



Australian Government
Department of Health
Therapeutic Goods Administration

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

Proprietary Product Name: Prevenar 13

Sponsor: Pfizer Australia Pty Ltd

February 2014

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- 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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List of abbreviations

Abbreviation	Meaning
7vPnC	7-valent pneumococcal conjugate vaccine
9vPnC	9-valent pneumococcal conjugate vaccine (experimental)
13vPnC	13-valent pneumococcal conjugate vaccine
23vPPV	23-valent pneumococcal polysaccharides vaccine
AE	Adverse Event
AOM	Acute Otitis Media
CDC	(US) Centers for Disease Control and Prevention
CI	Confidence Interval
CORE II	Clinical Operations Randomisation Environment II
CRF	Case Report Form
CRM ₁₉₇	cross-reacting material ₁₉₇ (nontoxic mutant form of diphtheria toxin)
DoB	Date of Birth
ELISA	Enzyme-linked immunosorbent assay
GCP	Good Clinical Practice
GMC	Geometric mean concentration
GMFR	Geometric mean field rise
GMT	Geometric mean titres
IgG	immunoglobulin G
IM	intramuscular
IPD	Invasive Pneumococcal Disease
LLOQ	lower limit of quantitation
LOD	limit of detection
NI	Non-inferiority
NP	nasopharyngeal

Abbreviation	Meaning
OM	otitis media
OPA	opsonophagocytic activity
PD	Pneumococcal Disease
Prevenar	7-valent pneumococcal conjugate vaccine
Prevenar13	13-valent pneumococcal conjugate vaccine
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
WHO	World Health Organisation
YK	Yukon Kuskokwim

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of Indications and PI changes
<i>Decision:</i>	Approved
<i>Date of decision:</i>	30 August 2013
<i>Active ingredient:</i>	Pneumococcal polysaccharide conjugate vaccine, 13-valent adsorbed: 13 capsular polysaccharide antigens of <i>Streptococcus pneumoniae</i> serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F-each individually conjugated to Diphtheria CRM ₁₉₇ protein
<i>Product name:</i>	Prevenar 13
<i>Sponsor's name and address:</i>	Pfizer Australia Pty Ltd, 38-42 Wharf Road West Ryde, NSW 2114
<i>Dose form:</i>	Suspension for Injection
<i>Strengths:</i>	Potency is expressed in terms of the amounts of each polysaccharide in the 0.5mL dose. The vaccine contains 2.2 µg/dose of each of the serotypes, except for serotype 6B which is present at 4.4 µg/dose.

<i>Container:</i>	1 mL glass syringe
<i>Pack sizes:</i>	Packs of 1 and 10
<i>Approved therapeutic use:</i>	Active immunisation for the prevention of disease caused by <i>Streptococcus pneumoniae</i> 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. ¹
<i>Route of administration:</i>	Intramuscular (IM) injection
<i>Dosage:</i>	The proposed dosage regimen for the additional age group is a single 0.5 mL dose, irrespective of their immunisation status for Prevenar (7-valent pneumococcal vaccine). In cases where the subjects have been previously vaccinated with one or more doses of Prevenar, it is recommended the dose of Prevenar 13 be given at least 8 weeks after the last dose of Prevenar.
<i>ARTG number:</i>	158450

Product background

Prevenar 13 is a suspension for injection containing pneumococcal capsular polysaccharides for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F, each individually conjugated to diphtheria CRM₁₉₇ protein and adsorbed on aluminium phosphate. It was developed as a successor of 7-valent pneumococcal vaccine (Prevenar). It is currently approved for use in the prevention of disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in children aged 6 weeks to 5 years, and in adults aged 50 years and older.

Prevenar 13 was registered in Australia in March 2010 and has been used in the National Immunisation Program since July 2011. The initial approved indication was for use in infants and children aged 6 weeks up to 5 years. No direct evidence of efficacy was provided. Instead, serum concentrations of anticapsular immunoglobulin G (IgG) measured using enzyme-linked immunosorbent assay (ELISA) was used as a correlate for efficacy of all vaccine serotypes. Opsonophagocytic antibody (OPA) was also used for functional antibody assessment². Two pivotal studies showed that Prevenar 13 had an antibody stimulation 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 invasive pneumococcal disease (IPD) caused by the additional serotypes contained in the

¹ The **full indications** are now read as:

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.

² The OPA antibody assay provides an *in vitro* measurement of the ability of serum antibodies to eliminate pneumococci by promoting complement-mediated phagocytosis and is believed to reflect relevant *in vivo* mechanisms of protection against pneumococcal disease. OPA antibody titres are expressed as the reciprocal of the highest serum dilution that reduces survival of the pneumococci by at least 50%.

vaccine (Miller et al, 2011³; cited in Australian Immunisation Handbook 10th edition 2013).

In October 2011 the indications for Prevenar 13 were extended to include adults aged 50 years and over. Approval was based on the demonstration of non-inferiority of serum antibody responses to Prevenar 13 when compared with the 23-valent pneumococcal polysaccharide vaccine (Pneumovax 23) for common serotypes in two pivotal studies. The primary endpoint employed in the studies was serotype specific OPA titers 1 month post vaccination. There are currently no data on clinical outcomes for Prevenar 13 in this age group but a study examining its efficacy against pneumonia in adults is underway (Hak et al 2008⁴; cited in Australian Immunisation Handbook 10th edition 2013).

The current application seeks to extend indications to include active immunisation for the prevention of pneumococcal disease (including invasive disease, pneumonia and acute otitis media) caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F in children aged 6 to 17 years of age. The sponsor also seeks to include information in the *Pharmacology (Mode of Action)* section of the Product Information (PI) about the prevention of nasopharyngeal carriage of *S. pneumoniae* serotypes.

Regulatory status

The product received initial Australian Register of Therapeutic Goods (ARTG) Registration on 29 March 2010.

An extension of indication (EOI) to include children and adolescents aged 6-17 years was approved in the European Union (EU) in December 2012 and in the USA in January 2013. The inclusion of information about nasopharyngeal carriage in the EU Summary of Product Characteristics (SmPC) was approved in November 2012. The approved text in the EU SmPC contains results from the ACTIV surveillance study conducted in France as a postmarketing requirement. At the time of writing this overview, no submission has been made in the USA to include nasopharyngeal carriage data in US Prescribing Information. Applications for the EOI and the inclusion of information about nasopharyngeal carriage in product labelling are under review by Health Canada.

The following table summarises the international regulatory status of this product.

Table 1. International regulatory status of Prevenar 13

Market	Variation to Indication	Status
USA	Invasive Disease Pediatric 6 weeks - 5 years Otitis Media Pneumonia Pediatric 6 weeks - 5 years	Approved 24/2/10
	Invasive Disease Adult 50+ Pneumonia-adult	Approved 30/12/11

³ Miller E, Andrews NJ, Waight PA, Slack MP, George RC. Effectiveness of the new serotypes in the 13-valent pneumococcal conjugate vaccine. *Vaccine* 2011; **29**: 9127-31.

⁴ Hak E, Grobbee DE, Sanders EA, et al. Rationale and design of CAPITA: a RCT of 13-valent conjugated pneumococcal vaccine efficacy among older adults. *Netherlands Journal of Medicine* 2008; **66**: 378-83.

Market	Variation to Indication	Status
Europe	Invasive disease, adult aged from 18 to 49 Years	Approved 09/07/13
	Invasive Disease Pediatric 6 weeks - 5 years Otitis Media Pneumonia Pediatric 6 weeks - 5 years	Approved 9/12/09
	Invasive disease, adult aged 50 years and older	Approved 24/10/11
Canada	Invasive disease, pediatric aged from 6 Weeks to 5 Years	Approved 21/12/09
	Invasive Disease Adult 50+	Approved 13/01/12
	Invasive disease, adult aged from 18 to 49 Years	Under review
Switzerland	Invasive Disease Adult 50+	Withdrawn. Swissmedic, would not accept OPA results as a surrogate marker of efficacy. A resubmission will be made once data from the CApiTA study (~80k adults) are available.
	Invasive Disease Pediatric 6 weeks - 5 years Otitis Media Pneumonia Pediatric 6 weeks - 5 years	Approved 12/08/10
NZ	Invasive Disease Pediatric 6 weeks - 5 years Otitis Media Pneumonia Pediatric 6 weeks - 5 years	Approved 25/3/10
	Invasive Disease Adult 50+ Pneumonia-adult	Approved 31/05/12

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

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

The sponsor submitted an extensive clinical summary with a reasoned argument for a change to the extension of age indication and change in Product Information (PI) wording for nasopharyngeal carriage. The following is a summarised extract from their clinical summary document.

Extension of age

Pfizer has developed the 13-valent pneumococcal vaccine (13vPnC, Prevenar13) as a successor of 7-valent pneumococcal vaccine (7vPnC, Prevenar) for use in infants and young children to prevent pneumococcal disease (invasive pneumococcal disease, IPD and acute otitis media, AOM) caused by the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) contained in the vaccine. To overcome the limited immunogenicity of pneumococcal polysaccharide vaccines, the protein conjugation technology was applied to the development of 7vPnC and 13vPnC. Each of the pneumococcal polysaccharides is covalently conjugated to the diphtheria cross-reactive material 197 (CRM₁₉₇), which acts as an immunologic carrier.

While there has been a significant reduction in IPD since the introduction of Prevenar in young children up to 5 years of age, there remains a significant burden of disease in children and adolescents 6 to 17 years of age. In the USA, the Centers for Disease Control and Prevention (CDC) estimated that in 2007, 1300 cases of IPD occurred annually in this age group (population 54 million) and between 52.4% and 61.3% were caused by 13vPnC serotypes.⁵ A study from the USA found that approximately 10% of patients admitted to a paediatric hospital with IPD were aged between 5 to 10 years.

The 7vPnC has demonstrated a high degree of efficacy against IPD in infants and young children; published studies have reported efficacy and effectiveness against pneumonia. 13vPnC has been licensed subsequently for children up to 5 years of age, with an expectation of effectiveness for all serotypes. The introduction of 13vPnC in the USA began in March 2010. An analysis of the quarterly incidence of IPD (cases per 100,000) in 2010 to 2006-2008 (baseline) showed that among children <2 years, overall and 13vPnC serotype rates were significantly lower ($p < 0.0001$) in the fourth quarter of 2010 when compared to baseline (13vPnC serotypes 8.5 cases versus 24.1 cases). The authors

⁵ Evaluator Comment: Based on Australian census data 2010, the number of children aged 6 to 17 years in Australia is approximately 4 million. Using the CDC calculations this would amount to an estimate of 96 IPD cases annually of which 52 to 61% would be caused by 13vPnC serotypes.

concluded that these preliminary findings are consistent with early effects of 13vPnC on IPD among young children. These observations are in line with those made in England and Wales after the introduction of 13vPnC in the National Immunisation Program. Evaluation of the immune response after 13vPnC in children and adolescents 6 to 17 years of age in Study 6096A1-3011 indicates that 13vPnC immunisation would likely confer similar benefits for this population.

Children with underlying conditions such as chronic heart or lung disease, diabetes and others have an increased risk of pneumococcal disease. The relative risk of children with a predisposing medical condition (diabetes, asthma) is often 2 to 4 fold, when compared to the healthy population of the respective age group. Vaccination with 23-valent pneumococcal polysaccharide vaccine (23vPPV) of at risk and high risk children and young adults has been recommended. However, the degree of protection afforded by 23vPPV remains a critical issue. The 13vPnC would provide a new alternative to protect children and adolescent 6 to 17 years of age who are at increased risk for pneumococcal disease. There is also a smaller group of children with complex immunocompromising conditions (HIV, sickle cell disease) who have an increased risk for pneumococcal infections.

The Australian Immunisation Handbook (9th Ed)⁶ has not been updated to include information regarding 13vPnC. The current recommendation is for children with specified underlying medical conditions to receive 2 doses of 7vPnC followed by a dose of 23vPPV.

