5.08 DTPa-hepB-IPV-Hib VACCINE 0.5mL pre-filled syringe; HEXAXIM®; Sanofi-aventis Australia Pty Ltd

1 Purpose of Application

1.1 The submission requested National Immunisation Program (NIP) listing for Hexaxim (antigens against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive infections caused by Haemophilus influenzae type b, DTPa-hepB-IPV-Hib) as a primary vaccine course.

2 Requested listing

2.1

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
DTPa-hepB-IPV-Hib VACCINE 0.5mL pre-filled syringe	1	0	$[redacted]	Hexaxim® Sanofi Pasteur

NIP listing
Primary vaccination series at 2, 4 and 6 months of age

2.2 Listing was requested on a cost-minimisation basis compared to Infanrix Hexa.

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

3 Background

3.1 TGA status: Hexaxim was registered by the TGA on 11 September 2014 for the 'vaccination of infants from six weeks of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive infections caused by Haemophilus influenzae type b. Use of this vaccine should be in accordance with the national recommendation as per the current Immunisation Handbook'.

3.2 The PBAC has not previously considered Hexaxim for any indication.

4 Clinical place for the proposed therapy

4.1 Hexaxim (DTPa-hepB-IPV-Hib) 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.

4.2 The submission positioned Hexaxim as an alternative to Infanrix Hexa when used as the primary course for DTPa-hepB-IPV-Hib vaccination.

4.3 At the November 2014 PBAC meeting, the PBAC recommended a change to the NIP schedule to include a DTPa booster (Infanrix) at 18 months of age.

5 Comparator

5.1 Infanrix Hexa.

The main differences between Hexaxim and Infanrix Hexa are:

- Hexaxim 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
- Hexaxim has a lower diphtheria toxoid content compared to Infanrix Hexa (≥20 vs ≥30 IU). The diphtheria toxoid levels in Hexaxim are lower than current international standards (≥ 30 IU)
- Hexaxim includes two pertussis antigens (pertussis toxoid, filamentous haemagglutinin) versus Infanrix Hexa which includes three pertussis antigens (pertussis toxoid, filamentous haemagglutinin, pertactin)
- Hexaxim includes a novel Hepatitis B surface antigen while Infanrix Hexa includes a previously well-established antigen
- Hexaxim has a higher Hib polysaccharide content compared to Infanrix Hexa (12mcg vs 10mcg).

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 that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on four head-to-head randomised trials comparing immunogenicity outcomes between Hexaxim and Infanrix Hexa when used as a three-dose primary vaccination series in infants (A3L11, A3L12, A3L17, A3L24). Additional longer-term extension studies from the key trials were identified during the evaluation (A3L21, A3L27).

