PUBLIC SUMMARY DOCUMENT
Product: PNEUMOCOCCAL POLYSACCHARIDE CONJUGATE VACCINE, 13-valent adsorbed, injection, 0.5 mL, pre-filled syringe, Prevenar-13®
Sponsor: Wyeth Australia Pty Limited
Date of PBAC Consideration: July 2010

1. Purpose of Application

The submission sought listing on the National Immunisation Program (NIP), as a replacement for Prevenar (7-valent pneumococcal vaccine), for vaccination against pneumococcal disease in infants.

2. Background

Prevenar 13, the 13-valent pneumococcal vaccine, had not previously been considered by the PBAC.

3. Registration Status

Prevenar 13 was TGA registered on 29 March 2010 for active immunisation for the prevention of disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (including invasive disease, pneumonia and acute otitis media) in infants and children from 6 weeks up to 5 years of age.

4. Listing Requested and PBAC's View

The submission stated that it is intended that Prevenar 13 will replace Prevenar on the NIP and the requested NIP indication is the same as Prevenar as follows:

"Immunisation against pneumococcal disease in infants and children at 2, 4 and 6 months of age, with medically at risk children receiving a fourth dose at 12 months."

5. Clinical Place for the Proposed Therapy

S. pneumoniae is a bacterial pathogen responsible for invasive pneumococcal disease (IPD) such as bacteraemia and meningitis and non-invasive pneumococcal disease (non-IPD) such as pneumonia, acute otitis media and sinusitis depending on the site of infection. IPD is a major cause of morbidity and mortality particularly in children aged less than 2 years, with a 20% case-fatality rate for pneumococcal meningitis. IPD caused by serotypes not covered by the currently available vaccines, predominantly 19A, have been increasing.

It was proposed that Prevenar 13 would provide an alternative 13-valent conjugate vaccine with broader serotype coverage against pneumococcal disease for vaccination of infants and children compared to the 7-valent (Prevenar) and 10-valent (Synflorix) vaccines currently listed on the NIP.

6. Comparator

The submission nominated Prevenar (three dose schedule, 3+0) as the main comparator and Synflorix (four dose schedule, 3+1) vaccine as a secondary comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented five randomised trials (004, 006, 011, 003, 3005) for the primary comparison of Prevenar 13 and Prevenar in infants receiving a primary series of pneumococcal vaccination (3 dose vaccination schedule).

Supportive evidence for the secondary indirect comparison was based on two trials (Vesikari and Wysocki) comparing a four dose schedule (3+1) of Synflorix with a four dose schedule (3+1) of Prevenar. All trials reported immunogenicity outcomes only.

The trials included in the submission are in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation
004	CSR 6096A1-004	28 August 2008
006	CSR 6096A1-006/ CSR-69237 Infant	1 August 2008
003	CSR 6096A1-003/ CSR-62926 Infant and Toddler	7 July 2008
011	CSR 6096A1-011/ CSR-70616 Infant Cohort 1	10 October 2008
3005	CSR6096A1-009/ CSR-74251 Infant	6 November 2008
Vesikari T, et al	Immunogenicity of the 10-Valent Pneumococcal Non-typeable Haemophilus influenzae Protein D Conjugate Vaccine (PHiD-CV) Compared to the Licensed 7vCRM Vaccine.	*The Paediatric Infectious Disease Journal* 2009; 28(4): S66-S76.
Wysocki J, et al	Immunogenicity of the 10-Valent Pneumococcal Non-typeable Haemophilus influenzae Protein D Conjugate Vaccine (PHiD-CV) When Coadministered With Different Neisseria meningitidis Serogroup C Conjugate Vaccines	*The Paediatric Infectious Disease Journal* 2009; 28(4): S77-S88.

8. Results of Trials

Comparative efficacy was assessed using four surrogate outcome measures in both the primary (versus Prevenar) and secondary (versus Synflorix) comparison:

- Immunoglobulin G (IgG) responders using enzyme-linked immunosorbent assay (ELISA) for assessment of immunogenicity. Differences in immune response (IgG antibody concentration) between Prevenar 13 and Prevenar were expressed in terms of the percentage of subjects with pneumococcal antibody concentrations of ≥0.35µg/mL. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% confidence interval of the difference between groups (Prevenar 13 minus Prevenar) was ≤ -10%. The difference in responder rates between Prevenar 13 and Synflorix in the indirect comparison was expressed in terms of both ≥0.35µg/ml and ≥0.2µg/ml.

- Mean geometric concentration (GMC) using ELISA. Differences between Prevenar 13 and Prevenar or Synflorix were expressed as the ratio of the GMCs for each serotype. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the ratio was ≥0.5 (2-fold test).

- OPA responders measured by opsonophagocytic assay (OPA). Differences between Prevenar 13 and Prevenar or Synflorix were expressed in terms of the percentage of subjects achieving an OPA antibody titre of ≥1:8.

- Mean geometric titre (GMT) measured by OPA. Differences between Prevenar 13 and Prevenar or Synflorix, were expressed as the ratio of the GMTs for each serotype.

