

**5.05 DIPHTHERIA, TETANUS, PERTUSSIS, HEPATITIS B,  
POLIOMYELITIS AND HAEMOPHILUS INFLUENZAE  
TYPE B CONJUGATE VACCINE (DTPa-HB-IPV-Hib),  
0.5 mL pre-filled syringe,  
Vaxelis<sup>®</sup>,  
Sanofi-aventis Australia PTY LTD**

**1 Purpose of submission**

- 1.1 The Category 2 submission requested National Immunisation Program (NIP) listing for Vaxelis, a hexavalent vaccine containing antigens against diphtheria (D), tetanus (T), pertussis (Pa), hepatitis B (HB), poliomyelitis (IPV) and invasive infections caused by *Haemophilus influenzae* Type b (Hib) (DTPa-HB-IPV-Hib) as a primary vaccine course in infants at 2, 4 and 6 months of age, and in children less than 10 years of age who have not previously received DTPa-HB-IPV-Hib vaccination.
- 1.2 Listing was requested on the basis of a cost-minimisation approach versus Infanrix Hexa<sup>®</sup> (DTPa-HB-IPV/Hib). The key components of the clinical issue addressed by the submission are summarised in Table 1.

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Infants aged around 2, 4 and 6 months of age; and Children less than 10 years of age who have not previously received DTPa-HB-IPV-Hib vaccination
Intervention	A three dose course of Vaxelis hexavalent vaccine (DTPa-HB-IPV-Hib) adjuvanted
Comparator	A three dose course of Infanrix Hexa hexavalent vaccine (DTPa-HB-IPV-Hib) adjuvanted
Outcomes	Immunogenicity: Vaccine-induced antibody responses against antigens included in Vaxelis, proportion of individuals achieving post-vaccination antibody titres above established thresholds and geometric mean antibody titres (GMTs).  Coadministration: Immune responses when administered with other routine infant vaccines Safety: proportion of subjects with solicited/unsolicited adverse events by severity and potential relationship to vaccination.
Clinical claim	In the target population of infants aged around 2, 4 and 6 months, a three dose primary series of Vaxelis will provide non-inferior comparative effectiveness and safety to Infanrix Hexa. Although clinical trial evidence is limited for the proposed catch-up population (children less than 10 years of age), it is reasonable to extrapolate this non-inferiority to the proposed catch-up setting based on biological plausibility and real world experience.

Source: Table 1-1, p12 of the submission.

DTPa = tetanus, diphtheria, acellular pertussis; HB = hepatitis B; IPV = inactivated polio virus; Hib = *Haemophilus Influenzae* type B

## 2 Background

### **Registration status**

- 2.1 **TGA status at time of PBAC consideration:** Vaxelis is not registered as a primary vaccine course in infants or catch up vaccine in children, and the submission was made under the TGA/PBAC Parallel Process. The proposed TGA indication is as follows:

Vaxelis (DTPa-HB-IPV-Hib) is indicated for primary and booster vaccination in infants and toddlers from the age of 6 weeks, against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by *Haemophilus influenzae* type b (Hib). The use of Vaxelis should be in accordance with official recommendations.

- 2.2 The TGA Delegate noted in the Delegate's Overview that all predefined acceptability of response targets and non-inferior immunogenicity criteria were satisfactorily met and that the overall adverse effects profile was consistent with that expected of a DTPa-HB-IPV-HiB vaccine. The TGA Delegate considered that the data supported the proposed indication and vaccination schedule.

### 3 Requested listing

#### Requested listing on the National Immunisation Program.

<b>Vaxelis (DTPA-HB-IPV-HIB (PRP-OMPC), 5mL pre-filled Luer-Lock syringe.</b>					
<b>NIP listing: Primary vaccination<sup>a</sup> series at 2, 4 and 6 months of age, and catch up immunisation of unvaccinated children less than 10 years of age.</b>					
<b>Population requested</b>	<b>Number of doses, timing (primary series)</b>	<b>Booster frequency</b>	<b>Program setting (all that apply)</b>	<b>Implications for other NIP vaccines</b>	<b>Price per dose</b>
All infants from 6 weeks of age regardless of medical risk factors or indigenous status	3 doses (primary series) in the current schedule at 2,4 and 6 months	Not requested	GPs OR treating specialist OR child/community health clinic	Unchanged (alternative brand only)	To be advised based on Nationally Negotiated Price for the Infanrix Hexa comparator
All children up to age 10 eligible for catch-up doses according to the 'no jab no pay' provisions in the NIP Determination which apply to items listed for use in infants	In children aged <10 years, the number of doses administered is influenced by the age at which they start catch-up vaccination, the number of doses needed, and the minimum intervals between doses according to the Australian Immunisation Handbook.	Not requested	GPs OR treating specialist OR child/community health clinic	Unchanged (alternative brand only)	To be advised based on Nationally Negotiated Price for the Infanrix Hexa comparator

Source: p28, Section 3.2 of the ATAGI Pre-submission Advice for Vaxelis (Final version)

<sup>a</sup>The ATAGI pre-submission advice noted that there was no evidence to support a mixed schedule. The 3-dose series should be given using either Vaxelis or Infanrix Hexa.

GP = General practitioner; NIP = National Immunisation Program; PRP = polyribosyl-ribitol-phosphate; OMPC = Outer membrane protein complex (*Neisseria meningitidis*).

- 3.1 The current NIP schedule includes a booster dose of DTPa and Hib vaccine to be administered at 18 months.
- 3.2 The submission noted that the current NIP price of Infanrix Hexa is confidential, and that upon receipt of a positive recommendation by PBAC, the Sponsor would endeavour to match the revealed NIP list price of Infanrix Hexa. The submission further assumed that the two vaccines would subsequently be included in a national procurement process. The actual price paid for Vaxelis would depend on the outcome of the competitive tender process.
- 3.3 No changes were proposed to the current catch-up program for DTPa, HB, IPV, or Hib vaccines.
- 3.4 The submission did not provide clinical evidence to support interchangeability between Vaxelis and Infanrix Hexa. The Australian Technical Advisory Group on Immunisation (ATAGI) considered that children who have commenced Vaxelis or

Infanrix Hexa should continue receiving the same vaccine for their 4 and 6 month scheduled doses if possible (p58 of the ATAGI advice to PBAC).

