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Product name: **Prevenar**
Procedure No. EMEA/H/C/000323/II/0076

SCIENTIFIC DISCUSSION

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1. Introduction

Prevenar was approved in the EU in the indication active immunisation of infants and young children from 2 months of age up to 2 years of age against invasive pneumococcal disease (IPD) (including sepsis, meningitis, bacteraemic pneumonia, bacteraemia) caused by the 7 pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F and 23F contained in the vaccine. . In 2004, the CHMP adopted a positive opion to extend the therapeutic indications to the age range from 2 to 5 years of age.

The scope of this extension of the indication application was to include acute otitis media (AOM. The target population was deemed the same for the current indications and AOM and it was not anticipated that the additional indication would result in any change in the use of the vaccine.

The CHMP considered that the supplementary follow-up data from the pivotal pre-licensure clinical trials demonstrated that Prevenar has effects on the incidence of AOM, pneumococcal AOM, and serotype-specific pneumococcal AOM in young children aged <2 years, in particular, on the more severe forms of the disease. In addition, post-marketing data from the United States (US) indicated significant public health benefit by reductions of hospital and outpatients visits, antibiotic prescriptions and tympanostomy tube placement since the implementation of Prevenar for routine infant immunisation. These data have been further supported by a very recent large ecological study which showed that AOM visits rates declined by 20% in children <2 years of age after the introduction of Prevenar *(Grijalva CG et al. 2006)*.

After the assessment of the data included in the submission of the variation application, the CHMP requested the MAH to respond to a request for supplementary information. The main points that needed to be clarified were as follows:

- The MAH was asked to perform a recalculation of data to show absolute benefits
- The extrapolation of US data to a European setting needed to be justified
- The MAH was asked to present plans for surveillance serotype replacement in NPH carriage/AOM, shifts in microbiology and resistance patterns
- Furthermore, the MAH was asked to discuss a selection of publications with negative results
- The MAH was also asked to present an update on serotype epidemiology/coverage in the EU

The MAH responded in November 2006 and the responses were assessed by the CHMP.

The Vaccine Working Party (VWP) also discussed the variation procedure in the light of the assessment of the MAH's responses on its January 2007 meeting. The VWP supported the Rapporteur's and Co-Rapporteur's conclusions, however recommended a revised wording of the SPC sections 4.1. and 4.4. The VWP recommended to revise the indication by including the AOM indication as a part of the overall indication and to revise section 4.4 by including information with regards to the immune response following the administration a 23-valent pneumococcal polysaccharide vaccine after priming with Prevenar.

1.2 Clinical aspects

S. pneumoniae is one of the three bacterial pathogens most commonly encountered in AOM, with the seven vaccine serotypes contributing to approximately 60 to 80 % of pneumococcal-associated AOM. Furthermore, these serotypes account for most of the antibiotic- resistant clinical isolates.
Most children will experience AOM, defined as the acute infection of the middle ear with rapid onset of signs and symptoms.

Differences in case definitions, observation time periods and population characteristics between studies explain the diversity of published data on incidence rates of AOM. For these reasons, studies are not usually comparable. Nevertheless, it is commonly acknowledged that approximately 20 to

60 % of infants experience an episode of AOM by the age 12 months, and most children, 40 to 85 %, by the time that they reach 2 years of age. The greatest incidence of AOM occurs between 6 and 12 months of age.

Before the introduction of Prevenar into the US, 40 to 50% of samples from children with AOM grew S. pneumoniae. The Finnish Otitis Media (FinOM) trial, which was assessed for the initial MA, showed that approximately 60% of pneumococcal isolates from the controls were vaccine serotypes.

Based on available data in the scientific literature, the CHMP considered that although the clinical effect appeared to be limited, the disease burden that is potentially vaccine preventable is substantial because of the high incidence of AOM among children.

At the time of the initial evaluation of the Marketing Authorisation, taking into account the available data from trials at this time point, the CHMP was of the opinion that although Prevenar had a clear effect against AOM caused by the vaccine serotypes (VE of 57 %), the overall impact on otitis media of 6-7 % was too low to grant the indication of AOM prevention.

However, the protection afforded by the vaccine against otitis was understood as an add-on beneficial effect by the CHMP that was to be described in the SPC section 5.1.

1.2.1. Clinical data:

To support the extension of the indication for this variation, the MAH used the data from several published studies. Two pre-licensure pivotal studies evaluated the role of Prevenar in the prevention of AOM in infants and toddlers in California (NCKP) and Finland (FinOM), respectively. These studies were fully assessed by the CHMP for the granting of the initial Marketing Authorisation of Prevenar.

FinOM trial:
This trial was conducted in 1662 healthy infants in Finland randomised to receive either Prevenar or a control vaccine (hepatitis B vaccine), at 3, 4, 6 and 12 months of age, alongside with the other vaccines recommended for infants in Finland (*Eskola J et al, 2001*). Parents were instructed to bring their child to the study clinic whenever the child presented with clinical signs and symptoms suggesting a respiratory tract infection or an AOM. When middle ear effusion was suspected, myringotomy was systematically performed, and a middle ear fluid sample was obtained for 93% of patients' visits due to AOM.

FinOM follow up study
Children originally enrolled in the FinOM trial that had completed 24 months of follow-up and were still living within the study area were invited to participate in this follow- up study at 4- 5 years of age, which primarily evaluated the efficacy of Prevenar for tympanostomy tube placement. The clinical phase of the FinOM vaccine trial ended in March 1999, and subjects' parents were informed of their child's vaccination status (Prevenar or control) in late September 1999.

Northern California Kaiser Permanente (NCKP) trial
The effectiveness of Prevenar in reducing the incidence of AOM was also investigated in the NCKP trial, which was primarily designed to assess vaccine efficacy against invasive pneumococcal diseases. Between October 1995 and August 1998, 37,868 healthy, 2- month- old infants were enrolled in this study, and received either Prevenar or a control vaccine at 2, 4, 6 and 12- 15 months of age, concomitantly with other recommended infant vaccines *(Black et al, 2000)*. Clinical AOM (without microbiological confirmation) was evaluated as a secondary endpoint.

NCKP follow up study
The impact of Prevenar on otitis media at NCKP was reported in a separate publication from the IPD efficacy trial, and included the experience in subjects followed for up to 3.5 years after immunisation. The main outcome measures for AOM included visits for otitis, frequent visits for otitis, and

tympanostomy tube procedures. As in the main trial, the diagnosis of AOM was not standardized but was ascertained by review of physician exam checklists and healthcare databases.

The submission was also supported by the following published studies:

- two US population-based surveillance studies ("Population based impact in Tennessee and New York" (*Poehling et al.)* and "Experience in a rural community in Kentucky" (*Block SL et al.)*
- a study on the impact of Prevenar vaccination on the microbiology of AOM ("Changes in frequency and pathogens causing acute otitis media in 1995-2003. (*Casey JR, et al.),*
- a cohort comparison study to determine changes in the microbiology of otitis media before (1992- 1998) and after (2000- 2003) community- wide implementation of Prevenar as part of routine care for all infants in a large (6- 7 clinician) paediatric practice in central rural Kentucky ("Community- wide vaccination with the heptavalent pneumococcal conjugate significantly alters the microbiology of otitis media", (*Block SL, et al.).*
- a study on AOM due to penicillin-nonsusceptible Streptococcus pneumoniae before and after the introduction of the pneumococcal conjugate vaccine (*McEllistrem MC et al).*

The MAH further submitted a review of post-marketing surveillance data including the following studies:

- Active Bacterial Core (ABC) surveillance data from the Centres for Disease Control and Prevention (CDC)
- Post- introduction surveillance data of IPD caused by serotype 19A (publication by *Pai et al.)*
- Data from the NCKP post- marketing study on serotype- specific IPD incidence

1.2.1.1 Efficacy data

Table 1 gives an overview on the main trials submitted in this variation.

