5.04 PERTUSSIS VACCINE-ACELLULAR, COMBINED WITH DIPHTHERIA AND TETANUS TOXOIDS (DTaP), 0.5 mL vial, 1, Tripacel®, Sanofi-aventis Australia Pty Ltd.

1 Purpose of Application

1.1 The submission requested National Immunisation Program (NIP) listing for the Pertussis Vaccine-Acellular, combined with Diphtheria and Tetanus Toxoids (Adsorbed) (DTaP) vaccine at approximately 18 months for the prevention of pertussis.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
PERTUSSIS VACCINE-ACELLULAR, COMBINED WITH DIPHTHERIA AND TETANUS TOXOIDS (ADSORBED) (DTAP) 0.5 ml injection	1	0	$[redacted]	TRIPACEL® Sanofi Pasteur
NIP listing Booster dose for infants aged approximately 18 months				

2.1 The listing was requested on a cost minimisation basis compared to Infanrix (DTPa), recommended as an 18-month booster at the November 2014 PBAC meeting.

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

3 Background

3.1 The DTaP vaccine was approved by the TGA in 1998. Until 2003, the treatment schedule for DTaP included a booster dose at approximately 18 months. In 2003, with the introduction of the booster dose for adolescents (15-17 year), the 18 months dose was removed.

3.2 The Australian Technical Advisory Group on Immunisation provided pre-PBAC submission advice in June 2014, which indicated that it endorses the re-instatement of a booster dose of DTaP-containing vaccine onto the NIP schedule.

3.3 At the November 2014 meeting, the PBAC recommended DTPa (Infanrix) as an 18 months booster.

4 Clinical place for the proposed therapy

4.1 Pertussis is a highly infectious disease of the upper respiratory tract, caused by the bacterial organism Bordetella pertussis. Currently, there are five scheduled childhood doses of pertussis vaccine. The first three occur in infancy at 2 months, 4 months, and 6 months. Two booster shots are given at 4 years and 15 years.

4.2 The submission proposed a revenue-neutral, clinically equivalent, alternate vaccine as an additional booster of pertussis vaccine at 18 months of age.

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

5 Comparator

5.1 The submission nominated DTPa (Infanrix) as an 18-month booster. The ESC accepted this was the appropriate comparator.

5.2 The differences in pertussis antigen between DTaP (Tripacel) and DTPa (Infanrix) are:

- DTaP includes four pertussis antigens (pertussis toxoid, filamentous haemagglutinin, pertactin and fimbriae 2 + 3 (FIM) versus DTPa which includes three pertussis antigens (pertussis toxoid, filamentous haemagglutinin and pertactin);
- DTaP has lower pertussis antigens level (pertussis toxoid 10 µg, filamentous haemagglutinin 5 µg and pertactin 3 µg) compared to DTPa (pertussis toxoid 25µg, filamentous haemagglutinin 25 µg and pertactin 8 µg).

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 one small head-to-head randomised trial with 1 year follow-up (comprising a series of concurrent comparisons of 12 acellular Pertussis Vaccines including Tripacel and Infanrix), to a single whole cell Pertussis vaccine (Pichichero, Deloria, et al. 1997); and a naïve comparison of 13 trials including either DTPa or DTaP (Harlperin 1996, Halperin 1995, PHASE IIC, Chatterjee 2012, Guerra 2009, Study PERTB9301, Halperin 1994, Pichichero 1996, Nolan 2004, Trofa 2011, Schmitt 1998, Trofa 2011, NCT00289913 and Schmitt 1996).