Some of the highest rates of IPD ever reported in the world were in young central Australian Aboriginal children before the availability of conjugate vaccine. As well as higher rates of IPD, a wider range of serotypes are responsible for disease in Aboriginal and Torres Strait Islander children, resulting in a lower percentage of cases (<60%) caused by serotypes included in the 7vPnC. A booster dose of 23vPPV at 18 to 24 months is currently recommended for Indigenous children living in areas of high incidence. There has been a rapid decline in invasive pneumococcal disease in Indigenous children since the introduction of the 7vPnC in 2001 (Australian Immunisation Handbook).⁶ An extension of age indication, if proven, would have a benefit for this subset of the Australian population.

Nasopharyngeal colonisation and carriage

Colonisation with *Streptococcus pneumoniae* in the nasopharynx is the necessary first step in the pathogenesis of all types of pneumococcal disease (PD), whether invasive (such as sepsis, meningitis, arthritis) or mucosal (for example otitis media, pneumonia). Studies suggest that nasopharyngeal (NP) colonisation early in life may result in increased susceptibility to pneumococcal infections, specifically to acute otitis media, later in life. Data from randomised controlled trials and from observational studies of pneumococcal conjugate vaccines that is, 7vPnC, 13vPnC and the experimental 9-valent pneumococcal conjugate vaccine (9vPnC) have shown a reduction in NP colonisation by vaccine serotypes after vaccination. The result of this effect is a reduction of transmission of *S pneumoniae*, leading to an indirect effect (herd protection) and to the reduction in transmission of antibiotics resistant strains. Thus, the protection conferred by pneumococcal conjugate vaccines results from:

1. Direct protection against invasive disease caused by vaccine-type serotypes, which is mediated through functional antibodies
2. Reduction of NP colonisation in the individual and thus a reduction of transmission to unvaccinated subjects or “herd protection”

⁶<[http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/78CDF41C283426A8CA2574E40020CCAB/\\$File/handbook-9.pdf](http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/78CDF41C283426A8CA2574E40020CCAB/$File/handbook-9.pdf)>

Prevention of pneumococcal NP colonisation has emerged as a relevant surrogate marker of vaccine efficacy of 7vPnC and 13vPnC against pneumococcal disease, including invasive disease as well as the biological basis for the additional benefits listed above for pneumococcal vaccines.

Evaluator Comment:

The critical factor here is differentiating between a reduction in nasopharyngeal acquisition (colonisation) by pneumococcal serotypes versus a reduction in the nasopharyngeal carriage of the bacteria. This difference also has implications in terms of showing herd immunity.

A quick PubMed⁷ literature search shows that there have been a number of theories postulated for the herd immunity effect that has been shown with 7vPnC. The conclusion of these studies was that it was not yet clear if NP carriage plays a pivotal role in 'herd protection'. In addition, several studies that undertook long-term follow-up of subjects and their families post 7vPnC and found that the drop in NP carriage rates initially seen following vaccination could not be reproduced >2 years post-vaccine.

There is currently no evidence to show that the effect results in a reduction in transmission of *S. pneumoniae* antibiotic resistant strains.

Contents of the clinical dossier

The clinical submission was confined to clinical information related to the extension of indications and application for an additional mode of action to be added to the PI.

The submission contained the following clinical information:

- 1 pivotal efficacy study for the extension of indications to include 6 to 17 year olds (6096A1-3011 also referred to as Study 3011).
- 2 pivotal efficacy studies for the inclusion of nasopharyngeal carriage (6096A1-3006, 6096A1-3010; also referred to as Studies 3006 and 3010 in this AusPAR).

Paediatric data

The submission deals exclusively with a paediatric population and includes data on infants and children aged 2 months to 17 years.

Good clinical practice

All three studies were conducted in accordance with the International Conference on Harmonisation (ICH), Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki.

Pharmacokinetics

Studies providing pharmacokinetic data

There were no new pharmacokinetic data submitted with this application.

⁷ PubMed is a free search engine accessing primarily the MEDLINE database of references and abstracts on life sciences and biomedical topics.

Pharmacodynamics

Studies providing pharmacodynamic data

There were no new pharmacodynamic data submitted with this application.

Efficacy

Dosage selection for the pivotal studies

The dose selected for the pivotal studies is in line with the current dosage indications; 0.5 mL of vaccine containing 2.2 µg/dose of each of the serotypes, except for serotype 6B which is present at 4.4 µg/dose. Up to four doses of Prevenar 13 are administered with a typical regimen being 3 infant doses at 2, 4 and 6 months and a toddler dose at 12 months of age.

Introduction

Clinical efficacy for Prevenar 13 is based on a surrogate immunogenicity marker. This standard was established during the initial approval of the Prevenar 13 vaccine and is based on non-inferiority of immunogenicity profiles to Prevenar.

Evaluator's conclusions on clinical efficacy (immunogenicity) for extension of indication (age 6 to 17 years)

The pivotal efficacy study (6096A1-3011) assessed the safety and immunogenicity of Prevenar13 in children aged 5-17 years. The primary immunogenicity analysis involved a complex design that compared Group 3 (children aged 5 to 10 years) against a historical cohort of similarly aged children who received Prevenar OR Prevenar13. For this analysis immunoglobulin G (IgG) titres were used as an indicator of immunogenicity.

Immunogenicity in the oldest cohort (aged 10 to 17 years) was assessed by comparing Group 3 and Group 4 OPA Geometric Mean Titres (GMTs) (secondary outcome). In addition to these results, numerous calculations were performed assessing antibody titres, pre and post-vaccination antibody levels, OPA GMTs and reverse cumulative distribution curve (RCDC). A major limitation of the study is the ability to show immunogenicity in an older cohort of children who have already acquired immunity to many of the serotypes available in the vaccine.

The key immunogenicity findings were:

- The serotype-specific GMCs were higher in the cohort of children aged 5 to 10 years who received 13vPnC (Group 3) compared to a similarly aged historical cohort who received 7vPnC. The serotype-specific geometric mean ratios for the 7vPnC serotypes⁸ ranged from 2.51 for serotype 23F to 5.66 for serotype 6B.
- The serotype-specific GMCs were higher in the cohort of children aged 5 to 10 years who received 13vPnC (Group 3) compared to a similarly aged historical cohort who received 13vPnC. The serotype-specific geometric mean ratios for 13vPnC serotypes ranged from 1.23 for serotype 1 to 3.17 for serotype 19A.
- For Group 4 (children aged 10 to 17 years) immunogenicity data was based on OPA GMTs comparisons to the 13vPnC data from Group 3. All serotypes were found to be

⁸ Sponsor comment: "These results refer to the data for the 7 serotypes common to both vaccines."

non-inferior except for serotype 3 where the lower limit of the 95% CI for the ratio between OPA GMTs was 0.48.

- Sensitivity analysis (comparison between the evaluable and all-available immunogenicity populations) generally confirmed the results.
- Results for the IgG antibody titres for both Group 3 and 4 showed that for all serotypes subjects achieved IgG titres ≥ 0.35 $\mu\text{g/mL}$ post-vaccination (98.9% to 100.0%).
- The majority of subjects in Group 3 also had IgG antibody titres ≥ 1.0 $\mu\text{g/mL}$ for the 13vPnC serotypes. Serotype 3 had the lowest number of subjects with titres ≥ 1.0 $\mu\text{g/mL}$ with 80.5%.
- Pre-vaccination IgG titres for 13vPnC serotypes for Group 4 suggested that many subjects had already been exposed to the 13vPnC pneumococcal serotypes with the proportion of subjects with IgG concentrations ≥ 0.35 $\mu\text{g/mL}$ pre-vaccination being between 43 to 99%. The proportion of subjects with pre-vaccination antibody titres ≥ 1.0 $\mu\text{g/mL}$ was also high (23 to 96%).

Based on the key immunogenicity findings, the vaccine shows immunogenicity for the age Group 10 to 17 years although many children, particularly in the older age group are likely to have already come into contact with the serotypes present in the vaccine.

Evaluator's conclusions on effect of Prevenar 13 on nasopharyngeal carriage of *S. pneumoniae*

Two pivotal studies (3006, 3010) and one post-marketing surveillance study (ACTIV) provide evidence to support the PI change.

Study 3006 was a Phase III, randomised, active-controlled, double-blind, multi-site study in healthy infants. The study was designed as a parallel-group study in which subjects were randomly assigned to 2 groups in a 1:1 ratio to receive either 13cPnC or 7vPnC. The study was generally well designed and implemented and found that there was a statistically significant difference in NP colonisation of 13vPnC serotypes between the two groups (7vPnC versus 13vPnC). In particular, the study showed a reduction in the colonisation of 19A and 6A' serotypes. A number of other analyses were performed, however, the study was not powered to detect a difference in these tests and they should be viewed as exploratory results only.

Study 3010 was a Phase III, multicentre, open-label study to evaluate the immunogenicity and safety of 13vPnC and the impact of 13vPnC on the incidence of IPD and NP colonisation in healthy Alaskan native children in the Yukon Kuskokwim (YK) Delta region of Alaska. Unfortunately due to cultural factors and the timing of the implementation of the 13vPnC vaccine, the study suffered severely from poor subject recruitment. The immunogenicity portion of the study is based on a handful of cases and no conclusions can be drawn from this data. The surveillance data is also limited by poor study numbers. In addition, an unusually low prevalence of IPD in the YK Delta population in 2009 makes interpreting the change in serotype prevalence over time, difficult. Overall this study adds very little weight to the evidence presented in Study 3006.

ACTIV is an ongoing postmarket surveillance study assessing the prevalence of 13vPnC serotypes in NP swabs of subjects presenting with acute otitis media. The study found a statistically significant decrease in the prevalence of 13vPnC serotypes, particularly serotype 19A amongst children presenting with acute otitis media following the introduction of Prevenar 13. This study is the only study to directly support the PI change. Although the results provide some evidence to support the hypothesis that Prevenar 13 reduces the carriage of *S. pneumoniae* serotypes present in the 13vPnC vaccine, it is not sufficient on its own. The study should ideally be supported by more robust studies in the

form of randomised controlled trial or alternatively, long term (5 year) follow-up data from postmarket studies from a cross-section of the global community.

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies

In the pivotal efficacy study (6096A1-3011), the following safety data were collected:

- Local reactions (redness, swelling and tenderness);
- Systemic events (including fever, decreased appetite, irritability, increased sleep, decreased sleep and hives [urticaria]) and the use of antipyretic medications to prevent or treat symptoms. Adverse events were recorded via an electronic (e) diary for 7 days after vaccination. A 6 month follow-up telephone interview recorded any newly diagnosed chronic medical conditions as adverse events (AEs).
- All serious AEs (SAEs) were reported from the time of enrolment through the 6-month follow-up.

Local reactions were assessed by a severity scale. For tenderness the range was; no discernible tenderness, tenderness present or tenderness interfering with limb movement. For redness and swelling, the parent/legal guardian measured the actual size of the reaction with a calliper and recorded the measurement (range 1-14 caliper units). A calliper unit represented 0.5 cm. The measurements for redness and swelling were categorised as absent (no redness or swelling present), mild (1-4 caliper units), moderate (5-14 caliper units) or severe (>14 caliper units).

Temperature was collected at bedtime daily for 7 days after vaccination and at any time during the 7 days that fever was suspected. Temperature was measured and recorded to 1 decimal place and then categorised according to the following terms and scale:

- Absent <38.0°C;
- Mild ≥38°C to ≤39°C;
- Moderate ≥39°C to ≤40°C;
- Severe >40.0°C.

Pivotal studies that assessed safety as a primary outcome

No studies assessed safety as a primary outcome.