- 3.5 ATAGI (p29 of the ATAGI advice to the PBAC) noted that all the monovalent Hib vaccines approved, which will be used as a booster vaccine at 18 months of age, are polyribosyl-ribitol-phosphate tetanus (PRP-T) vaccines, while Vaxelis uses polyribosyl-ribitol-phosphate conjugated to the outer membrane protein complex of *Neisseria meningitidis* (PRP-OMPC). The evidence provided in support of the safety and effectiveness of schedules that combine different types of Hib conjugate vaccines (Hib PRP-OMPC and Hib PRP-T) was of limited relevance given the comparator (Pentacel).
- 3.6 Regarding the concomitant use of other vaccines, ATAGI noted the following (p29 of the ATAGI advice to the PBAC):
- No clinically important interference was observed when Vaxelis is concomitantly administered with rotavirus vaccines, pneumococcal conjugate vaccines, the measles-mumps-rubella-varicella (MMRV) vaccine and two different meningococcal C vaccines (MenC-TT and MenC-CRM).
  - Concomitant use of Vaxelis has not been studied with quadrivalent meningococcal serogroups A, C, W and Y strains (MenACWY) vaccines; these are funded under the NIP for vaccination at 12 months of age (Nimenrix®) and are available through private prescription from 6 weeks of age<sup>a</sup>. MenACWY is strongly recommended for all healthy infants (indigenous and non-indigenous) and infants at increased medical risk<sup>b</sup> from 6 weeks of age. Also, there was also no evidence to support concomitant use with 4CMenB (four-component MenB vaccine; Bexsero®) and influenza vaccines.
- 3.7 ATAGI (p1 of the ATAGI advice to PBAC) considered that inclusion of Vaxelis on the National Immunisation Program (NIP) as a 3+1 schedule (2, 4, 6, and 18 months), with inclusion of a hexavalent booster (DTPa-HB-IPV-Hib) at 18 months might be beneficial to overcome potential waning of long term immunity to hepatitis B after the primary immunisation course, noting that a booster for hepatitis B is currently not listed on the NIP. However, the submission did not propose listing of Vaxelis for use as a booster on the NIP. The pre-PBAC Response stated that the inclusion of a hexavalent booster (DTPa HB IPV Hib) at 18 months represents a significant change to the current

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<sup>a</sup> FactSheet: Meningococcal vaccines for Australians: Information for immunisation providers. National Centre for Immunisation Research and Surveillance (NCIRS).

[https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKewiniuHe9p71AhUQgtgFHsTAukQFnoECAIQAAQ&url=https%3A%2F%2Fwww.ncirs.org.au%2Fsites%2Fdefault%2Ffiles%2F2019-04%2FMeningococcal\\_FactSheet\\_April2019\\_Final.pdf&usg=AOvVaw1p4PSru2Enp-Z2Xr5glluh](https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKewiniuHe9p71AhUQgtgFHsTAukQFnoECAIQAAQ&url=https%3A%2F%2Fwww.ncirs.org.au%2Fsites%2Fdefault%2Ffiles%2F2019-04%2FMeningococcal_FactSheet_April2019_Final.pdf&usg=AOvVaw1p4PSru2Enp-Z2Xr5glluh) (Accessed 7 January 2022).

<sup>b</sup> Increased risk of meningococcal disease, including inherited defects or deficiency of properdin or complement components, current or future treatment with eculizumab, functional or anatomical asplenia, HIV infection and haematopoietic stem cell transplant (FactSheet National Centre for Immunisation Research and Surveillance (NCIRS)).

schedule which has been in place for almost 10 years and had not been raised by either ATAGI or the Immunisation Branch with Sanofi prior to being discussed in ATAGI's pre-submission advice. The pre-PBAC Response noted that consultation with relevant stakeholders would be required to ensure any implications of this proposed change to the schedule are fully considered and indicated the sponsor was willing to work with the Department, ATAGI and PBAC towards this objective.

## 4 Population and disease

- 4.1 Implementation of nationally funded immunisation programs in Australia since the 1950s has resulted in a significant decline of vaccine-preventable diseases (VPD), including those prevented by hexavalent vaccines (tetanus, pertussis, diphtheria, poliomyelitis, hepatitis B and *Haemophilus influenzae* type b).
- 4.2 Vaxelis (a DTPa-HB-IPV-Hib vaccine) is a combination bacterial/viral vaccine that induces the production of antibodies against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive infections caused by *Haemophilus influenzae* type b.
- 4.3 The submission positioned Vaxelis as an alternative to Infanrix Hexa when used as the primary course in infants at 2, 4 and 6 months of age for DTPa-HB-IPV-Hib vaccination.
- 4.4 At the November 2014 PBAC meeting (paragraph 7.1, Public Summary Document, November 2014 PBAC Meeting), the PBAC recommended including an 18-month booster dose of the DTPa vaccine (Infanrix®) on the NIP for the prevention of pertussis on the basis of cost-effectiveness compared with the comparator schedule without the booster. The NIP had previously included a booster dose of DTPa at approximately 18 months until 2003, when it was removed with the introduction of the booster dose for adolescents (15-17 years). The PBAC considered the removal of the 18-month dose may have contributed to resurgence in pertussis notifications in Australia between 2008 and 2012.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## 5 Comparator

- 5.1 The submission appropriately nominated Infanrix Hexa as the main comparator. Infanrix Hexa is currently the only hexavalent vaccine supplied on the NIP. Infanrix Hexa has not been previously considered by the PBAC. Hexaxim, another hexavalent vaccine listed on the NIP since October 2015 (on the basis of non-inferiority to Infanrix Hexa), is not currently available or supplied in Australia. ATAGI advised that Hexaxim will not be continued (p3 of the ATAGI advice to PBAC).
- 5.2 The main differences between Vaxelis and Infanrix Hexa are:
  - Vaxelis is available as a liquid suspension in a pre-filled syringe (ready to use) while Infanrix Hexa is available as a lyophilized powder (Hib component) + liquid suspension (DTPa-HBV-IPV component) and requires reconstitution before use;

- Vaxelis has a lower threshold for diphtheria toxoid content compared to that for Infanrix Hexa ( $\geq 20$  vs  $\geq 30$  IU). The threshold for diphtheria toxoid levels in Vaxelis are lower than current international standards ( $\geq 30$  IU)<sup>c</sup>.
- The number and amount of pertussis antigens: For pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN), Vaxelis has a lower antigen content than Infanrix Hexa (PT 20  $\mu\text{g}$  vs. 25  $\mu\text{g}$ , FHA 20  $\mu\text{g}$  vs. 25  $\mu\text{g}$ , and PRN 3  $\mu\text{g}$  vs. 8  $\mu\text{g}$ ). On the other hand, Vaxelis contains additional pertussis antigens (fimbriae types 2 and 3 (FIM2/3)) compared to Infanrix Hexa. The pre-PBAC Response noted the TGA clinical evaluator considered that the FIM types 2 and 3 antigens may provide added protection compared to those without FIM antigens (such as Infanrix Hexa or Hexaxim) (p58, TGA Clinical Evaluation Report (CER)). The pre-PBAC Response considered that Vaxelis may provide additional clinical utility against a disease which remains one of Australia's most challenging vaccine-preventable diseases, noting that FHA-negative and PRN-negative *B. pertussis* were observed in Australia during the 2013–2017 pertussis epidemic.
- The quantity of PRP in Hib and its carrier protein: Vaxelis has lower Hib polysaccharide content compared to Infanrix Hexa (3  $\mu\text{g}$  compared to 10  $\mu\text{g}$ ). The Vaxelis Hib component is conjugated to the outer membrane protein complex of *Neisseria meningitidis* (OMPC) (PRP-OMPC) compared to tetanus toxoid (TT) for Infanrix Hexa (PRP-TT).

For more detail on PBAC's view, see section 7 PBAC outcome.

## 6 Consideration of the evidence

### **Sponsor hearing**

6.1 There was no hearing for this item.

### **Consumer comments**

6.2 The PBAC noted and welcomed the input from organisations (2) via the Consumer Comments facility on the PBS website. The comments from the Global Healthy Living Foundation Australia (GLHF Australia) noted that reducing the vaccination burden in terms of number of injections with a hexavalent vaccine such as Vaxelis may in turn increase vaccine uptake and increase completion of vaccine series. GLHF Australia noted that the introduction of a second hexavalent combination vaccine would allow choice, improve consumer access and introduce competitiveness in the market for

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<sup>c</sup> World Health Organization. Annex 4 - Recommendations to assure the quality, safety and efficacy of diphtheria vaccines (adsorbed). Replacement of Annex 2 of WHO Technical Report Series, No. 800, and Annex 5 of WHO Technical Report Series, No. 927.

