Australian Public Assessment Report for Pneumococcal polysaccharide conjugate vaccine, 13-valent adsorbed

Proprietary Product Name: Prevenar 13

Sponsor: Pfizer Australia Pty Ltd

September 2014
About the Therapeutic Goods Administration (TGA)

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- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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# Contents

List of the most common abbreviations used in this AusPAR ______ 4

I. Introduction to product submission ________________________ 6
  Submission details ________________________________________ 6
  Product background ______________________________________ 6
  Product Information ______________________________________ 8

II. Quality findings ________________________________________ 8

III. Nonclinical findings ____________________________________ 8

IV. Clinical findings ________________________________________ 8
  Introduction ____________________________________________ 8
  Pharmacokinetics _________________________________________ 10
  Pharmacodynamics _________________________________________ 10
  Dosage selection for the pivotal studies ______________________ 10
  Efficacy ________________________________________________ 10
  Safety _________________________________________________ 11
  First round benefit-risk assessment _________________________ 12
  First round recommendation regarding authorisation _________ 14
  Clinical questions _______________________________________ 14
  Second round evaluation of clinical data submitted in response to questions_ 14

V. Pharmacovigilance findings ______________________________ 14
  Risk management plan ___________________________________ 14

VI. Overall conclusion and risk/benefit assessment ____________ 17
  Background _____________________________________________ 17
  Quality _________________________________________________ 18
  Nonclinical _____________________________________________ 18
  Clinical ________________________________________________ 18
  Risk management plan ____________________________________ 27
  Risk-benefit analysis _____________________________________ 28
  Outcome _______________________________________________ 35

Attachment 1. Product Information ___________________________ 36
Attachment 2. Extract from the Clinical Evaluation Report ______ 36
### List of the most common abbreviations used in this AusPAR

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>7vPnC</td>
<td>7-valent pneumococcal conjugate vaccine</td>
</tr>
<tr>
<td>13vPnC</td>
<td>13-valent pneumococcal conjugate vaccine</td>
</tr>
<tr>
<td>23vPS</td>
<td>23-valent pneumococcal polysaccharide vaccine</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>CAP</td>
<td>community-acquired pneumonia</td>
</tr>
<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CO</td>
<td>clinical overview</td>
</tr>
<tr>
<td>CRM197</td>
<td>cross-reacting material 197 (nontoxic mutant form of diphtheria toxin)</td>
</tr>
<tr>
<td>CSR</td>
<td>clinical study report</td>
</tr>
<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>GMCs</td>
<td>geometric mean concentrations</td>
</tr>
<tr>
<td>GMFR</td>
<td>geometric mean fold rise</td>
</tr>
<tr>
<td>GMT</td>
<td>geometric mean titre</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>IgG</td>
<td>immunoglobulin G</td>
</tr>
<tr>
<td>IPD</td>
<td>invasive pneumococcal disease</td>
</tr>
<tr>
<td>LLOQ</td>
<td>lower limit of quantitation</td>
</tr>
<tr>
<td>MAA</td>
<td>Marketing Authorisation Application</td>
</tr>
<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Meaning</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>NIP</td>
<td>National immunisation program</td>
</tr>
<tr>
<td>OPA</td>
<td>opsonophagocytic activity</td>
</tr>
<tr>
<td>RCDC</td>
<td>reverse cumulative distribution curve</td>
</tr>
<tr>
<td>SAP</td>
<td>statistical analysis plan</td>
</tr>
<tr>
<td>SCD</td>
<td>sickle cell disease</td>
</tr>
<tr>
<td>SmPC</td>
<td>summary of product characteristics</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>VT</td>
<td>vaccine type</td>
</tr>
</tbody>
</table>
I. Introduction to product submission

Submission details

Type of submission: Extension of indications to include adults 18-49 years old
Decision: Approved
Date of decision: 27 May 2014
Active ingredients: Pneumococcal capsular polysaccharides for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, each individually conjugated to diphtheria CRM$_{197}$ protein and adsorbed on aluminium phosphate.

Product name: Prevenar 13
Sponsor’s name and address: Pfizer Australia Pty Ltd
38-42 Wharf Road
West Ryde NSW 2114

Dose form: Suspension for intramuscular injection
Strengths: 2.2 µg of polysaccharides for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F and 4.4 µg of polysaccharides for serotype 6B.

Container: Prefilled syringe
Pack sizes: 1 and 10s

Approved therapeutic use: Active immunisation for the prevention of pneumococcal disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in adults and children aged more than 6 weeks of age.

The use of Prevenar 13 should be guided by official recommendations.

Route of administration: Intramuscular (IM)
Dosage: 0.5 mL (see Product Information for details of Immunisation Schedules)

ARTG number: 158450

Product background

This AusPAR describes the application by the sponsor, Pfizer Australia Pty Ltd, to extend the indications for Prevenar 13 to include active immunisation for the prevention of pneumococcal disease caused by Streptococcus pneumoniae (S. pneumoniae) serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F in adults 18 to 49 years of age. The proposed indications are as follows:
Active immunisation for the prevention of disease caused by Streptococcus pneumonia 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.

Active immunisation for the prevention of pneumococcal disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in adults aged 18 years and older.

The use of Prevenar 13 should be guided by official recommendations.

The sponsor has also requested to include additional information in relation to the use of Prevenar 13 in high risk populations, such as pre-term infants, children and adolescents with sickle cell disease and human immunodeficiency virus (HIV) infected adults. These changes have now been approved by the European Medicines Agency (EMA).

*S. pneumoniae* is considered to be a leading cause of invasive pneumococcal disease (IPD), acute otitis media (AOM) and bacterial pneumonia. The protection afforded by Prevenar 13 vaccination is mediated by the induction of antibodies against the pneumococcal capsular serotypes in the vaccine. There are well-established conditions associated with an increased risk of pneumococcal disease. These are identified in the Australian Immunisation Handbook and include immuno-compromising conditions such as chronic cardiac disease, chronic lung disease and diabetes mellitus.

The currently approved indication for Prevenar 13 in Australia is for infants and children 6 weeks to 17 years old and adults 50 years and older and reads as follows:

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 to 17 years of age.

Active immunisation for the prevention of pneumococcal disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in adults aged 50 years and older.

The use of Prevenar 13 should be guided by official recommendations.

**Regulatory status**

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 16 March 2010. At the time the TGA considered this application, a similar application had been approved in USA, Europe and Canada (see Table 1 for details).

**Table 1. International Regulatory status**

<table>
<thead>
<tr>
<th>Market</th>
<th>Indication</th>
<th>Date</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>High risk groups (pre-term infants, children with sickle cell disease, and HIV-infected adults)</td>
<td>February 2013</td>
<td>Approved</td>
</tr>
<tr>
<td>Europe</td>
<td>Adults aged 18-49 years of age</td>
<td>30 September 2012</td>
<td>Approved</td>
</tr>
<tr>
<td></td>
<td>High risk groups (pre-term infants, children with</td>
<td>20 December</td>
<td></td>
</tr>
<tr>
<td>Market</td>
<td>Indication</td>
<td>Date</td>
<td>Status</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
<td>--------------</td>
<td>----------</td>
</tr>
<tr>
<td></td>
<td>sickle cell disease, and HIV-infected adults)</td>
<td>2012</td>
<td>Approved</td>
</tr>
<tr>
<td>Canada</td>
<td>Adults aged 18-49 years of age</td>
<td>4 April 2013</td>
<td>Approved</td>
</tr>
<tr>
<td></td>
<td>High risk groups (pre-term infants, children with sickle cell disease, and HIV-infected adults)</td>
<td>10 April 2014</td>
<td>Approved</td>
</tr>
</tbody>
</table>

**Product Information**

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

**II. Quality findings**

There was no requirement for a quality evaluation in a submission of this type.

**III. Nonclinical findings**

There was no requirement for a nonclinical evaluation in a submission of this type.

**IV. Clinical findings**

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

**Introduction**

**Clinical rationale**

On 2 December 2008, the Marketing Authorisation Holder (MAH) submitted an application to the European Medicines Agency (EMA) for 13-valent pneumococcal conjugate vaccine (13vPnC, Prevenar 13), through the centralised procedure in the EU. A positive opinion was adopted on 24 September 2009 by the Committee for Medicinal Products for Human Use (CHMP). The current adult indication for 13vPnC covers adults aged 50 years and older. The MAH is now submitting a Type II variation in multiple countries to expand the adult indication to include adults aged 18 to 49 years. With this expanded coverage, the adult indication would be extended to cover all adults aged 18 years and older.
The epidemiological data contained in this submission is mainly from Europe and the United States. In these countries, as in Australia, there is still a significant burden of IPD in subjects 18 to 49 years of age. The incidence of IPD, according to population-based data from England and Wales, ranged from $4.7 \times 10^5$ to $11.0 \times 10^5$ in the 2009/2010 season. Available data indicate that about 50% of all cases may be caused by 13vPnC serotypes. It is also true that the incidence of pneumococcal pneumonia in subjects 18 to 49 years is largely underestimated because valid microbiological tests are not routinely available. Estimates from clinical studies indicate CAP incidences range between $44/10^5$ and $134/10^5$, of which roughly 40% are due to *S. pneumoniae*. Administrative data indicate that hospitalisations for CAP or 'all cause-pneumonia' are in the magnitude of $30/10^5$ to $60/10^5$ and roughly 40% are due to *S. pneumoniae*; of these 57% have been identified as 13vPnC serotypes in the only study assessing pneumococcal serotypes in patients with CAP using multiple microbiological methods. Epidemiological data in Australia is similar. Herd protection effects from pneumococcal conjugate vaccines are also seen in the group aged 18 to 49 years.

There are subjects with diverse types of 'risks' for severe pneumococcal infections. These risks encompass various types of immune deficiencies (with or without a remaining ability to produce protective antibodies), non-immunologically determined other underlying diseases and conditions, as well as various life style factors. While details may vary for such 'risk subjects,' pneumococcal vaccination is recommended in virtually all European countries. Currently for adults aged 18 to 49 years only 23vPS is available, although it is well known that the polysaccharide vaccine does not offer high and long lasting protection and hypo-responsiveness is a concern. Subjects age 18 to 49 years in certain at-risk groups have significant risk for pneumococcal diseases and 13vPnC has an estimated 60% coverage of serotypes causing IPD in these subjects.

### Contents of the clinical dossier

The sponsor provided Study 6115A1-004, which compared the immunogenicity, tolerability, and safety of Prevenar 13 and 23vPS in adults 60 to 64 years of age (Cohort 1) who had not previously been vaccinated with 23vPS, using a randomised, double-blind design. The study also included a cohort of subjects 50 to 59 years of age (Cohort 2), and a cohort of subjects 18 to 49 years of age (Cohort 3, approximately 900 subjects). Cohorts 2 and 3 received open-label Prevenar 13.

The sponsor also submitted 3 clinical studies on the use of Prevenar 13 in populations with specific conditions associated with increased risk of pneumococcal disease. The information proposed is derived from the final study reports for the studies listed below.