Dose-response and non-pivotal efficacy studies

Study 6096A1-3010

Measures of reactogenicity (solicited local reactions and systemic events) were collected for 7 days after 13vPnC vaccination. Adverse events were collected for all subjects from day of consent until the final study follow-up telephone call, scheduled at 6 months after the last 13vPnC vaccination.

Study 6096A1-3006

Adverse events, specifically medically important adverse events, adverse events resulting in withdrawal, adverse events associated with antibiotic use (excluding topical antibiotics) and severe adverse events were collected. AEs were recorded from the signing of the informed consent form to the last study visit.

Other studies evaluable for safety only

None.

Postmarketing experience

Two studies were presented in the sponsor's *Clinical Safety Summary* with postmarket data.

The ACTIV Surveillance Study is a national surveillance study of pneumococcal NP colonisation in children with acute otitis media (AOM). It was initiated in France with the licensing of 7vPnC and extended for 13vPnC which was introduced into France between June and September 2010.

The study enrolled 943 infants between October 2010 and May 2011 with AOM; 651 received at least 1 dose of 13vPnC and 285 received 7vPnC only; 7 children were not vaccinated.

Among children vaccinated with at least 1 dose of 13vPnC, overall pneumococcal colonisation and colonisation by the 6 additional serotypes not in 7vPnC were significantly lower when compared with that of children exclusively vaccinated with 7vPnC (53.9% versus 64.6%, $p=0.002$, and 9.5% versus 20.7%, $p<0.001$, respectively). There were also significantly lower colonisation rates of serotypes 19A, 7F and 6C.

The sponsor concludes that in young children (<2 years of age) with AOM 13vPnC has an impact on overall pneumococcal colonisation, as well colonisation of individual serotypes 19A, 7F and 6C.

A second postmarket study looked at NP colonisation in children <5 years in Atlanta, Georgia. NP colonisation was assessed prior to the introduction of 13vPnC (2009) and after vaccine introduction (July 2010-September 2011). A total of 776 children who presented to an emergency department were enrolled in the study. Results from 3 time periods were compared and susceptibility of isolates to antimicrobial agents were evaluated.

Prior to 13vPnC introduction 31% of children <5 years were colonised with *S. pneumoniae*; 22% of isolates were 13vPnC-type, mostly serotype 19A. Of the 776 children enrolled after 13vPnC introduction 225 (29%) were colonised with *S. pneumoniae*, with serotype 19A making up 18% of serotypes isolated. Overall *S. pneumoniae* colonisation rates were unchanged throughout the study but the rate of colonisation of serotype 19A declined from 26.7% (period 1) to 11.9% (period 2) to 4.4% (period 4), $p=0.0047$. Colonisation rates for 13vPnC serotypes combined declined significantly from 30% (period 1) to 15.3% (period 2) to 4.4% (period 3), $p=0.0006$.

The sponsor concludes that after introduction of 13vPnC, 13vPnC-type serotypes significantly declined in young children, primarily due to a decline in serotype 19A.

Evaluator's overall conclusions on clinical safety

Safety data is available from all three studies submitted with this application; however, only data from Study 6096A1-3011 (pivotal study) is relevant to the extension of age indication.

Safety endpoints were assessed by the subjects/carers through an e-diary, filled out nightly for 7 days following vaccination and a 6 month follow-up telephone interview. There are numerous inherent problems with patient-reported outcome (PRO) data, particularly for its potential for selection bias. PRO and in particular e-diaries rely on patient motivation to obtain relevant outcome data; subjects with 'events' are more likely to report and therefore the potential for selection bias is high. Such selection bias would

be more likely to favour 'adverse event' reporting so, if anything, results would not favour the vaccine. In Study 6096-3011, this type of selection bias seems to have been minimised as there was 75% compliance with the e-diary with no obvious difference in reporting rates between groups.

Local reactions seem to have been consistent with known AE reporting across other vaccines.

Headaches and gastroenteritis seem to be rare but important adverse events associated with the vaccine in this age group. These events have been added to the PI for this age group which is appropriate.

Overall the safety evaluation for this vaccine in the age groups 5 to 18 years seems appropriate.

First round benefit-risk assessment

First round assessment of benefits

The benefits of an extension to the age indication are:

- Increased coverage for older children at increased risk of pneumococcal disease for example children with predisposing medical conditions
- Increased coverage for older children in 'at risk' populations for example Aboriginal and Torres Strait Islanders

First round assessment of risks

The risks of an extension of age indication:

- Burden of disease from pneumococcal disease less in older age groups; inherent risks of vaccination (local reactions, systemic reactions) may not be justified when underlying burden of disease so small
- Many children >10 years have already been exposed to pneumococcal serotypes present in 13vPnC vaccine. Immunogenicity data is therefore difficult to interpret.

First round assessment of benefit-risk balance

The benefit-risk balance of an extension of age indication, given the proposed usage, was favourable.

First round recommendation regarding authorisation

The evaluator recommended the extension of age indication for Prevenar 13.

There is insufficient evidence presented to show that Prevenar 13 reduces the rate of carriage of pneumococcal serotypes present in the 13vPnC vaccine. There is some evidence to suggest that 13vPnC vaccination prevents colonisation of 13vPnC.

List of questions

Following the First Round clinical evaluation, the evaluator posed several questions to the sponsor. The sponsor's responses to these questions and the evaluator's second round evaluation of the answers is included below.

Second round evaluation of clinical data submitted in response to questions

Question 1

In the primary analysis the index group (Group 3) had significantly better GMC results compared to the study 3005 7vPnC and 13vPnC GMC results. In all cases the ratio of geometric mean concentrations was substantially higher than the non-inferiority cut-off level of 0.5 (lower limit of the 2 sides 95%CI). Why does the 13vPnC vaccine seem to be performing so much better in this group of children, the expectation would be for the vaccines to be substantially equivalent?

The sponsor stated that higher immune responses were seen in the index group as they were previously vaccinated with 7vPnC. In addition, higher immune responses in older children are expected due to a mature immune system.

The sponsor's answer provided adequate explanation for the difference in results seen.

Question 2

Two different cohorts of children were used for the comparator in the primary analysis; what was the rationale behind this decision, why wasn't the Study 3005, 13vPnC population used for all serotypes? Please provide calculation and analysis of the 7vPvC serotypes with this group of children.

The comparison with Study 3005 allowed bridging of the two populations (infants and children 6 weeks to 5 years) and represented the largest and most robust dataset for comparison with the infants and children vaccinated in Study 3011.

The sponsor's response was considered to be adequate.

Question 3

No power calculations were included in the sample size calculations for Study 3006; please provide evidence that the study was adequately powered to detect a difference between groups.

Power calculations were provided by the sponsor, sample sizes of 820 subjects per group would provide at least 90% power to show that the reduction of new acquisitions (6A and 19A combined) 1 year after the toddler dose in subjects receiving 13vPnC is statistically significantly greater than the reduction in subjects receiving 7vPnC, assuming a 2-sided type I error rate of 0.05 and a dropout rate of at most 12%.

Table 2. Power to detect reduction in 6A or 19A carriage with type 1 error rate=0.05 and 820 subjects/group

Assumed Carriage Rate in 7vPnC	Power for Detecting Reduction of			
	27.5%	30%	40%	50%
0.30	96%	98	>99%	>99%
0.24	90%	94%	>99%	>99%
0.2	82%	88%	>99%	>99%
0.15	67%	75%	95%	>99%

Question 4

All results from Study 3006 and 3010 related to NP acquisition of S. pneumoniae serotypes. What evidence is there to support the link between reduction in NP acquisition and reduction in NP carriage at a population level?

The sponsor provided a recent paper (Simell *et al*, 2012)⁹ that provides a review of the evidence supporting pneumococcal carriage at the individual level as an immediate and necessary precursor to pneumococcal disease. The review suggests that there is a casual link between carriage and disease.

The sponsor defines *acquisition* and *colonisation* in a similar manner to Simell *et al*. that is; *acquisition* is the time when a pneumococcal strain establishes itself within the host and *ongoing NP colonisation* describes carriage.

According to the sponsor, Study 3006 showed significant reduction in NP acquisition. The impact of the vaccine on prevalence (carriage) was a significantly lower NP prevalence in the 13vPnC group than in the 7vPnC group for 6A, 6C and 19A combined. For single serotypes, 13vPnC recipients had significantly lower levels of 6A and 19A. There was no statistically significant difference between the common serotypes, with the exception of serotype 19F which had a lower prevalence in the 13vPnC group compared with the 7vPnC group.

The sponsor concluded that “*a similar correlation between acquisition and carriage should exist in the general population with the use of 13vPnC in paediatric vaccination programs.*”

Evaluator Comment:

Study 3006 found that 13vPnC reduced the acquisition of serotypes, as well as, the ongoing prevalence of serotypes 6A, 6C and 19A combined, and serotype 19F at an individual level. Prevalence data was secondary analysis and the study was not powered to detect this result, however, the results support the hypothesis that a decrease in 13vPnC serotypes acquisition and carriage are both associated with Prevenar13.

Study 3010 suffered from poor study recruitment and results from this study should be seen as exploratory.

The post-market study, ACTIV, found a reduction in the carriage of 13vPnC serotypes in French children vaccinated exclusively with the 13vPnC vaccine compared to children exclusively vaccinated with the 7vPnC.

The sponsor proposed that a link be drawn between the individual data provided in Study 3006 and the postmarket population data provided in the ACTIV study. This link provides evidence that 13vPnC may reduce the carriage of serotypes 6A, 6C and 19A. This link is also supported by the article by Simell *et al*.¹⁰ However, from the evidence provided the link should be considered as an association only and not a causal pathway.

Question 5

Question removed on agreement with sponsor and evaluator.

Question 6

Results from Study 3010 ‘Proportion of Carriage of Typeable Pneumococci Comprised of 6 Additional Serotypes in 13vPnC children <5 Years of Age’ and ‘Proportion of Carriage of Typeable Pneumococci Comprised of 6 Additional Serotypes in 13vPnC Adult Population ’ do not have reference ranges included. Please provide 95% CI reference ranges for the percentages provided for all years (March 2010, 2008, 2009 and 2010).

⁹ Simell B *et al* (2012). The fundamental link between pneumococcal carriage and disease. *Expert Rev Vaccines* 11: 841-855.

¹⁰ Simell B *et al* (2012). The fundamental link between pneumococcal carriage and disease. *Expert Rev Vaccines* 11: 841-855.

The data was analysed by the CDC's Arctic Investigation Program and the summary provided to the sponsor did not contain the reference ranges and 95% CI requested by the evaluator.

Question 7

For Study 3010, the comparison for pre and post-vaccine NP carriage rates for YK Delta adult cohort were made between the average of the 2008 to 2009 data and the 2010 data. What was the justification for performing the analysis this way?

The sponsor stated that averages were used to establish a stable baseline; however, it did not make a significant difference to the results due to low variability between 2008 and 2009 data.

Question 8

The incidence of IPD in the YK Delta population dropped unexpectedly in 2009. This may have been due to natural annual variance. What is the likely effect or association of a decrease in seasonal IPD on the nasopharyngeal rates of pneumococci?

The sponsor suggested that seasonal differences were mitigated by conducting the cross-sectional carriage surveys annually at the same time, and in the same villages and clinic sites, where a cross section of the population was enrolled for NP swab collection. Data could then be compared to trends in serotype specific disease rates using the ongoing invasive pneumococcal disease (IPD) surveillance operated by CDC in Alaska.

Evaluator Comment:

The effect of seasonal variation in disease may still have been a factor in the results presented in Study 3010 which compared only 4 years of data. Long-term trends will detect any seasonal variation in the Alaskan group over time (10 years), however, the potential interaction of seasonal variation and the vaccine effectiveness cannot be separated over such a short time period.

Second round benefit-risk assessment**Second round assessment of benefits**

The answers provided by the sponsor to questions raised at the end of the First Round Evaluation served to clarify the clinical trial data and did not affect the benefits previously described. Accordingly, the benefits of 13vPnC are unchanged from those identified in the *First Round Assessment of benefits*.