[https://www.who.int/biologicals/vaccines/Diphtheria\\_Recommendations\\_TRS\\_980\\_Annex\\_4.pdf?ua=1](https://www.who.int/biologicals/vaccines/Diphtheria_Recommendations_TRS_980_Annex_4.pdf?ua=1) ; 2014 [accessed 14 December 2021].

critical vaccines. The comments from the Immunisation Foundation of Australia noted that prefilled syringes help make the vaccination process quicker for children, potentially reducing anxiety, and that the earlier and more robust immune response for Hib with Vaxelis is likely to be beneficial to the health of Aboriginal and Torres Strait Islander children, given that they are at higher risk of contracting Hib disease. The PBAC noted that this advice was supportive of the evidence provided in the submission.

### **Clinical studies**

- 6.3 The submission was based on two head-to-head randomised trials comparing immunogenicity and safety outcomes between Vaxelis and Infanrix Hexa (V419-007 and V419-008 (herein referred to as Studies 007 and 008, respectively)) when given concomitantly with Prevnar 13<sup>®d</sup> (both trials), RotaTeq<sup>®e</sup> (both trials), Rotarix<sup>®</sup> (Study 008 only), and ProQuad<sup>®f</sup> (Study 007 only) in a 2, 3 and 4 month primary dose series (3+1; Study 007) and a 2 and 4 month primary dose series (2+1; Study 008) followed by a 11-12 month booster for both studies. The time points of the dosing schedule differed between the key studies and the proposed Australian setting. The ATAGI advised that the difference between the trial setting and proposed Australian setting in terms of dosing schedule is unlikely to affect vaccine efficacy and safety.
- 6.4 The proposed dosing schedule for the primary series (identical to that for Infanrix Hexa) is at 2, 4 and 6 months. No booster dose was proposed in the submission.
- 6.5 Supportive evidence provided in the submission included:
- Extension Study PRI03C - a non-randomised parallel group study that assessed the long-term persistence of hepatitis B and pertussis antibody responses in healthy 4 to 5-year-old children approximately 4 years after the primary series and booster vaccination from Studies 007 (3+1 schedule), and 008 (2+1 schedule). Given the comparator was Infanrix Hexa in the primary key studies, this study was considered relevant in terms of longer term data.
  - Studies 005 and 006 - two randomised trials (based in the US) to evaluate the safety and immunogenicity of Vaxelis compared with Pentacel<sup>®</sup> (DTPa-IPV-Hib pentavalent vaccine) plus Recombivax HB<sup>®</sup>, when given concomitantly with Prevnar 13 and RotaTeq in a 2, 4 and 6 month primary dose series schedule. Although the time points of the dosing schedule for the primary series are similar to those proposed in Australia, the relevant comparator (Infanrix Hexa) was not assessed in these studies. The trial comparators, Pentacel and Recombivax HB, are not in use in Australia. Thus Studies 005 and 006 do not inform the comparative effectiveness and safety with regard to the submission comparator.

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<sup>d</sup> Pneumococcal conjugate vaccine

<sup>e</sup> Rotavirus vaccine

<sup>f</sup> Measles, Mumps, Rubella, and Varicella combination vaccine

6.6 Details of the studies presented in the submission are provided in Table 2.

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Key studies (direct comparison with Infanrix Hexa)</b>		
Study 007	A phase III randomized, double-blind, active-comparator controlled clinical trial to study the safety, tolerability, and immunogenicity of V419 in healthy infants when given at 2, 3, 4, and 12 months (V419-007)	July 2014
	Vesikari T et al. A phase III Randomized, Double-blind, Clinical Trial of an Investigational Hexavalent Vaccine Given at Two, Three, Four and Twelve Months	Pediatr Infect Dis J. 2017; 36:209-215
Study 008	A phase III randomized, double-blind, active-comparator controlled clinical trial to study the safety, tolerability and immunogenicity of V419 in healthy infants when given at 2, 4, and 11 to 12 months.	July 2014
	Silfverdal S et al. A phase III randomized, double-blind, clinical trial of an investigational hexavalent vaccine given at 2, 4, and 11-12 months	Vaccine 2016; 34(33):3810-6
<b>Supportive study – Extension to direct comparison Studies 007 and 008.</b>		
Extension PRI03C	Long-Term Persistence of Hepatitis B and Pertussis Antibody Responses in Healthy 4 To 5 Year-Old Children Previously Vaccinated With a 2-Dose Or 3-Dose Infants Series and Toddler Dose With Vaxelis or Infanrix hexa. Follow up of infants included in Studies 007 and 008.	September 2017
	Vesikari T et al. Hepatitis B and pertussis antibodies in 4- to 5-year-old children previously vaccinated with different hexavalent vaccines	Hum Vaccin Immunother. 2020; 16(4):867-874
<b>Other supportive studies (non-comparative to Infanrix Hexa)</b>		
Study 005	A phase III randomized, open-label, active-comparator controlled clinical study to evaluate the safety, tolerability, and immunogenicity of V419 in infants when given at 2, 4, and 6 months concomitantly with Prevnar 13™ and RotaTeq™.	March 2014
	Marshall GS et al. Immunogenicity, Safety, and Tolerability of a Hexavalent Vaccine in Infants.	Pediatrics. 2015; 136(2): e323-32.
Study 006	A phase III randomized, partially double-blind, active-comparator-controlled, lot-to-lot consistency clinical study to evaluate the safety, tolerability, and immunogenicity of V419 in healthy infants when given at 2, 4, and 6 months concomitantly with Prevnar 13™ and RotaTeq™.	May 2014
	Block, S. L. et al. Lot-to-lot Consistency, Safety, Tolerability and Immunogenicity of an Investigational Hexavalent Vaccine in US Infants.	Pediatr Infect Dis J. 2017; 36(2):202–208.

Source: Table 2.2, p25 of the submission

6.7 The key features of the direct randomised trials are summarised in Table 3.

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
<b>Vaxelis vs Infanrix Hexa</b>					
Study 007	1217	R, DB 13 mths	Low	Healthy infants	Immune response (antibody levels) and AEs
Study 008	1315	R, DB 12-13 mths	Low	Healthy infants	Immune response (antibody levels) and AEs

Source: Sections 2.3-2.4 of the submission.

DB = double blind; R = randomised; AE = adverse event.