- 6096A1-4001 (B1851037): preterm infants
- 6096A1-3014 (B1851013): children and adolescents aged 6 to <18 years with sickle cell disease (SCD), previously immunised with 23-valent pneumococcal polysaccharide vaccine (23vPS)

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• 6115A1-3017 (B1851028): human immunodeficiency virus (HIV)-infected adults aged 18 years and over, previously immunised with 23vPS.

Paediatric data
The submission includes paediatric efficacy and safety data.

Good clinical practice
This submission has compliance with good clinical practice.

Pharmacokinetics
No new data submitted.

Pharmacodynamics
No new data submitted.

Dosage selection for the pivotal studies
The standard dose of 0.5 mL was used.

Efficacy

Studies providing efficacy data
The sponsor submitted 3 clinical studies on the use of 13vPnC in populations with specific conditions associated with increased risk of pneumococcal disease:

• 6096A1-4001 (B1851037): preterm infants
• 6096A1-3014 (B1851013): children and adolescents aged 6 to <18 years with sickle cell disease (SCD), previously immunised with 23-valent pneumococcal polysaccharide vaccine
• 6115A1-3017 (B1851028): human immunodeficiency virus (HIV)-infected adults aged ≥18 years previously immunised with 23vPS

Evaluator’s conclusions on efficacy

For active immunisation for the prevention of invasive disease caused by Streptococcus pneumoniae in adults (aged 18 years and older).

In Study 6115A1-004 Cohort 3 the primary immunological comparisons were the serotype-specific opsonophagocytic activity (OPA) geometric mean titres (GMTs) for the 13 pneumococcal serotypes contained in 13vPnC, when measured 1 month after study vaccine administration in subjects 18 to 49 years of age in Cohort 3 relative to those in subjects 60 to 64 years of age in Cohort 1. The results demonstrated that all 13 serotypes elicited immunologic responses in Cohort 3 that were non-inferior to those in Cohort 1 and were statistically significantly higher in Cohort 3 for all serotypes except serotype 3.

In addition, the immune response in each of the 3 age subgroups of Cohort 3 was statistically significantly higher than the response among subjects in Cohort 1 for all serotypes except serotype 3, which elicited a non-inferior response. Among the age subgroups, OPA GMTs were
generally highest for subjects in the 18 to 29 year old subgroup and lowest in the 40 to 49 year old subgroup, indicating higher antibody responses with younger age.

The serotype-specific geometric mean fold rise (post-vaccination OPA GMT/pre-vaccination OPA GMT) was generally similar or higher in the 18 to 49 year old group relative to that of the 60 to 64 year old group, at 1 month and 1 year after vaccination.

After vaccination, the proportion of subjects achieving a serotype-specific OPA titre ≥ lower limit of quantification (LLOQ) in Cohort 3 was non-inferior to that of Cohort 1 for all 13 serotypes and was statistically significantly greater for all serotypes, except for serotype 3.

A high antibody response in Cohort 3 was still present 1 year after vaccination. Except for serotype 3, the OPA GMTs were higher for Cohort 3 than for Cohort 1 one year after vaccination and were still well above baseline (pre-vaccination) levels.

**For use in preterm infants**

Most preterm subjects (Group 1) and those born at term (Group 2) achieved immunoglobulin type G (IgG) antibody concentrations ≥ 0.35 µg/mL 1 month after the infant series (>85%) and 1 month after the toddler dose (>97%) for at least 10 serotypes. After the infant series, IgG concentrations elicited by 13vPnC were somewhat lower in preterm infants compared with term infants, although OPA GMTs were similar in the 2 groups indicating that the immune response is likely to be adequate to provide protection against disease.

While post-toddler dose responses varied by serotype and with gestation age, there is good evidence of adequate priming among preterm infants given 13vPnC in a 2, 3 and 4 month schedule when compared with that of infants born at term.

**In children and adolescents with SCD**

Children and adolescents between 6 and 18 years of age with SCD who were previously immunised with 23vPS had significant increases in both IgG binding and functional antibody (OPA) after both 1 dose and 2 doses of 13vPnC. The addition of a second dose of 13vPnC given 6 months after the first dose resulted in IgG geometric mean concentrations (GMCs) that were similar to or lower than those seen after Dose 1. Serotype-specific OPA responses after the second 13vPnC dose were comparable or higher than those after the first dose, suggesting a potential positive impact on maturation of functional antibody response for at least some serotypes after the second dose but the differences were modest and the clinical significance is uncertain.

Overall these data suggest that a 2-dose regimen of 13vPnC given 6 months apart does not enhance pneumococcal immune responses beyond those of a single dose of 13vPnC.

**For adults with HIV infection**

HIV infected subjects previously immunised with 23vPS responded to 13vPnC at each of 3 vaccine doses and immune responses remained above initial baseline levels (before Dose 1) throughout the study. The immune response after vaccine Dose 3 was either stable or increased relative to the response after Dose 2 or Dose 1. However, the clinical significance of the increased immune response (statistically significant for most serotypes) after Dose 3 is unknown. The number of previous 23vPS doses had no impact on the immune response.

**Safety**

**Studies providing safety data**

The following studies provided evaluable safety data:

- Study 6115A1-004; all cohorts.
**Patient exposure**

The data supporting age expansion are from 899 subjects vaccinated in Study 6115A1-004. The most relevant information for this age extension submission is for Cohort 3 (ages ≥18 years to 49 years [up to the 50th birthday) of a single trial, Study 6115A1-004.

**Postmarketing data**

There is no marketing experience for 13vPnC in the age extension age group.

**Evaluator’s conclusions on safety**

The safety of 13vPnC administered to the 18 to 49 year old subjects in Cohort 3 was compared with the safety of the 13vPnC vaccine administered to the older subjects (60 to 64 years old and 50 to 59 years old) in Cohorts 1 and 2, respectively. The safety of 13vPnC administered to subjects in each of the age subgroups in Cohort 3 was also assessed. Local reactions and systemic events occurring within 14 days after vaccine administration were reported by higher percentages of subjects in Cohort 3 compared with the older subjects in Cohorts 1 and 2. In the age subgroups in Cohort 3, in general, the percentages of subjects with local reactions and systemic events were generally highest in the youngest (18 to 29 year old) age subgroup.

In relation to the percentages of subjects who reported adverse events (AEs) within approximately 1 month after vaccination, there were no differences between Cohort 3 and the older cohorts or within the age subgroups in Cohort 3. The percentage of subjects reporting any AEs at the 6 month follow-up contact was slightly lower in Cohort 3 (0.3%) than in Cohort 2 (1.5%) and Cohort 1 (2.9%).

These findings were consistent with those expectable post vaccination and no new safety issues were identified. An acceptable safety profile was demonstrated for the administration of 13vPnC to subjects 18 to 49 years of age.

In the studies in special populations (premature infants, children and adolescents with SCD and adults with HIV infection), there were also no unexpected safety issues identified.

In Study 6096A1-4001 there was a high incidence of local reactions, more so in the toddler dose than in the infant series, consistent with immunological priming. These were generally mild and resolved quickly (as did the related systemic events). There were however two documented febrile convulsions. In both these infants, there were thought to be concomitant infections. This study did not suggest any new or unexpected safety signal among preterm infants compared with their term counterparts.

In Study 6096A1-3014 in children and adolescents with SCD, the reported local and systemic reactions were also consistent with the known and expected ones post vaccination and there were no unanticipated reactions or AEs. The AE and serious adverse events (SAE) data in the study reflected the underlying condition of SCD.

In Study 6115A1-3017 in HIV infected adults, an acceptable safety profile was demonstrated for the administration of 13vPnC in subjects aged 18 years and older previously immunised with 23vPS. No new safety issues were identified in this population after administration of 3 doses of 13vPnC.

**First round benefit-risk assessment**

**First round assessment of benefits**

Study 6115A1-004 Cohort 3 evaluated the immunogenicity and safety of 13vPnC to support extension of the indication for 13vPnC to subjects 18 years to 49 years of age who had not
received prior 23vPS vaccination. The primary immunological comparisons were the serotype-specific OPA GMTs for the 13 pneumococcal serotypes contained in 13vPnC, when measured 1 month after study vaccine administration in subjects 18 to 49 years of age in Cohort 3 relative to those in subjects 60 to 64 years of age in Cohort 1. The results demonstrated that all 13 serotypes elicited immunologic responses in Cohort 3 that were non-inferior to those in Cohort 1 and were statistically significantly higher in Cohort 3 for all serotypes except serotype 3.

In addition, the immune response in each of the 3 age subgroups of Cohort 3 was statistically significantly higher than the response among subjects in Cohort 1 for all serotypes except serotype 3, which elicited a non-inferior response.

Among the age subgroups, OPA GMTs were generally highest for subjects in the 18 to 29 year old subgroup and lowest in the 40 to 49 year old subgroup, indicating higher antibody responses with younger age.

A high antibody response in Cohort 3 was still present 1 year after vaccination. Except for serotype 3, the OPA GMTs were higher for Cohort 3 than for Cohort 1 one year after vaccination and were still well above baseline (pre vaccination) levels.

Even though the proportion of subjects with risk conditions for pneumococcal disease was generally low in Cohort 3 with percentages as follows: asthma, 5.2%; cardiac disorders 3.3%; and diabetes mellitus, 2.9%, according to previously submitted data, these types of risk conditions are not expected to negatively impact the immune response to vaccination with 13vPnC. The marketing authorisation holder (MAH) had previously compared (descriptive comparison) the responses of subjects with risk conditions (cardiovascular, pulmonary, renal diseases, diabetes mellitus) to those of non-risk subjects in the 2 older cohorts (aged 60 to 64 years and 50 to 59 years, 23vPS-naïve) in Study 6115A1-004; in 60 to 64 year old, 23vPS-naïve subjects in Study 6115A1-3010; and in 23vPS-preimmunised subjects ≥70 years of age in Study 6115A1-3005. The results for subjects at risk and for those not at risk were similar and confirmed that immuno-competent subjects with these underlying diseases elicit antibody responses to 13vPnC that are similar to those of healthy subjects.

In the efficacy data submitted for inclusion in the PI, comparable immunogenicity and safety is also shown in all at risk groups studied (preterm infants, children and adults with SCD and HIV infected adults).

**First round assessment of risks**

The risk analysis for 13vPnC in the proposed usage showed:

- An acceptable safety profile was demonstrated for the administration of 13vPnC to subjects 18 to 49 years of age.
- Safety and tolerability of 13vPnC administered to subjects aged 18 to 49 years in Cohort 3 was compared with the safety and tolerability of 13vPnC administered to older subjects aged 60 to 64 years and 50 to 59 years in Cohorts 1 and 2, respectively.
- Local reactions and systemic events occurring within 14 days after vaccine administration were, in general, reported by higher percentages of subjects in Cohort 3 compared with the older subjects in Cohorts 1 and 2.
- In the age subgroups of Cohort 3, the percentages of subjects with local reactions were generally highest in the youngest (aged 18 to 29 years) subgroup. Medical care was only required for a few subjects and these subjects had mild or moderate symptoms; that is, none had severe pain or limitation of arm movement.
- Local reactions generally did not last more than 2.8 days for Cohort 3. Fever was reported in 7.2% of subjects of Cohort 3 and was generally mild or moderate except for 1 case of fever.
therapeutic goods administration

>40° in the subgroup aged 30 to 39 years. The mean durations of systemic events also were
generally similar for the 3 cohorts and did not exceed 5.5 days in Cohort 3 overall.