Tab. 1: Summary of NCKP and FinOM outcomes in otitis media, with follow-up data

	NCKP Pre-licensure	**NCKP Follow-up**	**FinOM**	**FinOM Follow-up**
N	37,868	37,754	1662	1490 (756 primary)
Design	Randomised, double-blind, active control; clinical AOM ascertainment via computerized database		Randomised, double-blind, active control	
Schedule	2, 4, 6, 12-15 months		2, 4, 6, 12 months	
Study Vaccine	Prevenar		Prevenar	
Control Vaccine	Meningococcal serogroup C Conjugate		Hepatitis B	
Follow-up	October 1995-April 30, 1998	Through April 1999; avg. age 26.1±9.4 months	6.5 to 24 months of age	24 months to 4-5 years
Primary OM Outcome	Number of OM episodes in fully-vaccinated per-protocol follow-up time	-Number of OM visits -Tube procedures	Number of vaccine serotype (VST) AOM episodes	Tympanostomy tube placement, ascertained by visit, medical records, and hospital records

	NCKP Pre-licensure		NCKP Follow-up		FinOM		FinOM Follow-up	
Secondary OM Outcomes	-Frequent OM -Tube placement -Spontaneously draining OM with culture		-Frequent OM -Antibiotic prescriptions		- Vaccine-related serotype (VRST) episodes - Non-vaccine serotype (NVST) episodes - Other organism		-Tube placement ascertained by hospital records only -Tube placement associated with cOME	
Myringotomy criteria	None				Systematic for all subjects diagnosed with clinical AOM (visibly abnormal TM + at least 1 sign of acute infection)			
Diagnostic procedure	N/A				Middle ear fluid (MEF) for bacterial culture and serotyping			
Results (Vaccine Efficacy, %); Comments			Overall incidence of AOM: - PP: 1.85/p-y PCV7, 2.0 control - ITT: 1.69/p-y PCV7, 1.81 control		2596 clinical episodes; overall incidence of AOM: - 1.16/p-y Prevenar - 1.24/p-y control MEF obtained for 92% of all visits			
	PP	**ITT**	**PP**	**ITT**	**PP**	**ITT**	**Primary**	**Secondary**
OM visits (95% CI)	8.9	7.8	7.8 (5.4, 10.2)	7.0	N/A			
OM episodes	7.0	6.4	6.6	5.8	6.0, with MEF, 7.0			
Frequent OM (95% CI)	9.3-22.8 (n=5451)	9.1-12.3	Range, 10 to 24; persistent (>60 d): 22.0		16 (-6, 35)	9 (-12, 27)	18 (1, 32); OME: 50 (15, 71)	Not reported
Tube placement (95% CI)	20.1 (n=432)	20.3	24.2 (11.7, 36)	23.2 (11.3, 33.5)	4 (-19, 23)		39 (4, 61); OME: 49 (-7, 76)	44 (19, 62); OME: 63 (28, 81)
Culture confirmed VST (95% CI)	66.7 (p=0.077); n=16 (12 controls)	64.7 (p=0.035) n=23 (17 controls)	Not reported		57 (44, 67) Range, 25 to 84; significant for serotypes 6B, 14, 23F		N/A	N/A
Cross-reactive VST	N/A	N/A	N/A		51 (27, 67) Range, -103 to 75%; significant for serotype 6A		N/A	N/A
NVST (95% CI)	N/A	N/A	N/A		-33 (-80, 1)		N/A	N/A
Other organism	N/A	N/A	N/A		*H. flu*, -11 (-34, 8); *M. cat* -1 (-19, 15)		N/A	N/A

FinOM trial

The Finnish Otitis Media (FinOM) trial was a randomised, double-blind, active control tympanocentesis study specifically designed to evaluate the efficacy of Prevenar in acute otitis media. In this

trial, 1662 subjects were randomly assigned to receive either Prevenar or hepatitis B vaccine (as placebo) at 2, 4, 6, and 12 months of age, and were followed for otitis media outcomes through 24 months of age.

The primary endpoint of this trial related to pneumococcal otitis media caused by vaccine serotypes. Vaccine efficacy against episodes of AOM caused by vaccine serotypes was 57 % (95 % CI: 44, 67). In view of the risk associated with an early onset of AOM in life, it was considered noteworthy that efficacy estimate for the interval between the third and fourth dose, representing the second semester of life, was 57 % (95 % CI: 36, 72) against episodes caused by vaccine serotypes.

Serotype- specific estimates ranged from 25 % for serotype 19F to 84 % for serotype 6B. A reduction of 51 % (95 % CI: 27, 67) was also demonstrated for AOM due to cross-reactive serotypes, with a serotype- specific efficacy estimate that was only significant for serotype 6A, 57 % (95 % CI: 24, 76). There was a statistically significant increase (33 %), in the number of episodes due to non- vaccine serogroups. Overall, vaccine efficacy was 34 % (95 % CI: 21, 45) for any type of pneumococcal AOM. A total of 2596 episodes of AOM were recorded during the per-protocol (PP) specified follow-up from 6.5 to 24 months of age. A statistically non- significant 6 % reduction in the incidence of all clinical AOM episodes was noted among the vaccine group, 1.16 versus 1.24 episodes / child-year in the control group. Nevertheless, there were 118 clinical AOM episodes prevented per 1000 children vaccinated before they reached the age of 2 years.

It was noted that the observed 6 % reduction in the number of all AOM episodes contrasted to the higher efficacy rate of 15 to 20 %.

When considering all microbiologically proven episodes in the FinOM trial, among the vaccine group there were 186 less cases of AOM due to vaccine serogroup pneumococci, whereas there were 30 more cases due to non-vaccine serogroup pneumococci and 30 more cases due to H. influenzae and M. catarrhalis. Consequently, the net reduction was 126 cases.

Moreover, the fact that this 6 % vaccine efficacy estimate was not statistically significant could have been the result of the small size of the trial. The data from the FinOM trial were extrapolated to the population of children aged less than 2 years living in the 25 Member States of the EU (birth cohort statistics, preliminary estimates for 2005, Eurostat 01- 2006). Applied to a birth cohort of 4,816,400 infants, the number of clinical episodes of AOM would be 8,958,400 per year in the 6- to 24- month-old age group. The projected number of vaccine- prevented AOM episodes in this age group would be about 568,300 in any one year, considering that 118 clinical episodes of AOM would be prevented in the first two years of life per 1,000 vaccinated children.

As to whether serotype replacement occurred or whether previously co-colonising serotypes had actually increased in density with the absence of dominant serotypes could not be established. It was discussed that if serotype replacement does occur, the relatively limited number of serotypes associated with invasive diseases in children suggests that only a small number of these are intrinsically virulent. Furthermore, antibiotic resistance was associated with a few serotypes that are represented in Prevenar and it was considered that replacing serotypes are likely to be susceptible to most commonly used antibiotics.