6.4 Details of the trials presented in the submission are provided in the table below.

Trials and associated reports included in the submission

Trial ID	Protocol title/ Publication title	Publication citation
A3L11	Sanofi Pasteur Clinical Study Report (2009). Lot-to-Lot Consistency Study of DTaP-IPV-Hep B-PRP-T Vaccine Administered at 2-4-6 Months of Age in Healthy Mexican Infants	Internal study report
	Sanofi Pasteur (2014). Lot Consistency Study of DTaP-IPV-HB-PRP~T Vaccine Administered at 2-4-6 Months of Age in Healthy Infants	Clinicaltrials.gov record (NCT00404651)
	Aquino AG et al (2012). A fully liquid DTaP-IPV-Hep B-PRP-T hexavalent vaccine for primary and booster vaccination of healthy Mexican children	Vaccine 30: 6492–6500
	Santos-Lima E et al (2013). Combined immunogenicity data for a new DTaP-IPV-Hep B-PRP-T vaccine (Hexaxim™) following primary series administration at 2, 4, 6 months of age in Latin America.	Vaccine 31: 1255–1258
A3L21	Sanofi Pasteur (2013). Study of the DTaP-IPV-Hep B-PRP~T Combined Vaccine Following a Primary Series of DTacP IPV-HepB-PRP-T or Infanrix Hexa™	Clinicaltrials.gov record (NCT00654901)
	Aquino AG et al (2012). A fully liquid DTaP-IPV-Hep B-PRP-T hexavalent vaccine for primary and booster vaccination of healthy Mexican children	Vaccine 30: 6492–6500
A3L12	Sanofi Pasteur Clinical Study Report (2009). Immunogenicity Study of a DTaP-IPV-Hep B-PRP-T Combined Vaccine in Comparison to Infanrix Hexa™, Both Concomitantly Administered with Prevnar™ at 2, 4, and 6 Months of Age in Thai Infants	Internal study report
	Sanofi Pasteur (2014). Comparison of a DTaP-IPV-HB-PRP~T Combined Vaccine to Infanrix™-Hexa, When Administered With Prevnar® in Thai Infants	Clinicaltrials.gov record (NCT00401531)
	Kosalaraksa P et al (2011). Immunogenicity and safety study of a new DTaP-IPV-Hep B-PRP-T combined vaccine cf a licensed DTaP-IPV-Hep B//PRP-T comparator, both concomitantly administered with a 7-valent pneumococcal conjugate vaccine at 2, 4, and 6 months of age in Thai infants	International Journal of Infectious Disease 15(4):e249-56
A3L17	Sanofi Pasteur Clinical Study Report (2009). Immunogenicity Study of DTaP-IPV-Hep B-PRP-T Combined Vaccine in Comparison to Infanrix Hexa™, at 2-4-6 Months of Age in Healthy Peruvian Infants	Internal study report
	Sanofi Pasteur (2014). Study of DTaP-IPV-Hep B-PRP~T Combined Vaccine Compared to Infanrix®Hexa in Healthy Peruvian Infants	Clinicaltrials.gov record (NCT00831753)
	Lanata C et al (2012). Immunogenicity and safety of a fully liquid DTaP-IPV-Hep B-PRP-T vaccine at 2–4–6 months of age in Peru.	Journal of Vaccines and Vaccination 3(1):1000128.
	Santos-Lima E et al (2013). Combined immunogenicity data for a new DTaP-IPV-Hep B-PRP-T vaccine (Hexaxim™) following primary series administration at 2, 4, 6 months of age in Latin America.	Vaccine 31: 1255–1258
A3L24	Sanofi Pasteur Clinical Study Report (2012). Lot-to-Lot Consistency Study of DTaP-IPV-Hep B-PRP-T Vaccine Administered at 2-4-6 Months of Age in Healthy Latin American Infants Concomitantly with Prevenar™ and Rotarix™	Internal study report
	Sanofi Pasteur (2014). A Study of DTaP-IPV-Hep B-PRP-T Vaccine Given With Prevenar™ and Rotarix™ in Healthy Latin American Infants	Clinicaltrials.gov record (NCT01177722)
A3L27	Sanofi Pasteur (2014). Study of the Booster Effect of DTaP-IPV-Hep B-PRP~T Combined Vaccine or Infanrix Hexa™ and Prevenar™ in Healthy Infants	Clinicaltrials.gov record (NCT01444781)

6.5 The key features of the included trials are summarised in the table below.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Hexaxim vs. Infanrix Hexa when used as a primary vaccination series (2, 4, 6 months of age)					
A3L11/A3L21	1,189	R, PB, PG, MC 6 mths + extension	Low	Healthy Mexican infants	Immune response (antibody levels)
A3L12	412	R, PB, PG, MC 6 mths	Low	Healthy Thai infants	Immune response (antibody levels)
A3L17	263	R, PB, PG, SC 6 mths	Low	Healthy Peruvian infants	Immune response (antibody levels)
A3L24/A3L27	1,376	R, PB, PG, MC 6 mths + extension	Low	Healthy Latin American infants	Immune response (antibody levels)
Meta-analysis (vaccine course)	3,240	A3L11, A3L12, A3L17, A3L24			
Meta-analysis (2nd year of life)	1,987	A3L21/A3L27			

Abbreviations: MC, multi-centre; PB, partially blinded (parent/observer); PG, parallel group; R, randomised; SC, single-centre
Source: Constructed during the evaluation

6.6 The trials recruited healthy infant populations from Colombia, Costa Rica, Mexico, Peru and Thailand. The Commentary noted that it was unclear whether differences in vaccination schedules, ethnicity and natural exposure may affect the applicability of results to the Australian setting.

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

Comparative effectiveness

6.7 The main outcome of the submission was the proportion of patients achieving target seroprotection/seroconversion antibody levels.

6.8 The submission presented intention-to-treat meta-analyses based on patients receiving at least one vaccine dose. However during the evaluation, the per-protocol results (based on patients receiving a full vaccine course) from each trial were extracted and meta-analysed as these were the nominated main analyses in each of the trial reports.