- The percentages of subjects reporting AEs were not different among the 3 cohorts of Study
6115A1-004 or among the age subgroups within Cohort 3. At the 6 month follow-up contact
slightly fewer subjects reported AEs in Cohort 3 (0.3%) than in Cohort 2 (1.5%) and Cohort
1 (2.9%). Most AEs were the types of diseases and conditions commonly observed among
adults in these age groups. There were few reports of related AEs, severe or life threatening
AEs, or SAEs and incidences were similar in Cohort 3 as in Cohort 1 and Cohort 2.

- There were no deaths or AEs that led to withdrawal from the study in Cohort 3.

- In the safety data submitted with the three other studies in at-risk groups, no new safety
alerts were identified and most of the adverse events reflected the background
conditions/risks associated with the primary diseases in these groups.

First round assessment of benefit-risk balance

The benefit-risk balance of 13vPnC, given the proposed usage, was considered to be favourable.

First round recommendation regarding authorisation

The clinical evaluator recommended licensing of 13vPnC for use in adults 18 to 49 years of age
for the prevention of pneumococcal disease.

Clinical questions

No questions were posed by the clinical evaluator.

Second round evaluation of clinical data submitted in response to questions

As the clinical evaluator had no questions for the sponsor, there was no second round clinical
evaluation required.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU RMP Version 7.0, dated 13 June 2013, with
an Australian Specific Annex (ASA) Versions 1.0 (dated 18 June 2013) and 2 (dated 11
December 2013) which were reviewed by the TGA’s Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the clinical aspects of the Safety Specification by the OMA, the
summary of the Ongoing Safety Concerns, as specified by the sponsor, is given in Table 2.
Table 2. Summary of ongoing safety concerns

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>a) Increased fever rates when 13vPnC is co-administered Infanrix hexa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b) Anaphylaxis/hypersensitivity</td>
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<tr>
<td></td>
<td>c) Convulsions/seizures</td>
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<tr>
<td></td>
<td>d) Apnoea</td>
</tr>
<tr>
<td>Important potential risks</td>
<td>a) Lack of effect in subjects who are fully vaccinated</td>
</tr>
<tr>
<td>Important missing information</td>
<td>a) Unanticipated safety signals (including the onset of rare events) not seen in clinical trials of 13vPnC (including wheezing as part of post-approval safety study).</td>
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<tr>
<td></td>
<td>b) Effectiveness of 13vPnC</td>
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<td></td>
<td>c) Potential changes in the epidemiology of nonvaccine S. pneumoniae serotypes that may occur.</td>
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<tr>
<td></td>
<td>d) Safety and immunogenicity in high-risk populations:</td>
</tr>
<tr>
<td></td>
<td>i) Pneumococcal vaccine naïve HIV-infected subjects.</td>
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<tr>
<td></td>
<td>ii) Subjects with bone marrow transplant</td>
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<td></td>
<td>e) Impact of 13vPnC on nasopharyngeal carriage (infants/children)</td>
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<tr>
<td></td>
<td>f) Effect of antipyretics on immune response to vaccination (infants/children)</td>
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<td></td>
<td>g) Safety of more than 1 dose of 13vPnC in adults administered &gt;1 year apart.</td>
</tr>
<tr>
<td></td>
<td>h) Vaccine exposure during pregnancy and lactation</td>
</tr>
</tbody>
</table>

Abbreviations: HIV = human immunodeficiency virus. NPC = nasopharyngeal carriage.
Note: The labeled events of apnoea, convulsions/seizures, and anaphylaxis/hypersensitivity are being presented in the “Important identified risks” section in the new format of the RMP for clarity, whereas in the previous version (6.0) of the RMP they were presented in Section C, which was not clearly within identified or potential risks.

Content of the pharmacovigilance submission

The sponsor proposes routine pharmacovigilance activities to monitor all the specified ongoing safety concerns, including the use of an adverse event follow-up form for the important potential risk: ‘Lack of effect in subjects who are fully vaccinated’. Additional pharmacovigilance activities are also proposed to further monitor and characterise all the specified ongoing safety concerns, except for the important identified risk: ‘Increased fever rates when 13vPnC is co-administered Infanrix hexa’ and the important missing information: ‘Vaccine exposure during pregnancy and lactation’.

The sponsor has concluded that routine risk minimisation activities are sufficient for all the specified ongoing safety concerns, except for the important missing information: ‘Unanticipated safety signals (including the onset of rare events)’, ‘Potential changes in the epidemiology of nonvaccine S. pneumonia serotypes that may occur’ and ‘Effect of antipyretics on immune response to vaccination (infants/children) for which no risk minimisation activities are applied.

Reconciliation of issues outlined in the RMP report

The rationale for the specified changes to the ongoing safety concerns from those previously accepted would appear reasonable. Notwithstanding the evaluation of the clinical aspects of the Safety Specification, it is considered that this list of ongoing safety concerns is acceptable.

The sponsor’s conclusion that routine risk minimisation activities are sufficient for all the specified ongoing safety concerns except for some of the important missing information is similar to what was previously accepted. This currently continues to be acceptable.

The sponsor’s handling of the potential for medication error using routine pharmacovigilance and routine risk minimisation activities is considered satisfactory.

In regard to the proposed routine risk minimisation activities, the draft product information document is considered satisfactory.
In regard to the proposed routine risk minimisation activities, the draft consumer medicine information is considered satisfactory.

Table 3 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR’s evaluation of the sponsor's responses.

Table 3. Reconciliation of issues outlined in the RMP report

<table>
<thead>
<tr>
<th>Recommendation in RMP evaluation report</th>
<th>Sponsor's response</th>
<th>OPR evaluator's comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The ongoing studies are not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore the related study protocols have not been requested for review. Nevertheless these studies will either generate safety data that will simply support the known safety profile of the medicine or generate data that will provoke applications to amend the Australian registration details. To this end the sponsor should provide an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia.</td>
<td>An attachment to the Australian Specific Annex (ASA) was prepared by the sponsor and included with their response. The requested list of forthcoming studies and their anticipated dates for submission in Australia was provided.</td>
<td>This is acceptable.</td>
</tr>
<tr>
<td>2. The sponsor should provide a tabular 'Summary of the Risk Management Plan in Australia' in a revised ASA, including reference to specific wording pertaining to the routine risk minimisation activities for all the specified ongoing safety concerns in the proposed Australian PI and CMI.</td>
<td>The sponsor states: 'Attachment 2 of the ASA (provided with this response) lists the text from the PI and CMI that address the specified ongoing safety concerns, as listed in the Risk Management Plan (Part VI, section 6.1.4).’</td>
<td>Attachment 2 [of the ASA] only addresses the important identified risks and none of the important potential risks or important missing information as listed in the EU RMP. This remains an outstanding issue.</td>
</tr>
</tbody>
</table>

Summary of recommendations

It is considered that the sponsor’s response to the TGA request for further information has not adequately addressed all of the issues identified in the RMP evaluation report.
**Issues in relation to the RMP**

The sponsor was advised to provide a tabular ‘Summary of the Risk Management Plan in Australia’ in a revised ASA, including reference to specific wording pertaining to the routine risk minimisation activities for all the specified ongoing safety concerns in the proposed Australian PI and CMI (see Point 2 in Table 3 above). The sponsor should correct this oversight before this application is approved.

**Advice from the Advisory Committee on the Safety of Medicines (ACSOM)**

ACSOM advice was not sought for this submission.

**Suggested wording for conditions of registration**

**RMP**

The European Risk Management Plan Version 7.0 (dated 13 June 2013), with an Australian Specific Annex (ASA) Version 2.0 (dated 11 December 2013), must be implemented.

**VI. Overall conclusion and risk/benefit assessment**

The submission was summarised in the following Delegate’s overview and recommendations:

**Background**

Prevenar 13 was first registered in Australia in March 2010. The initial approved indication was for use in infants and children aged 6 weeks up to 5 years to prevent diseases (including invasive disease, pneumonia and acute otitis media) caused by the 13 streptococcus pneumonia serotypes. No direct evidence of efficacy was provided. Instead, serum concentrations of anticapsular IgG measured using enzyme-linked immunosorbent assay (ELISA) was used as a correlate for efficacy. OPA was also used for functional antibody assessment. Two pivotal studies showed that Prevenar 13 had an antibody response profile comparable to that of Prevenar from which it was deduced that its preventive efficacy was the same for the shared serotypes. Protective antibody responses for the 6 new serotypes were also considered to be acceptable. Since then, early data from Prevenar 13 use in England and Wales in 2011 have shown an impact against IPD caused by the additional serotypes contained in the vaccine. In August 2013, the indications for Prevenar 13 were extended to children and adolescent 6 to 17 years of age for prevention of pneumococcal disease (including invasive disease, pneumonia and acute otitis media) caused by the 13 streptococcus pneumoniae serotypes and the approval was based on immunogenicity data comparison; Serotype specific ELISA IgG GMCs measured 1 month post vaccination were compared to corresponding data from a historical cohort enrolled in Study 6096A1-3005.

In October 2011 the indications for Prevenar 13 were extended to adults aged over 50 years for the prevention of pneumococcal disease. The extension of indication was based on the demonstration of non-inferiority of the OPA antibody responses to Prevenar 13 when compared with Pneumovax 23 (the 23-valent pneumococcal polysaccharide vaccine-23vPS) for common serotypes in two pivotal studies. The primary endpoint used in the studies was serotype specific OPA titres 1 month post Prevenar 13 versus the OPA response to 23vPS in subjects aged 60 years and older; this comparison was considered relevant as the protective efficacy in this population was demonstrated for the 23vPS in previous studies. A postmarketing randomised controlled trial (CAPITA) examining the protective efficacy of Prevenar 13 in adults was started and on 24 February 2014, Pfizer announced that CAPITA has achieved its objective in

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demonstrating the efficacy of Prevenar 13 against first episode of vaccine type community acquired pneumonia (CAP), non-invasive CAP and invasive pneumococcal disease (IPD).

**Quality**

There was no requirement for a quality evaluation in a submission of this type.

**Nonclinical**

There was no requirement for a nonclinical evaluation in a submission of this type.

**Clinical**

**Efficacy**

**Study 6115A1-004**

This was a Phase III, randomised, active-controlled, modified double blind trial evaluating the safety and immunogenicity of a 13vPnC compared to a 23vPS in adults 60 to 64 years of age (Cohort 1) who were naive to 23vPS, using a randomised, double-blind design. The study also included a cohort of subjects 50 to 59 years of age (Cohort 2) and a cohort of subjects 18 to 49 years of age (Cohort 3). Both of these groups received open-label 13vPnC.