The CHMP highlighted that in the assessment of the initial application for the Marketing Authorisation it was acknowledged that Prevenar displayed efficacy against AOM caused by vaccine serotypes (VE: 57%). Although the MAH argued that a slight reduction in percent could possibly translate into a very high total number of otitis cases prevented, the small overall impact on total number of otitis media episodes (6%, non-significant) was considered insufficient to justify an indication at the time of the initial MA.

The observed shifts in carriage of serotypes and AOM were considered as early warnings suggesting that the non-vaccine serotypes could increase, replace the vaccine serotypes and cause disease leading to a reduction in vaccine efficacy. The virulence/susceptibility to penicillin of the non-vaccine strains might change or increase in this scenario. The MAH therefore committed at the time of the initial MA

to closely monitor serotype replacement in the post-authorisation period. Furthermore, the MAH now committed to provide annual reports from the pneumococcal surveillance programmes run by public health institutions in the EU to CHMP (see section III of this report)

*FinOM follow-up trial (**Palmu AAI et al,**)*

All children enrolled in FinOM who were still living the study area in February 2001 (N= 1490) were invited to a single- follow- up visit.

The Primary Analysis Data Set included 756 children (403 Prevenar recipients and 353 controls; mean age, 58 months; mean time since last vaccine dose, 46 months) who accepted the invitation for the follow-up visit and were examined at the study clinic; upon examination they were enrolled in the FinOM Follow- up Study. Additionally, to assess the effect of potential selection bias among subjects accepting the follow-up invitation, a Secondary Analysis Data Set was defined, which included an analysis of tympanostomy tube procedures performed in all children enrolled in FinOM who were still living in the study area (through June 2001).

Primary and secondary endpoints
The primary endpoint was tympanostomy tube placement, whether unilateral or bilateral (considered as one event if both tubes were placed at the same time).
A secondary endpoint was tympanostomy tube placement associated with chronic otitis media with effusion (cOME), representing the most severe cases.

Results
In this long-term follow-up, efficacy against at least one episode of AOM after the age of 24 months was only 8% (95% CI: -2 to 16%). However, efficacy increased with increasing disease frequency and increasing severity. In longer duration follow-up, efficacy for recurrent AOM (defined as at least 3 episodes) after 24 months was 18% (95% CI: 1 to 32%) and for chronic otitis media with effusion, 50% (95% CI: 15 to 71%).

While in the clinical phase of the FinOM trial, there was no difference in the rate of tympanostomy tube placements between vaccinees and controls (12.0 events/100 person-years vs. 12.7 events/100 person-years, respectively, vaccine efficacy (VE) was 4%, (95% CI: -19 to 23%)), the rate of tympanostomy tube placement among Prevenar recipients in the Primary Analysis Data Set after the age of 24 months was 3.5 per 100 person-years and was 5.7 per 100 person-years among controls, for a vaccine efficacy for tympanostomy tube placement after age 24 months through 4-5 years of age of 39% (95% CI: 4 to 61%).

In those associated with cOME, VE was 49% (95% CI: -7 to 76%). Similar results were observed for the Secondary Analysis Data Set (which included all children at risk for surgery in the study area hospitals, N=1490), with vaccine efficacy for all tympanostomy tube placements of 44% (95% CI: 19 to 62%), and for tympanostomy tube placement associated with cOME of 63% (95% CI: 28 to 81%).

In the original assessment of infants during the period from 2 months up to 24 months, the vaccine did not show preventive efficacy against tympanostomy tube placement (VE: 4%). In contrast, the follow-up study of the FinOM trial demonstrated that Prevenar was associated with a significant reduction in tympanostomy tube placement from 2 to 4-5 years of age (VE: 39%-44%). The CHMP therefore concluded that this finding indicated long-term persistence of vaccine efficacy until at least the age of 5 years.

The observed difference in VE between the follow-up periods could be explained by markedly different thresholds for surgery between the 2 time periods. The rate of surgery was 2.6 times higher in the control group during the first period, possibly due to the strict follow-up of children during vaccination and easy access to tube surgery.

The number of overall AOM events after the age of 24 months (VE 8%, p=NS) was concordant with the primary period of the FinOM (6%). However, for the children with recurrent AOM after 24 months, VE was 18% (p=significant). The higher vaccine efficacy (50%) against tube placement associated with cOME suggests that pneumococci play an important role in this more severe form of otitis disease.

NCKP trial:

Between October 1995 and August 1998, 37,868 healthy, 2-month-old infants were enrolled in this study, and they received either Prevenar or a control vaccine at 2, 4, 6 and 12-15 months of age, concomitantly with other recommended infant vaccines. With regard to otitis media, the NCKP study relied on healthcare utilisation databases to document otitis visits and did not use standard clinical criteria for the diagnosis, however the diagnosis was ascertained by review of physician exam checklists.

The primary endpoint of the study was efficacy for vaccine-serotype invasive pneumococcal disease (IPD), though additional endpoints included a variety of AOM parameters such as number of visits and impact on recurrent disease.
A planned interim evaluation by the Study Advisory Committee of 17 cases of invasive disease caused by vaccine serotype in fully vaccinated subjects revealed IPD efficacy of 100% in the Prevenar arm. Case ascertainment continued through 40 cases of IPD in fully vaccinated subjects, and final analysis demonstrated a per-protocol efficacy for vaccine-serotype IPD of 97.4% (95% CI, 82.7 to 99.9%), with efficacy in the intent-to-treat (ITT) analysis of 93% (95% CI, 79.6 to 98.5%).

The per-protocol efficacy for AOM visits was 8.9% (95% CI, 5.8 to 11.8%). While this study was not designed to evaluate pneumococcal otitis media (because tympanocentesis was not routinely performed, so the aetiology of any given AOM episode could not be confirmed), the investigators were able to report a 66.7% efficacy against vaccine-serotype AOM in a small number of subjects with spontaneously draining ears (n=16 per-protocol cases, p=0.077).

The primary analysis was the overall incidence of AOM episodes (new visits) during the per protocol follow-up. From the beginning of the study in October 1995 through the end of April 1998 a total of 16,124 AOM episodes were identified in 11,849 Prevenar (7VPnC) children versus 17,405 AOM episodes in 11.897 children receiving control vaccine (Meningococcal C conjugate (MnCC) vaccine).

The overall incidence of AOM episodes was reduced from 1.72 episodes per child year in MnCC recipients to 1.60 episodes per child-year in the 7VPnC recipients, a 7.0% (95% CI: 4.1 to 9.7%; p<0.0001) overall reduction, which represents a prevention of 12 episodes per 100 child-years. The incidence of AOM decreased over time in both vaccine groups reflecting the increasing age of the subjects. A lower incidence was seen in the 7VPnC group for all but one time point throughout the follow-up period.

In the assessment of the initial Marketing Authorisation it was acknowledged that the effectiveness of Prevenar against otitis media was demonstrated in this trial across all endpoints except ruptured eardrums. The risk reduction (7% PP, 6.4% ITT) of the primary outcome measure was low although statistically significant, representing prevention of 12 episodes per 100 child-years.