Meta-analysis of seroprotection and seroconversion rates (Per-protocol population)

Outcome	Hexaxim	Infanrix Hexa	RR (95% CI)	RD (95% CI)
Patients with Anti-D ≥ 0.01 IU/mL at end of primary course	1912/1948 (98%)	753/754 (100%)	0.98 (0.94, 1.02) I^2 = 94%	-0.02 (-0.06, 0.02) I^2 = 94%
Patients with Anti-D ≥ 0.01 IU/mL in 2nd year of life	921/955 (96%)	308/321 (96%)	0.99 (0.92, 1.06) I^2 = 75%	-0.01 (-0.07, 0.05) I^2 = 75%
Patients with Anti-T ≥ 0.01 IU/mL at end of primary course	1815/1815 (100%)	623/623 (100%)	1.00 (1.00, 1.00) I^2 = 0%	0.00 (-0.00, 0.00) I^2 = 0%
Patients with Anti-T ≥ 0.01 IU/mL in 2nd year of life	950/951 (100%)	320/320 (100%)	1.00 (0.99, 1.01) I^2 = 0%	-0.00 (-0.01, 0.00) I^2 = 0%
Patients with Anti-PT ≥ 4 fold increase at end of primary course	1673/1799 (93%)	570/619 (92%)	1.01 (0.98, 1.03) I^2 = 0%	0.01 (-0.02, 0.03) I^2 = 0%
Patients with Anti-PT ≥ LLQ in 2nd year of life	693/767 (90%)	225/257 (88%)	1.03 (0.98, 1.09) I^2 = 0%	0.03 (-0.02, 0.07) I^2 = 0%
Patients with Anti-FHA ≥ 4 fold increase at end of primary course	1714/1784 (96%)	573/614 (93%)	1.02 (1.00, 1.05) I^2 = 13%	0.02 (-0.00, 0.04) I^2 = 10%
Patients with Anti-FHA ≥ LLQ in 2nd year of life	773/773 (100%)	253/255 (99%)	1.01 (1.00, 1.02) I^2 = 0%	0.01 (-0.00, 0.02) I^2 = 0%
Patients with Anti-Hep B ≥ 10 mIU/mL at end of primary course	1927/1944 (99%)	754/755 (100%)	1.00 (0.99, 1.00) I^2 = 0%	-0.01 (-0.01, 0.00) I^2 = 19%
Patients with Anti-Hep B ≥ 10 mIU/mL in 2nd year of life	926/963 (96%)	319/324 (98%)	0.97 (0.93, 1.02) I^2 = 50%	-0.03 (-0.07, 0.01) I^2 = 46%
Patients with Anti-Polio 1 > 8 1/dil at end of primary course	1805/1806 (100%)	616/616 (100%)	1.00 (1.00, 1.00) I^2 = 0%	-0.00 (-0.00, 0.00) I^2 = 0%
Patients with Anti-Polio 1 > 8 1/dil in 2nd year of life	827/837 (99%)	275/278 (99%)	1.00 (0.99, 1.01) I^2 = 0%	-0.00 (-0.01, 0.01) I^2 = 0%
Patients with Anti-Polio 2 > 8 1/dil at end of primary course	1804/1804 (100%)	616/616 (100%)	1.00 (1.00, 1.00) I^2 = 0%	0.00 (-0.00, 0.00) I^2 = 0%
Patients with Anti-Polio 2 > 8 1/dil in 2nd year of life	836/838 (100%)	278/278 (100%)	1.00 (0.99, 1.01) I^2 = 0%	-0.00 (-0.01, 0.00) I^2 = 0%
Patients with Anti-Polio 3 > 8 1/dil at end of primary course	1803/1804 (100%)	613/615 (100%)	1.00 (1.00, 1.01) I^2 = 0%	0.00 (-0.00, 0.01) I^2 = 0%
Patients with Anti-Polio 3 > 8 1/dil in 2nd year of life	800/837 (96%)	275/278 (99%)	0.97 (0.95, 0.98) I^2 = 0%	-0.03 (-0.05, -0.02) I^2 = 0%
Patients with Anti-PRP ≥ 0.15 mcg/mL at end of primary course	1888/1950 (97%)	733/755 (97%)	1.00 (0.99, 1.01) I^2 = 0%	0.00 (-0.01, 0.01) I^2 = 0%
Patients with Anti-PRP ≥ 0.15 mcg/mL in 2nd year of life	746/961 (78%)	257/323 (80%)	0.97 (0.91, 1.03) I^2 = 0%	-0.02 (-0.07, 0.02) I^2 = 0%