Second round assessment of risks

The answers provided by the sponsor to questions raised at the end of First Round Evaluation served to clarify the clinical trial data and did not affect the risks previously described. Accordingly, the risks of 13vPnC are unchanged from those identified in *First Round Assessment of risks*.

Second round assessment of benefit-risk balance

The benefit-risk balance of an extension of age indication, given the proposed usage, was considered to be favourable.

Second round recommendation regarding authorisation

The key immunogenicity findings presented show that for the age Group 10 to 17 years the 13vPnC is likely to be effective in eliciting an immune response to the 13vPnC serotypes. Many children in this age group are likely to have already come into contact with the serotypes present, however; children without previous contact are likely to mount a strong response to the serotypes. In addition, the safety profile of the vaccine in this age group shows that children aged 10 to 17 years may experience mild-moderate, self-limiting adverse events similar to those associated with many vaccines. The balance of risks to benefits of the vaccine was considered to be favourable and the evaluator recommended that the age indication be extended to include this age group.

The sponsor provided three studies to support their proposal to update the PI to introduce the concept that 13vPnC reduced NP disease by decreasing the NP carriage of 13vPnC serotypes. Study 3006 provides individual data showing that 13vPnC vaccination decreases acquisition of 6A, 6C and 19A combined individually and may decrease carriage of 13vPnC serotypes when compared to children vaccinated with 7vPnC. Study 3010 was intended to provide population data showing a link between vaccination and decreased carriage rates, however the study suffered from poor recruitment and the results reported should be considered exploratory only. A postmarket surveillance study shows reduction of 13vPnC serotype carriage in children with otitis media following the introduction of 13vPnC however, no individual data exists.

It was not clear to the evaluator whether individual data from one study and population data from a second is sufficient to draw a causal link between 13vPnC vaccine and carriage of 13vPnC serotypes. There is almost certainly an association between 13vPnC vaccine, acquisition of 13vPnC serotypes and carriage of 13vPnC serotypes. However, association does not prove causation and in the absence of more concrete data the evaluator was reluctant to approve the proposal to include “nasopharyngeal carriage” in the mode of action section of the PI.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing safety Concerns which are shown at Table 3.

Table 3. Summary of Ongoing safety Concerns

Important identified risks	<ul style="list-style-type: none"> · Increased fever rates when 13vPnC is co-administered Infanrix hexa · No other important identified risks requiring further follow-up have been identified.
Important potential risks	<ol style="list-style-type: none"> 1. Unanticipated safety signals (including the onset of rare events) not seen in clinical trials of 13vPnC. 2. Vaccine failure in subjects who are fully vaccinated according to local recommendations.

<p>AEs not associated with 13vPnC in clinical trials or with 7vPnC in postauthorisation observational safety studies, but are included in the Prevenar SmPC</p>	<p><u>Infants/children</u></p> <ol style="list-style-type: none"> 1. Wheezing diagnoses 2. Apnea 3. Convulsions/seizures 4. Anaphylaxis/hypersensitivity
<p>Important missing information</p>	<ol style="list-style-type: none"> 1. Effectiveness of 13vPnC consistent with the high effectiveness of 7vPnC vaccine (infants/children). 2. Effectiveness of 13vPnC (adults). 3. Long-term vaccine effectiveness. 4. Potential changes in the epidemiology of nonvaccine <i>S pneumoniae</i> serotypes that may occur (infants/children). 5. Safety and immunogenicity in high risk populations: <ol style="list-style-type: none"> a. HIV-infected subjects b. Premature infants born at <37 weeks of gestational age. c. Immunocompromised subjects including those with bone marrow transplant and sickle cell disease 6. Age group (18 to <50 years). 7. Impact of 13vPnC on nasopharyngeal carriage, including monitoring replacement with non-vaccine serotypes and non-pneumococcal bacteria in the nasopharyngeal flora of children. 8. No evidence of an association between wheezing diagnoses and vaccination was noted in postmarketing trials with 7vPnC or in clinical trials with 13vPnC; however, wheezing diagnoses will be monitored post authorisation (infants/children). 9. Pediatric transition plan. 10. Effect of antipyretics on immune response to vaccination (infants/children). 11. Safety of more than 1 dose of 13vPnC in adults administered >1 year apart. 12. Vaccine exposure during pregnancy and lactation.

OPR reviewer comment

It was noted that from the previously evaluated EU Risk Management Plan for 13-Valent Pneumococcal Conjugate Vaccine (13vPnC), Version 4.0 dated 18 November 2010 by the TGA, the following changes have occurred to the Ongoing Safety Concerns (Table 4):

Table 4. Changes to Ongoing Safety Concerns since previous TGA evaluation

Ongoing safety concerns	<p>Added to 'Important identified risks'</p> <ul style="list-style-type: none"> · Increased fever rates when 13vPnC is co-administered Infanrix hexa <p>Modified in 'Important missing information'</p> <ul style="list-style-type: none"> · f) Age group (>5 to <50 years) to f) Age group (18 to <50 years) <p>Removed in 'Important missing information'</p> <ul style="list-style-type: none"> · h) Safety of more than 4 doses of CRM-based pneumococcal conjugate vaccine when 13vPnC is administered for protection against the 6 additional serotypes in subjects previously vaccinated with a primary series of 7vPnC (infants/children) · i) Immunogenicity of 1 booster dose of 13vPnC against the 6 additional serotypes after a primary series of 7vPnC (infants/children)
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For the added Important identified risk 'Increased fever rates when 13vPnC is co-administered Infanrix hexa', it was recommended that the sponsor propose adequate and appropriate risk minimisation activities.

For the removal of Important missing information h) above the sponsor states:

This safety concern has been addressed in completed studies 6096A1-3010 (P46 042), 3011 groups 1 and 2 (FU2 18.2), and 3021 (P46 09), which have been submitted. Results in each study showed acceptable safety and tolerability and support the update to section 4.2 of the SmPC (shown below). Young Children (12-59 months) completely immunized with Prevenar (7-valent): Young children who are considered completely immunised with Prevenar (7-valent) should receive one dose of 0.5 ml of Prevenar 13 to elicit immune responses to the 6 additional serotypes. This dose of Prevenar 13 should be administered at least 8 weeks after the final dose of Prevenar (7-valent) (see section 5.1).(see RMP page 276).

This was considered to be acceptable.

For the removal of i) above the sponsor states:

This safety concern has been addressed in completed studies 6096A1-008 (FUM009) and 3012(P46 041), which have been submitted. Results showed that a single 13vPnC dose after a 7vPnC primary series elicited appropriate antibody levels against the 6 additional serotypes (see section 1.2.4.2). These data support the update to section 4.2 (Posology and method of administration) of the SmPC shown below. Prevenar 13 vaccine schedule for infants and children previously vaccinated with Prevenar (7-valent) (Streptococcus pneumoniae serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) Prevenar 13 contains the same 7 serotypes included in Prevenar, using the same carrier protein CRM197. Infants and children who have begun immunisation with Prevenar may switch to Prevenar 13 at any point in the schedule.

This was considered to be acceptable.

Pharmacovigilance plan

Proposed pharmacovigilance activities

The sponsor has proposed routine pharmacovigilance with the addition of clinical trials, a pharmacoepidemiology/epidemiology study and follow-up questionnaires.

All studies in the Prevenar 13 pharmacovigilance plan are either currently ongoing or completed. It is expected that results of completed studies will be communicated to the TGA via Periodic Safety Update Reports (PSURs) and updates to the RMP at the same time as other regulatory agencies. Studies, as part of the Prevenar 13 pharmacovigilance plan, have been reviewed previously by the TGA for which EU RMP Version 4.0 dated 18 November 2010 were submitted.

For the Important potential risk 'Vaccine failure in infants/children and adults who are fully immunized according to local recommendations', the sponsor is conducting (as also per previously evaluated EU RMP Version 4.0) a follow-up questionnaire of vaccine failure reports to ascertain whether serotype information was collected.

Risk minimisation activities

No additional risk minimisation activities were proposed by the sponsor in Australia for Prevenar 13.

Routine risk minimisation activities were considered acceptable to mitigate the risks associated with Prevenar 13 by the OPR evaluator.

The following table (Table 5) summarises the OPR's evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the second round OPR evaluation of the sponsor's responses.

Table 5. Reconciliation of issues outlined in the RMP report. Table continued across two pages.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
1. It was recommended that the sponsor implement EU RMP Version 5.0 dated 4 September 2012 [data lock point 9 July 2012] with Australian Specific Annex and any future updates as a condition of registration.	The sponsor acknowledged and agreed to the evaluator's comment.	This was considered to be acceptable.
2. For the important identified risk 'Increased fever rates when 13vPnC is co-administered Infanrix hexa', it was	The sponsor stated that the Prevenar 13 Core Data Sheet has recently been updated to include information regarding the concomitant administration of Prevenar 13 and Infanrix.	This was considered to be acceptable and the Delegate was requested to

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p>recommended that the sponsor propose adequate and appropriate risk minimisation activities as found in the EU SmPC¹¹. It is important to inform Healthcare Professionals of the risk of higher rates of febrile reactions when Prevenar 13 and Infanrix hexa are administered concomitantly.</p>	<p>As a result, the Prevenar 13 Product Information will be updated accordingly, as part of a Safety-Related Notification. The approved text will then be added to the Product Information associated with this current application, after the Delegate's Overview has been received.</p>	<p>consider this assurance when the final PI and CMI are negotiated during the processing of this application.</p>
<p>3. It has been reported¹² that a higher risk of febrile seizures associated with the concomitant administration of Prevenar 13 and trivalent influenza vaccine (TIV) compared to when these vaccines were given alone on separate days in children 6-59 months of age. It is important that Healthcare professionals and also parents of</p>	<p>The sponsor claimed that the single analysis that identified this interaction has some significant methodological issues, and the US Food and Drug Administration (FDA) is currently developing a Mini-Sentinel study to examine this further. The sponsor notes that similar findings have not been presented for the subsequent influenza season (2011-2012) which had the same TIV formulation, or in this most recent season (2012-2013) which has a different TIV formulation. The sponsor wonders whether this result was a spurious one or due to other factors that were not accounted for. However, the sponsor felt that changing the</p>	<p>The sponsor's justification and position appeared reasonable, although the Delegate was requested to consider this recommendation when the final PI and CMI are negotiated during the processing of this application.</p>

¹¹ The EU SmPC lists in 4.4 *Special warnings and precautions for use, Infants and children aged 6 weeks to 5 years*:

When Prevenar 13 is administered concomitantly with Infanrix hexa (DTPa-HBV-IPV/Hib), the rates of febrile reactions are similar to those seen with concomitant administration of Prevenar (7-valent) and Infanrix hexa (see section 4.8). In addition, in the EU SmPC Section 4.8, Undesirable effects, Infants and children aged 6 weeks to 5 years (see page 6): In a clinical study in infants vaccinated at 2, 3, and 4 months of age, fever $\geq 38^{\circ}\text{C}$ was reported at higher rates among infants who received Prevenar (7-valent) concomitantly with Infanrix hexa (28.3% to 42.3%) than in infants receiving Infanrix hexa alone (15.6% to 23.1%). After a booster dose at 12 to 15 months of age, the rate of fever $\geq 38^{\circ}\text{C}$ was 50.0% in infants who received Prevenar (7-valent) and Infanrix hexa at the same time as compared to 33.6% in infants receiving Infanrix hexa alone. These reactions were mostly moderate (less than or equal to 39°C) and transient.

¹² Tse A, Tseng HF, Greene SK, Vellozzi C, Lee GM. Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010–2011. *Vaccine* 2012; 30:2024-2031

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
patients are notified of this risk. It was recommended the sponsor address the risk in the <i>Precautions</i> section of the proposed Australian PI.	labelling is not appropriate at this time and notes that there is existing information in the labelling about both convulsions and febrile convulsions.	