The CHMP highlighted that AOM is an extremely common disease resulting in around 25 million visits to physicians (US) per year, which equates the reduction of 6% with 1.5 million visits.
Efficacy was more promising in the group with recurrent and potentially more serious otitis (tube placement) (20.3%). However, the otitis part of the NCKP trial suffered from important deficiencies, since there were no pre-specified criteria for the diagnosis and no bacteriologic confirmation.

NCKP follow up study (Fireman B et al.)

In this study, the overall incidence of AOM among controls was higher than that reported in Finland, with a rate of 1.8 otitis media visits/ person-year. In particular, at the period of greatest incidence, from 8 to 12 months of age, the rate for boys and girls together in the control group was 22 to 24 visits per 100 children per month.

Children receiving Prevenar had reduced number of otitis visits than controls in every age group, race, sex, and season examined. While the absolute reduction of otitis visits was modest (7.8%; 95% CI, 5.4 to 10.2% for the per- protocol analysis), efficacy improved with increasing severity, so that efficacy for recurrent otitis increased in proportion to increasing frequency of episodes over a six- month period – from 5% for prevention of a first otitis visit (95% CI, 3 to 7%), to 10% for at least 3 visits, to 26% for 10 or more visits in the previous 6 month period.

Tympanostomy tube placement, a surrogate marker for severe, recurrent, and/ or difficult-to-treat otitis media, was reduced by 23.2% (95% CI, 11.3 to 33.5%) in the ITT analysis, and by 24.2% (95% CI, 11.7 to 35%) in the PP analysis.

Additionally, the investigators were able to document reductions in antibiotic prescriptions among Prevenar recipients, by 5.4% (95% CI, 4 to 6.7%) in the follow- up starting after the first dose, and by 5.7% (95% CI, 4.2 to 7.2%) after the primary series. Greater reductions were observed among Prevenar recipients in prescriptions for "second-line" antibiotics, which included antimicrobials other than amoxicillin, trimethoprim/sulfamethoxazole, and erythromycin ethylsuccinate/sulfisoxizole (12.6% for all follow- up time; 95% CI, 9.6 to 15.6%). It was estimated that from the first dose through 3.5 years, Prevenar prevented a total of 35 antibiotic prescriptions per 100 children vaccinated per protocol.

This longer-term follow-up of the NCKP trial examined whether effectiveness of Prevenar waned after age 24 months and whether it varied by race, sex, clinic, season, year and partial immunization. As for the "original" trial data there were no pre-specified criteria for the diagnosis and no bacteriologic confirmation of the diagnosis. Thus, the results were considered applicable on clinically diagnosed otitis in usual care.

From the submitted documentation for this variation application, it was not clear on which basis the participants for the NCKP were chosen. The MAH was therefore asked to clarify this item in order to exclude any bias. The MAH responded that no significant differences between the groups with respect to age or level of compliance with the study protocol were observed. Additionally, the MAH pointed out that findings regarding otitis media at NCKP were reported in two separate publications that used different data lock points.

The overall extent of reduction in otitis episodes (7% (95% CI: 4 to 9%)) observed in this follow-up study was consistent with that of the primary NCKP trial (7%) and that of the FinOM trial (6%). Hence, there was no indication that vaccine effectiveness waned during the follow-up time. However, when examined by age and calendar month there was a tendency of waning with age, as the vaccine reduced otitis visits by 3.7% in children aged 24 to 42 months. However, when this finding was examined closer it was not monotonic or statistically significant. Children in the vaccine group followed up during ages 3 to 3.5 years had 11.3% fewer visits than controls. Similar to other studies, the otitis visits peaked at 8 to 12 months of age.
The authors of this publication estimated that Prevenar prevented 43 otitis visits by 3.5 years of age for every 100 children vaccinated as recommended.

The vaccine reduced frequent AOM by a percentage that increased with frequency. The effect on frequent otitis visits was equal to that on tympanostomy tube placement (23-24%), which however varied with sex and race due to different risks and thresholds for inserting tubes. The vaccine efficacy against tympanostomy tube placement was consistent with that of the first follow-up period of the NCKP trial (VE: 20%). The vaccine, thus, had a larger magnitude of efficacy against the most severe form of otitis media. A decreased use of antibiotics in vaccinated subjects has also been observed,

which the CHMP considered as clinical relevant as AOM is currently the most common indication for antibiotic prescription for children.

In conclusion, the CHMP found no evidence of waning efficacy against AOM up to the age of 3 to 3.5 years. The vaccine efficacy was greater against complicated cases of AOM, i.e. recurrent otitis and otitis requiring tube surgery (VE: 23%).

The CHMP considered also that the results of the NCKP trial further suggest that age was not a factor, since VE was 20% in the initial period (2-24 months) and 23% in the second follow-up period in both the per-protocol (PP) and ITT analyses. Estimates of tube replacement efficacy, thus, seemed consistent in both follow-up trials (of NCKP and FinOM).

Additional supportive data

The MAH submitted the following publications as additional supportive data:

Population based impact in Tennessee and New York; (*Poehling K.A. et al)*
This study had the objective to determine the population impact of pneumococcal conjugate vaccine (PCV) on pneumococcal-related diseases, including pneumonia and otitis media.
Using administrative data from Tennessee Medicaid and 3 commercial insurance plans in upstate New York, annual rates of medical visits for pneumococcal-related diseases (pneumococcal and non-specific pneumonia and invasive disease; otitis media) and pneumococcal- unrelated diseases (other acute respiratory illnesses) were measured. Disease rates before (1995 – 2000 in Tennessee; 1998–2000 in New York) and after (2000 – 2002) the licensure of Prevenar in the US were calculated for children aged <2 years (eligible for PCV) and those 3 to 5 years (not routinely given PCV).

Adding PCV to the childhood immunization schedule was associated with a 10-fold greater reduction in pneumonia and a 100-fold greater reduction in otitis media than the previously reported reduction in culture-confirmed invasive pneumococcal diseases of 1.3 episodes per 1000 children aged <2 years. The CHMP considered that although additional studies are needed to confirm the impact of routine immunization with PCV on pneumococcal-related disease, these results suggest that its impact was substantially greater than the effects on invasive disease alone.

Experience in a rural community in Kentucky; *(Block SL et al.)*
This study assessed the reduction in annual rates of acute otitis media (AOM) episodes and antibiotic days during the first three years of life before and after widespread use of conjugated heptavalent pneumococcal vaccine (pcv7) in a closed community.

The study was carried out in a sole paediatric private practice, which cares for approximately 2/3 of all children born in a rural Kentucky community. The study was a retrospective case cohort comparison of all children consecutively born seeking routine ambulatory care during 2 intervals:
Cohort 1 (n= 274) was born (1993- 1994) before and Cohort 2 (n= 221) was born (2000-2001) after the widespread use of pcv7 in the practice.

The nearly uniform adequate dosing of pcv7 in a closed population of mostly daycare children was associated with 28% and 26% reduction in total antibiotic days and overall antibiotic days for AOM, respectively. The mean total of AOM episodes was also significantly reduced by 19%, with pcv7 benefits persisting into Year 3 of life.

Changes in frequency and pathogens causing acute otitis media in 1995-2003. (*Casey JR, et al.)*
This 9-year, prospective study (1995-2003) was undertaken in a community-based private practice in Rochester, USA, to evaluate trends in pathogens causing persistent or treatment-resistant AOM and the antimicrobial susceptibilities in the context of both changes in AOM treatment guidelines (high dose amoxicillin) and the introduction of Prevenar. 551 children with persistent AOM (PAOM, defined as clinical failure within 30 days of an antibiotic treatment course) or treatment-resistant AOM (AOMTF, defined as those who were treatment failures after 48 hours on therapy) underwent

tympanocentesis to identify bacterial isolates. Only children who had received amoxicillin as initial antimicrobial therapy were eligible to participate in the study.