Abbreviations: Anti-D, diphtheria toxoid antibodies; Anti-FHA, filamentous haemagglutinin antibodies; Anti-Hep B, hepatitis B antibodies; Anti-Polio, poliovirus antibodies; Anti-PRP, polyribosylribitol phosphate polysaccharide antibodies; Anti-PT, pertussis toxoid antibodies; Anti-T, tetanus toxoid antibodies; CI, confidence interval; LLQ, lower limit of quantitation; RD, risk difference; RR, relative risk

Source: Constructed during the evaluation

Note: Non-inferiority margin was defined as a risk difference lower CI limit > −0.10 for Anti-D, Anti-T, Anti-PT, Anti-FHA, Anti-Hep B, Anti-PRP and a risk difference lower CI limit > −0.05 for Anti-polio Types 1, 2, 3. The longer-term A3L21 and A3L27 extension studies (i.e. results in 2nd year of life) were not designed to assess the comparative non-inferiority of treatments

6.9 Hexaxim was non-inferior to Infanrix Hexa in terms of immunogenicity against the common antigen for the six targeted diseases at the end of the primary course (based on historical margins previously accepted by the FDA for other multi-component vaccines).

6.10 There was substantial unexplained heterogeneity between included trials in terms of anti-diphtheria response (although results were still within the nominated non-inferiority margin).

6.11 The clinical importance of the pertussis results was unclear as there are no established thresholds for antibody response to pertussis antigens that can be used as a surrogate for protection.

6.12 The comparative longer-term durability of protection in terms of polio (booster at 4 years of age) and hepatitis B (booster at 10-15 years of age) is unclear but is unlikely to be a major issue as the risk of exposure is low in Australian children.

6.13 A lower proportion of patients achieved target seroconversion levels to concurrent rotavirus vaccination in the Hexaxim treatment arm (77.7%; 95% CI 71.2%, 83.3%) compared to the Infanrix Hexa treatment arm (87.9%; 95% CI 77.5%, 94.6%). The clinical importance of this observed difference is unclear.

Comparative harms

6.14 Meta-analyses of safety data were conducted during the evaluation. Treatment with Hexaxim was associated with a higher incidence of solicited injection-site reactions (primarily mild-to-moderate pain, erythema and swelling) compared to Infanrix Hexa (RD 0.05; 95% CI, 0.02, 0.08). The incidence of solicited systemic reactions, unsolicited events and serious adverse events appeared to be similar between treatment arms although there was some heterogeneity across the trials.

Clinical claim

6.15 The submission described Hexaxim as non-inferior in terms of comparative efficacy and safety compared to Infanrix Hexa.

6.16 In the pre-submission advice, the Australian Technical Advisory Group on Immunisation (ATAGI) advised that there is currently insufficient information to determine whether there are relevant clinical differences between this vaccine and the comparator (particularly in regards to pertussis which has no accepted thresholds for antibody response that can be used as a surrogate for protection). However, ATAGI suggested that potential clinical differences may be offset by the availability of a DTPa booster at 18 months. The PBAC recommended the addition of an 18-month DTPa booster to the NIP at the November 2014 meeting. ATAGI also recommended increased surveillance of the real-world effectiveness of both vaccines.

6.17 The PBAC considered that the claim of non-inferior comparative effectiveness and comparative safety was reasonable, in the context of an 18-month DTPa-containing booster being available on the NIP.

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

Economic analysis

6.18 The submission presented a cost-minimisation analysis comparing Hexaxim 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 0.5mL doses of Hexaxim = 3 x 0.5mL doses of Infanrix Hexa

The Commentary noted that the calculation of equi-effective doses is reasonable.

6.19 The requested cost minimised price of Hexaxim is exactly equal to the assumed NIP list price of Infanrix Hexa ($[redacted], based on the last known historical price).

6.20 The submission suggested that there may be lower vaccination program costs associated with Hexaxim due to reduced preparation times (pre-filled syringe, ready for use) compared to Infanrix Hexa (lyophilized powder and liquid suspension, requires reconstitution before use).

6.21 The submission suggested that there may also be potential savings associated with having two vaccines competing for the DTPa-hepB-IPV-Hib market under the NIP.

Drug cost/patient/course

6.22 The cost per course for both Hexaxim and Infanrix Hexa was estimated to be $[redacted] (3 doses per course).

Estimated PBS usage & financial implications

6.23 This submission was not considered by DUSC.

The submission used an epidemiological approach to estimate the utilisation/financial implications associated with the NIP listing of Hexaxim.