- 6.8 The main outcome of the submission was the proportion of patients achieving target seroprotection/seroconversion antibody levels which were based on established correlates/surrogates of protection for diphtheria, tetanus, polio, Hib and Hep B antigens. There are no known established correlates of protection for pertussis.
- 6.9 The non-inferiority of the vaccine-induced response rate was tested individually for each component involved, by rejection of the null hypothesis, or equivalently by establishing that the lower limit of the 2-sided 95% confidence interval (CI) for response rate difference between the 2 groups (Vaxelis group minus Infanrix Hexa group) for each component was greater than the prespecified limit.
- 6.10 Non-inferiority margins were based on clinical meaningfulness of the difference between the groups being compared. The margin for response rate was 5 percentage points for antigens with an expected response rate >95% and 10 percentage points for antigens with an expected response rate ≤95% (p22 of the TGA CER). Pertussis FIM 2/3 are not components of the comparator Infanrix Hexa, and therefore was not an endpoint for the non-inferiority hypothesis.
- 6.11 Overall, the endpoints, prespecified non-inferiority margins, and methods of statistical analysis were reasonable. ATAGI noted (p1 of the ATAGI advice to PBAC) that correlates of protection were accepted as indicators of presumptive seroprotection. However, the relationship between immunological markers and clinical protection against disease of any severity remains insufficiently defined for the pertussis vaccine components.
- 6.12 In the March 2015 PBAC consideration of Hexaxim (Paragraph 7.5, Public Summary Document, March 2015 PBAC Meeting), the advice from ATAGI was that for the pertussis antigens PT and FHA, as there were no established correlates of protection, a ≥4-fold increase in titre above baseline was used to indicate seroconversion. Further, ATAGI noted the relationship between immunological markers and clinical protection against severe or any disease was not well defined for pertussis vaccines.

## ***Comparative effectiveness***

### **Study 007**

- 6.13 Primary immunogenicity results for the comparison between Vaxelis and Infanrix Hexa in Study 007 are summarised in Table 4. Immunogenicity analyses were based on the Per Protocol Revised Window (PP-RW) population<sup>§</sup>, and not on the number of randomised patients. Response was reported at one month post-Dose 3 (i.e. at 5

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<sup>§</sup> All subjects who met the inclusion criteria, who were not protocol violators, who received vaccinations within acceptable day ranges, and had serology results within the specified day ranges, were included in the PP immunogenicity analyses. PP-RW (Per Protocol Revised Window) population was defined as the PP population using a blood draw sample window of Days 28 to 51 following Dose 3 or the Toddler dose.

months) and one month post-Toddler dose (i.e. about 12 months). Primary analysis for antigen response specific to pertussis was limited to the post-Toddler dose.

**Table 4: Study 007: Immunogenicity response of Vaxelis vs. Infanrix Hexa at 1-month post-Dose 3 and post-Toddler dose (PP-RW population)**

Timepoint	Antigen	Endpoint	Estimated response, n (%)		Estimated difference, % (95% CI)	NI margin, %	NI criteria met/not met
			Vaxelis (N=598)	Infanrix Hexa (N=590)			
1 month post-Dose 3 (one month following the infant series [visit4])	Hib (PRP)	% with titre $\geq 0.15 \mu\text{g/mL}$	550 (98.36)	521 (86.99)	11.37 (8.44, 14.68)	-10	Met
	Diphtheria (D)	% with titre $\geq 0.01 \text{ IU/mL}$	542 (99.81)	517 (99.80)	-0.00 (-0.95, 0.96)	-10	Met
	Tetanus (T)	% with titre $\geq 0.01 \text{ IU/mL}$	538 (100.00)	519 (100.00)	0.00 (-0.71, 0.74)	-5	Met
	IPV1	% with Nab $\geq 1:8$ dilution	547 (100.00)	528 (99.81)	0.19 (-0.15, 1.07)	-5	Met
	IPV2	% with Nab $\geq 1:8$ dilution	547 (99.82)	530 (99.62)	0.19 (-0.69, 1.21)	-5	Met
	IPV3	% with Nab $\geq 1:8$ dilution	545 (100.00)	525 (100.00)	0.00 (-0.70, 0.73)	-5	Met
1 month post-Toddler dose	HBsAg	% with titre $\geq 10 \text{ mIU/mL}$	551 (99.64)	531 (99.06)	0.58 (-0.49, 1.85)	-10	Met
	PT	% seroresponse <sup>a</sup>	543 (99.82)	523 (98.49)	1.33 (0.32, 2.86)	-10	Met
	FHA	% seroresponse <sup>a</sup>	542 (97.22)	524 (99.81)	-2.59 (-4.39, -1.29)	-10	Met
	PRN	% seroresponse <sup>a</sup>	543 (98.89)	523 (98.86)	0.03 (-1.40, 1.52)	-10	Met

Source: Table 2.20, p42 of the submission.

<sup>a</sup>Seroresponse was defined as follows: if pre-vaccination antibody concentration was  $<4\text{X LLOQ}$ , then the post-vaccination antibody concentration was  $\geq 4\text{X LLOQ}$ ; If pre-vaccination antibody concentration was  $\geq 4\text{X LLOQ}$ , then the post-vaccination antibody concentration was  $\geq$  pre-vaccination levels.

CI = Confidence interval; FHA = Filamentous hemagglutinin; FIM = Fimbriae types 2 and 3; HBsAg = Hepatitis B surface antigen; IPV = Inactivated poliovirus; IU = International unit; Nab = Neutralizing antibodies; NI = Non-inferiority; PP-RW = Per-protocol-revised window population; PRN = Pertactin; PRP = Polyribose ribitol phosphate (Haemophilus B conjugate); PT = Pertussis toxin; LLOQ = lower limit of quantification.

- 6.14 For the primary analyses, the group difference (Vaxelis group minus Infanrix Hexa group) met the prespecified non-inferiority margin for all prespecified endpoints, indicating that Vaxelis was non-inferior to Infanrix Hexa group.
- 6.15 For the primary analysis of Hib (PRP), the group difference in response rate (anti-PRP  $\geq 0.15 \mu\text{g/mL}$ ) between Vaxelis and Infanrix Hexa (at one month post-Dose 3) was 11.37% (95% CI: 8.44%, 14.68%;  $p < 0.001$ ), favouring Vaxelis over Infanrix Hexa. It is unclear whether this was due to the different PRP antigen forms between the two hexavalent vaccines. In Vaxelis, PRP (3  $\mu\text{g}$ ) was conjugated to the outer membrane protein complex (OMPC 50  $\mu\text{g}$ ) of *Neisseria meningitidis* compared to Infanrix Hexa where PRP (10  $\mu\text{g}$ ) was bound to tetanus toxoid (TT  $\sim 25 \mu\text{g}$ ).
- 6.16 Tertiary immunogenicity analyses showed that the anti-PRP geometric mean titre (GMT) was significantly higher in subjects who received Vaxelis compared to subjects

who received Infanrix Hexa at one month post-Dose 3 (3.90 vs 0.65) and at Month 12 pre-Toddler dose (1.19 vs 0.24). However, the higher anti-PRP GMT in Vaxelis was not sustained after the post-Toddler (booster) dose; the anti-PRP GMT was lower in subjects who received Vaxelis (6.79 (95% CI: 6.11 to 7.54)) versus subjects who received Infanrix Hexa (21.39 (95% CI: 18.77 to 24.37)). This may be indicative of more rapid waning of immunity against PRP in the Vaxelis group. However, an early high Hib response with an OMPC-based vaccine may benefit indigenous infants in whom the disease burden is higher at an early age.