The study had three general observations for primary care practitioners who manage children in the US:

1) The frequencies of PAOM and AOMTF have declined in the US in the period 2001-2003 when Prevenar was introduced compared with the 6 years prior,

2) Within this subgroup of children with PAOM and AOMTF, a shift in causative pathogens has been observed, with H. influenzae becoming predominant in this population (though S. pneumoniae was still important), and

3) The proportion of *S. pneumoniae* isolates resistant to penicillin also declined

The authors noted that the decrease in both PAOM and AOMTF in their practice coincided with the introduction of Prevenar.

No information is available regarding the serotypes of S. pneumoniae isolated from PAOM and AOMTF in this study. However, the finding that penicillin non-susceptibility among isolated pneumococci declined since the introduction of Prevenar may perhaps be expected. Five of the 7 serotypes included in Prevenar are commonly penicillin resistant, and the vaccine has the potential to reduce the frequency of AOM caused by penicillin non-susceptible S. pneumoniae overall.

Community-wide vaccination with the heptavalent pneumococcal conjugate significantly alters the microbiology of otitis media. ***(Block SL, et al.)***
The objective of this cohort comparison study was to determine changes in the microbiology of otitis media before (1992- 1998) and after (2000-2003) community- wide implementation of Prevenar as part of routine care for all infants in a large (6-7 clinician) paediatric practice in central rural Kentucky, USA. For each cohort, there were approximately 2600- 2900 visits for AOM annually among children of all ages. Convenience samples of children aged 7-24 months who underwent tympanocentesis were prospectively assessed.
Clinical criteria for tympanocentesis included a visibly abnormal tympanic membrane plus the addition of at least one of the following:

1) prominent severe symptoms of AOM (crying, fussiness, altered sleep, otalgia, and/ or fever);
2) recurrent symptomatic or asymptomatic AOM unresponsive to previous antimicrobial therapy; or
3) ill appearance. Middle ear fluid was also collected for culture from spontaneous otorrhea or otorrhea through tympanostomy tubes of <48 hours' duration.

The CHMP considered that this study had limitations by its lack of a randomised placebo control group, the small sample size, particularly regarding the pneumococcal serotypes recovered and a selected study population for tympanocentesis. Furthermore, the CHMP pointed out that historical data and bacteriological data from myringotomy (most often available in complicated otitis cases) have to be used to document the impact of Prevenar on bacterial AOM incidence. In the study only 10% of the children had received the 4th vaccine dose, which has to be taken in consideration since the booster dose was considered important for long-term protection, in particular for mucosal disease.

This study focused on children with severe or refractory AOM. There was a substantial drop in all-bacterial AOM (rate difference -10.3; rate change -49%). Furthermore, there was a pronounced change in the proportion of otopathogens recovered in vaccinated children ages 7-24 months, particularly in children with known risk factors for AOM. Comparing pathogens pre- and post-PCV7, the proportion of S pneumoniae decreased from 48% to 31% and non-typable H. influenzae increased from 41% to 56%. Beta-lactamase-producing H. influenzae increased primarily in the population who had recently been treated with antibiotics. Thus, the proportion of gram-negative bacteria became 2-fold more

frequent than pneumococci in the post-Prevenar era, and three-fourths of organisms in AOM antibiotic failures were H. influenzae, which has implications for antibiotic selection to treat AOM.

The combined proportion of vaccine plus vaccine-related serotypes remained unchanged between cohorts. Although vaccine serotypes diminished by nearly half, this was offset by an increase of the vaccine-cross-reactive serotypes 6A and 19A. Furthermore these 2 serotypes accounted for 32% of penicillin-resistant strains. Unlike the FinOM trial no replacement with non-vaccine serotype was observed. However, the number of pneumoccocal isolates in the study was limited.

In the post-marketing surveillance studies of invasive pneumococcal disease in the US, an increase of serotype 19A disease has been noted. The finding of an increase of serotype 6A was unexpected, especially as cross-protection against this serotype was seen in the FinOM trial (VE: 57%) and in post licensing IPD studies. Vaccine-induced cross-protection against IPD and AOM caused by serotype 6A has been shown in the pre-licensure efficacy trials and in the post-licensure surveillance studies. With respect to vaccine protection against Nasopharyngeal (NP) carriage of serotype 6A, results have been conflicting but the accumulated evidence now suggests that Prevenar provided no protection. On the basis of these observations, the SPC has been amended with regards to use of vaccine serotype coverage instead of serogroup, which was considered appropriate by the CHMP.

Acute otitis media due to penicillin-nonsusceptible Streptococcus pneumoniae before and after the introduction of the pneumococcal conjugate vaccine. (*McEllistrem et al.*)
The primary focus of this study was to evaluate whether the proportions of AOM due to penicillin nonsusceptible S. pneumoniae (PNSP), Prevenar serotypes, vaccine-related serotypes, and non-vaccine serogroups changed over the period 1999- 2002. Additionally, molecular analysis was performed on a subset of isolates. Isolates were recovered from children with spontaneous otorrhea during an episode of AOM, during myringotomy or tympanostomy tube placement, during tympanocentesis performed for treatment-resistant AOM, or during tympanocentesis performed after the clinical diagnosis of AOM in a clinical trial. Isolates were collected from 505 cases of AOM due to S. pneumoniae from 5 sites in the US.

Overall, this multi-centre observational study demonstrated that the proportion of AOM in this population caused by PNSP did not change over this time period, and confirmed the findings of earlier studies in which an increase in the proportion of cases due to non-vaccine serogroups was observed. However, a significant decrease in the number of vaccine serotype isolates was observed over the time period overall ($p<0.01$), and specifically for serotypes 6B ($p= 0.03$), 14 ($p= 0.01$), and 23F ($p< 0.01$); no change was observed for serotypes 9V (6 isolates per year for 1999, 2000, and 2002, with 2 isolates in 2001) and 19F (21, 25, 20 and 28 isolates per year, respectively). Significant reductions in vaccine serotype disease correlated with number of doses of Prevenar received (= 1 dose vs. 2- 4 doses) overall ($p< 0.01$) and for serotypes 6B ($p= 0.02$) and 14 ($p= 0.03$). The major limitation of this study was the select nature of the isolates evaluated; that is, only approximately half of isolates were from patients with spontaneous otorrhea, and the remainder were from tympanostomy and/or myringotomy procedures. While those isolates from patients with spontaneously draining ears may represent more "typical" AOM, there was likely to be enrichment for pneumococcal AOM, and also PNSP and non-vaccine serogroups; in this study population, the true impact of pneumococcal vaccination on routine AOM could not be assessed.

Further supportive studies on following immunisation with 23-valent polysaccharide vaccines

Multiple publications have described studies on the effect of administering Prevenar and 23-valent pneumococcal polysaccharide vaccine (23vPS) on recurrent AOM among unvaccinated children 1 to 7 years of age who have had previous episodes of AOM (Veenhoven R, et al. 2003, van Heerbeek N et al. 2006, *Brouwer et al. 2005*). An Israeli study looked at the effect of a candidate 9-valent pneumococcal vaccine (9vPnC) on respiratory infections among toddlers aged 12 to 35 months attending daycare. (*Dagan et al. 2001, Dagan et al. 2002*) Both the authors Veenhoven and Dagan have raised the issue of 'replacement' by S. aureus after vaccinating with Prevenar.