Australian Specific Annex to the Risk Management Plan

The Prevenar 13 Risk Management Plan (RMP) is a global plan that considers clinical studies and spontaneous reports from across the world to investigate and monitor safety. The RMP considers safety issues and information, regardless of region or country and is therefore appropriate and applicable to the Australian market.

Pfizer Australia does not intend to conduct any additional risk minimisation activities in Australia in relation to Prevenar 13's use in children and adolescents. The patient population and demographics do not differ particularly between Australia and Europe. In addition, there are no significant differences in the clinical information proposed in the European SmPC compared to the Australian PI. The risk minimisation activities in the European RMP are therefore considered to be appropriate for the Australian market, with one exception. There is mention of communications to healthcare professionals in Europe, regarding the transition from Prevenar (7-valent) to Prevenar 13. In Australia, communications were made to healthcare professionals in middle of 2011 regarding the transition to Prevenar 13. However, as the State health departments are responsible for the implementation of the immunisation program, the communications were sent by the State health departments.

Summary of recommendations

It was considered that the sponsor's response to the TGA's request for information has adequately addressed all of the issues identified in the RMP evaluation report.

Outstanding issues

Issues in relation to the RMP

There were no outstanding issues in relation to the RMP for this submission.

Advice from the Advisory Committee on the Safety of Vaccines (ACSOV)

The Advisory Committee on the Safety of Vaccines (ACSOV) advice was not sought for this submission.

Suggested wording for conditions of registration

RMP

The European Risk Management Plan Version: 5.0 dated 4 September 2012 with an Australian Specific Annex, to be revised as specified in the sponsor's correspondence dated 28 March 2013, must be implemented.

PSUR

An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The reports are to at least meet the requirements for Periodic Safety Update Reports (PSURs) as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-Periodic Safety Update Report, Part VII.B. "Structures and processes". Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The annual submission may be made up of two Periodic Safety Update Reports each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

VI. Overall conclusion and risk/benefit assessment

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

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

Extension of indication to children aged 6 to 17 years. Study 6096A1-3011

The current submission is based on results from clinical Study 6096A1-3011, an open-label study designed to evaluate the safety, tolerability, and immunogenicity of Prevenar 13 administered to healthy children aged >15 months to <2 years (Group 1); ≥ 2 years to <5 years (Group 2); ≥ 5 years to <10 years (Group 3); and ≥10 years to <18 years (Group 4). Data were only presented for Groups 3 and 4 as they form the basis of the proposed extension of indication. Children aged 5 through 9 years were previously vaccinated with at least one dose of Prevenar, whilst children aged 10 through 17 years were pneumococcal vaccine-naïve. A total of 598 subjects were enrolled across the 2 groups; 299 in Group 3 (mean age at enrolment 7.4 years [range 5 to 10 years]; 68.4% White) and 299 in Group 4 (mean age at enrolment 13.7 years [range 10 to 18 years]; 78% White).

Immune response was assessed approximately 1 month after subjects received a single dose of Prevenar 13. Immunogenicity was measured using ELISA serum concentrations of anticapsular immunoglobulin G (IgG) for each pneumococcal serotype. In addition,

functional antibody titres for the 13 pneumococcal serotypes were determined using serum OPA assays. Safety was assessed over the first 7 days following vaccination (through the use of an e-diary) and at a 6-month telephone follow-up.

Serotype specific ELISA IgG geometric mean concentrations (GMCs) measured 1 month post-vaccination were compared to corresponding data from a historical cohort enrolled in Study 6096A1-3005¹³. Study 6069A1-3005 included approximately 1050 Prevenar 13 vaccinated subjects contributing data to the evaluable post toddler immunogenicity analyses. In addition, that study included a Prevenar control arm. For the primary analysis, ELISA IgG concentrations from the Prevenar control group in Study 6096A1-3005 were used for a non-inferiority comparison with Prevenar 13 for the 7 common serotypes in Group 3 as this provides a direct link to Prevenar immunogenicity. The criterion for non-inferiority for a given serotype was met if the lower limit of the 2-sided 95% CI for the ratio of geometric mean concentrations (Group 3 confirmatory cohort relative to study 6069A1-3005) was >0.05. The data from Group 4 was then compared to Group 3 OPA responses.

Groups 3 and 4 were split into exploratory and confirmatory cohorts. The exploratory cohort comprised the first 100 subjects in each group and their data were used to obtain reference IgG antibody concentrations for children aged 5-17 years. The confirmatory cohort comprised the next 200 subjects in each group and their data were used to validate the exploratory cohort results.

Immunogenicity results

In children aged 5 through 9 years (Group 3):

- For the Prevenar 13 confirmatory cohort, IgG GMCs measured 1 month after vaccination were non-inferior to the post toddler responses in the Prevenar (7-valent) group from Study 6096A1-3005 for the 7 common serotypes and also non-inferior to the combined Prevenar 13 groups from study 6096A1-3005 for the 6 additional serotypes; and
- 100% of subjects achieved IgG concentrations ≥ 0.35 $\mu\text{g/mL}$ for the 7 common serotypes and 98.9% to 100% subjects achieved IgG concentrations ≥ 0.35 $\mu\text{g/mL}$ for the 6 additional serotypes. Of note, most subjects appeared to have already acquired immunity to the additional serotypes 5, 6A and 19A pre vaccination. There were similar findings for the proportion of subjects achieving IgG concentrations ≥ 1.0 $\mu\text{g/mL}$.

In children aged 10 through 17 years (Group 4):

- OPA GMTs 1 month after vaccination were non-inferior to OPA GMTs in Group 3 (that is, the 5 through 9 year old group) for all 7 common serotypes and, with the exception of serotype 3, for the 6 additional serotypes;
- Although not discussed in the CER, IgG GMCs measured 1 month after vaccination for the Group 4 Prevenar 13 confirmatory cohort were also non-inferior to the post toddler responses in the Prevenar group from Study 6096A1-3005 for the 7 common serotypes and also non-inferior to the combined Prevenar 13 groups from study 6096A1-3005 for the 6 additional serotypes; and

¹³ Study 6096A1-3005 was a Phase III, randomised, double blind, lot consistency study included in the submission for the initial marketing application in Australia. Healthy infants (approximately 2 months of age at first vaccination) received 1 dose (0.5 mL) of either Prevenar 13 or Prevenar at each of the 4 vaccination visits and a concomitant dose of Pediarix (diphtheria, hepatitis B, pertussis, polio and tetanus) and Hib vaccine at the 2, 4 and 6 month visits, and with measles, mumps and rubella (MMR), varicella and hepatitis A vaccines at the 12-month visit. The mean age at which the subjects received the toddler dose was 12.4 months.

- 98.9% to 100% of subjects achieved IgG concentrations ≥ 0.35 $\mu\text{g/mL}$ for the 7 common serotypes and 97.2% to 100% subjects had IgG concentrations ≥ 0.35 $\mu\text{g/mL}$ for the 6 additional serotypes. However many subjects appeared to have already acquired immunity to most of the serotypes present in Prevenar 13, and at least 40% of subjects had antibody concentrations ≥ 1.0 $\mu\text{g/mL}$ to at least one of the additional vaccine sero-types prior to vaccination. These subjects were pneumococcal vaccine-naïve and these findings suggest previous exposure.

The clinical evaluator considered the vaccine possessed adequate immunogenicity for the proposed age group although many children, particularly in the older age group, are likely to have already come into contact with the serotypes present in the vaccine.

Safety

Local reactions occurred for the majority of subjects in both age groups (Group 3: 89.6%; Group 4: 90.5%) but were mostly mild or moderate in severity and resolved within 3 days. Tenderness at the injection site was most frequently reported, followed by redness and swelling.

Systemic events (fever, decreased appetite, irritability, increased sleep, decreased sleep, and hives [urticaria]) were reported for approximately 50% subjects in each group (Group 3: 47.2%; Group 4: 51.4%) and most of these resolved within 3 days. These most commonly comprised irritability, decreased appetite and increased sleep in both age groups plus decreased sleep in the older age group (Group 4). Any fever was reported in 4.2% subjects in Group 3 and 5% subjects in Group 4. Severe fever ($>40^{\circ}\text{C}$) was reported by 1 (0.5%) subject in each group.

Beyond 7 days, the reported adverse events (AEs) were generally consistent with childhood illnesses common in the respective age groups. There were few treatment-related AEs, severe or life-threatening AEs or serious AEs (mostly infections) reported and the incidences were similar among Group 3 and Group 4. There were no deaths or AEs that led to withdrawal from the study.

The clinical evaluator concluded that local reactions were consistent with those reported for other vaccines. Headaches and gastroenteritis were found to be rare but important adverse events associated with the vaccine in the 6 to 17 year age group and the evaluator noted these events have been added to the PI for this age group.

Clinical evaluation conclusion

Overall, the clinical evaluator concluded Prevenar 13 is likely to be effective in eliciting an immune response to the 13 *S. pneumoniae* serotypes in the 6 to 17 year age group, with an acceptable safety profile. It was noted that many children in this age group, particularly those >10 years of age, are likely to have already come into contact with the serotypes within the vaccine. However, children without previous contact mounted a strong response to the serotypes. The balance of benefits and risks of the vaccine was considered to be favourable and the evaluator recommended that the proposed extension of indications be approved.

Other changes to the PI: Effect on nasopharyngeal *S. pneumoniae* serotypes

Data submitted in support of the proposed PI statements about nasopharyngeal carriage of *S. pneumoniae* were generated from:

- 2 Phase III studies: 6096A1-3006 and 6096A1-3010; and

- 2 post marketing surveillance studies: ACTIV, conducted in France (Cohen et al, 2012^{14,15}) and a US study conducted in Atlanta, Georgia (Desai et al, 2012¹⁶). Copies of these 2 studies were not submitted. They were simply summarised in the Module 2 *Summary of Clinical Safety*. Of particular note, the article by Desai et al 2012 is an abstract.

Study 6096A1-3006 was a randomised, active-controlled, double-blind Phase III study in healthy infants conducted in Israel which showed the proportion of subjects with newly identified nasopharyngeal acquisition¹⁷ of *S. pneumoniae* serotypes 6A' (serotypes 6A + 6C) and/or 19A at 1 month after infant series vaccination to 24 months of age was statistically significantly lower for Prevenar 13 than for Prevenar (20.0% versus 36.0%; RR 0.56 (95%CI: 0.47 – 0.65)). The proportions of subjects with new acquisition of single serotypes 1, 6A', 6A, 6C, 7F and 19A were also significantly lower for Prevenar 13 than for Prevenar. For serotype 3, no difference was observed between the 2 vaccines. Assessment of colonisation by serotype 5 was not possible because of insufficient number of events. No difference was detected in the acquisition of non-vaccine serotypes between groups (RR 1.08 (95%CI: 1.02 - 1.15)). Prevalence of nasopharyngeal colonisation with the *S. pneumoniae* serotypes present in Prevenar 13 was assessed at 7, 12, 13, 18 and 24 months of age as secondary immunogenicity outcomes. There was a significantly lower prevalence of serotypes 6A' or 19A following vaccination with Prevenar 13 than Prevenar at each time point. Otherwise, no difference was observed for any serotype common to both Prevenar 13 and Prevenar, and absolute numbers for the additional serotypes in Prevenar 13 were small making interpretation of odds ratios difficult.

Study 6096A1-3010 was an open-label Phase III study conducted with the primary objective of evaluating of the impact of Prevenar 13 vaccination on the incidence of IPD in healthy native children aged 6 weeks to <5 years in the YK Delta region of Alaska. A total of 373 children were enrolled and vaccinated with Prevenar 13 using an age-appropriate dose schedule from January 2009 to March 2010¹⁸. Only 10% of eligible children in the YK Delta region were enrolled.