Estimated budget impact of Hexaxim to the NIP

Current budget impact model	Year 1 (2015)	Year 2 (2016)	Year 3 (2017)	Year 4 (2018)	Year 5 (2019)
Infants aged < 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infants who are fully immunised (91.4%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated uptake of Hexaxim (50%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Hexaxim doses (3 per patient)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost of Hexaxim ($[redacted] per dose)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost of Infanrix Hexa substituted doses[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to the NIP	$0	$0	$0	$0	$0

Abbreviations: NIP, National Immunisation Program

[a] Based on identical utilisation to Hexaxim

6.24 The submission claimed that listing Hexaxim would be cost-neutral to the NIP. Estimates presented in the submission may not be representative of actual utilisation/financial implications as both the estimated uptake and price of Hexaxim will be dependent on the national tender procurement process for the NIP.

Financial Management – Risk Sharing Arrangements

6.25 The submission did not propose a risk sharing arrangement.

7 PBAC Outcome

7.1 The PBAC recommended the listing of Hexaxim on the National Immunisation Program (NIP) 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, on a cost-minimisation basis that 3 x 0.5mL doses of Hexaxim is equi-effective 3 x to 0.5mL doses of Infanrix Hexa, when an 18-month DTPa-containing booster is available on the NIP.

7.2 The PBAC noted the pre-submission and post-submission advice from the Australian Technical Advisory Group on Immunisation (ATAGI).

7.3 The PBAC accepted that Infanrix Hexa was the most appropriate comparator.

7.4 The PBAC noted that the submission provided clinical evidence based on head-to-head randomised trials between Hexaxim and Infanrix Hexa. The PBAC noted the advice from ATAGI that differences in the clinical trial settings for Hexaxim are unlikely to affect applicability of the results to the Australian setting.

7.5 The PBAC noted, based on the per-protocol analysis, that Hexaxim was non-inferior to Infanrix Hexa in terms of immunogenicity against each of the six targeted diseases at the end of the primary course, based on historical margins previously accepted by the FDA for other multi-component vaccines. The advice from ATAGI observed that correlates of protection were accepted as indicators of presumptive seroprotection: diphtheria and tetanus (≥0.01 IU/mL), polio types 1–3 (≥8 1/dil), hepatitis B (≥10

mIU/mL) and Hib (≥0.15 µg/mL). For the pertussis antigens PT and FHA, as there are 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 is not well defined for pertussis vaccines.

7.6 The PBAC considered the rate of adverse events was reasonable in the context of vaccination.

7.7 The PBAC noted that, based on the clinical evidence available, the ATAGI advised that it cannot 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. This is particularly in relation to protection against pertussis, and notes that it is difficult to be definitive in relation to this issue due to the limited evidence available. The most notable point of difference responsible for this uncertainty is the inclusion of two rather than three pertussis antigens in the vaccine. In addition, the diphtheria toxoid content of the vaccine is noted to be lower than the present comparator. Limited evidence from persistence and booster studies, and post-marketing studies of similar products, suggest 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.

7.8 The PBAC recalled that it recommend 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.

7.9 The PBAC noted that a positive recommendation for Hexaxim would provide a potential second supplier of childhood DTPa-hepB-IPV-Hib vaccines in Australia.

7.10 The PBAC did not agree with the submission that there may be lower vaccination program costs associated with Hexaxim due to reduced preparation times (pre-filled syringe, ready for use) compared to Infanrix Hexa (lyophilized powder and liquid suspension, requires reconstitution before use). During the preparation of Infanrix Hexa, the PBAC noted that the health care professional may discuss aspects of the vaccination with parents of the vaccinee. These discussions would be expected to occur, irrespective of the vaccine used.

7.11 The PBAC noted the advice from ATAGI that if Hexaxim is included on the NIP with high uptake, ongoing monitoring of vaccine safety and studies to assess vaccine effectiveness will be required.

Outcome:
Recommended

8 Recommended listing

8.1 List Hexaxim on the NIP for a 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.

9 Context for Decision

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

10 Sponsor's Comment

Sanofi Pasteur welcomes the PBAC's recommendation to include Hexaxim (DTPa-hepB-IPV-Hib) as a primary vaccine course for the prevention of diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive infections caused by Haemophilus influenzae type b in the National Immunisation Program. As well as being registered by the TGA Hexaxim is the only hexavalent vaccine that is WHO prequalified vaccine.