One study of *Dagan et al* studied one or two doses of 9vPnC in older, previously unvaccinated, children who were already attending day care. In 2003, these investigators concluded their series of papers by suggesting that any national immunization program should include surveillance for the reduction of antibiotic use, reversal of the current increase in resistance in the community or replacement by non-vaccine serotype, antibiotic resistant S. pneumonia.

In the studies of *Dagan et al*, a high risk population for respiratory infections was studied namely day care attendees. In this population a 17% reduction of otitis episodes was demonstrated, which was higher than in the FinOM trial. The CHMP considered that use of the broader 9vPnC was not an explanation for this finding, since serotypes 1 and 5 were not considered as otitis pathogens. Another important observation in the vaccinated cohort was a decrease in antibiotic treatment for respiratory illnesses including otitis (20% risk reduction), which was most pronounced in children below 3 months of age. It was noted that despite an increase in non-vaccine serotypes a reduced risk of lower and upper respiratory infections and AOM was observed.

Discussion of efficacy data

The submitted literature data demonstrated that the efficacy estimates:

- Against microbiologically-proven AOM caused by vaccine serotypes varied from 57 to 67 %,
- Against all clinical AOM episodes ranged from 6 to 8 %,
- Against recurrent clinical AOM episodes ranged from 9 to 23 %, and
- Against tympanostomy tube placement ranged from 4 to 49 %.

While in the NCKP and FinOM studies, clinical AOM reduction was modest overall (6-7%), frequent otitis was reduced by 20% in the NCKP study. The observed 24% reduction in PAOM and AOMTF observed in the study by *Casey et al.* was consistent with the reduction observed in severe frequent otitis media in NCKP.

The CHMP considered that Prevenar prevents 6-7% of all AOM and this was rather consistent in the presented data. This effect on AOM was rather small in the total reduction of AOM any cause. It was clear that Prevenar was not an AOM preventing vaccine, Prevenar prevents "only" pneumococcal AOM an thus, the CHMP discussed whether this clear effect should be mentioned in section 4.1 or should be mentioned as it was for the time being in section 5.1. Having seen the submitted data on both severe AOM, e.g. tube placement therapy, the CHMP agreed that the data were sufficient to include otitis media in section 4.1 of the SPC as the MAH adequately responded to the RSI and limited the indication to pneumococcal AOM only.

The CHMP requested the MAH also to further study the available literature and to provide an in depth analysis of all negative trials. The MAH responded that in addition to the pneumococcal conjugate vaccine clinical trials and the post-introduction surveillance studies already described, further studies were reviewed to complete the description of the impact of Prevenar on AOM.

Contradictory results on the efficacy of vaccination with Prevenar (followed by 23-valent polysaccharide pneumococcal vaccine) for recurrent AOM in older children (n=383, aged 1-7 years) were obtained in a Dutch study (*Veenhoven et al 2003)* In this study 58% of the children in the vaccine group had at least one AOM episode (recurrence rate 1.1 episode per person-year) vs. 56% of the controls (recurrence rate 0.83 episode per person-year).

Thus, there was no decrease of AOM in the pneumococcal vaccine group compared with controls. The number treated with tympanostomy tubes during the 18-month follow-up was also similar in both groups. Nasopharyngeal carriage of vaccine serotypes fell substantially in the vaccine group, whereas overall carriage of pneumococci was not affected due to an increase of non-vaccine serotypes (types 11, 15 and 16). However, S. pneumoniae was isolated more commonly in the middle-ear fluid of controls (21% vs. 14%; vaccine serotypes 9% vs. 4%). The main differences between this trial and the

NCKP and FinOM studies were age at vaccination, booster vaccination with a polysaccharide vaccine and study population including only children with a history of recurrent otitis.

In the study by *Veenhoven et al*. a clinically relevant reduction of tube surgery was observed (-39%). The vaccine efficacy persisted long-term during the follow-up period up to age 5 years. However, the CHMP considered that the contradictory results described by Veenhoven et al needed to be further addressed by the MAH.

Following the assessment of the MAH's responses, the CHMP considered that the use of the 23-valent polysaccharide vaccine as booster in the study by Veenhoven et al had abrogated the effect of the conjugated pneumococcal vaccine, since the number of episodes of AOM was significantly decreased during the 6 months after receipt of the 7-valent vaccine and before the booster vaccination, whereas no effect could be seen after the booster. The known hyporesponsiveness induced by polysaccharide vaccines was considered to be a potential cause of this phenomenon. The selection of high risk children with recurrent AOM could also impact efficacy of the vaccine and it might be necessary to vaccinate at infant age before major otitis morbidity.

The MAH submitted further publications in their response describing similar studies on the effect of administering Prevenar and 23-valent pneumococcal polysaccharide vaccine (23vPS) on recurrent AOM among unvaccinated children 1 to 7 years of age who have had previous episodes of AOM.

Based on the review of the additional data provided by the MAH, the CHMP considered that use of the 23vPS as booster seemed to have abrogated the effect of the conjugated vaccine, since the number of episodes was significantly decreased during the 6 months after the 7-valent vaccine and before booster vaccination in one study. The CHMP highlighted that the known hyporesponsiveness induced by polysaccharide vaccines might be the cause of this phenomenon.

Furthermore, the CHMP considered that inclusion of older children with an already established recurrent AOM disease also affected the vaccine efficacy negatively.

No change in the overall pneumococcal carriage rate (50% of children in both groups) was noted despite a substantial decrease of vaccine serotypes, which was due to an increase in non-vaccine serotypes. This shift in serotypes occurred mainly in the youngest children that received 2 doses of Prevenar. Less effect of vaccination on pneumococcal carriage was seen in older children.

No influence on the carriage rate of other pathogens such as H. influenzae or M. catarrhalis was observed in this study. The *Van Heerbeck* study likewise showed no efficacy of combined pneumococcal conjugate/polysaccharide vaccination against recurrence of OME in older children 2 to 8 years of age.

A recent study by *Kempen et al 2006* in Belgian children using a similar design as the studies above confirmed the lack of beneficial effect of combined vaccination on AOM episodes in older children with recurrent AOM.

The effect of 9vPnC on NP carriage *described by Dagan et al.* showed a marked protection against carriage of vaccine serotypes, but this was coupled with an increase in non-vaccine serotypes. The authors stated that the clinical significance of the replacement of non-vaccine serotypes was not clear. Antibiotic resistance was mainly found in the 5 serotypes included in the 7 and 9-valent vaccine (6B, 9V, 14, 19F and 23 F) and a significant decrease in carriage rate of antibiotic-resistant pneumococci was observed.

The CHMP highlighted that the results by Dagan et al. underline the need for close and long-term monitoring of pneumococcal serotype epidemiology and disease during widespread use of the conjugated pneumoccocal vaccine.

Overall, the CHMP concluded that Prevenar should not be used as a therapeutic measure for older ´otitis prone´ children but as a prophylactic measure in infancy.