As 23vPS is not generally recommended in the younger adult age groups, 13vPnC antibody responses in Cohorts 2 and 3 were not directly compared to responses after 23vPS, but were compared to antibody responses elicited by 13vPnC in the 60 to 64 year age group (Cohort 1). As Cohort 1 included a direct comparison to 23vPS, this design allowed for indirect comparison of antibody responses in cohorts 2 and 3 to 23vPS.

Approximately 370 subjects were to be enrolled in the 13vPnC group in Cohort 1 and 370 subjects were to be enrolled in Cohort 2. In the original protocol, approximately 370 subjects were to be enrolled in Cohort 3, but the protocol was amended to increase enrolment in this cohort to 900 subjects. In Cohort 3, subjects were stratified into 3 age subgroups: subgroup 1 (18 to 29 years), subgroup 2 (30 to 39 years), and subgroup 3 (40 to 49 years), with each subgroup to enrol around 300 subjects. Serology was assessed at one month and one year post vaccination. This report includes data for Cohort 3, with immunogenicity comparison to Cohort 1 subjects who received 13vPnC, and with safety comparisons to subjects in Cohort 1 and 2 who received 13vPnC. Full details regarding the methods and the complete results for Cohorts 1 and 2 were presented in a separate study report.

Subjects were excluded if they had previously been vaccinated with any licensed or experimental pneumococcal vaccine, had a documented *S. pneumoniae* infection within the past 5 years, had any other disorder that precluded them from participating in the study, or had any of the other exclusion criteria specified in the protocol. Subjects with pre-existing stable disease (as specified in the protocol) were eligible to enrol.

The primary study objective with respect to Cohort 3 was to demonstrate that the immune response to the 13 serotypes in the 13vPnC in Cohort 3 (18 to 49 year old) is non-inferior to the immune response to 13vPnC in Cohort 1 (60 to 64 year old) as measured by serotype specific OPA titres 1 month after vaccination. The secondary and exploratory objectives were described in page 9 and 10 of the CER.

For Cohorts 1, 2, and 3, blood samples were obtained before study vaccine administration at Visit 1 (Day 1), approximately 1 month after vaccination and approximately 1 year after vaccination. Serum OPA titres for the 13 serotypes were determined for all subjects for blood
samples collected at baseline and 1 month post vaccination. In addition, OPA titres were
determined for blood samples collected at 1 year post vaccination for randomly selected subsets
of 100 subjects in each cohort and vaccine group. Serum concentrations of serotype-specific IgG
were determined for each of the 13 serotypes using ELISA. IgG concentrations were determined
for all 3 blood samples (baseline, 1 month and 1 year post vaccination) for the same subsets of
100 subjects selected for the 1 year post vaccination OPA analyses.

The evaluable immunogenicity population included all subjects who were randomised, received
the vaccine and had at least 1 valid and determinate assay result for antibody response to any
pneumococcal serotype as well as a pre vaccination blood drawn on the same day as the day of
vaccination or within 15 days prior to Day 1, and had no other major protocol violation. The all-
available immunogenicity population included all subjects who had at least 1 valid and
determinate assay result related to the proposed analysis.

The primary endpoint for the Cohort 3 and Cohort 1 comparison was the serotype-specific OPA
GMTs 1 month after vaccination. Non-inferiority was declared if the lower limit (LL) of the 2-
sided, 95% confidence interval (CI) for the GMTs ratio (Cohort 3/Cohort 1) was greater than 0.5
(2 fold criterion). Statistical significance was demonstrated if the LL of the 2-sided, 95% CI for
the GMT ratio was >1. The secondary endpoint for the Cohort 3 and Cohort 1 comparison was
the proportion of subjects achieving an OPA titre > LLOQ for each serotype one month after
vaccination.

A total of 899 people in Cohort 3 were vaccinated (300 in 18 to 29 age group, 298 in 30 to 39
year old age group, and 301 in 40 to 49 year old age group). Of the 900 subjects assigned to
Cohort 3, the majority were vaccinated (99.9%), completed the 1 month blood draw (98.1%)
and completed the 6 month contact (94.9%). Of the 854 subjects in Cohort 3 who completed the
6 month contact, 352 subjects were not scheduled to have a 1 year visit and 502 subjects were
scheduled to have a 1 year visit. There were 469 subjects who completed the 1 year blood draw
in Cohort 3. Similar results were seen for the Cohort 3 age subgroups.

Results for the primary immunogenicity endpoint

The evaluable immunogenicity population for Cohort 1 and 3 comprised a total of 1285
subjects: 411 in Cohort 1 and 874 in Cohort 3. The demographic characteristics of the evaluable
immunogenicity population were similar to those in the overall population. The immune
responses after 13vPnC vaccination to subjects in Cohort 3 were non-inferior to those in Cohort
1, as measured by serotype-specific OPA GMTs 1 month after vaccination (the lower limit of the
95% CI for the GMT ratio >0.5, see the table below).
Other immunogenicity endpoints

The immune response in each of the 3 age subgroups of Cohort 3 was statistically significantly higher than the response among subjects in Cohort 1 for all serotypes except serotype 3. Among the age subgroups, OPA GMTs were generally highest for subjects in the 18 to 29 year old subgroup and lowest in the 40 to 49 year old subgroup, indicating higher antibody responses with younger age.

The serotype specific geometric mean fold rise (post vaccination/pre vaccination) was generally similar or higher in the 18 to 49 year old group relative to that of the 60 to 64 year old group, at 1 month and 1 year after vaccination.

After vaccination, the proportion of subjects achieving a serotype-specific OPA titre ≥LLOQ in Cohort 3 was non-inferior to that of Cohort 1 for all 13 serotypes and was statistically significantly greater for all serotypes, except for serotype 3.

With regard to the persistence of the antibody response, a decrease in OPA GMTs was observed from 1 month to 1 year post vaccination but titres at 1 year remained higher than titres before vaccination for both Cohorts 3 and Cohort 1. Antibody response curves for Cohort 3 were higher than those for Cohort 1 for all serotypes except for serotype 3. In general the OPA antibody response curves were highest for subjects in the 18 to 29 year old subgroup and lowest in the 40 to 49 year old subgroup.

IgG results supported those of the OPA analysis. In Cohort 3, IgG GMCs for all serotypes in 13vPnC were non-inferior to those of Cohort 1 measured 1 month after vaccination. The same pattern of response was observed for each age subgroup. Among the age subgroups in general the IgG GMCs were highest for subjects in the 18 to 29 year old subgroup and lowest in the 40 to 49 year old subgroup.

IgG results supported those of the OPA analysis. In Cohort 3, IgG GMCs for all serotypes in 13vPnC were non-inferior to those of Cohort 1, measured 1 month after vaccination. The same pattern of response was observed for each age subgroup. Among the age subgroups in general the IgG GMCs were highest for subjects in the 18 to 29 year old subgroup and lowest in the 40 to 49 year old subgroup.

Study 6096A1-4001 in preterm infants

Study 6096A1-4001 was an open-label, multicentre and parallel-group study. The study compared the safety, tolerability, and immune response to 4 doses of 13vPnC in preterm infants.
to that of infants born at term. The two groups were defined as follows: Group 1: preterm infants aged <37 weeks of gestation; Group 2: term infants aged ≥37 weeks of gestation. In addition, Group 1 was divided into the following preterm subgroups: Group 1A- 32≤ GA <37 weeks, Group 1B - 29≤ GA <32 weeks; Group 1C - GA <29 weeks. All subjects in each group were to receive 13vPnC at 2, 3, 4 and 12 months of age. Subjects received 1 dose (0.5 mL) of 13vPnC at each vaccination visit (Visits 1, 2, 3, and 5).

The primary objective was to describe the immune response to 13vPnC at 1 month after the infant series in preterm infants compared to that of infants born at term. A secondary objective was to describe the serotype-specific immune response to 13vPnC at 1 month after the toddler dose in preterm infants compared to term infants.

The blood samples were collected from all subjects at 3 time points, that is, 1 month after the third dose, just before the toddler dose and 1 month after the toddler dose. This study is ongoing and 2 additional blood samples will be obtained at 12 months and 24 months after the toddler dose. Serotype-specific OPA titres were measured by the OPA assay while serotype specific IgG antibodies concentrations were measured by ELISA.

Immunogenicity analyses were performed for 2 populations. The primary immunogenicity population was the evaluable immunogenicity population, which consisted of eligible subjects who received all the assigned vaccinations, had blood drawn within required time frames, had at least 1 valid and determinate assay result for the proposed analysis, received no prohibited vaccines, and had no major protocol violations. The all-available immunogenicity population consisted of subjects who had at least 1 valid and determinate assay result for the proposed analysis. All subjects who received at least 1 dose of 13vPnC were included in the safety population.

The immunogenicity analyses are described by summary statistics, that is, GMCs, GMTs, or geometric mean fold rise (GMFRs) along with 95% CIs by group. For each serotypes, the proportion of the subjects achieving IgG concentration ≥0.35 μg/mL at 1 month after the infant series was calculated along with an exact, 2-sided 95% CI. The difference in the proportion between the 2 groups was computed along with exact, unconditional, 2-sided 95% CI. The analyses were performed similarly for the results 1 month after the toddler dose. In addition, the serotype-specific fold rise in antibody concentration from the pre toddler dose to 1 month after the toddler dose was derived for each subject and summarized using GMFR along with 2-sided 95% CI. The 2 groups were compared by computing the ratio of the GMFR along with 2-sided 95% CI.

Of the 200 total subjects (100 in each group) assigned to receive the vaccine, all were vaccinated at each dose of the infant series, 99 preterm infants (Group 1) and 97 term infants (Group 2) were vaccinated at the toddler dose. In Group 1, 52% of preterm infants were males and in Group 2, 45% were males. All subjects in each group were categorised as White. The mean chronological age at first vaccination was 1.8 months in preterm infants and 1.5 months in term infants. The mean gestational age in Group 1 was 30.8 weeks and in Group 2 was 39.4 weeks. Mean weight at birth was 1.6 kg in Group 1 and 3.3 kg in Group 2. Distributions by race and gender were not notably different for each dose.

Results of the primary immunogenicity endpoint

The primary analysis population (evaluable immunogenicity population) comprised a total of 99 subjects in Group 1 and 98 in Group 2 at the infant series. At the toddler dose, 88 subjects in each group were included in the evaluable immunogenicity population. The primary immunogenicity endpoint was the proportion of the subjects in each group achieving IgG concentration ≥0.35 μg/mL measured 1 month after the infant series for each serotype. The same endpoint was assessed at 1 month after the toddler dose.

At 1 month after the infant series, the proportions of subjects achieving serotype specific IgG antibody concentrations ≥0.35 μg/mL were generally similar (>85%) in preterm infants (Group
1) and in term infants (Group 2) for 10 of 13 serotypes. For serotypes 6B, 5, and 6A the proportion of responders in Group 1 was statistically significantly lower than in Group 2. The proportion of responders was not notably different in each of the age subgroups, that is, Group 1A, 1B and 1C, although the highest proportions were consistently observed in Group 1A.