Trial results were reported separately and pooled according to the vaccination schedule; 1) studies that used a 2-4-6 month vaccination schedule and 2) all studies.

Primary Comparison: Prevenar 13(3+0) versus Prevenar (3+0)

ELISA IgG Responders

Based on the all trial pooled analysis of ELISA IgG responders, non-inferiority was demonstrated for all common serotypes and five out of the six additional serotypes in Prevenar 13 when compared to Prevenar. However, non-inferiority was not demonstrated for serotype 3.

ELISA GMC

The meta-analysis of ELISA GMC for all trials and trials with 2-4-6 month vaccine schedule demonstrated that all common serotypes met the non inferiority criteria for the GMC ratio. Five out of the six additional serotypes in Prevenar 13 were non-inferior compared to Prevenar and serotype 3 did not meet the non-inferiority criteria.

OPA Responders

The meta-analysis of OPA responders in trials 003, 004 and 006 found there were no statistically significant differences for the percentage of subjects with OPA titres ≥1:8 for all common serotypes. All six additional serotypes in Prevenar 13 demonstrated statistical superiority over Prevenar.

Mean Geometric Titre

The meta-analysis of OPA GMT for all trials and trials with 2-4-6 month vaccine schedule found no statistically significant differences for OPA responders (OPA titres ≥1:8) for serotypes 9V, 14, 18C, 19F and 23F. However, serotypes 4 and 6B were found to be statistically inferior in the pooled analysis of all studies, and serotype 4 was found to be statistically inferior in the pooled analysis of 2-4-6 trials. All of the additional serotypes in Prevenar 13 demonstrated statistical superiority over Prevenar.

Secondary Comparison: Prevenar 13 (3+0) vs Synflorix (3+1)

ELISA IgG responders and GMC

The pooled results for IgG responders found no statistically significant differences for all common serotypes in terms of both the relative risks and absolute risk differences between Prevenar 13 and Synflorix, using Prevenar as the common reference. Among the three additional serotypes found in Synflorix, serotypes 1 and 7F in Prevenar 13 were statistically superior to Synflorix, while there was a statistically non-significant difference for serotype 5. Serotypes 6A and 19A were statistically superior in Prevenar 13.

For the GMC outcome, four out of the six common serotypes demonstrated statistical superiority in Prevenar 13. Serotype 19F was found to be statistically inferior. All additional serotypes were found to be statistically superior in Prevenar 13.

OPA Responders and GMT

For OPA responders, the pooled analysis found there was no statistically significant difference for all common serotypes. Among the additional serotypes, Prevenar 13 was statistically inferior for 7F and statistically superior to Synflorix for 6A and 19A.

For further PBAC comments on these results, see Recommendation and Reasons.

The safety analysis, based on 12 studies with a total of 4428 infants vaccinated with Prevenar 13 and 2457 infants vaccinated with Prevenar, demonstrated that Prevenar 13 is non-inferior with respect to local and general adverse events. There were no differences in the overall adverse events during infant series, between infant series, during toddler dose and after the toddler dose. The incidence of serious adverse events was 4.5% or less for each vaccine group, with most considered unrelated to the administration of the vaccine. In total, there were 13 serious adverse events judged by study investigators to be related to study vaccines, seven in the Prevenar 13 groups and six in the Prevenar group. Overall, the number of withdrawals from the trials due to adverse events was low. Comparative safety of Prevenar 13 and Synflorix was not assessed in the indirect comparison. The submission did not undertake an extended assessment of comparative harms for Prevenar 13 compared to Prevenar or Synflorix, respectively.

9. Clinical Claim

The submission described Prevenar 13 (3+0) as non-inferior in terms of comparative immunogenicity and non-inferior in terms of safety over Prevenar (3+0) and Synflorix (3+1).

The submission claimed that the key incremental benefit of Prevenar 13 over Synflorix would be a substantial reduction in disease caused by subtypes 19A and 6A. Consequently, Prevenar 13 should provide clinically meaningful protection against IPD and non-IPD caused by these additional serotypes.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

A stepped economic evaluation was presented. The model estimated the number of cases of IPD (meningitis or bacteraemia), inpatient and outpatient community acquired pneumonia (all-cause) and otitis media (all-cause) by age group.

The results of the economic evaluations show that the number of illnesses occurring following vaccination with Prevenar 13 is consistently less than is estimated to occur following vaccination with either Synflorix or Prevenar.

The submission also presented a cost-effectiveness analysis including all costs. The submission claimed that Prevenar 13 provides additional cost-savings compared to Synflorix and Prevenar on the basis of reduced numbers of cases of IPD, community acquired pneumonia and otitis media.

For PBAC's view, see Recommendation and Reasons.

11. Estimated NIP Usage and Financial Implications

The submission estimated the likely number of patients per year to be greater than 200,000 in Year 5. The evaluation estimated a net cost to the NIP of less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended listing on the National Immunisation Program (NIP) of this new presentation of pneumococcal vaccine (Prevenar 13) under the same circumstances of use as the existing NIP listed pneumococcal 7-valent vaccine (Prevenar). The PBAC further recommended that Prevenar 13 pre-filled syringes should be priced to achieve parity between a complete course of Prevenar 13 and a complete course of the 10-valent vaccine (Synflorix) taking into account the proportion of the Prevenar 13 targeted population who will require a fourth dose and including the $7 cost of administering this dose at an existing vaccination point.