Surveillance studies

In the USA, the incidence of invasive pneumococcal disease (IPD) has been actively monitored since 1995 by the Active Bacterial Core (ABC) surveillance system of the Centres for Disease Control and Prevention (CDC).

CDC case- control effectiveness study
To evaluate the impact of Prevenar since its launch, the CDC conducted a case-control study to assess the post-licensure effectiveness of Prevenar immunization program in young children, both overall as well as by serotype. In this study, a case was defined as IPD that occurred in a 3- to 59-month-old child residing in one of the regions under ABC active surveillance, with isolation of pneumococcus from a sterile site and serotyping of the isolate. Cases were identified from January 2001 to May 2004. At least three controls per case were matched by age and by mother's residence.
Children were considered as vaccinated if they had received at least one dose of Prevenar and, for both cases and controls, a dose of vaccine had to have been administered at least 2 weeks before onset of the case to validate the case.

Compared to no vaccination, effectiveness against invasive disease caused by vaccine-related serotypes was 43% (95 % CI: 6, 66). In particular, serotype-specific efficacy estimate was 76 % (95 % CI: 39, 90) for 6A. Although, this estimate is lower than that observed for 6B, 94 % (95 % CI: 77, 98), these data also indicate statistically significant cross-protection. By contrast, for serotype 19A, estimate of vaccine efficacy was only 26 % (95 % CI: - 45, 62), revealing an absence of cross protection.

Because of the small number of cases, it was not possible to assess whether cross-protection could be extended to related serotypes within vaccine serogroups other than serogroups 6 or 19.

Post- introduction surveillance of IPD caused by serotype 19A
A publication by *Pai et al* provided additional evidence for poor cross-protection against serotype 19A afforded by Prevenar. The incidence of IPD caused by serotype 19A in the CDC/ABC areas was under continuous surveillance from July 1999 to June 2004. While the rate of all IPD in children less than 5 years of age decreased from 88.7 in July 1999 to 22.4 cases/ 100,000 between by June 2004, the estimated rate of IPD due to 19A increased over this period from 2.6 to 6.5 cases/ 100,000, with a rate ratio [RR] of 2.5 (95 % CI: 1.7, 3.7). This experience was accompanied by the expansion of a clonal complex (CC199) that already had predominated before the introduction of Prevenar, as well as an increased diversity of clonal types among the isolates of serotypes 19A. Clonal expansion may provide evidence of serotype switching from vaccine serotypes to serotype 19A. In conclusion, these findings confirm that Prevenar provided little or no cross-protection against serotype 19A IPD in children.

Post-introduction surveillance at the NCKP organisation

Data from the NCKP post- marketing study on serotype-specific IPD incidence (rate per 100,000 person years) is available for children less than 5 years of age from the pre- licensure (April 1996- March 2000) to the post- licensure period (April 2000- March 2005) of Prevenar. For serotype 6A IPD, the incidence fell from 3.07 to 0.58 over this time (an 81 % reduction in rate). For 19A, by contrast, the incidence increased slightly from 1.32 to 1.75 over this period, indicative of no cross- protection against this serotype. There were insufficient numbers for evaluation of cases due to other vaccine-related serotypes, although overall there were fewer such cases in the post- licensure period.

Discussion of surveillance studies

The CHMP pointed out that although the MAH has provided argumentation that the effect size observed in the US may still be of substantial public health benefit for the US situation, in the absence of any relevant epidemiological data and effectiveness data from the European Union, these

conclusions could not be extrapolated to the European setting. The MAH was therefore asked to submit data on the vaccine use in EU countries with respect to effectiveness against IPD and AOM following widespread use of Prevenar. The main focus was on possible shifts in the incidence of vaccine serotypes, vaccine-related serotypes, non-vaccine serotypes and penicillin non-susceptible S. pneumoniae (PNSP) strains.
The MAH presented data from Spain (*Calbo E, et al.*), Germany (ESPED), France (EPIBAC) and presented an overview on further national surveillance programs in Norway, UK,Italy, Switzerland (countries with 3-dose schedule) as well as further networks in France, Germany and Spain (countries with 4-dose schedule)

Results of an EU wide survey funded by the EU project on pneumococcal disease (PnC - EURPO) has recently summarized all publicly funded national surveillance programs across the EU and presents, in tabular form, the data elements being collected by each program (Pebody RG et al. 2006)
The CHMP considered that the available data are still very limited since few countries have implemented universal immunisation of children below 2 years of age.

In Spain, vaccine uptake had remained low and IPD is not a reportable disease in all regions of Spain.
In one Spanish study (*by Calbo E et al*), no overall decrease in the rate of IPD was observed despite reductions in disease caused by some vaccine serotypes. In contrast, serogroup 19 isolates were found in equal numbers before and after Prevenar introduction, but it was not known whether this was due to an increase in serotype 19A strains as has been seen in the US.
An unexpected finding was an increase of empyema caused by non-vaccine serotype 1, which, however, also has been observed in other regions regardless of the use of Prevenar. The data from Spain were difficult to interpret due to limitations in the surveillance methods and the low percentage of children vaccinated. The data warrants further close monitoring of the effectiveness of the vaccine.
Monitoring of IPD in Germany through the ESPED surveillance system was considered to provide valuable data after the introduction of universal vaccination of all infants in 2006. So far epidemiological data have shown that serotype coverage of Prevenar in 2004 was 66% in the age group 0-23 months and 64% in the age group 24-59 months.
The EPIBAC data from France demonstrated significant reductions for pneumococcal bacteremia (29%) and meningitis (39%) in children below 2 years of age during a period when Prevenar was only recommended for use in high-risk children.

In conclusion, The MAH´s response was accepted by the CHMP. The limited data from Europe so far available were considered difficult to interpret due to the low vaccine uptake, which precludes any comparison with the US situation at this time. Since routine immunisation has only recently been implemented in several EU countries, data on long-term effectiveness and serotype replacement will have to be awaited. The MAH therefore agreed with the CHMP to commit that annual reports will be provided to CHMP for the national surveillance systems.

1.2.1.2 Safety Data

The MAH did not submit new safety data for this type II variation. The pharmacovigilance plan has been previously reviewed during the r`enewal procedure and the PSUR cycle has been set on every two years.

The CHMP considerered that there is no change to the safety profile. The vaccine will continue to be used in the same target population for which the vaccine is currently approved, and no increase in the extent of use of the product is foreseen, therefore no amendment to the Risk Management Plan was considered necessary.

1.3 Overall Discussion and conclusion

Two major issues were initially identified by the CHMP pertaining to efficacy in AOM:

firstly the extent of benefits of the vaccine in the otitis indication was not considered sufficiently justified and data were to be presented as absolute benefit per 100 children vaccinated,
and secondly in the absence of any relevant epidemiological data and effectiveness data from the European Union, the CHMP questioned whether the US experience could be extrapolated to the European setting.

Other concerns included potential risks with 7vPnC vaccination such as serotype replacement and microbiological shifts to gram-negative organisms in naso-pharyngeal carriage and AOM. Surveillance studies including close monitoring of AOM and carriage with respect to serotype replacement and bacteriological shifts as well as patterns of antibiotic resistance in the EU also needed to be outlined by the MAH.

The MAH responded that the absolute benefit per 100 children vaccinated, with 18 to 25 AOM episodes prevented per 100 children vaccinated as well as a reduction of outpatient medical visits for AOM with 20%, was deemed clinically relevant considering the high disease burden that otitis media represents in clinical practice. It has been estimated that up to 90% of all children will experience an episode of AOM before the age of 5 years.