- 6.17 Additional tertiary immunogenicity analyses, at one month post-Dose 3 (post primary series), were also presented in the CSR for Study 007. Seroresponse rates were significantly lower in the Vaxelis group compared to the Infanrix Hexa group (with non-overlapping 95% CIs) for the following pertussis components:
- PRN: Vaxelis 86.74% (95% CI: 83.55%, 89.52%) versus Infanrix Hexa 92.32% (95% CI: 89.65%, 94.48%); and
  - FHA: Vaxelis 89.02% (95% CI: 86.03%, 91.55%) versus Infanrix Hexa 96.65% (95% CI: 94.70%, 98.04%).
- 6.18 Secondary analysis for the concomitant administration with ProQuad (MMRV combination vaccine) indicated that the group difference in rates (Vaxelis with ProQuad group vs. Infanrix Hexa with ProQuad group) met the prespecified non-inferiority criteria for all prespecified endpoints, indicating that Vaxelis was non-inferior to Infanrix Hexa when used concomitantly with ProQuad.

### Study 008

- 6.19 Immunogenicity analyses were based on the PP-RW population<sup>h</sup>. Response was reported at one month post-Dose 2 (i.e. 5 months) and one month post-Toddler dose (i.e. about 12 months).
- 6.20 In Study 008, the proportion of subjects with anti-PRP  $\geq 1.0$   $\mu\text{g}/\text{mL}$ , at one month post-Dose 2, was 72.86% for the Vaxelis group versus 26.66% for the Infanrix Hexa group (Vaxelis group minus Infanrix Hexa group: 46.20% (95% CI: 41.05, 51.06); p-value  $< 0.001$ ); the lower limit of the 2-sided 95% CI for the difference in response rates was  $> 0$ , thus  $> -10\%$ , indicating that both non-inferiority and superiority criteria were met.
- 6.21 Non-inferiority analysis of Vaxelis antigen responses versus Infanrix Hexa, one month post-Toddler dose (about 12 months), is presented in Table 5. In the current Australian clinical practice setting (NIP), booster doses limited to DTPa and monovalent Hib are administered at 18 months only.

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<sup>h</sup> All subjects who met the inclusion criteria, who were not protocol violators, who received vaccinations within acceptable day ranges, and had serology results within the specified day ranges, were included in the PP immunogenicity analyses. PP-RW (Per Protocol Revised Window) population was defined as the PP population using a blood draw sample window of Days 28 to 51 following Dose 2 or the Toddler dose.

**Table 5: Study 008: Antigen immunogenicity of Vaxelis vs Infanrix Hexa, 1 month post-Toddler dose (around 12 months of age) (PP-RW population)**

Time	Antigen	Endpoint	Estimated response, n (%)		Estimated difference, % (95% CI)	NI margin, %, NI criteria met/not met
			Vaxelis (N=638)	Infanrix Hexa (N=642)		
1 month post-Toddler dose	PRP	% with titre $\geq 1.0 \mu\text{g/mL}$	454 (89.80)	478 (91.06)	-1.27 (-5.13, 2.52)	-10, Met
	Diphtheria	% with titre $\geq 0.1 \text{ IU/mL}$	590 (98.62)	578 (99.83)	-1.21 (-2.54, -0.22)	-10, Met
	Tetanus	% with titre $\geq 0.1 \text{ IU/mL}$	589 (99.83)	577 (100.00)	-0.17 (-0.95, 0.50)	-5, Met
	IPV1	% with Nab $\geq 1:8$ dilution	591 (99.32)	580 (99.83)	-0.51 (-1.59, 0.34)	-5, Met
	IPV2	% with Nab $\geq 1:8$ dilution	591 (99.83)	579 (100.00)	-0.17 (-0.96, 0.49)	-5, Met
	IPV3	% with Nab $\geq 1:8$ dilution	590 (99.49)	579 (99.65)	-0.16 (-1.20, 0.82)	-5, Met
	HBsAg	% with titre $\geq 10 \text{ mIU/mL}$	377 (98.14)	391 (98.73)	-0.59 (-2.66, 1.35)	-10, Met
	PT	% seroresponse <sup>a</sup>	566 (99.11)	561 (99.64)	-0.54 (-1.79, 0.49)	-10, Met
	FHA	% seroresponse <sup>a</sup>	582 (97.40)	571 (99.13)	-1.73 (-3.47, -0.26)	-10, Met
	PRN	% seroresponse <sup>a</sup>	582 (96.86)	572 (98.28)	-1.42 (-3.42, 0.39)	-10, Met

Source: Table 2.36, p58 of the submission  
PP-RW (Per-protocol-revised window) population.

<sup>a</sup>Seroresponse was defined as follows: if pre-vaccination antibody concentration was <LLOQ, then the post-vaccination antibody concentration was  $\geq$ LLOQ; If pre-vaccination antibody concentration was  $\geq$ LLOQ, then the post-vaccination antibody concentration was  $\geq$ pre-vaccination levels (the pre-vaccination level was defined as the antibody titre at pre-Dose 1)

FHA = Filamentous hemagglutinin; FIM = Fimbriae types 2 and 3; HBsAg = Hepatitis B surface antigen; IPV = Inactivated poliovirus; IU = International unit; LLOQ = Lower limit of quantification; Nab = Neutralising antibodies; NI = Non-inferiority PRN = Pertactin; PRP = Polyribose ribitol phosphate; PT = Pertussis toxin.

- 6.22 The difference in response rates (Vaxelis group minus Infanrix Hexa group) was met the prespecified non-inferiority margin for all prespecified endpoints, indicating that Vaxelis was non-inferior to Infanrix Hexa at one month post-Toddler dose.
- 6.23 The Committee for Medicinal Products for Human Use (CHMP, European Medicines Agency (EMA)) assessment report for Vaxelis; EMA/CHMP/72003/2016) presented data from Study 008 on anti-pertussis responses (FHA, PRN, FIM antigens) for Vaxelis and Infanrix Hexa at various timepoints, and noted that prior to the Toddler dose, the pertussis response rates for all shared antigens were lower in the Vaxelis group compared to those in the Infanrix Hexa group. After the Toddler dose (booster), the pertussis antibody response rates were similar between the groups.
- 6.24 A similar trend was observed for the response rates and GMTs of IPV1 and IPV3. At one month post-Dose 2, the response rates and GMTs of IPV1 and IPV3 were lower in the Vaxelis group. However, the response rates to all three poliovirus antigens were similarly high (>99%) in both groups one month post-Toddler dose.
- 6.25 Regarding concomitant use of Rotarix, immune responses to Rotarix in subjects who received Vaxelis were non-inferior to those observed for Rotarix plus Infanrix Hexa at one month post-Dose 2.
- 6.26 At one month post-Dose 2, the anti-HBsAg GMT was lower in the Vaxelis group compared to the Infanrix Hexa group and was also lower than that observed in study 007. There was a trend towards lower anti-HB immune responses in the Vaxelis group

compared to the Infanrix Hexa group. The TGA clinical evaluator noted that the clinical significance of this is unclear since immunological memory persists beyond the detection of antibodies and the persistence of anti-HBs antibodies may therefore not be the most appropriate surrogate of long term protection (p35, TGA CER). The long term persistence of anti-HBs immunity may need to be evaluated in future studies.

