dis J 2006, 25, 1001-7.

[x] Hansen J, Black S, Shinefield H et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than 5 years of age for prevention of pneumonia; updated analysis using world health organisation standardized interpretation of chest radiographs. Pediatr Infect Dis J 2006, 25, 779-781.

[xi] Grijalva CG. Decline in pneumonia admissions after routine childhood immunization with pneumococcal conjugate vaccine in the USA: a time-series analysis. Lancet 2007, 369, 1179-86.

[xii] Nelson JC, Whitney CG, Yu O et al. Impact of the introduction of pneumococcal conjugate vaccine on rate of community acquired pneumonia. ISPPD April 2005, SYL 05.

[xiii] Zhou F, Kyawmh, Shefer A et al. Health care utilization for pneumonia in young children after routine pneumococcal conjugate vaccine use in the United States. Arch Pediatr Adoles Med 2007, 161, 1162-68.

xiv Poehling KA, Lafleur BJ, Szilagyi PG et al. Population-based impact of pneumococcal conjugate vaccine in young children. Pediatrics 2004, 114, 755-61.

APPENDIX 2:

Opinion of the High Council for Public Health relating to the vaccination schedule for the heptavalent pneumococcal conjugate vaccine

(October 17, 2008)

This opinion complements the opinion of the Superior Council for Public Health in France, transmissible diseases section, of May 19, 2006, relating to the vaccination with the heptavalent pneumococcal conjugate vaccine of children under the age of 2 and children aged 2 to 5,

And after taking into account the report of the technical vaccinations committee work group on vaccination with the heptavalent pneumococcal conjugate vaccine.

Vaccination with the heptavalent pneumococcal conjugate vaccine (PCV_7) was initially recommended in France in March 2002 for children under the age of 2 affected by diseases with conditions exposing them to an elevated risk of invasive pneumococcal infections (IPI) or related to their form of day care. In July 2006, this recommendation was extended to all children under the age of 2. The vaccination schedule adopted in France is currently 3 injections at the age of 2, 3, 4 months and a booster dose at the age of 12-15 months.

According to EPIBAC data collected between 2001 and 2006, the incidence of pneumococcal meningitis and infections among children under the age of 2 decreased from 8.0 to 6.0 cases per 100,000 (p=0.04) and from 21.8 to 17.5 cases per 100,000 (p=0.007) respectively ([i]). The decrease observed was 25% for pneumococcal meningitis and 20% for pneumococcal infections. At the same time, the incidence of pneumococcal meningitis and infections did not decrease in older children and adults. Similarly, according to data from the GPIP/ACTIV National observatory for childhood bacterial meningitis, a 28.4% decrease in the number of cases of pneumococcal meningitis was observed in children aged 2 to 24 months between 2001-2002 and 2005 ([ii]).

Other various elements encourage an increase in vaccination coverage in France: reimbursements of PCV_7 for children under the age of one increased by 20% between 2005 and 2006 and the proportion of children given a full priming vaccination, estimated as 44% in the first quarter of 2006, was 56% one year later according to two surveys on a sampling of children aged 6 to 12 months ([iii]). The influence of the number of injections on vaccination coverage has not been explored.

The safety profile does not differ to other vaccines: essentially painful reactions at the injection site (in around one third of children), a temperature exceeding 38℃ and vomiting (in around a quarter of them). Severe allergic reactions are rare ([iv]).

An alternative vaccination schedule, comprised of two doses for the priming vaccination of infants under the age of 1 followed by one booster dose, has been validated by the European Medicines Agency (EMEA).

- **Data concerning the two-dose priming vaccination schedule followed by one booster dose**

Immunogenicity data

- In eight studies, the percentage of children showing a level of antibodies determined by Elisa as ≥ 0.35 µg/ml[13] one month after the second dose of the vaccine in the context of a two-dose priming vaccination schedule is comparable for 5 of the vaccine serotypes (4, 9V, 14, 18C and 19F) to the percentage observed one month after the third dose in the three-dose priming vaccination schedule ([v, vi, vii, viii, ix, x, xi, xii]). However, all the studies, excluding non-controlled trials on British infants, show a significantly lower response for serotypes 6B and 23F after two doses.