After the toddler dose, the proportions of subjects achieving IgG ≥0.35 μg/mL in Group 1 and in Group 2 were 97.67% or higher in both groups for 12 of 13 serotypes (exception: serotype 3, 70.59% preterm versus 79.31% term). The proportion of responders in each preterm subgroup was comparable to those of Group 1 overall.

Results of OPA antibody titres

The proportion of subjects achieving OPA antibody titres ≥ Lower limit of quantification (LLOQ) at 1 month after the infant series was >90% in both groups for 10 of 13 serotypes (all but serotypes 1, 5 and 9V). There were no statistical differences between groups for 12 of 13 serotypes (all but serotype 5: 67.5% preterm, 83.5% term). Ninety percent or more subjects in each preterm subgroup achieved an OPA response ≥LLOQ for the majority of serotypes. The proportion of responders in Group 1A was similar to, or higher than, that of the other 2 subgroups.

After the toddler dose, more than 95% of subjects in Group 1 and Group 2 achieved an OPA antibody titre ≥LLOQ for all serotypes except serotypes 1 (both groups) and 19F (preterm). The proportion of subjects achieving an OPA titre ≥ LLOQ at 1 month after the toddler dose was >90% for at least 10 of 13 serotypes in each preterm subgroup. For most serotypes, the proportion of responders was similar among the 3 subgroups.

Serotype 3: Unlike IgG results, the proportion of subjects achieving OPA antibody titre ≥LLOQ for serotype 3 after the infant series was 100% in Group 1 and 95.35% in Group 2 and after the toddler dose was 100% in the Group 1 and 98.73% in Group 2.

Study 6096A1-3014 in children and adolescents with Sickle Cell Disease (SCD)

Study 6096A1-3014 was a Phase III, multicentre, open-label, single-arm study in children (≥6 to <18 years of age) with SCD who had been previously immunised with at least 1 dose of 23vPS. The primary objective was to evaluate the immune response 1 month after 2 doses of 13vPnC, spaced 6 months apart, compared to 1 month after 1 dose of 13vPnC as measured by fold rise in serotype-specific IgG geometric mean concentrations (GMCs) in those children who had previously been immunised with at least 1 dose of 23vPS.

The inclusion criteria required that all subjects be between the ages of ≥6 to <18 years, have a diagnosis of SCD by haemoglobin (Hb) electrophoresis or polymerase chain reaction (PCR); and documentation to show vaccination with 23vPS at least 6 months before enrolment. Subjects with a history of hematopoietic stem cell transplantation were excluded. In this study, subjects received 1 dose of 13vPnC at Visit 1, followed by a second dose 182 to 224 days later at Visit 3.

Of the 158 subjects assigned to receive the vaccine, all were vaccinated at Dose 1 and 146 subjects were vaccinated at Dose 2. Of the 158 subjects vaccinated at Dose 1, 146 subjects had previously received 1 dose of 23vPS and 12 subjects had received 2 or more doses of 23vPS. Of all vaccinated subjects, slightly more subjects were male (51.9%) and the majority were categorised as Black or African American (42.4%) or White (35.4%); 22.2% were categorised as other. Mean age at vaccination was 13.3 years (age range 6.0 years to 17.9 years).

The primary immunogenicity endpoint was the geometric mean fold rise (GMFR) in IgG GMC from 1 month after dose 1 to 1 month after dose 2 (GMC dose 2/GMC dose 1) along with the 2-sided 95% CI for each serotype. The immunogenicity analysis includes results in subjects with >1 prior dose of 23vPS and in the subset of subjects who had received only 1 previous dose of 23vPS. In the other subset of subjects who received 2 or more previous doses of 23vPS, immunogenicity results were not summarised because there were too few subjects (12
Subjects). The evaluable immunogenicity population was the primary analysis population and comprised 138 (87.3%) subjects at Vaccination 1.

Results for the primary immunogenicity endpoint (GMFR Dose 2/Dose 1)

Dose 2/Dose 1 comparison: the GMFR in the IgG GMC from 1 month after dose 1 to 1 month after dose 2 (that is, GMC post dose 2/GMC post dose 1) was assessed for each serotype. IgG GMCs were higher after Dose 1 than after Dose 2 for all serotypes, except for 19F. GMFRs were less than 1 for 12 of 13 serotypes and ranged from 0.70 to 1.05. For 9 of 13 serotypes (all but 6B, 19F, 23F, and 6A) IgG GMCs were statistically significantly lower after Dose 2 than after Dose 1 (that is, upper limit for 95% CI for the GMFR was <1). Comparable results were observed in the subset of subjects who received only 1 previous 23vPS dose.

Post dose/pre dose comparison: when GMFRs (post dose/pre dose) for Dose 1 and Dose 2 were compared, the ratios of GMFRs (Dose 2 GMFR/dose 1 GMFR), and the upper limits of the 95% CIs for the ratios, were less than 1 for each serotype, indicating that GMFRs were statistically significantly lower after Dose 2 than after Dose 1 for all serotypes. This result was also observed in the subset of subjects pre-immunised with only 1 dose of 23vPS.

Results of OPA GMTs and GMFRs

OPA GMTs after Dose 1 and after Dose 2 were notably higher than that before each respective 13vPnC dose. GMFRs for Dose 1 (post dose 1/pre dose 1) ranged from 3.5 to 40.3. GMFRs for Dose 2 (post dose 2/pre dose 2) ranged from 1.3 to 3.4. OPA GMTs before and after Dose 1 and Dose 2 were not notably different in the subgroup of subjects pre-immunised with 1 23vPS dose. OPA GMTs rose after each vaccination from pre-vaccination titres. Although OPA GMTs had declined at pre-vaccination 2 from titres achieved after the first vaccination, GMTs remained higher than at baseline. In contrast to IgG GMCs, after the second dose of 13vPnC, OPA GMTs were similar to (5 serotypes) or higher (8 serotypes) than titres after Dose 1.

Dose 2/Dose 1 comparison: the GMFR in the OPA GMTs from 1 month after Dose 1 to 1 month after Dose 2 were similar or higher after Dose 2 compared with GMTs after Dose 1. GMFRs (that is, GMT post dose 2/GMT post dose 1) ranged from 0.9 to 1.4. For 4 of 13 serotypes the lower limit of the 95% CI for the GMFR was >1, indicating that titres for these serotypes (1, 7F, 9V, 23F) were statistically significantly higher after Dose 2 than after Dose 1. Comparable results were observed in the subset of subjects with 1 previous 23vPS dose.

Post dose/pre dose comparison: when GMFRs (GMT post dose/ GMT pre dose) for Dose 1 and Dose 2 were compared, the ratios of GMFRs (Dose 2 GMFR/Dose 1 GMFR), and the upper limits of the 95% CIs for the ratios, were < 1 for each serotype, indicating that the fold rise from pre to post vaccination was statistically significantly lower for Dose 2 than for Dose 1 for all serotypes. This result was also observed in the subset of subjects pre-immunised with only 1 dose of 23vPS.

Comparison to healthy subjects

Following TGA request, the sponsor provided the comparison of the immune responses after a single dose of 13vPnC in this study (6096A1-3014) with the immune responses in healthy children and adolescents observed in Study 6096A1-3011. The comparison shows that the immune responses in subjects with SCD were similar to those of healthy subjects in the same age range. Study 6096A1-3011 was submitted to the TGA as part of a submission to support expansion of the Prevenar 13 indication to include children and adolescents aged 6 years to 17 years.

Study 6115A1-3017 in adults with HIV infection

Study 6115A1-3017 was a Phase III, open-label, single-arm trial in which HIV-infected subjects previously immunised with the 23vPS vaccine received 3 doses of 13vPnC given at 6 month
intervals. The study was to determine the number of 13vPnC doses that are needed to induce an
acceptable immune response in HIV infected subjects who had previously been immunised with
23vPS. The primary immunogenicity endpoint was the immune response 1 month after 3
doses of 13vPnC, given 6 months apart, compared to the response 1 month after 2 doses of
13vPnC, as measured by the fold rise in serotype-specific IgG GMCs in those HIV-infected
subjects. The primary objective was to compare the immune responses one month post Dose 3
versus the response one month post Dose 2 in these patients.

There were 2 immunogenicity analysis populations: evaluable immunogenicity and all-available
immunogenicity population. The study was stratified by number of previous 23vPS vaccination.
Of the 331 subjects assigned to receive study vaccine, 329 subjects were vaccinated at Dose 1;
300 subjects were vaccinated at Dose 2, and 279 were vaccinated at Dose 3. Of all subjects
vaccinated at Dose 1, 160 subjects had previously received 1 dose of 23vPS and 169 subjects
had received 2 or more doses of 23vPS.

### Table 5. Actual vaccine administered

<table>
<thead>
<tr>
<th>Actual Vaccine Administered</th>
<th>≥1 Previous Dose of 23vPS N=331</th>
<th>1 Previous Dose of 23vPS N=162</th>
<th>≥2 Previous Doses of 23vPS N=169</th>
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</thead>
<tbody>
<tr>
<td>13vPnC</td>
<td>379</td>
<td>128</td>
<td>151</td>
</tr>
<tr>
<td>13vPnC</td>
<td>484</td>
<td>179</td>
<td>205</td>
</tr>
<tr>
<td>None</td>
<td>21</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>13vPnC</td>
<td>29</td>
<td>8.8</td>
<td>6.3</td>
</tr>
<tr>
<td>None</td>
<td>2</td>
<td>0.9</td>
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</tbody>
</table>

Note: Subjects 3017-001-000209 and 3017-014-000734 were enrolled but not vaccinated.

Distributions by race, sex and age were not notably different between the 2 groups based on
23vPS pre immunisation status. Overall, the subjects in the 2 subgroups were similar with
respect to HIV status at baseline. The majority of subjects contracted HIV through sexual contact
and were receiving highly active antiretroviral therapy (HAART) at baseline. The mean length of
time since the HIV diagnosis was 13.0 years. The mean CD4+ cell counts at the first and second
baseline assessments were 599.0/mm³ and 604.5/mm³, respectively. The mean viral load at the
first and second baseline assessments was 463.0 copies/mL and 630.3 copies/mL.

The evaluable immunogenicity population was the primary analysis population and comprised
a total of 255 (77.0%) subjects at Vaccination 1. The immunogenicity endpoints were IgG GMCs
and OPA GMTs at 1 month after 3 doses of 13vPnC versus 1 month after 2 doses and the
respective GMFRs (Dose 3/Dose 2) or (Dose 2/Dose 1). Additional endpoints were: IgG GMCs
and OPA GMTs 1 month after 2 doses versus 1 dose of 13vPnC and the respective GMFRs (post
dose 2/post dose 1); and IgG GMCs and OPA GMTs immediately before and 1 month after each
dose and the respective GMFRs (post dose/pre dose).