A secondary objective of the study was the characterisation of serotypes and antimicrobial resistance patterns of *S. pneumoniae* found on nasopharyngeal swabs. The primary endpoint for this part of the study was the proportion of subjects with nasopharyngeal carriage of the Prevenar 13 serotypes, summarised for subjects aged <2 years, < 5 years and other age groupings in children and adults. Baseline data were used from an ongoing Alaskan investigator sponsored study of nasopharyngeal colonisation with *S. pneumoniae* that commenced in February 2008. For this part of the study, 453 swabs were collected from 225 children aged <5 years living in villages participating in the YK Delta region clinical trial. It was found that the proportion of children <5 years of age carrying any of the 6 additional serotypes in Prevenar 13 decreased from 30% in 2008-2009 to 16% in 2010 ($p < 0.002$). This was mostly due to a reduction in the proportion of subjects with serotype 19A. During this same period, there was no significant difference in carriage of

¹⁴Cohen R, Levy Corinne L, Bingen E, et al. Impact of 13-valent pneumococcal conjugate vaccine on pneumococcal nasopharyngeal carriage in children with acute otitis media. *Ped Infect Dis* 2012; 31(3): 297-301.

¹⁵ACTIV Surveillance network for nasopharyngeal carriage of Streptococcus Pneumoniae in children with AOM and in healthy children. Association Clinique et Therapeutique du Val de Marne, ACTIV; 2011. Report 2010-2011 (Year 10, 5 October 2010 to 27 April 2011, Paris, France:): 1-69.

¹⁶Desai AP, Sharma D, Crispell E, et al. Pneumococcal (sp) nasopharyngeal carriage in the immediate post-PCV-13 era in children presenting to the emergency department in Atlanta, Georgia. International Symposium on Pneumococci and Pneumococcal Diseases, ISPD; 11-15 March 2012; Iguazu Falls, Brazil, Abstract #665.

¹⁷A newly identified acquisition was defined based upon observation of a positive culture during the observation visits if one was not positive at baseline.

¹⁸ Prevenar 13 became commercially available in the United States in March 2010 at which time the trial ceased.

any of the 6 additional serotypes in those populations that did not begin to use Prevenar 13 until licensure in 2010.

Carriage data from persons 18 years and older in the village populations participating in the clinical trial suggested a decrease in the 6 additional serotypes in Prevenar 13 amongst the adult population. Nasopharyngeal colonisation decreased from 23% in 2008-2009 (26% in 2008, 20% in 2009) to 12% in 2010 ($p < 0.02$). Carriage among adults in villages not participating in the clinical trial rose slightly from 18% (19% in 2008, 18% in 2009) to 21% but this difference was not statistically significant.

The ACTIV Surveillance Study of pneumococcal nasopharyngeal serotypes in children with acute otitis media enrolled 943 infants between October 2010 and May 2011. A total of 651 children received at least 1 dose of Prevenar 13; 285 received Prevenar; and 7 were not vaccinated. Among children vaccinated with at least 1 dose of Prevenar 13, overall pneumococcal colonisation and colonisation by the 6 additional serotypes not in Prevenar were significantly lower when compared with that of children exclusively vaccinated with Prevenar (53.9% versus 64.6%, $p = 0.002$; and 9.5% versus 20.7%, $p < 0.001$, respectively). There were also significantly lower colonisation rates of serotypes 19A, 7F and 6C.

In another post-marketing study, *Desai et al 2012* examined nasopharyngeal colonisation in children <5 years in Atlanta, Georgia prior to and after the introduction of Prevenar 13. Overall, *S. pneumoniae* colonisation rates were unchanged throughout the study (22% prior to Prevenar 13 vs. 29% after introduction of Prevenar 13). However, colonisation rates for 13vPnC serotypes combined declined significantly from 30% (period 1) to 15.3% (period 2) to 4.4% (period 3), $p = 0.0006$; whilst the rate of colonisation with serotype 19A declined from 26.7% (period 1) to 11.9% (period 2) to 4.4% (period 4), $p = 0.0047$.

Clinical evaluation conclusion

The evaluator concluded that the ACTIV post-market surveillance study was the only study to directly support the proposed PI change. Although the results provided some evidence to support the hypothesis that Prevenar 13 reduces the carriage of *S. pneumoniae* serotypes present in the 13vPnC vaccine, it was not considered to be sufficient on its own. The evaluator thought the study should ideally be supported by more robust random controlled trials (RCTs) or alternatively long term (5 year) follow-up data from postmarket studies from a cross-section of the global community.

The clinical evaluator recommended that the changes not be approved as proposed and suggested “*retaining the original wording “the prevention of nasopharyngeal colonisation by vaccine-type serotypes”*”, stating that the link between acquisition and carriage is associative only and that no causal link had been made. [Note: The current approved PI does not contain a statement about effect of the vaccine on nasopharyngeal colonisation. It is not clear whether the evaluator misconstrued that there was such a statement already in the PI or was referring to the statement as originally proposed by the sponsor. Confusion may have arisen because the sponsor appears to have inserted a statement about effect of the vaccine on nasopharyngeal colonisation and then relocated it and changed ‘colonisation’ to ‘carriage’ using tracked changes, so it could have appeared that it was approved wording of the PI that was being amended].

Risk management plan

The proposed RMP and Australian Specific Annex were reviewed by the TGA’s Office of Product Review (OPR) and there are no outstanding issues. The advice of the Advisory Committee on the Safety of Vaccines (ACSOV) was not sought for this submission. It has been recommended that implementation of the European Risk Management Plan Version: 5.0 dated 4 September 2012 with an Australian Specific Annex (revised as specified in the

sponsor's correspondence dated 28 March 2013), be a condition of approval. The Delegate accepted the evaluator's recommendation.

The RMP evaluator also made 2 recommendations with respect to the proposed PI:

- The PI should contain information about the risk of higher rates of febrile reactions when Prevenar 13 and Infanrix hexa are administered concomitantly. This was agreed by the sponsor and an amendment of the PI to this effect was recently approved by the TGA.

The *Precautions* section of the PI should also advise Healthcare Professionals that a higher risk of febrile seizures has been reported in association with the concomitant administration of Prevenar 13 and trivalent influenza vaccine (TIV) when compared to when these vaccines were given alone on separate days in children 6-59 months of age. In response the company noted that no such findings were apparent for the subsequent influenza season (2011-2012) which had the same TIV formulation or in the most recent season (2012-2013) which has a different TIV formulation and pointed to significant methodological issues with the data. It has been noted that the US FDA is currently developing a Mini-Sentinel study to examine this further and in the meantime the existing PI statements about both convulsions and febrile convulsions provide adequate risk minimisation. The risk was estimated to be about 18 excess cases per 100 000 doses for those aged 6-59 months, with a peak of 45 per 100 000 doses for those aged 16 months. Given the sponsor's arguments and the relatively low increase in risk, this seems reasonable.

Risk-benefit analysis

Summary of issues

EOI for the use of Prevenar 13 in children aged 6 to 17 years

- The submission is supported by immunogenicity data from a single clinical study in children ≥ 5 to 17 years of age;
- IgG GMC responses in the ≥ 5 to <10 years of age group were clearly non-inferior, even superior to the responses in toddlers, both against the 7 serotypes in common with Prevenar and the 6 additional serotypes. This provides a bridge to a population where efficacy has been demonstrated;
- OPA GMTs obtained 1 month after vaccination of subjects aged >10 years were non-inferior to OPA GMTs in the 5 through 9 year old group for all 7 common serotypes and, with the exception of serotype 3, for the 6 additional serotypes. Most of the subjects aged >10 years appeared to have already acquired immunity to most of the serotypes present in Prevenar 13, with at least 40% of subjects having antibody concentrations ≥ 1.0 $\mu\text{g/mL}$ prior to vaccination. Benefit in this group may be relatively limited;
- No new safety signals were identified in this age group.

Inclusion of nasopharyngeal carriage data in the PI

- The sponsor proposes including the effect of Prevenar 13 on nasopharyngeal carriage of vaccine-type serotypes as one of its modes of action for affording protection against invasive pneumococcal disease.
- The data relevant to such a claim (obtained in patients with acute otitis media) demonstrate an association but are too limited to conclude cause and effect.

- It is also unclear to what extent data obtained in patients with acute otitis media can be extrapolated to normal children and for other types of invasive pneumococcal disease.

The Delegate proposed that the data from these studies should be summarised in the *Clinical Trials* section of the PI rather than presented as being a mode of action.

Delegate considerations

Extension of indication to children aged 6 to 17 years

The key points to note with respect to this submission are:

- as was the case with the two previous submissions for Prevenar 13, this submission is based on comparative immunogenicity data (with Prevenar) rather than effect on disease endpoints which are extremely difficult to assess because of ethical considerations and sample size requirements;
- the submission is supported by immunogenicity data from a single clinical study in children ≥ 5 to 17 years of age; and
- there are no established serological correlates of protection in children ≥ 5 and 17 years of age.

Overall the results of this study demonstrate robust immune responses that are very likely to be protective in children 6-17 years of age as follows:

- the IgG GMC responses in the ≥ 5 to <10 years of age group were clearly non-inferior, even superior to the responses in toddlers, both against the 7 serotypes in common with Prevenar and the 6 additional serotypes. This provides a bridge to a population where efficacy has been demonstrated.
- in pneumococcal vaccine-naïve children aged 10 through 17 years of age, OPA GMTs were non-inferior to the 5 through 9 year old group for all 7 common serotypes and, with the exception of serotype 3, for the 6 additional serotypes. Also, non-inferiority of IgG GMC compared to Prevenar was demonstrated. The primary comparison for this group (OPA GMT versus the 5 through 9 year old group) is reasonable because protection is mediated by opsonophagocytic antibodies. This approach was used to extend the indication to adults >50 years of age.

However, most of the subjects aged >10 years appeared to have already acquired immunity to most of the serotypes present in Prevenar 13, with at least 40% of subjects having antibody concentrations ≥ 1.0 $\mu\text{g/mL}$ prior to vaccination. Given these subjects were pneumococcal vaccine-naïve, these findings suggest previous exposure. This indicates actual benefit of the vaccine for healthy individuals in this age group may be limited. It is of interest to note that Australian Technical Advisory Group on Immunisation (ATAGI) recommends that pneumococcal vaccine is not recommended for children in this age group who do not have a medical condition(s) associated with an increased risk of IPD, with the exception of older Indigenous children (aged >15 years) who have an increased risk of IPD, especially in the Northern Territory.

Although no immunogenicity, efficacy or safety data have been presented for at-risk children in this age group, it would be reasonable to expect that the benefits of Prevenar 13 in those children who are immunocompromised or have other underlying conditions would be greater, as the risk of pneumococcal infections as well as the associated morbidity and mortality is higher in such patients. For example, it is known that immunocompromised patients unable to mount an adequate immune response to pneumococcal capsular antigens, including those with asplenia, have the highest risk of

IPD. Also, patients with chronic heart or lung disease, diabetes, asthma, HIV and sickle cell disease have a significantly elevated risk of pneumococcal diseases.

No new safety signals were identified in the 6 through 17 years age group compared to the currently approved cohorts and given the demonstrated immunogenicity profile for this age group the benefit-risk balance was considered to be favourable. The ACPM was asked whether it agreed with this assessment of the data.

Other changes to the PI - nasopharyngeal carriage of *S. pneumoniae* serotypes

The sponsor submitted data from 4 studies in support of the proposed changes to the PI - 6096A1-3006, 6096A1-3010, ACTIV and the Atlanta study(Desai et al, 2012).¹⁶ However, the data proposed for inclusion in the PI are from only 2 of those studies; 6096A1-3006 and the ACTIV study. Appropriately, the sponsor is not proposing to include data contained within the abstract by Desai et al 2012, as this is unsuitable for evaluation, or data from Study 6096A1-3010. Study 6096A1-3010 suffered from poor subject recruitment and the immunogenicity portion of the study was based on a handful of cases and no conclusions can be drawn from this data. The surveillance data was also limited and this coupled with unusually low prevalence of IPD in the Yukon Delta population in 2009 made interpreting the change in serotype prevalence over time difficult.