- One month after the booster dose, antibody responses are similar for the 7 serotypes, whatever the priming vaccination schedule; the extent of the increase in antibody concentrations after a PCV_7 booster dose or after a dose of the VPC_9[14] vaccine at the age of 12 months demonstrates the production of a priming vaccination-acquired immune memory in both cases ([v, xii]).

Field efficacy data regarding invasive pneumococcal infections (IPI)

- In the United States, a retrospective case-control study conducted by the CDC during intermittent periods of vaccine shortages between 2001 and 2004 (booster dose temporarily suspended then third dose of priming vaccination) ([xiii]) estimated that the efficacy of the PCV_7 vaccination programme for children given the "2 + 1" form was 98% (95% CI: 75 to 100) and 100% with the "3 + 1" form (insignificant difference).

- In Quebec, after the introduction in December 2004 of PCV_7 vaccination for all infants with a "2 + 1" programme (at 2, 4 and 12 months) together with a "3 + 1" programme (at 2, 4, 6 and 12 months) for children with a condition exposing them to an elevated risk of IPI, and a catch-up programme for children aged under 5 ([xiv]), the vaccine's efficacy against vaccine serotype IPI was estimated as 93% (95% CI: 75 – 88) after two priming vaccination doses in non-risk children. In children at risk (5% of the general population), the efficacy of three PCV_7 doses was 100% (95% CI: 90 – 100). The vaccination cover, excluding catch-up, was estimated as 89.6% (86.3 – 92.3) in 2006. The overall incidence of invasive pneumococcal infections decreased by 72.5% in children under 2 years, compared with the data available for the pre-vaccination period 2003-2004.

- In England and Wales, wide-scale vaccination of infants with the PCV_7 was introduced from September 2006 with the "2 + 1" form (at 2, 4 and 13 months) from the start. Children aged under 8 months were given the "2 + 1" form; children aged 8 to 24 months were given a single vaccine dose from the age of 13 months, i.e. a reduced catch-up programme in comparison to the two doses recommended 2 months apart for this age group ([xv]).

On January 7, 2008, the field efficacy of the 2-dose vaccination programme (using the adjusted Broome method) was 89% (95% CI: 72 – 96) and 72% for 6B alone (95% CI: 16 – 93). Out of 8 children given two doses of PCV_7 during the first year and who presented with an IPI, 4 were due to serotype 6B. No vaccinations were reported to fail among children given the booster dose ([xvi]). The vaccination cover between October and December 2007 was estimated as 90.01% for 2 doses and 79.9% for the booster ([xv]).

- In July 2006, Norway introduced wide-scale vaccination of infants, from the outset based on the "2 + 1" form (at 3, 5 and 12 months) in conjunction with an initial catch-up programme for children aged 3 to 6 months. On January 1, 2008, Norwegian authorities estimated that 90%

[13] For each vaccine serotype, antibody concentration threshold recommended by the World Health Organisation for the evaluation of new conjugated pneumococcal vaccines.
[14] 9-valency pneumococcal vaccine

of children over the age of 6 months had been given at least two vaccine doses and 80% of children over the age of 13 months had been given the three recommended doses. The incidence of IPI due to vaccine serotypes in children under 2 fell from 47.1 out of 100,000 during the pre-vaccination period to 13.7 out of 100,000 in 2007, resulting in an estimated 74% efficacy rate (95% CI: 57 – 85) ([xvii]). The incidence of non-vaccine serotype IPI did not increase significantly. No vaccines were reported to fail after the administration of the two recommended priming vaccination doses.