### IgG results

**Comparison between doses**

IgG GMCs after Dose 3 of 13vPnC were similar to, or higher than, those after Dose 1. IgG GMCs
were statistically significantly higher (that is, lower limit of 95% CI for GMFR [post Dose 3/post
Dose 1] >1) after dose 3 than after Dose 1 for 10 of the 13 serotypes (all but 1, 7F, 18C). GMFRs
ranged from 1.02 to 2.33. The results were similar in the 2 subgroups, that is, those pre
immunised with one 23vPS dose or with 2 or more 23vPS doses.

After Dose 2, IgG GMCs were generally higher than those after Dose 1, and the increase was
statistically significant for 10 of the 13 serotypes (all but 1, 7F, 18C). GMFRs ranged from 0.93 to
2.07. A similar pattern of response was observed in the 2 subgroups.

IgG GMCs after Dose 3 were generally higher than those after Dose 2, with statistically
significant increases observed for 6 of the 13 serotypes (serotypes 6A, 6B, 9V, 18C, 19F, 23F).
GMFRs ranged from 0.94 to 1.25. A similar pattern of response was observed in the two 23vPS-preimmunised subgroups.

**Comparison of GMFRs**

When GMFRs (post dose/pre dose) for Dose 1 and Dose 2 were compared, the ratios of GMFRs (Dose 2 GMFR/Dose 1 GMFR), and the upper limits of the 95% CIs for the ratios, were less than 1 for each serotype, indicating that GMFRs were statistically significantly lower after Dose 2 than after Dose 1 for all serotypes. The results were similar in each 23vPS pre immunised subgroup. The comparison of GMFRs (post dose/pre dose) for Dose 2 and Dose 3 showed no notable difference in fold rise for each dose.

**OPA results**

For each serotype, OPA GMTs rose after each vaccination from pre-vaccination titres. Although OPA GMTs declined over the 6 month period between doses, at each pre vaccination time point GMTs remained higher than at baseline (before Vaccination 1). In general, the OPA GMTs after Dose 2 and Dose 3 were similar to or higher than those after Dose 1.

**Comparison between doses**

For subjects pre immunised with more than 1 dose of 23vPS, the OPA GMTs after Dose 3 were higher than those after Dose 1; post dose 3 GMTs were statistically significantly higher (that is, lower limit of 95% CI for GMFR >1) for 10 of the 13 serotypes (all but 1, 4, 5). The results were similar in the two 23vPS-preimmunised subgroups.

OPA GMTs after Dose 2 were generally higher than those after Dose 1 and the increase was statistically significant for 7 of the 13 serotypes (3, 6A, 6B, 9V, 19A, 19F, 23F). A similar pattern of response was observed in the 2 subgroups.

OPA GMTs after Dose 3 were generally higher than those after Dose 2, with significant increases observed for 7 of the 13 serotypes (1, 3, 6A, 6B, 9V, 18C, 23F). A similar pattern of response was observed in the two 23vPS-preimmunised subgroups.

**Comparison of GMFRs**

When GMFRs (post dose/pre dose) for Dose 1 and Dose 2 were compared, the ratios of GMFRs (Dose 2 GMFR/Dose 1 GMFR), and the upper limits of the 95% CIs for the ratios, were less than 1 for each serotype, indicating that GMFRs were statistically significantly lower after Dose 2 than after Dose 1 in the evaluable population. In each 23vPS-preimmunised subgroup GMFRs were statistically significantly lower after Dose 2 for 11 of 13 serotypes (all but serotypes 3 and 23F in each subgroup).

The comparison of GMFRs (post dose/pre dose) for Dose 2 and Dose 3 showed no notable difference in fold rise for 10 of 13 serotypes; GMFRs were statistically significantly lower after dose 3 relative to dose 2 for serotypes 19A, 19F, 23F .The results observed in each 23vPS-preimmunised subgroup were comparable to those of the overall evaluable population.

**Comparison to healthy subjects**

Following TGA request, the sponsor provided the comparison of the IgG and OPA data following Dose 1 in this study (6115A1-3017, in ≥18 years) with the data from Study 6115A1-004 (ages 60 to 64, 50 to 59 years, and 18 to 49 years, as these age groups span the age range of the HIV-infected subjects). The IgG and OPA responses in Study 6115A1-3017 were generally lower than in the healthy 23vPS-naïve adults in Study 6115A1-004 for most serotypes. No data are available for an age matched healthy 23vPS-preimmunised population, as 23vPS is not indicated in younger healthy adult populations.
Clinical safety

The data supporting age expansion are from 899 subjects vaccinated in Study 6115A1-004. The most relevant information for this age group is for Cohort 3 (18 to 49 years old). The safety of 13vPnC administered to the 18 to 49 year old subjects in Cohort 3 was compared with the safety of the 13vPnC vaccine administered to the older subjects (60 to 64 years old and 50 to 59 years old) in Cohorts 1 and 2, respectively. The safety of 13vPnC administered to subjects in each of the age subgroups in Cohort 3 was also assessed. Local reactions and systemic events occurring within 14 days after vaccine administration were reported by higher percentages of subjects in Cohort 3 compared with the older subjects in Cohorts 1 and 2. In the age subgroups in Cohort 3, in general, the percentages of subjects with local reactions and systemic events were generally highest in the youngest (18 to 29 year old) age subgroup. In relation to the percentages of subjects who reported AEs within approximately 1 month after vaccination, there were no differences between Cohort 3 and the older cohorts, or within the age subgroups in Cohort 3. The percentage of subjects reporting any AEs at the 6 month follow-up contact was slightly lower in Cohort 3 (0.3%) than in Cohort 2 (1.5%) and Cohort 1 (2.9%). These findings were consistent with those expectable post vaccination and no new safety issues were identified. An acceptable safety profile was demonstrated for the administration of 13vPnC to subjects 18 to 49 years of age. No deaths were reported for subjects in Cohort 3, or in Cohort 2. One (1) subject in Cohort 1 died due to pancreatic cancer and liver cancer, which was considered unrelated to study vaccine. SAEs occurring within approximately 1 month after vaccination were reported for 2 subjects (migraine, basal cell carcinoma) in Cohort 3, for 2 subjects (cellulitis, ovarian cancer) in Cohort 2 and for 1 subject (haemangioma) in Cohort 1. In Cohort 3, the migraine was reported by a subject in the 30 to 39 year old age group and the basal cell carcinoma was reported by a subject in the 40 to 49 year old age group.

Except for the SAE of migraine reported by the subject in Cohort 3, none of the serious AEs reported within 1 month after vaccination in Cohorts 1, 2, and 3 were considered by the investigator to be related to study vaccine and all of the SAEs were thought to have resolved. SAEs were reported at the 6 month follow-up contact for 2 subjects (0.2%) in Cohort 3, for 5 subjects (1.2%) in Cohort 2 and for 12 subjects (2.9%) in Cohort 1. In Cohort 3, the types of SAEs reported at the 6 month follow-up contact included reproductive system and breast disorders and injury, poisoning and procedural complications. A SAE in the category of injury, poisoning and procedural complications was also reported in Cohort 2. In Cohort 3, the SAE of hip fracture was reported by 1 subject and the SAE of ovarian cyst ruptured was reported by 1 subject in the 18 to 29 year old subgroup. Both these SAEs were severe, neither was considered to be related to study vaccine and both of the SAEs resolved. No AEs that led to withdrawal were reported for Cohort 3, Cohort 2 or for subjects who received 13vPnC in Cohort 1.

In the studies in special populations (premature infants, children and adolescents with SCD and adults with HIV infection), there were also no unexpected safety issues identified.

Safety in Study 6096A1-4001 (premature infants), there was a high incidence of local reactions (more than half of the subjects in each group experienced local reactions), more so even in the toddler dose than in the infant series, consistent with immunological priming. These were generally mild and resolved quickly (as did the related systemic events). Local reactions occurred in similar percentages of subjects in both groups. Overall systemic events were reported for similar percentages of subjects in each group, and the majority of events were mild with fewer than 10% of subjects in either group reporting a severe reaction. Infections and infestations accounted for the majority of AEs reported in both groups at each time point, followed by Gastrointestinal disorders, which occurred more often in preterm infants. The AE/SAE profile observed in this study generally reflects known and expected AEs occurring among young infants, such as respiratory infections (including RSV), especially those born prematurely. There were however, two documented febrile convulsions, one in pre-term group and one in the term baby group. In both these infants, there were thought to be concomitant
infections. At the onset of the febrile convulsions, the subjects were 12 and 14 months of age, respectively. Each subject had a simultaneous adverse event on the day of the febrile convulsion, including respiratory tract infection and bronchopneumonia, respectively. This study did not suggest any new or unexpected safety signal among preterm infants compared with their term counterparts.

Safety in Study 6096A1-3014 in children and adolescents with SCD, local reactions were reported by the majority of subjects after Dose 1 and Dose 2. After both doses most local reactions were mild or moderate in severity, and mean duration was less than 3.2 days. Pain of severe intensity was reported by 11.1% of subjects after Dose 1 and by 15.9% after Dose 2. Systemic events were also reported by the majority of subjects after both doses. Systemic events of severe intensity reported by more than 10% of subjects were muscle pain, fatigue, and headache. Most cases of fever were mild in severity. SAEs were reported in 25.3% of subjects after Dose 1 and in 7.9% of subjects after Dose 2. The majority of SAEs reported after each dose were classified as congenital, familial and genetic disorders; all subjects in this category had sickle cell anaemia with crisis, which was reported more frequently after Dose 1 than after Dose 2. Other SAEs after Dose 1 were most frequently categorised as Infections and infestations (7.6%). All SAEs resolved. The AE and SAE data in the study reflected the underlying condition of SCD. The reported local and systemic reactions were consistent with the known and expected ones post vaccination and there were no unanticipated reactions or AEs. No deaths occurred during the vaccination phase of the study.

The analysis of safety in Study 6115A1-3017 presented no notable safety concerns for HIV infected adults subjects who received 1, 2 and 3 doses of 13vPnC. Local reactions occurring after vaccine administration were as expected; injection site pain was the most frequently occurring local reaction after each vaccination. In general, there did not appear to be a trend toward increasing frequency or mean duration of reactions over the 3 vaccine doses. The most frequently reported individual AEs were upper respiratory tract infection (7.0%), fatigue (4.0%), diarrhoea (3.3%), bronchitis (3.3%) and rash (3.3%). The AEs were consistent with events expected in an adult HIV population. There was no increase in frequency or mean duration of systemic events over the 3 vaccine doses. The incidence of fever was less than 10% after each vaccine dose and most reports of fever were mild. In general, there were no differences in local reactions or systemic events between subjects with 1 previous dose of 23vPS and those with ≥2 previous doses of 23vPS. The majority of AEs reported after any doses were consistent with events expected in an adult HIV population. There were few related AEs, severe or life threatening AEs, or AEs that led to withdrawal reported. There were no deaths, and none of the SAEs or AEs that led to withdrawal was considered related to the study vaccine.

**Risk management plan**

The sponsor has submitted an EU-RMP Version 7.0, dated 13 June 2013, with ASA version 1.0, dated 18 June 2013 in support of the current application.