#### **Supportive extension study - PRI03C**

- 6.27 The proportion of individuals who showed  $\geq 10$  mIU/mL of anti-HBsAg antibody was lower in the Vaxelis group compared to Infanrix Hexa group. The difference was not statistically significant in those who were previously immunised with the 3+1 schedule from Study 007 (noting there was marginal overlap between the 95% CIs), but statistically significant (i.e. non-overlapping 95% CIs) in those previously immunised with the 2+1 schedule from Study 008.
- 6.28 In the TGA application to register Vaxelis, the Sponsor argued that the lower anti-HBsAg antibody levels, observed in the Vaxelis group from Study PRI03C, was unlikely to be clinically significant, given that hepatitis B vaccine responders exhibit immune memory against the disease even in the absence of circulating antibody years after initial vaccination. Upon request from the TGA clinical evaluator for further details on this issue (p59, TGA CER Round 2), the Sponsor provided further information and data which were deemed acceptable to the TGA clinical evaluator.
- 6.29 The percentage of children showing anti-pertussis antibodies based on  $\geq$  lower limit of quantification ( $\geq$ LLOQ) to PT was significantly higher in the Vaxelis group than in the Infanrix Hexa group. However, there were lower percentages of subjects with antibodies to FHA and PRN antigens in the Vaxelis group compared to the Infanrix Hexa group, although the differences were not statistically significant.
- 6.30 The Pre-PBAC Response noted the TGA clinical evaluator considered that the waning of seroresponse against some of the antigens in Vaxelis is likely to be a feature of all hexavalent vaccines and is not thought to be of significant clinical consequence at this stage (p59, TGA CER).

#### **Supportive studies 005 and 006**

- 6.31 In the two supporting trials, Vaxelis was administered at 2, 4 and 6 months of age, which is the timing more relevant to the Australia schedule, with a booster dose at 15 months of age. However, the results have limited applicability in terms of the comparator (Pentacel and Recombivax HB) used in the studies.
- 6.32 The difference in antibody response rates for Vaxelis compared with Pentacel and Recombivax HB, measured one month following the three-dose primary vaccinations series, met the non-inferiority criteria for all antigens of Vaxelis except for the FHA pertussis component:
- Study 005: GMT ratio Vaxelis/Control (Pentacel + Recombivax HB): 0.64 (95% CI: 0.59, 0.70); NI margin=0.67).

- Study 006: GMT ratio Vaxelis/Pentacel: 0.67 (95% CI: 0.62, 0.73); NI margin=0.67).

6.33 In Study 006, Vaxelis did not meet the non-inferiority criteria versus Pentacel following post-Toddler dose for geometric mean concentration (GMC) values of PRN.

6.34 Notably, the ATAGI pre-submission advice stated that in Study 006, higher anti-PRP GMCs for the post-toddler dose were demonstrated when Vaxelis (PRP-OMPC), used in the primary series, was boosted with PRP-TT in the second year of life, in comparison with an infant series containing PRP-TT conjugates only (Pentacel has PRP-TT rather than PRP-OMPC).

### Comparative harms

6.35 The results for overall adverse events (AEs) from a pooled analysis of safety data from Study 007 and Study 008 are summarised in Table 6.

**Table 6: Summary of pooled analysis of safety – Study 007 and Study 008**

AEs after any dose	Vaxelis (N=1263)		Infanrix Hexa (N=1264)		Difference (95% CI)
	n	%	n	%	
Subjects vaccinated and had safety follow-up	1263		1262		
One or more AEs (day 1-15 following each hexavalent vaccination)	1253	(99.2)	1254	(99.4)	-0.2 (-0.9, 0.5)
Injection-site AEs (day 1–15)	1155	(91.4)	1130	(89.5)	1.9 (-0.4, 4.2)
Solicited injection-site AEs (day 1–5)	1144	(90.6)	1121	(88.8)	1.7 (-0.6, 4.1)
Systemic AEs (day 1–15)	1247	(98.7)	1251	(99.1)	-0.4 (-1.3, 0.4)
Solicited systemic AEs (day 1–5)	1239	(98.1)	1242	(98.4)	-0.3 (-1.4, 0.7)
Unsolicited systemic AEs (day 1-15)	795	(62.9)	777	(61.6)	1.2 (-2.4, 4.9)
Vaccine-related AEs (day 1–15 following each hexavalent vaccination)	1251	(99.1)	1247	(98.8)	0.2 (-0.6, 1.1)
Injection-site AEs (day 1–15)	1155	(91.4)	1130	(89.5)	1.9 (-0.4, 4.2)
Solicited injection-site AEs (day 1–5)	1144	(90.6)	1121	(88.8)	1.7 (-0.6, 4.1)
Systemic AEs (day 1–15)	1230	(97.4)	1230	(97.5)	-0.1 (-1.3, 1.2)
Solicited systemic AEs (day 1–5)	1226	(97.1)	1227	(97.2)	-0.1 (-1.5, 1.2)
Unsolicited systemic AEs (day 1-15)	482	(38.1)	440	(34.9)	3.2 (-0.5, 6.8)
SAEs (day 1-15 following each hexavalent vaccination)	22	(1.7)	20	(1.6)	0.1 (-0.9, 1.2)
SAEs, any	29	(2.3)	32	(2.5)	-0.3 (-1.5, 1.0)
Serious vaccine-related AEs	4	(0.3)	4	(0.3)	0.0 (-0.5, 0.5)
Deaths	0	(0.0)	0	(0.0)	0.0 (-0.3, 0.3)
Discontinued due to an AE	1	(0.1)	8	(0.6)	<b>-0.6 (-1.2, -0.1)</b>
Discontinued due to a vaccine-related AE	0	(0.0)	5	(0.4)	<b>-0.4 (-0.9, -0.1)</b>
Discontinued due to a SAE	1	(0.1)	3	(0.2)	-0.2 (-0.6, 0.2)
Discontinued due to a serious vaccine-related AE	0	(0.0)	2	(0.2)	-0.2 (-0.6, 0.1)

Values shown in bold indicate statistical significance.

Source: Table 2.59, p72 of the submission.

AE = adverse event; SAE = serious adverse event

6.36 Overall, except for small differences that were unlikely to be clinically meaningful, the safety data were generally similar between the Vaxelis and Infanrix Hexa groups.

### **Clinical claim**

6.37 The submission claimed that it concurred with the ATAGI pre-submission advice that:

- Vaxelis is a safe and suitable alternative to Infanrix Hexa for use as primary immunisation at 2, 4 and 6 months of age, in accordance with the current NIP schedule, provided that a DTPa/Hib booster is provided at 18 months of age;
- From an immunological perspective, Vaxelis is at least non inferior to Infanrix Hexa in eliciting immune responses against all vaccine-included antigens at the end of the primary course to 4 months based on presumptive correlates of protection, noting that these do not exist for pertussis;
- Vaxelis can be coadministered with other routine paediatric vaccines, including Rotarix or RotaTeq, Prevenar 13 and ProQuad, however data regarding concomitant use with other potentially relevant meningococcal and influenza vaccines are not yet available.

6.38 The ATAGI pre-submission advice noted (p29) the following:

- Clinically relevant interference has not been observed with concomitant administration of Vaxelis and any of the following vaccines: rotavirus vaccines (RV1 and RV5), pneumococcal conjugate vaccines (7- and 13-valent), MMRV (measles, mumps, rubella, and varicella) vaccine and two different meningococcal C vaccines (MenC-TT and MenC- CRM).
  - There is no evidence to support the concomitant use of Vaxelis with i) influenza vaccines, and ii) MenACWY and 4CMenB. Concomitant use of Vaxelis in infants with 4CMenB is currently being investigated.