In all

The slightest immunogenicity of serotypes 6B and 23F in the 2-dose priming vaccination schedule should be compared with clinical field data. The clinical impact of using a "2 + 1" vaccination schedule in wide-scale national vaccination programmes has been evaluated by the Americans, Canadians, British and Norwegians in a context of fast, substantial vaccination coverage, catch-up vaccinations for certain countries (Quebec, Britain and Norway) and perhaps an indirect effect (group immunity). The field efficacy data concerning the 2 + 1 programmes were reported with a priming vaccination comprising two doses two months apart.

In Quebec and Britain a 2-dose priming vaccination schedule was set up for children aged 2 and 4 months corresponding to the schedule possible in France.

Furthermore, the data only concerns populations of infants not at risk. There is no specific immunogenicity and/or clinical efficacy evaluation for such a schedule for children with co-morbidities exposing them to an especially high risk of IPI. For premature infants, the only data currently available encourages maintaining a "3 + 1" schedule.

- **Estimated impact of changing the vaccination schedule on the number of IPI in France**

The number of additional cases of pneumococcal meningitis and bacteraemia expected in children under the age of 1 with the 2 + 1 schedule compared to the number of cases expected with the 3 + 1 schedule has been estimated using:

1) immunogenicity data from a randomised controlled trial comparing the response acquired after priming vaccination through 2 or 3 doses of PCV_7 for each of the 7 PCV_7 serotypes;

2) the estimated number of cases of pneumococcal meningitis and bacteraemia in 2001-2002 among children under 1 year of age according to the Epibac network as an estimation of the risk faced by an unvaccinated newborn child of suffering from pneumococcal meningitis or bacteraemia;

3) the distribution of serotypes of isolated strains of meningitis or bacteraemia in children under one in 2001-2002 or in 2005-2006 and addressed to the national pneumococci reference centre;

4) a theoretical vaccination coverage of 80%.

The number of expected additional cases would be no more than 5 additional cases of pneumococcal meningitis and 10 additional cases of pneumococcal bacteraemia per year among children under one. These additional cases constitute at most a 12% decrease in the overall foreseen benefit of PCV_7 vaccination, as far as IPI are concerned, among children under one, and would result in no more than 0.8 additional deaths per year. This data is an upper estimate of the negative impact of changing the foreseen vaccination schedule in France, namely because the indirect effects of PCV_7 vaccination on the frequency of infections and the distribution of serotypes in those not vaccinated have not been factored into this estimate.

Furthermore, the decrease in the number of injections can but improve vaccination coverage, by diminishing any fears that parents and vaccinators may have, by reducing both local adverse effects and cutting the cost to families.

- **The High Council for Public Health repeats that vaccination with the heptavalent pneumococcal conjugate vaccine is recommended for all children under the age of 2 to prevent invasive pneumococcal infections.**

  In this context, the High Council for Public Health recommends applying the following vaccination schedule: two separate injections, two months apart, at the age of 2 and 4 months, and one booster dose at the age of 12 months. This booster dose may, for example, be given on the same day as the first dose of the trivalent measles-mumps-rubella vaccine in two different injection sites.

  The High Council for Public Health stresses the need to achieve the highest possible vaccination coverage for the first two doses and the booster.

- **For premature infants and those at a high risk of catching an invasive pneumococcal infection[15], the High Council for Public Health recommends maintaining a vaccination schedule comprised of three injections one month apart (the first injection at the age of 2 months), followed by a booster dose between 12 and 15 months.**

- **For children aged two to five years and who have a high risk of catching an invasive pneumococcal infection[13] and children eligible for a cochlear implant or carrying cochlear implants, and who have not already been vaccinated, the High Council for Public Health repeats that it recommends a vaccination schedule comprised of two doses of the heptavalent conjugate vaccine two months apart, followed, at least two months after this second dose, by a dose of the 23-valent polysaccharide vaccine.**

- **The High Council for Public Health stresses the importance of continuing:**
  - **monitoring of serotypes and the sensitivity of strains to antibiotics,**
  - **monitoring of nasopharyngeal carriage data,**
  - **epidemiological monitoring of the incidence of invasive pneumococcal infections,**
  - **pharmacovigilance monitoring.**

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