The MAH provided also an update on studies with "negative" results. The main features of these studies enrolling older children (1-8 years) were that
i) the children had established recurrent or severe AOM disease and/or
ii) the use of mixed vaccination schedules. The administration of a 23-valent polysaccharide vaccine as booster after priming with the 7-valent conjugate vaccine is known to induce hyporesponsiveness and was a plausible cause of the negative study outcomes.

Considering the accumulated data, the MAH was requested to propose a modification of the SPC section 4.4 to warn against the possible negative effects of using mixed vaccination schedules with conjugated and polysaccharide vaccines. In the MAH´s response to the RSI, a modified text was proposed, which was agreed after further revision.

A consistent observation in the NP carriage studies was the replacement of vaccine serotype with non-vaccine types after vaccination and in the FinOM trial it was shown that some of these serotypes resulted in middle-ear disease. Further studies have shown that replacement disease with nonvaccine serotypes has only occurred at low frequencies. The magnitude of the benefit of vaccination at this stage was considered to be higher than the risk of replacement.

The extent of indirect effects (herd immunity) induced by the vaccine has been demonstrated in the US surveillance studies, as twice as many IPD cases were prevented as through direct effects. The herd effects were presumably attained by reduced carriage of vaccine serotypes in children <2 years of age, who constitute the prime group for transmission of S. pneumoniae infection in the community. Thus, the CHMP considered that these effectiveness data concerning IPD are also relevant to the AOM indication.

Since routine infant immunisation has only recently been implemented in several EU countries (UK, Netherlands, Germany, France, Belgium and Norway), data on long-term effectiveness and serotype replacement will have to be awaited. An overview of all surveillance studies planned by the National Public Health authorities was provided. The majority of studies concerned IPD, but the one study in France that was considered relevant for the otitis indication is funded by the MAH. It was proposed to extend this study until 2011 and to expand with respect to bacteriologic and clinical endpoints. This was considered an important follow-up study to evaluate antibiotic resistance, bacteriological shifts and serotype replacement disease in AOM.

In conclusion, the AOM indication was considered approvable and the MAH agreed to the final modifications required to the SPC as requested by the CHMP.

1.4 Benefit-Risk assessment.

Based on the presented data for the extension of the indication to include otitis media in infants and children from 2 months of age to 2 years of age the CHMP considers that the benefit/risk remains unchanged. The target population was considered the same for both indications and an otitis indication will not result in any change in the use of the vaccine.

2. CHANGES TO THE PRODUCT INFORMATION

As this variation is finalised in parallel with variation EMEA/H/C/000323/II/0090, the changes adopted in parallel are also included in the Annexes.

The MAH agreed with the CHMP on the following changes to the Product Information:

SPC section 4.1
Following the VWP discussions, the CHMP agreed to include acute otitis media as part of the overall indication rather than including it under a separate paragraph. The MAH agreed with the CHMP on the revised wording.

SPC section 4.4
The VWP and the CHMP agreed that the wording regarding hyporesponsiveness following vacination with a 23vPS vaccine needed to be revised to better reflect the current state of knowledge.

Furthermore, the MAH agreed with the CHMP that a wording on the low vaccine efficacy in overall AOM has been included in this section. The Package Leaflet has been updated accordingly.

Package Leaflet

The CHMP discussed the appropriate wording reflecting the statement on the comparably low efficacy in all AOM in section 4.4 of the SPC and proposed to re-word the statement in order to reflect the fact more correctly. The MAH agreed with the change proposed by the CHMP.

For detailed changes refer to the present/ proposed Appendix and final approved highlighted SPC/ PL attached to the CHMP AR.

3. CONCLUSION

On 1 February 2007 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet based on the observations and the appropriate conclusions.

REFERENCES

- Block S, Hedrick J, Harrison C, Tyler R, Smith A, Findlay R, Keegan E. Community-wide vaccination with the heptavalent pneumococcal conjugate significantly alters the microbiology of acute otitis media. Pediatr Infect Dis J 2004; 23(9), 829-317.
- Brouwer et al. Consecutive Prevenar and 23vPS vaccination in children 1 to 7 years of age with a history of recurrent AOM: impact on the child's quality of life . Pediatrics 2005:115:273-9)
- Casey J, Pichichero M. Changes in frequency and pathogens causing acute otitis media in 1995-2003. Pediatr Infect Dis J 2004; 23(9): 824-828
- Calbo E, et al. Invasive pneumococcal disease among children in a health district of Barcelona: early impact of pneumococcal conjugate vaccine. Clin Microbiol Infect 2006;12:867-72.
- Dagan R, et al. 9vPnC vaccination in children 12 to 35 months of age attending daycare: effect on nasopharyngeal carriage al JID2002:927-36;
- Dagan R, et al. Effect of a nonavalent conjugate vaccine on carriage of antibiotic-resistant Streptococcus pneumoniae in day-care centers. Ped Infect Dis J 2003;22:532-9)
- Dagan R, Sikuler-Cohen M, Zamir O, Janco J, Givon-Lavi N, Fraser D. Effect of a conjugate pneumococcal vaccine on the occurrence of respiratory infections and antibiotic use in day-care Eskola center attendees. Pediatr Infect Dis J 2001; 20: 951-8
- J, Kilpi T, Palmu A, Jokinen J, Haapakoski J, Herva E, Takala A, Käyhty H, Karma P, Kohberger R, Siber G, Mäkelä H. Efficacy of a pneumococcal conjugate vaccine against acuteotitis media. N Engl J Med, 2001; 344(6): 403-409
- Fireman B et al. Impact of the pneumococcal conjugate vaccine on otitis media. Pediatr Infect Dis J 2003;22:10-16
- Grijavla CG et al. National Impact of universal childhood immunisation with pneumococcal conjugate vaccine on outpatient medical care visits in the United States. Pediatrics 2006, 18, 3 (Sept 3):865-73).
- McEllistrem MC, 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 Jun 15;40(12):1738-44.
- Pai R et al. Postvaccine genetic structure of S. pneumoniae serotype 19A from children in the United States. J Infect Dis 2005; 192, 1988-95
- Palmu AAI et al, The seven-valent pneumococcal conjugate vaccine reduces tympanostomy tube placement in children. Pediatr Infect Dis J 2004;23:732-8
- Pebody RG, et al. Pneumococcal disease surveillance in Europe. Eurosurveillance 2006; 11:171-8
- Poehling K, Lafleur B, Szilagyi P, Ewards K, Mitchel E, Barth R, Schwartz B and Griffin M. Population-based impact of pneumococcal conjugate vaccine in young children. Pediatrics, 2004, 114: 755-76131.
- Van Heerbeek N et al. Consecutive Prevenar and 23vPS vaccination in children 2 to 8 years of age with a history of recurrent AOM: effect on recurrent otitis media with effusion (OME). Pediatrics 2006; 117:603-8
- Van Kempen et al. Pneumococcal conjugate vaccination in children with recurrent acute otitis media: a therapeutic alternative? Int J Ped Otolaryngol 2006;70:275-85
- Veenhoven R, et al. Effect of conjugate pneumococcal vaccine followed by polysaccharide pneumococcal vaccine on recurrent acute otitis media: a randomised study. Lancet 2003; 361, 2189-95