6.39 The Pre-Sub Committee Response (p1) noted that the investigation into concomitant use with 4cMenB has been completed and data are expected to be published in May 2022.

6.40 Overall, the therapeutic conclusion was consistent with the ATAGI pre-submission advice with additional issues worth noting:

Across the key studies (Study 007: 3+1 schedule; Study 008: 2+1 schedule), Vaxelis demonstrated:

- For the one month post-primary series (5 months of age)
  - Acceptable seroresponses to D, T, IPV, Hib antigens (Study 007);
  - Non-inferiority of D, T, IPV, Hib antigen response compared to Infanrix Hexa (Study 007); and
  - Potential superiority of Hib PRP antigen response compared to Infanrix Hexa (Study 007, 008).
  - Lower FHA and PRN seroresponses compared to Infanrix Hexa (95% CI not overlapping) post-primary series (tertiary analysis from Study 007). While the clinical relevance of the pertussis data remains uncertain in the absence of an

established correlate of protection, the ESC noted that a booster dose in the second year of life (available at 18 months of age in Australia) complements the primary vaccination scheme.

- For the one month post-toddler dose (about 12 months of age), noting that a booster dose limited to DTPa/Hib is available at 18 months only in Australia,
  - Acceptable seroresponses to all Vaxelis antigens (Study 007, 008);
  - Non-inferiority for all pertussis antigens and Hepatitis B response (HBsAg) compared to Infanrix Hexa (Study 007, 008); and
  - Non-inferiority of all Vaxelis responses compared to Infanrix Hexa (Study 008).
- Superior seroresponse to the Hib PRP-OMPC antigen (Vaxelis) compared with PRP-TT (Infanrix Hexa) after the primary series, but similar or lower seroresponses after the booster dose. However, earlier antibody response with OMPC-based vaccines may benefit indigenous infants in Australia where the disease burden is higher at an early age.
- AEs generally appeared similar between the Vaxelis and Infanrix Hexa groups. However, there were no safety data on the use of Vaxelis in children > 15 months. The ATAGI pre-submission advice i) noted that this will be relevant if the vaccine is used in a catch-up schedule for children under ten years of age, and ii) recommended that if Vaxelis is included on the NIP, ongoing monitoring of vaccine safety and efficacy is required. The pre-PBAC Response noted that to date, no specific safety signals have been reported in the EU in relation to use in children over 15 months.

6.41 In the March 2015 PBAC consideration of Hexaxim, the PBAC noted the following:

- Based on the clinical evidence available, the ATAGI advised that it could not conclude with certainty that a primary series using Hexaxim will be equally efficacious compared to a primary series of Infanrix Hexa in the Australian setting, particularly for protection against pertussis, and notes that it is difficult to be definitive in relation to this issue due to the limited evidence available. The reasons for this uncertainty included the lower number of pertussis antigens (two rather than three) in the vaccine and the lower diphtheria toxoid content, compared to the comparator Infanrix Hexa. ATAGI also noted that limited evidence from persistence, booster, and post-marketing studies of similar products, suggested that over the longer term, any potential reduction in efficacy following a primary series of Hexaxim would be best mitigated by inclusion of a routine 18 month booster dose of a DTP-containing vaccine (Paragraph 7.7, Public Summary Document (PSD) for Hexaxim, March 2015 PBAC Meeting).
- The PBAC also recalled that it recommended an 18-month DTP-containing vaccine booster at its November 2014 PBAC meeting and agreed with ATAGI that Hexaxim should only be made available on the NIP where a DTP-containing vaccine is available at the 18-month schedule point.

- 6.42 The PBAC noted that Vaxelis met the pre-specified non-inferiority criteria for all pre-specified endpoints for the primary analyses in Study 007 and Study 008, at 1 month post-dose 3 and 1 month post-toddler dose timepoints. Overall, the PBAC considered it was reasonable to conclude that Vaxelis was non-inferior to Infanrix Hexa in terms of effectiveness.
- 6.43 The PBAC considered that the clinical data provided supported the claim of noninferior safety of Vaxelis compared to Infanrix Hexa.

**Economic analysis**

- 6.44 The submission used a cost-minimisation approach (CMA) comparing Vaxelis with Infanrix Hexa when used as a three-dose primary vaccination series in infants. The equi-effective doses were based on the recommended dosing regimens outlined in the relevant Product Information documents, which are the same as the doses used in the included clinical trials:

3 x 0.5 mL doses of Vaxelis = 3 x 0.5 mL doses of Infanrix Hexa.

The proposed equi-effective doses are reasonable.

- 6.45 The submission used a proxy price of \$ [REDACTED] in the CMA as the assumed NIP list price of Infanrix Hexa, which is the current market price of Infanrix Hexa provided by the Royal Children’s Hospital Melbourne. The results of the CMA are summarised in Table 7.

**Table 7: Results of the cost-minimisation for a three-dose primary vaccination series in infants**

		Infanrix Hexa	Vaxelis	Source/calculation
A	Vaccine cost per dose (Royal Children’s Hospital Melbourne)	\$ [REDACTED]	\$ [REDACTED]	Infanrix Hexa = market price Vaxelis = C / B
B	Injections	3	3	Three-dose primary vaccination series in infants
C	Total cost for primary course	\$ [REDACTED]	\$ [REDACTED]	Infanrix Hexa = A * B Vaxelis = assumed equal to Infanrix Hexa

Source: Table 3.1, p82 of the submission

- 6.46 The submission suggested that there may be lower vaccination program costs associated with Vaxelis due to reduced preparation times (pre-filled syringe, ready for use) compared to Infanrix Hexa (lyophilised powder and liquid suspension, requires reconstitution before use).
- 6.47 The submission also suggested that there may also be potential savings associated with having two vaccines competing for the DTPa-HB-IPV-Hib market under the NIP.

**Vaccine cost/patient/course**

- 6.48 The cost per course for both Vaxelis and Infanrix Hexa was estimated to be \$ [REDACTED] (3 doses per course).

### Estimated NIP usage & financial implications

- 6.49 This submission was not considered by DUSC.
- 6.50 The submission used a market share approach to estimate the usage of Vaxelis and its financial implications to the NIP. The key inputs for financial estimates are summarised in Table 8.

**Table 8: Key inputs for financial estimates**

Data	Value and source	Comment
<b>Eligible population</b>		
Primary program - Children aged 2-6 months	Yr 1: 348,159 to Yr 6: 370,252 ABS population data (3222.0 Series B)	This source is appropriate.
Catch-up program - <10 years	Yr 1: 73,052 to Yr 6: 78,737 ABS population estimates for <10 years of age and uptake rates in primary and catch-up programs.	This calculation is appropriate.
<b>Uptake rates</b>		
Uptake rate – Primary program	95% Department of Health	This assumption is reasonable.
Uptake rate – Catch-up program	20% Assumption	This assumption is reasonable.
<b>Market share (with listing of Vaxelis)</b>		
Infanrix Hexa	50% each Assumption	Although the assumed market share is uncertain, there is no impact on the estimated financial implication to NIP given the direct substitution for Infanrix Hexa at the proposed same price.
Vaxelis		

Source: Section 4 workbook '4.1. Worksheet'

- 6.51 The submission estimated the number of eligible children for the primary and catch-up vaccination program based on ABS population projections for the years 2022-2027. All children under the age of 1 year were deemed eligible for the primary vaccination program. The number of children eligible for catch-up vaccination was based on unvaccinated children aged 1-9 years.
- 6.52 The submission further assumed that 95% of eligible infants would be vaccinated in the primary program, and 20% of unvaccinated children under 10 years of age would be vaccinated in the catch-up program. These are consistent with the current immunisation rates in Australia for both the programs.
- 6.53 Equal market share between Infanrix Hexa and Vaxelis was assumed after listing of Vaxelis. Given that Vaxelis is easy to administer and ready-made, it is possible that market share of Vaxelis will progressively increase over that for Infanrix Hexa. Nonetheless, there will be no impact on the estimated financial implications to the NIP due to the direct substitution at the same doses and prices. The estimated use and financial implications of Vaxelis are summarised in Table 9.