The only outstanding issue raised by the RMP evaluator is that the sponsor needs to provide a tabular ‘Summary of the Risk Management Plan in Australia’ in a revised ASA, including the important identified risks as well as the important potential risks/important missing information as listed in the EU-RMP (Part VI, section 6.1.4).

The European Risk Management Plan Version 7.0 (dated 13 June 2013), with an Australian Specific Annex (ASA) Version 2.0 (dated 11 December 2013), must be implemented.
Risk-benefit analysis

Delegate’s considerations

Adults 18 to 49 years old:

Study 6115A1-004 showed that the OPA responses to all 13 serotypes in Cohort 3 (18 to 49 years old) were non-inferior to the response in Cohort 1 (60 to 64 years old) and were statistically significantly higher in Cohort 3 for all serotypes except serotype 3. A high antibody response in Cohort 3 was still present 1 year after vaccination. Except for serotype 3, the OPA GMTs were higher for Cohort 3 than for Cohort 1 one year post vaccination and were still well above baseline (pre-vaccination) levels. The proportion of subjects with risk conditions for pneumococcal disease was generally low in Cohort 3 with percentages as follows: asthma 5.2%; cardiac disorders 3.3%; and diabetes mellitus 2.9%. However, according to previously submitted data, these types of risk conditions are not expected to negatively impact the immune response to vaccination with 13vPnC. The sponsor had previously compared (descriptively) the responses of subjects with risk conditions (cardiovascular, pulmonary, renal diseases, diabetes mellitus) to those of non-risk subjects in the 2 older cohorts (aged 60 to 64 years and 50 to 59 years, 23vPS-naïve) in Study 6115A1-004; in 60 to 64 year old, 23vPS-naïve subjects in Study 6115A1-3010; and in 23vPS-preimmunised subjects ≥70 years of age in Study 6115A1-3005. The results for subjects at risk and for those not at risk were similar and confirmed that immunocompetent subjects with these underlying diseases elicit antibody responses to 13vPnC that are similar to those of healthy subjects. Overall, based on the immune responses observed after vaccination with Prevenar 13 in adult 18 to 49 years old, Prevenar 13 is likely to offer protection against pneumococcal disease caused by the 13 serotypes in this age group (18 to 49 years old). It is acknowledge that the benefit of vaccinating healthy adults 18 to 49 years of age is limited as this age group has a low risk of contracting pneumococcal disease but the benefit is considered potentially greater in subjects of this age group with underlying co-morbidities who are at an increased risk of pneumococcal diseases. The use of Prevenar 13 should be guided by official recommendations taking into consideration the risk of pneumococcal disease in different age groups, underlying co-morbidities, as well as the variability of serotype epidemiology in different geographical areas.

Preterm infants:

Study 6096A1-4001 showed that most preterm subjects and those born at term achieved IgG antibody concentrations ≥0.35 μg/mL 1 month after the infant series (>85% ) and 1 month after the toddler dose (>97%) for at least 10 serotypes. After the infant series, IgG concentrations elicited by 13vPnC were somewhat lower in preterm infants compared with term infants, although OPA GMTs were similar in the 2 groups indicating that the immune response is likely to be adequate to provide protection against disease. The post toddler dose responses varied by serotype and with gestation age. It is not known whether immunological memory to all serotypes of Prevenar 13 is induced in pre-term infants.

Children and adolescents with SCD:

Study 6096A1-3014 showed that children and adolescents with SCD who were previously immunised with 23vPS had significant increases in both IgG antibody and OPA antibody after both 1 dose and 2 doses of 13vPnC. The addition of a second dose resulted in IgG GMCs that were similar to or lower than those seen after Dose 1. Serotype-specific OPA responses after the second dose were comparable or higher than those after the first dose, suggesting a potential positive impact on maturation of functional antibody response for at least some serotypes after the second dose but the differences were modest and the clinical significance is uncertain. The study results suggest that a 2-dose regimen of 13vPnC given 6 months apart does not enhance pneumococcal immune responses beyond those of a single dose of 13vPnC.
**Adults with HIV-infection:**

Study 6115A1-3017 showed that adults with HIV infection who previously immunised with 23vPS responded to 13vPnC at each of 3 vaccine doses and immune responses remained above initial baseline levels (before Dose 1) throughout the study. The immune response after Dose 3 was either stable or increased relative to the response after Dose 2 or Dose 1. However, the clinical significance of the increased immune response (statistically significant for most serotypes) after Dose 3 is unknown. The number of previous 23vPS doses had no impact on the immune response. The immune responses to Prevenar 13 observed in HIV infected adults were lower than the immune responses reported for healthy adults.

**Safety in the at risk groups:**

The three studies conducted in at risk groups did not reveal any new safety alerts and most of the adverse events reflected the background conditions/risks associated with the primary diseases in these groups. However, the interpretation of the safety results was difficult as only the study in pre-term infants included a control group. Therefore, the adverse events observed were expected, it was not possible to fully characterise the frequency of their occurrence relative to other populations.

**Delegate’s summary of issues**

**The use of Prevenar 13 in adults 18 to 49 years**

Study 6115A1-004 in adults is provided to support the application to extend the indications. In this study, immune response (OPA antibody titre) to Prevenar 13 in adults 18 to 49 years of age was shown to be non-inferior to the OPA responses in adult 60 to 64 years old. No new safety signals were identified in this age group.

**The use of Prevenar 13 in at risk individuals**

Study 6096A1-4001 showed that most preterm infants and term infants (>85%) achieved IgG antibody concentrations ≥0.35 μg/mL 1 month after the infant series and 1 month after the toddler dose for at least 10 serotypes. After the infant series, IgG CMCs elicited by Prevenar 13 were lower in preterm infants compared with term infants, although OPA GMTs were similar in the 2 groups indicating that the immune response is likely to be adequate. The immune responses to post toddler dose varied by serotype and with gestation age.

Study 6096A1-3014 in children and adolescent with sickle cell disease showed that the second dose of Prevenar 13 does not appear to enhance the immune response beyond those of a single dose of Prevenar 13.

Study 6115A1-3017 in HIV infected adults showed that after the second and third dose of Prevenar 13, immune responses were comparable or higher than those after the first dose.

**Delegate’s proposed action**

The Delegate had no reason to say, at this time, that the application to extend the indications for use of Prevenar 13 to adults 18 to 49 years old and to include the information of at risk groups should not be approved.

The European Risk Management Plan Version 7.0 (dated 13 June 2013), with an Australian Specific Annex (ASA) Version 2.0 (dated 11 December 2013), must be implemented.

**Delegate’s request for Advisory Committee on Prescription Medicines (ACPM) advice**

The committee is requested to provide advice on the following specific issues:
The use of Prevenar 13 in adults 18 to 49 years old

- Whether the ACPM consider the immunogenicity comparison (OPA response to Prevenar 13) between adults aged 18 to 49 and aged 60 to 64 is considered sufficient to support the use of Prevenar 13 in adults 18 to 49 years for the prevention of pneumococcal disease;
- Whether the use of Prevenar 13 in healthy adults 18 to 49 years for the prevention of pneumococcal disease has a favourable benefit-risk balance, considering there is a lower risk of pneumococcal disease in healthy adults of this age group (18 to 49)

The use of Prevenar 13 in at risk individuals

- Does the committee agree that vaccination with Prevenar 13 is of benefit for those at risk individuals, even though the immune responses might be lower in some at risk individuals (such as in HIV-infected subjects) than in healthy subjects?
- Does the committee agree with the following proposed dose regimen for at risk individuals?

  Individuals who may be at higher risk of pneumococcal infection (such as subjects with sickle cell disease or HIV infection) including those previously vaccinated with one or more doses of 23vPPV may receive at least one dose of Prevenar 13
- The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Introduction

In this pre ACPM response, Pfizer would like to provide comments on issues raised in the TGA Delegate’s Overview. In the following sections, the matters being addressed are identified by bold italic type.

Issues

The Delegate has sought advice from the Advisory Committee on Prescription Medicines (ACPM) on the following issues:

- **The Use of Prevenar 13 in Adults 18 to 49 Years Old-Immunogenicity of Prevenar 13**
  - Whether the ACPM consider the immunogenicity comparison (OPA response to Prevenar 13) between adults aged 18 to 49 and aged 60 to 64 sufficient to support the use of Prevenar 13 in adults 18 to 49 years for the prevention of pneumococcal disease.

Pfizer’s response

Study 6115A1-004 compared the immunogenicity of 13vPnC and 23vPS in adults 60 to 64 years of age (Cohort 1). The study also included a cohort of subjects 50 to 59 years of age (Cohort 2), and a cohort of subjects 18 to 49 years of age (Cohort 3), all of whom received open-label 13vPnC. Because 23vPS is not generally recommended in the younger adult age groups, 13vPnC antibody responses in Cohorts 2 and 3 were not directly compared to responses after 23vPS but were compared to antibody responses elicited by 13vPnC in the 60 to 64 year age group (Cohort 1). As Cohort 1 included a direct comparison to 23vPS, this design allowed for indirect comparison of antibody responses in Cohorts 2 and 3 to 23vPS.

Results from Study 6115A1-004 demonstrated that Prevenar 13 is immunogenic in both younger and older adults. In adults 60 to 64 years of age not previously vaccinated with 23vPS, 13vPnC was shown to be as immunogenic as 23vPS for the 12 common serotypes contained in 13vPnC, as measured by serotype-specific OPA geometric mean titres (GMTs) 1 month after vaccination; and 13vPnC was statistically significantly more immunogenic than 23vPS for 8 of the 12 common serotypes.
Among subjects 18 to 49 years of age, functional antibody responses (OPA GMTs) 1 month after vaccination were non-inferior to the responses in 60 to 64 year-old subjects for all 13 serotypes, and were statistically significantly higher for all serotypes except for serotype 3. In addition, immune responses in each of 3 age subgroups (18 to 29 years, 30 to 39 years, and 40 to 49 years), were statistically significantly higher than the response among subjects in Cohort 1 for all serotypes except serotype 3, which elicited a non-inferior response in the age subgroups. OPA GMTs were generally highest for subjects in the 18 to 29 year old subgroup and lowest in the 40 to 49 year old subgroup, indicating higher antibody responses with younger age.

The incidences of local and systemic events were somewhat higher in younger subjects than older subjects, which may be related to the higher antibody responses in younger subjects. However, the majority of events were mild and short lived and the sponsor concluded that overall Prevenar 13 demonstrated an acceptable safety profile.

Data from clinical studies suggest that the antibody responses elicited by 13vPnC in older adults (≥ 50 years of age) with chronic underlying diseases which put them at increased risk of pneumococcal disease, are similar to those of healthy adults of the same age. These results indicate that these at-risk subjects should experience the same benefit from vaccination with Prevenar 13 as healthy subjects. These results, along with the data from Study 6115A1-004, support the perspective that younger adults 18 to 49 years of age, including those with underlying medical conditions, may benefit from vaccination with Prevenar 13 during early adulthood.