In making this recommendation, the PBAC considered that Synflorix is the appropriate main comparator and Prevenar a secondary comparator, noting that, the 10-valent vaccine is the product most similar, in terms of serotype coverage, to Prevenar 13. Additionally, Prevenar is being removed from the NIP, so that the two vaccines which will be available for inclusion on the NIP in the future will be Synflorix and Prevenar 13, making the comparison with Synflorix the most relevant for PBAC consideration.

The PBAC was satisfied that, based on the surrogate outcome data presented in the submission and taking into account the advice from the Australian Technical Advisory Group on Immunisation (ATAGI), on-balance Prevenar 13 (3+0) is non-inferior with respect to immunogenicity and safety to Synflorix (3+1) and Prevenar (3+0), although some uncertainty remains as to whether the use of three dose schedule of Prevenar 13 might be associated with reduced immune persistence, in the common serotypes, compared to the four dose schedule of Synflorix and the three dose schedule of Prevenar.

The uncertainty around duration of protection arises because in the comparison of Prevenar 13 versus Prevenar, the meta-analysis of differences between Prevenar 13 and Prevenar using ELISA GMCs showed that, although all common serotypes met the non inferiority criteria for the GMC ratio, they were statistically inferior in Prevenar 13. Additionally, the meta-analysis of differences between Prevenar 13 and Prevenar using OPA showed Prevenar 13 to be statistically inferior to Prevenar for serotypes 4 and 6B in the pooled analysis of all studies, and statistically inferior for serotype 4 in the pooled analysis of the 2-4-6 month vaccine schedule studies. For the comparison of Prevenar 13 and Synflorix, based on comments provided by the ATAGI, the PBAC considered there may be a modestly higher level of immune persistence for serotypes 1, 4, 18C, 19F and 23F with the 4 dose Synflorix schedule than with the 3 dose schedule of Prevenar 13. Taken together, these results are suggestive of a lower duration of protection for Prevenar 13 compared to Prevenar or Synflorix.

The PBAC was sufficiently reassured by the ATAGI advice that *"assuming extrapolation from the Prevenar experience is reasonable, the herd immunity achieved by a 3-dose primary course of Prevenar 13 without a booster dose, is likely to substantially reduce the actual*

differences in effectiveness of vaccine programs observed at the population level following introduction of different pneumococcal conjugate vaccines" to recommend the Prevenar 13 be made available on the NIP on a three dose schedule, with a fourth dose at 12 months of age for medically at risk children.

The PBAC also considered the sponsor's request that the Committee acknowledge the clinical benefits claimed for Prevenar 13 over Synflorix and Prevenar by the submission. The PBAC considered that acceptance of this claim rested on acceptance that the surrogate immunogenicity data provided for Prevenar 13 translates into clinically important benefits and that the evidence to support the validity of this extrapolation is currently very uncertain. Additionally it is particularly problematic for the comparison of Prevenar 13 and Synflorix because the surrogate outcomes are derived from studies with different assays, resulting in even greater uncertainty.

The PBAC also noted that ATAGI had concluded that given the high current burden of invasive pneumococcal disease (IPD) caused by serotype 19A, the high absolute and relative immunogenicity of Prevenar 13 against this serotype is likely to result in clinical benefits for Prevenar 13 over Prevenar in non-indigenous children which outweigh possible reductions in Prevenar 13 efficacy against serotypes 6B and 19F. On the other hand, ATAGI considered the same clinical benefit unlikely to be realised in indigenous children in regions with high incidence of IPD, because there is greater serotype diversity and in these regions, 19A IPD has not increased since the introduction of Prevenar.

The PBAC noted that ATAGI additionally concluded that the potential clinical benefits for Prevenar 13 (3 dose schedule) over Synflorix (4 dose schedule) are much less certain, particularly for non-invasive diseases (primarily pneumonia and otitis media) but also for IPD. In this context, the PBAC noted that the POET study using a prototype of the Synflorix formulation, demonstrated a significant reduction in overall incidence of acute otitis media in fully vaccinated children less than 2 years of age, so there are clinical data available, albeit limited, which counter the submission's claim.

The PBAC concluded that overall the submission's claim of superiority was not sufficiently supported by the evidence provided. Whether the immunological differences between Prevenar, Synflorix and Prevenar 13 documented by the submission translate into different outcomes in practice can only be determined from clinical outcome data in large populations. The cost-effectiveness analysis provided with the current submission is therefore without adequate basis and was not considered further by the Committee.

The PBAC welcomed and noted the consumer comments provided in relation to the Prevenar 13 submission.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Wyeth is pleased that Prevenar 13 will be available on the National Immunisation Program. This will provide an important advance on existing pneumococcal vaccines, particularly with respect to its direct protection against serotype 19A, the serotype responsible for the greatest burden of invasive pneumococcal disease in Australia.