The sponsor proposed to include the data from Study 6096A1-3006 and the ACTIV study under the subheading *Mode of Action* in which the preliminary text states:

“The protection afforded by Prevenar 13 is mediated by:the prevention of nasopharyngeal carriage of vaccine-type serotypes”.

As noted by the clinical evaluator, ACTIV is the only study to directly support the proposed statement. The sponsor provided only a brief summary of that study within the submission. However, the article by Cohen et al 2012¹⁴ has been obtained by this Delegate and from this it was confirmed that the study was well conducted. Importantly, methods used for obtaining nasopharyngeal swabs and for the culture and typing organisms were appropriate and standardised, and the bacteriologic analyses undertaken in laboratories were blinded. Also, apart from patients’ age, the demographic characteristics (sex, day care attendance, number of siblings, use of antibiotics 3 months before enrolment and history of acute otitis media) were similar across the groups in the study. Tabulated results from ACTIV have been reproduced below. From the table it can be appreciated that, at the time at of presentation with acute otitis media, a significantly lower proportion of Prevenar 13-vaccinated children had overall pneumococcal serotypes identified from their nasopharyngeal swabs than children exclusively vaccinated with Prevenar, as well as the additional serotypes in Prevenar 13 (in particular serotypes 19A and 7F) and serotype 6C.

Table 6. Nasopharyngeal Carriage, Serotypes Distribution and Penicillin Resistance According to Vaccination status.

	PCV7 Vaccinated Only (Non PCV13 Vaccinated) n (%) [95% CI] n = 285	PCV13 Recipients					
		Adequately PCV13 Vaccinated n (%) [95% CI] n = 486	<i>P</i> ^a	Partially PCV13 Vaccinated n (%) [95% CI] n = 165	<i>P</i> ^b	PCV13 Vaccinated (≥1 Dose) n (%) [95% CI] n = 651	<i>P</i> ^c
<i>Streptococcus pneumoniae</i>	184 (64.6) [59.0–70.1]	266 (54.9) [50.5–59.4]	0.008	84 (50.9) [43.2–58.6]	0.004	351 (53.9) [50.1–57.8]	0.002
PCV7 serotypes	4 (1.4) [0.3–2.8]	12 (2.5) [1.1–3.9]	0.3	3 (1.8) [0–3.9]	0.7	15 (2.3) [1.1–3.5]	0.4
6 additional serotypes in PCV13	59 (20.7) [16.0–25.4]	48 (9.9) [7.4–12.8]	<0.001	14 (8.5) [4.2–12.8]	<0.001	62 (9.5) [7.3–11.8]	<0.001
19A	44 (15.4) [11.2–19.7]	39 (8.2) [5.8–10.7]	0.001	10 (6.1) [2.4–9.7]	0.003	49 (7.5) [5.5–9.6]	<0.001
7F	8 (2.8) [0.9–4.7]	2 (0.4) [0–1.0]	0.005	1 (0.6) [0–1.8]	0.1	3 (0.5) [0–1.0]	0.002
6A	0	2 (0.4) [0–1.0]	0.3	1 (0.6) [0–1.8]	0.2	3 (0.5) [0–1.0]	0.3
3	7 (2.5) [0.6–4.3]	5 (1.0) [0.1–1.9]	0.1	2 (1.2) [0–2.9]	0.4	7 (1.1) [0.3–1.9]	0.1
1	0	0		0		0	
5	0	0		0		0	
6C	24 (8.4) [5.2–11.7]	17 (3.5) [1.9–5.1]	0.003	7 (4.2) [1.1–7.4]	0.009	24 (3.7) [2.2–5.1]	0.003
Non-PCV13 serotypes (excluding 6C)	97 (34.0) [28.8–39.7]	189 (38.9) [34.7–43.3]	0.1	60 (36.4) [29.4–43.9]	0.4	250 (38.4) [34.7–42.2]	0.1
Predominant non-PCV13 serotypes ^d							
35B	12 (4.2) [1.9–6.6]	24 (4.9) [3.0–6.9]	0.6	3 (1.8) [0–3.9]	0.2	27 (4.2) [2.6–5.7]	0.08
15A	12 (4.2) [1.9–6.6]	30 (6.2) [4.0–8.3]	0.2	5 (3.0) [0.4–5.7]	0.5	35 (5.5) [3.8–7.3]	0.4
15BC	13 (4.6) [2.1–7.0]	24 (4.9) [3.0–6.9]	0.8	6 (3.6) [0.8–6.5]	0.6	30 (4.6) [3.0–6.2]	0.9
11A	11 (3.9) [1.6–6.1]	22 (4.5) [2.7–6.4]	0.7	4 (2.4) [0.5–4.8]	0.4	26 (4.0) [2.5–5.5]	0.9
Penicillin nonsusceptible							
Intermediate	79 (27.7) [22.5–32.9]	103 (21.2) [17.5–24.8]	0.04	28 (17.0) [11.2–22.8]	0.01	131 (20.1) [17.0–23.2]	0.01
Resistant	6 (2.1) [0.4–3.8]	8 (1.7) [0.5–2.8]	0.6	4 (2.4) [0.5–4.8]	0.8	12 (1.8) [0.8–2.9]	0.8

^a*P* compares PCV7 vaccinated only versus adequately PCV13 vaccinated.

^b*P* compares PCV7 vaccinated only versus partially PCV13 vaccinated.

^c*P* compares PCV7 vaccinated only versus PCV13 vaccinated.

^dCarried by more than 3% of infants.

Note: children were adequately vaccinated with PCV13 for their age if they had received 2 doses before 12 months or at least 1 dose after this age and the second one; children were partially PCV13 vaccinated if they had received 1 dose of PCV13 according to the French guidelines.

The Delegate considered that ACTIV can be accepted as providing reasonably robust results, although there are uncertainties that need to be considered in the context of the sponsor's proposed preliminary text:

- the length of time between last vaccination and the nasopharyngeal sampling was not reported and there is no way of telling whether the data represents recent acquisition or long term carriage of vaccine-specific serotypes – at best one can say whether a specific serotype was/was not present at that single point in time;
- these children had acute otitis media and the nasopharyngeal flora of normal children could be quite different, making generalisation to the wider target population problematic. Also, it is unclear whether such data can be extrapolated to pneumococcal disease other than acute otitis media; and
- no information was reported as to whether attempts were made to identify the pneumococcal strain in the middle ear fluid during the episode of acute otitis media and its concordance or otherwise with the strain(s) present in the nasopharyngeal sample.

Few studies in the literature have prospectively investigated the temporal relationship of pneumococcal acquisition and/or carriage with pneumococcal disease in the same study subjects. It is generally accepted that colonisation of the nasopharynx is a relatively frequent event, sometimes manifesting with mild respiratory symptoms in the very young but disease is rare. Many colonisation episodes are of short duration, however, longitudinal studies in adults and children have shown that persistent colonisation with a specific serotype over many months can occur and this eventually results in the development of capsule-specific serum IgG, which is thought to play a role in mediating clearance of bacteria from the nasopharynx. Carriage of the organism by young people is thought to be the main source of transmission. Factors that come into play in determining whether the pneumococcus causes invasive disease in an individual include the virulence

of the serotype/strain and host factors such as integrity of the nasopharyngeal epithelium, the effectiveness of mechanical clearance of the organism, type-specific immunity and intercurrent illness.

Simell et al 2012¹⁹ cited a number of longitudinal studies²⁰ that support the notion that nasopharyngeal carriage is a predisposing condition for mucosal pneumococcal disease. They concluded the main predisposing event for disease was likely to be recent acquisition (presumably as a result of the absence of type-specific immunity), rather than the prolonged carrier state. Of note, Cohen et al¹⁴ report the prevalence at a single point of time (that is, the time of presentation with acute otitis media) as 'carriage'. On the other hand Simell et al⁹ defines nasopharyngeal 'carriage' in terms of ongoing colonisation; which requires that the presence of a specific serotype be demonstrated at successive time points. It is therefore important that any statement in the PI clearly sets out what was actually demonstrated, so as to avoid any confusion as to what is meant by 'carriage'.

The Delegate agreed with the clinical evaluator that whilst an association has been demonstrated, cause and effect cannot be considered to have been conclusively established because of the limitations and uncertainties around the dataset outlined above. Furthermore, an impact has not been demonstrated for all vaccine-type serotypes.

For these reasons, the Delegate was of the view that the results of the ACTIV and 6096A1-3006 studies should not appear under the heading *Mode of Action* and the preliminary text should not be included in the PI.

However, it is important to document effects on nasopharyngeal serotypes as they give a sense of the indirect (herd) protection (that is, likely effectiveness of the vaccine rather than its mode of action). Thus, it would be acceptable for the results of the 2 studies to be reported within the *Clinical Trials* section of the PI under a heading "*Effect on nasopharyngeal S. pneumoniae serotypes*", as follows:

Effect on nasopharyngeal S. pneumoniae serotypes

In a randomised double-blind study, 930 infants received Prevenar 13 and 933 received Prevenar (7-valent) at 2, 4, 6 and 12 months of age in Israel. The proportion of subjects with a newly identified nasopharyngeal (NP) acquisition in each vaccine group was assessed at 7, 12, 13, 18 and 24 months. Prevenar 13 significantly reduced newly identified NP acquisition of the 6 additional serotypes (and serotype 6C) combined and of individual serotypes 1, 6A, 6C, 7F, 19A when compared with Prevenar. Among the common serotypes, a significant reduction in the proportion of

¹⁹ Simell B, Auranen K, Kayhty H et al. The fundamental link between pneumococcal carriage and disease. *Expert Rev. Vaccines* 2012; **11**(7): 841-855. (Copy included in the ACPM materials)

²⁰ Gray et al 1980 correlated acquisition episodes and carriage periods of the pneumococcus with culture-confirmed pneumococcal disease in a study of 82 infants. These subjects underwent routine monthly swabbing of the nasopharynx from birth up to 6 months of age and then at 2- to 3-month intervals until 2 years of age. Information was also collected about any disease episodes experienced by the children. Although prolonged duration of carriage was common, 74% of infections (mostly acute otitis media) were caused by serotypes found less than a month before the infection (*J. Infect. Dis.* 1980; **142**(6): 923-933).

Syrjanen et al 2006 followed 329 children from 2 months until 2 years of age in the Finnish Otitis Media (FinOM) cohort study, obtaining ten scheduled nasopharyngeal samples and comprehensive information about respiratory infection and aetiologically confirmed episodes of acute otitis media. The serotype causing the infection was found in 99% of simultaneous nasopharyngeal samples in affected children. During the weeks preceding respiratory infection, children with pneumococcal otitis media had a significantly lower frequency of carriage specific to the serotype/group causing the disease compared with children of the same age who carried pneumococci during a respiratory infection but did not have pneumococcal otitis media (*Pediatr. Infect. Dis. J.* 2005; **25**(11): 1032-1036).

Sleeman et al 2005 obtained biweekly nasopharyngeal samples from 213 infants from 2 weeks to 3 months of age and then at monthly intervals until 6 months of age. Pneumococcal acquisition was significantly associated with office visits to general practitioners for nonspecific respiratory infections, whereas there was no evidence for an association between carriage and physician visits (*Pediatr. Infect. Dis. J.* 2005; **24**(2): 121-127).

subjects with newly identified NP acquisition of serotype 19F was observed in the Prevenar 13 group compared with the Prevenar group. For the remaining 6 common serotypes, similar rates of NP acquisition were observed in both vaccines groups.