- **Benefit-Risk Balance of Prevenar 13**

  - Whether the use of Prevenar 13 in healthy adults 18 to 49 years for the prevention of pneumococcal disease has a favourable benefit-risk balance, considering there is a lower risk of pneumococcal disease in healthy adults of this age group (18 to 49).

**Pfizer's response**

As detailed in the sponsor's Clinical Overview, there is an increased risk for invasive pneumococcal disease (IPD) associated with certain life style and environmental factors (such as smoking, alcoholism, crowded living), a diverse array of primary and secondary immunodeficiencies (immune defects, asplenia or splenic dysfunction, human immunodeficiency virus [HIV] infection), as well as various types of underlying diseases and conditions (for example, premature birth, chronic cardiopulmonary diseases, liver failure).8,9 The odds ratio for the incidence of IPD in individuals with one or more risk factor(s), compared to those without risk factors, varies depending on the nature of the underlying disease. For example, in those aged 16 to 64 years, the odds ratios range from 2.3 (asplenia) to 61.2 (HIV infection), with incidences between 12 per 105 (asplenia) and 316 per 105 (HIV infection).9

While herd protection does occur in individuals at risk for pneumococcal diseases, those with a T-cell defect (specifically HIV-positive patients) appear to have a reduced ability to eliminate

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8Schmoele-Thoma BJ, L A; Greenberg, R N; Frenck, R. The immunogenicity of Prevnar 13 in immunocompetent older adults with stable underlying medical conditions is comparable to that in healthy older adults. Presented at: Infectious Diseases Society of America; October 17-21, 2012; San Diego, CA
pneumococci from their nasopharynx. Disease rates in such individuals are still in the magnitude as the incidences observed in non-risk subjects before the introduction of 7vPnC.

In addition to the morbidity from IPD, there is relevant morbidity from community-acquired pneumonia (CAP) in the age group under discussion, with incidences ranging from 16 to 80 per 105, of which up to 50% may be due to pneumococci.

Clinical studies have demonstrated that Prevenar 13 is immunogenic in subjects 18 to 49 years of age and has an acceptable safety profile similar to that observed in older age groups.

Although the benefit-risk balance is clearly positive, the degree of benefit that adults in this age group would have varies by both the individual risk a patient may have and the underlying prevalence of the disease in the population. Thus, approval for use in adults aged 18 to 49 years will allow Australian health authorities to make recommendations for the use of Prevenar 13 and will allow health care professionals to administer Prevenar 13 to patients based on their assessment of risk within the framework of an approved product label.

- **The Use of Prevenar 13 in at Risk Individuals-Benefit of Prevenar 13 in High Risk Groups**
  
  - Does the committee agree that vaccination with Prevenar 13 is of benefit for those at risk individuals, even though the immune responses might be lower in some at risk individuals (such as in HIV infected subjects) than in healthy subjects?

**Pfizer’s response**

The Australian Immunisation Handbook includes HIV infection and sickle cell disease (SCD) among the medical conditions considered to be ‘associated with the highest increased risk of invasive pneumococcal disease (IPD)’ (Category A). Preterm birth at <28 weeks gestation is included among Category B conditions, that is, those associated with an increased risk of IPD. It also states that, ‘despite their immunological immaturity, pre-term infants generally respond satisfactorily to vaccines...[and]...should be vaccinated according to the recommended schedule at the usual chronological age.’ It is recommended that individuals with these diseases or conditions be vaccinated with Prevenar 13.

The sponsor stated that (as outlined in the sponsor’s Clinical Overview), Study 6096A1-4001 demonstrates a positive benefit/risk profile of 13vPnC in preterm infants similar to that observed in infants born at term. This is supported by the immunogenicity results and a favourable safety profile in preterm infants comparable to those of term infants observed in this study, the demonstrated effectiveness of 7vPnC in premature infants, and the effectiveness of 13vPnC in infants and children. Study 6096A1-4001 confirms that 13vPnC is likely to confer

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similar protection against pneumococcal disease in infants born prematurely. Thus, 13vPnC represents an important option for protection of preterm infants against pneumococcal disease due to serotypes in the vaccine.

Study 6096A1-3014 demonstrates that, in children and adolescents ≥6 to <18 years of age with SCD who have been previously immunised with 23vPS, 13vPnC has a positive benefit/risk profile similar to that observed in healthy children and adolescents and other age groups (paediatric subjects 6 weeks to 5 years of age and adults 50 years and older) in which Prevenar 13 is currently indicated. Based on the positive impact of 7vPnC in children with SCD19, 20, 21, 22, 23 the demonstrated effectiveness of 13vPnC in younger children, and the comparable immunogenicity and favourable safety profile demonstrated in this study, Prevenar 13 is likely to confer similar protection against pneumococcal disease in children and adolescents ≥6 to <18 years of age with SCD. Therefore, for children and adolescents with SCD, Prevenar 13 represents an important option for protection against pneumococcal disease due to serotypes in the vaccine.

Study 6115A1-3017 demonstrates a positive benefit/risk profile for 13vPnC in HIV infected adults ≥18 years of age previously vaccinated with 23vPS. A single dose of 13vPnC has been shown to be immunogenic in HIV infected adults. The antibody responses were lower than responses in healthy subjects without prior 23vPS vaccination but were similar to responses in other populations previously vaccinated with 23vPS for which vaccination with 13vPnC is licensed. Additionally, the study showed that Prevenar 13 has an acceptable safety profile, similar to that observed in healthy subjects of comparable age.

In conclusion: although immune responses to 13vPnC may be lower in some at risk individuals such as in HIV infected subjects as compared with responses in healthy subjects not previously immunised with 23vPS, the positive risk-benefit profiles demonstrated in all 3 studies support the perspective that individuals at high and highest risk for pneumococcal disease will benefit from vaccination with Prevenar 13. This view is also consistent with the recommendations of the Australian Immunisation Handbook.

**Proposed Dose Regimen for 13vPnC**

- Does the committee agree with the following proposed dose regimen for at risk individuals? 'Individuals who may be at higher risk of pneumococcal infection (such as subjects with sickle cell disease or HIV infection) including those previously vaccinated with one or more doses of 23vPPV may receive at least one dose of Prevenar 13.‘

**Pfizer’s response**

The sponsor stated that (as outlined in the sponsor’s Clinical Overview), the clinical studies for subjects with sickle cell disease (6096A1-3014) and HIV infection (6115A1-3017) support the proposed dose regimen for at risk individuals:


Individuals who may be at higher risk of pneumococcal infection (such as subjects with sickle cell disease or HIV infection) including those previously vaccinated with one or more doses of 23vPPV may receive at least one dose of Prevenar 13.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register an extension of indications for a currently registered product.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered Prevenar 13 suspension for injection, containing pneumococcal polysaccharide conjugate vaccine, 13-valent adsorbed including 2.2 μg of polysaccharides for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F and 4.4 μg of polysaccharides for serotype 6B to have an overall positive benefit–risk profile for the indication;

Active immunisation for the prevention of pneumococcal disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in adults and children aged more than 6 weeks of age.

The use of Prevenar 13 should be guided by official recommendations.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- A statement in the Clinical Trials section of the PI and relevant sections of the CMI to reference the specific number of doses to treat high risk patients and quantify any benefit gained from the extra doses.

- A table in the Adverse Effects section of the PI and relevant sections of the CMI to reflect local and systemic adverse events for subjects 18 to 50 years of age.

- A statement in the Precautions section of the PI and relevant sections of the CMI to reference the age groups when discussing the potential increased risk of convulsions/floppy babies when using the vaccine with Infanrix Hexa.

- A statement in the Clinical Trials section of the PI to accurately reflect the immunogenicity numbers to inform the epidemiology.

- A statement in the CMI that pain after injection may prevent use of the arm.

- Amendment of the CMI to improve the way the side effects of the medicine are described to enable better understanding by consumers and inclusion of information applicable for use in Australia.

Specific advice

The ACPM advised the following in response to the specific Delegate’s questions on this submission:

The use of Prevenar 13 in adults 18 to 49 years old

- Whether the ACPM consider the immunogenicity comparison opsonophagocytic antibody (OPA) response to Prevenar 13 between adults aged 18-49 and aged 60-64 is considered
sufficient to support the use of Prevenar 13 in adults 18-49 years for the prevention of pneumococcal disease;

The ACPM noted that the submission used OPA geometric mean titres (GMTs) as the primary endpoint and not IgG serum concentrations which is recommended by most regulatory guidelines. However, the ACPM considered that both OPA and IgG results suggested immunogenicity in the 18 to 49 age group which was comparable to, or better than, in the 60 to 64 year age group.

- **Whether the use of Prevenar 13 in healthy adults 18-49 years for the prevention of pneumococcal disease has a favourable benefit-risk balance, considering there is a lower risk of pneumococcal disease in healthy adults of this age group (18-49).**

The ACPM noted that a much higher proportion of younger patients reported the adverse event of severe local pain, which lasted a few days. The ACPM considered that it was difficult to assess the balance between such transient side effects and the rare but potentially devastating pneumococcal disease.

**The use of Prevenar 13 in at risk individuals**

- **Does the committee agree that vaccination with Prevenar 13 is of benefit for those at risk individuals, even though the immune responses might be lower in some at risk individuals (such as in HIV infected subjects) than in healthy subjects?**

The ACPM noted that ‘at risk individuals’ were not a homogenous group. The data presented in sickle cell disease and in participants with HIV did not compare response with an appropriate healthy group but inclusion of the at risk groups is not included in the requested indication. The ACPM noted that the immunological responses in people with HIV appeared to be suboptimal compared to healthy adults but that patients with HIV are at a higher risk of disease, therefore, the magnitude of benefit (that is, the number needed to treat) is likely to be similar, if not better than, in healthy adults. However, there is no clinical outcome data to support this.

**Does the committee agree with the following proposed dose regimen for at risk individuals?**

- **Individuals who may be at higher risk of pneumococcal infection (such as subjects with sickle cell disease or HIV infection) including those previously vaccinated with one or more doses of 23vPPV may receive at least one dose of Prevenar 13**

The ACPM considered that the statement ‘at least one dose’ is not helpful and that the PI should to specify what dose is recommended and discuss the reasons for the recommendation and the incremental benefit of additional doses.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

**Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration of Prevenar13 containing pneumococcal polysaccharide conjugate vaccine 13 valent adsorbed 0.5mL syringe for the new indications:

*Active immunisation for the prevention of pneumococcal disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14.18C, 19A, 19F and 23F in adults and children aged more than 6 weeks of age.*

*The use of Prevenar 13 should be guided by official recommendations.*
Specific conditions of registration applying to these goods

Risk Management Plan (RMP)

For the Prevenar 13 containing pneumococcal polysaccharide conjugate vaccine 13 valent adsorbed (Submission Number PM-2013-01480-1-2); the European Risk Management Plan Version 7.0 (dated 13 June 2013), with an Australian Specific Annex (ASA) Version 2.0 (dated 11 December 2013), must be implemented in Australia.

Attachment 1. Product Information

The Product Information approved for main Prevenar 13 at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report