**Table 9: Estimated use of Vaxelis and financial implications to NIP**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of children vaccinated	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>	<sup>1</sup>
Number of doses <sup>a</sup>	<sup>2</sup>	<sup>2</sup>	<sup>2</sup>	<sup>2</sup>	<sup>2</sup>	<sup>2</sup>
<b>Estimated financial implications of Vaxelis</b>						
Cost to NIP	<sup>3</sup>	<sup>3</sup>	<sup>3</sup>	<sup>3</sup>	<sup>3</sup>	<sup>3</sup>
<b>Estimated financial implications for Infanrix Hexa</b>						
Cost to NIP	-  <sup>3</sup>	-  <sup>3</sup>	-  <sup>3</sup>	-  <sup>3</sup>	-  <sup>3</sup>	-  <sup>3</sup>
<b>Net financial implications</b>						
Net cost to NIP	<sup>4</sup>	<sup>4</sup>	<sup>4</sup>	<sup>4</sup>	<sup>4</sup>	<sup>4</sup>

Source: Section 4 workbook '4.2. Worksheet'

<sup>a</sup> 3 doses per child.

The redacted values correspond to the following ranges:

<sup>1</sup> 100,000 to < 200,000

<sup>2</sup> 500,000 to < 600,000

<sup>3</sup> \$50 million to < \$60 million

<sup>4</sup> \$0 to < \$10 million

6.54 The submission estimated that listing of Vaxelis on NIP will be cost neutral to the NIP given the direct substitution for Infanrix Hexa at the same price. This is reasonable.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## 7 PBAC Outcome

7.1 The PBAC recommended that diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b conjugate vaccine (DTPa-HB-IPV-Hib, Vaxelis) be a designated vaccine for the purposes of the *National Health Act 1953*, for the primary vaccination series against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive infections caused by *Haemophilus influenzae* type b at 2, 4 and 6 months of age. The PBAC also considered Vaxelis to be suitable for catch-up for children under 10 years of age. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of Vaxelis would be acceptable if it were cost-minimised against the nominated comparator, Infanrix Hexa.

7.2 The PBAC considered that the nominated comparator, Infanrix Hexa, was appropriate noting it is currently the only hexavalent vaccine supplied on the NIP.

7.3 The PBAC considered that having a second supplier of childhood DTPa-HB-IPV-Hib vaccines in Australia would be useful for managing risks associated with a sole supplier on the NIP.

7.4 The PBAC advised that the equi-effective doses were 1 x 0.5 mL Vaxelis at 2, 4 and 6 months and 1 x 0.5 mL Infanrix Hexa at 2, 4 and 6 months.

7.5 The PBAC noted that the time points of the dosing schedule in the key trials, Study 007 (2, 3 and 4 month primary dose series) and Study 008 (2 and 4 month primary dose series), differed to the proposed Australian setting. The PBAC noted the advice from

- ATAGI that the difference between the trial setting and proposed Australian setting in terms of dosing schedule is unlikely to affect vaccine efficacy and safety.
- 7.6 The PBAC noted that Vaxelis met the pre-specified non-inferiority criteria for all pre-specified endpoints for the primary analyses in Study 007 and Study 008, at 1 month post-Dose 3 and 1 month post-Toddler dose timepoints. Overall, the PBAC considered it was reasonable to conclude that Vaxelis was non-inferior to Infanrix Hexa in terms of effectiveness.
- 7.7 The PBAC noted that tertiary immunogenicity analyses from Study 007 and Study 008 prior to the Toddler dose indicated seroresponse rates were significantly lower in the Vaxelis group compared to the Infanrix Hexa group for pertussis antigens. The PBAC considered it was difficult to interpret the pertussis data given the absence of an established correlate of protection for pertussis; however, the PBAC considered that any potential reduction in efficacy following the primary series would be mitigated by the DTP-containing vaccine booster at 18 months currently listed on the NIP.
- 7.8 The PBAC noted that tertiary immunogenicity analyses from Study 007 indicated that anti-PRP GMT was lower in the Vaxelis group compared to the Infanrix Hexa group post-Toddler dose, despite anti-PRP GMT being significantly higher in the Vaxelis group compared to the Infanrix Hexa group pre-Toddler dose. The PBAC noted that the initial immune response may be due to the Hib antigen in Vaxelis being conjugated to the strongly immunogenic *Neisseria meningitidis* OMPC. The PBAC noted the TGA clinical evaluator considered that the lower post-Toddler dose GMT for Vaxelis is unlikely to have significant adverse impact in Australia, noting that similar numbers of individuals in the Vaxelis and Infanrix Hexa groups achieved the pre-specified  $\geq 0.15 \mu\text{g/mL}$  and  $\geq 1.0 \mu\text{g/mL}$  endpoints for PRP.
- 7.9 The PBAC considered that the clinical data provided supported the claim of noninferior safety of Vaxelis compared to Infanrix Hexa.
- 7.10 The PBAC acknowledged ATAGI's advice that inclusion of a hexavalent booster (DTPa-HB-IPV-Hib) at 18 months might be beneficial to overcome potential waning of long term immunity to hepatitis B after the primary immunisation course, noting that a booster for hepatitis B is currently not listed on the NIP. The PBAC considered that consultation with health professionals and other relevant stakeholders would be required prior to implementation of this change on the NIP.
- 7.11 PBAC noted that this submission is not eligible for an independent review as independent review is only relevant to requests for PBS listing.

**Outcome:**

Recommended

## 8 Recommended listing

8.1 Add new item to the Determination:

### Essential elements of the requested listing

Name, restriction, manner of administration, form	Nationally Negotiated Price	Proprietary name and manufacturer
Diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and <i>Haemophilus influenzae</i> type b conjugate vaccine, 0.5 mL pre-filled syringe	\$TBA	Vaxelis®, Sanofi-aventis (Australia) Pty Ltd
Vaccine may be provided to a child who is about 2, 4 or 6 months old*		

\* With a catch-up program for children under 10 years of age

***This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.***

## 9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## 10 Sponsor's Comment

Sanofi Pasteur welcomes the PBAC's recommendation to list diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b conjugate vaccine (DTPa-HB-IPV-Hib, Vaxelis) on the NIP. Since the PBAC's consideration, an additional study investigating the concomitant use of Vaxelis with 4CMenB has been completed and is awaiting publication. We will continue to work through the post-PBAC processes with the Department of Health and relevant stakeholders to realise the benefits to the NIP of having a second supplier of childhood DTPa-HB-IPV-Hib vaccines in Australia.