In the ACTIV surveillance study in France conducted following the introduction of Prevenar (7-valent) and subsequently Prevenar 13, the prevalence of pneumococcal serotypes in nasopharyngeal swabs was determined in 943 children at the time of presentation with acute otitis media (Cohen et al 2012). The prevalence of pneumococcal serotypes overall was significantly reduced in children vaccinated with Prevenar 13 compared with Prevenar. In addition, Prevenar 13 significantly reduced the prevalence of the 6 additional serotypes (and serotype 6C) combined and individual serotypes 6C, 7F, 19A when compared with Prevenar.

Request to ACPM

The Delegate requested the Advisory Committee on Prescription Medicines' advice on the following issues:

EOI for the use of Prevenar 13 in children aged 6 to 17 years

- Whether there is sufficient evidence of immunogenicity and safety to support the use of Prevenar 13 in subjects aged 6 to 17 years for the prevention of pneumococcal disease;
- Whether the use of Prevenar 13 in subjects aged 6 to 17 years for the prevention of pneumococcal disease has a favourable benefit-risk balance.

PI changes on the effect of Prevenar 13 on nasopharyngeal carriage of S. pneumoniae

- Whether the surveillance data generated from the ACTIV study, coupled with the randomised controlled trial data from Study 6096A1-3006, are sufficient to conclude that one of the modes of action through which Prevenar 13 achieves its protective effect against invasive pneumococcal disease is through the prevention of nasopharyngeal carriage of the vaccine-type serotypes;
- If the ACPM considers that such a claim is unsupported, does the ACPM consider that the data from these studies may still be presented in the PI under *Clinical Trials*, as proposed by the Delegate?
- The Committee was 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.

Pre ACPM preliminary assessment

The Delegate found no reason to say, at this time, that the application to extend the indications for use of Prevenar 13 to include subjects aged 6 to 17 years should not be approved for registration.

Response from sponsor

Prevenar 13 was first approved in Australia in March 2010 for use in infants and children aged 6 weeks to 5 years of age. Approval has since been granted for use in adults (50 years and over). The benefits of this vaccine follow on from those afforded by the 7-valent pneumococcal vaccine, Prevenar (approved January 2001) which facilitated a large reduction in invasive pneumococcal disease in all markets where it was made available.

In this submission, Pfizer Australia Pty Ltd has applied to extend the paediatric indication of PREVENAR 13 to:

“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.”

Both the clinical evaluator and the TGA Delegate have recommended the approval of this application for the proposed indication.

In this pre-ACPM response, Pfizer provided comments on matters raised in the TGA Delegate’s Overview. The matters being addressed are identified by bold italic type.

The Delegate has sought the advice of the ACPM as to whether:

- ***“there is sufficient evidence of immunogenicity and safety to support the use of Prevenar 13 in subjects aged 6 to 17 years for the prevention of pneumococcal disease***
- ***the use of Prevenar 13 in subjects aged 6 to 17 years for the prevention of pneumococcal disease has a favourable benefit-risk balance.”***

Pfizer’s comments on immunogenicity (Benefit):

The proposed extension of the indication to include children 6 to 17 years of age is supported by data from clinical Study 6096A1-3011. The immunogenicity results show that healthy children age 5 to 10 years previously vaccinated with Prevenar have non-inferior, even superior, IgG responses compared to toddlers receiving a booster dose of Prevenar 13 (primary objective). Likewise, healthy, previously unvaccinated children 10 to 17 years were shown to have non-inferior opsonophagocytic activity (OPA) responses compared to healthy children 5 to 10 years and toddlers (secondary objective).

Comparison to post toddler responses in infants provides a bridge to immunogenicity in a population with known efficacy. These data support a conclusion that Prevenar 13 will be efficacious in those 6 to 17 years of age.

Thus, as noted by the clinical evaluator, both the primary and secondary immunogenicity objectives were successfully achieved in Study 6096A1-3011. The clinical evaluator concluded, *“based on the key immunogenicity findings, the vaccine shows immunogenicity for the age Group 10 to 17 years although many children, particularly in the older age group, are likely to have already come into contact with the serotypes present in the vaccine”*.

The Delegate has stated: ***“However, most of the subjects aged >10 years appeared to have already acquired immunity to most of the serotypes present in Prevenar 13, with at least 40% of subjects having antibody concentrations $\geq 1.0 \mu\text{g/mL}$ prior to vaccination. Given these subjects were pneumococcal vaccine-naïve, these findings suggest previous exposure. This indicates actual benefit of the vaccine for healthy individuals in this age group may be limited.”***

It is not unexpected that 40% of these children had antibody concentrations $\geq 1.0 \mu\text{g/mL}$ for at least one of the additional vaccine serotypes prior to vaccination, as older children have a fully mature immune system and to varying extents have been exposed to pneumococci already. The epidemiology of *S pneumoniae* is such that the incidence of disease is low in the 6 to 17 years age group, with the majority of disease being at the extremes of age.

Pfizer appreciates the fact that IgG antibodies to most of the Prevenar 13 serotypes in children aged 10 to 17 years, as measured by ELISA were observed prior to vaccination. However, functional antibody levels measured by OPA GMTs in this group before vaccination were low and similar to that seen in subjects aged 5 to 10 years. Significant increases in functional antibody levels were also seen after vaccination in subjects aged >10 years.

It should also be noted that Prevenar 13 provides protection against a total of 13 serotypes and so having antibodies to some of the vaccine serotypes prior to vaccination

does not preclude an individual from gaining immunological benefit from vaccination with Prevenar 13.

The Delegate stated: ***“Although no immunogenicity, efficacy or safety data have been presented for at-risk children in this age group, it would be reasonable to expect that the benefits of Prevenar 13 in those children who are immunocompromised or have other underlying conditions would be greater, as the risk of pneumococcal infections as well as the associated morbidity and mortality is higher in such patients. For example, it is known that immunocompromised patients unable to mount an adequate immune response to pneumococcal capsular antigens, including those with asplenia, have the highest risk of IPD. Also, patients with chronic heart or lung disease, diabetes, asthma, HIV and sickle cell disease have a significantly elevated risk of pneumococcal diseases.”***

Pfizer agrees with the Delegate that “at-risk” children vaccinated with Prevenar 13 would stand to gain greater immunological benefit than healthy children. The risk of pneumococcal infections is higher, and the morbidity and mortality greater in indigenous populations, in immunocompromised children and in those with specific underlying conditions such as sickle cell disease, asthma and HIV infection. The availability of Prevenar 13 to children aged 6 to 17 years will, therefore, be of greater benefit to at-risk and indigenous populations. Currently, for “medically at risk” children 4 years old and indigenous teenagers 15 years and over, the National Immunisation Program funds the 23-valent pneumococcal polysaccharide vaccine (23vPPV). Although there are no data comparing immune responses in children 5 to 17 years of age between Prevenar 13 and 23vPPV, there are concerns in the literature regarding the efficacy of 23vPPV in at risk populations. Prevenar 13, which in contrast to 23vPPV, acts through T-cell dependent mechanisms and establishes immunological memory, represents an opportunity to better protect “at-risk” children in this age group. Although the use of Prevenar 13 in the 5 to 17 year age group has not yet been approved by the TGA, given the morbidity and mortality associated with high risk conditions, the Australian Immunisation Handbook (10th Edition 2013) recommends that children aged 5 to 18 years with a pre-existing chronic medical condition associated with the highest increased risk of IPD, receive Prevenar 13, dependent on prior pneumococcal vaccination history.

Pfizer’s comments on safety (Risk):

It is important to note that the risks of the proposed extension of age indication, identified by the clinical evaluator, do not represent a risk to the safety of the individual.

The safety and efficacy of Prevenar 13 has already been extensively established in children aged from 6 weeks to 5 years. The safety database in 5 to 17 year olds consists of 598 children from the pivotal study (6096A1-3011). There were no new safety signals reported with Prevenar 13 from this study. Furthermore, as noted by the clinical evaluator, the incidence of local reactions and systemic events were consistent with those of other vaccines.

Therefore, the current safety profile of Prevenar 13 is maintained in children aged 6 to 17 years. The results of Study 3011 demonstrate substantial immune responses that are protective in children 6 to 17 years of age and Prevenar 13 has been shown to have an acceptable safety profile in this population. The benefit-risk balance is therefore favourable.

Benefit – risk balance

Based on demonstrated immunogenicity in the proposed age group (6 to 17 year olds) and the corresponding absence of new or elevated incidences of adverse reactions reported, the sponsor believed that the benefit-risk balance is acceptable and is supportive of a positive outcome of this application.

Reduction of Nasopharyngeal Carriage

The Delegate has indicated that the proposed changes to the Mode of Action section of the PI are not acceptable. However, the data provided have been deemed worthy of inclusion in the Clinical Trials section of the PI. Therefore, the Delegate has proposed wording for inclusion in the Clinical Trials section.

Pfizer acknowledged the limitations of the ACTIV study in demonstrating the prevention of nasopharyngeal carriage, however, Study 6096A1-3006 clearly establishes prevention of colonisation (nasopharyngeal acquisition) and therefore the sponsor proposed to include the following text at the end of the Mode of Action section:

The protection afforded by Prevenar 13 vaccination is also mediated by the prevention of nasopharyngeal acquisition of vaccine-type serotypes (see Clinical Trials).

The sponsor agreed to include the Delegate's proposed text and tables in the *Clinical Trials* section, which present clinical data from the ACTIV and 6096A1-3006 studies, showing the effect of immunisation with Prevenar 13 on nasopharyngeal serotypes. These, and the other changes proposed by the Delegate have been made and are annotated in the PI that was included with the sponsor's response.

Conclusion

Prevenar 13, when administered to children of 5 to 17 years, is immunogenic and has an acceptable safety profile. Prevenar 13 has already been approved in the EU, USA and Canada for use in this age group and Pfizer Australia proposed the following indication for Prevenar 13 in Australia:

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.

The sponsor also proposed the inclusion of new text in the *Clinical Trials* section of the PI (see above), describing the effects of Prevenar 13 on nasopharyngeal serotypes.

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 ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Prevenar 13 suspension for injection containing pneumococcal purified capsular polysaccharides (2.2 µg each of serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 23F and 4.4 µg of serotype 6B) conjugated to a total of 32 µg of diphtheria CRM₁₉₇ protein to have an overall positive benefit-risk profile for the indication as proposed;

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.

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 PI and CMI and specifically advised on the inclusion of the following:

The data from the ACTIV study be included under *Clinical Trials* with a statement similar to the following:

- *Prevenar 13 is associated with the prevention of nasopharyngeal colonisation of vaccine type serotypes and this may contribute to mediation of protection against pneumococcal disease.*
- The ACPM agreed with the Delegate that it would not be appropriate to describe the effects on nasopharyngeal colonisation in the *Pharmacology (Mode of Action)* section

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 Prevenar 13 Vaccine containing pneumococcal polysaccharide conjugate vaccine 13 valent adsorbed 0.5 mL for the new indication: “*children from 6 weeks to 17 years of age.*”

The full indications now read 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.

Specific conditions applying to these therapeutic goods

Risk management plan

The Prevenar 13 Vaccine (containing 2.2 µg of pneumococcal purified capsular polysaccharides for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F and 23F and 4.4 µg of serotype 6B) Risk Management Plan (RMP), Version: 5.0 dated 4 September 2012 with an Australian Specific Annex, to be revised as specified in the sponsor’s correspondence dated 28 March 2013, included with submission PM-2012-02211-3-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The reports are to at least meet the requirements for Periodic Safety Update Reports (PSURs) as described in the European Medicines Agency’s Guideline on Good Pharmacovigilance Practices (GVP) Module VII-Periodic Safety Update Report, Part VII.B. “Structures and processes”. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The annual submission may be made up of two Periodic Safety Update Reports each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

Attachment 1. Product Information

The Product Information approved 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

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