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

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		
Pichichero, Deloria, et al. 1997	A Safety and Immunogenicity Comparison of 12 Acellular Pertussis vaccines and one whole-cellular pertussis vaccine given as a fourth dose in 15- to 20- month-old children.	Australian vaccine preventable disease epidemiological review series: pertussis, 2006-2012." CDI 38(3):E179.
Supplementary randomised trials		
(CANADA II CSR 1992) Halperin, Eastwood, et al. 1996	Adverse reactions and antibody response to four doses of acellular or whole cell pertussis vaccine combined with diphtheria and tetanus toxoids in the first 19 months of life.	Vaccine Vol. 14, No. 8, pp. 767-772.
Halperin, Mills, et al. 1995	Acellular pertussis vaccine as a booster dose for seventeen- to nineteen-month-old children immunized with either whole cell or acellular pertussis vaccine at two, four and six months of age.	Pediatr Infect Dis J. Sep;14(9):792-7.
PHASE IIC	Safety and Immunogenicity of two Connaught component pertussis vaccines in combination with diphtheria and tetanus toxoids adsorbed in children 2-6 months of age with a booster immunization at 18 months of age	PHASE IIC CSR
Chatterjee, et al. 2012); NCT00255047	Comparative immunogenicity and safety of different multivalent component pertussis vaccine formulations and a 5-component acellular pertussis vaccine in infants and toddlers: A randomized, controlled, open-label, multicenter study.	Vaccine 30;3360– 3368.
Guerra, et al. 2009	Safety and Immunogenicity of a Pentavalent Vaccine Compared With Separate Administration of Licensed Equivalent Vaccines in US Infants and Toddlers and Persistence of Antibodies Before a Preschool Booster Dose: A Randomized, Clinical Trial.	Pediatrics Volume 123, Number 1, pp. 301-315.
Study PERTB9301	Safety and Immunogenicity of two Connaught component pertussis vaccines in combination with diphtheria and tetanus toxoids adsorbed alone or in combination with haemophilius influenza B conjugate vaccine in children 17-19 months of age	Study PERTB9301 CSR
Halperin, Barreto, et al. 1994	Safety and Immunogenicity of a Five-Component Acellular Pertussis Vaccine With Varying Antigen Quantities.	Arch Pediatr adolesc med 148, Nov 1994, pp. 1220-1224.
Pichichero, Green, et al. 1996	Antibody Response and Reactions to Completion of a Four-dose Series with a Two- or Three-component Acellular Pertussis Vaccine Compared to Whole Cell Pertussis Vaccine.	Scand J Infect Dis 28: 159-163.
Nolan, Altmann, et al. 2004	Antibody persistence, PRP-specific immune memory, and booster responses in infants immunised with a combination DTPa–HBV–IPV/Hib vaccine.	Vaccine 23 (2004) 14–20.
Schmitt, Zepp, et al. 1998	Immunogenicity and reactogenicity of a Haemophilus in¯uenzae type b tetanus conjugate vaccine when administered separately or mixed with concomitant diphtheria-tetanus-toxoid and acellular pertussis vaccine for primary and for booster immunizations.	Eur J Pediatr 157: 208±214.
(Trofa, et al. 2011); NCT00197236	Immunogenicity and Safety of an Inactivated Hepatitis A Vaccine When Coadministered With Diphtheria-tetanus-acellular Pertussis and Haemophilus influenzae Type B Vaccines in Children 15 Months of Age.	Pediatr Infect Dis J 30: e164–e169.
NCT00289913	Concomitant Use of Hepatitis A Vaccine, Inactivated With Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate) and Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Given to Healthy Children 15 Months of Age (V251-068)	NCT00289913 CSR

Schmitt, Miischenborn, et al. 1996	Immunogenicity and Reactogenicity of a Bicomponent and a Tricomponent Acellular Pertussis-Diphtheria-Tetanus (DTaP) Vaccine in Primary Immunization and as Second Year Booster: A Double-Blind, Randomized Trial.	Int J Infect Dis 1:6-13.

Source: Section B.2, p19 of the submission.

6.5 The key features of the vaccine effectiveness studies are summarised in Table 2.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Outcome(s)
Pichichero, Deloria, et al. 1997	85 Total: 1374	Double-blind, randomised 1 year	Unclear	Immunogenicity Safety
(CANADA II CSR 1992) Halperin, Eastwood, et al. 1996	398	Double-blind, randomised 1-2 months	Low	Immunogenicity Safety
Halperin, Mills, et al. 1995	86	Double-blind, randomised 48 hours	Low	Immunogenicity Safety
PHASE IIC	545	Double-blind 28 days	Low	Immunogenicity Safety
Chatterjee, et al. 2012); NCT00255047	1975	randomised open-label 180 days	Unclear	Immunogenicity Fever rates; Safety
Guerra, et al. 2009	1249	randomised open-label 33 months	Unclear	Immunogenicity Safety
Study PERTB9301	763	partially blind 28 days	Unclear	Immunogenicity Safety
Halperin, Barreto, et al. 1994	91	Double-blind, randomised 48 hours	Unclear	Immunogenicity Safety
Pichichero, Green, et al. 1996	86	Double-blind, randomised 30 days	Unclear	Immunogenicity reactogenicity
Nolan, Altmann, et al. 2004	289	single-blind 30-48 days	Unclear	Immunogenicity reactogenicity
Schmitt, Zepp, et al. 1998	189	single-blind 28-35 days	Unclear	Immunogenicity reactogenicity
(Trofa, et al. 2011); NCT00197236	394	open label 6 months	Unclear	Immunogenicity Safety
NCT00289913	620	open label 14 days	Unclear	Immunogenicity
Schmitt, Miischenborn, et al. 1996	157	Double-blind, randomised 7 days	Unclear	Immunogenicity reactogenicity

Source: compiled during the evaluation

6.6 The submission presented Pichichero 1997 as the main clinical evidence, where vaccines similar to DTPa and DTaP were compared alongside an array of other DTaP vaccines against a single pertussis whole-cell vaccines (DTwP) vaccine (a total of 13 vaccines were tested). The submission also presented a naïve comparison of 13 selected trials including DTaP or DTPa. The ESC noted the high level of heterogeneity between the trials, including the fact that the naïve comparison included trials spanning a long time period (1994-2012), that there was a range of trial designs (double blind, single blind, partially blind, open-label), sample sizes (n=86 though to n=1975) and trial durations (from 48 hours to approximately 1 year), and that the there were differences in both the definitions and follow up reporting

periods for AEs. Furthermore, there were systematic differences in potential baseline prognostic factors between trials included in the naïve comparison (e.g. co-administration of Haemophilus influenzae type B vaccine (Hib), inactivated polio vaccine (IPV), and Hepatitis B vaccine (HepB)), not all trials reported items including age, race, concomitant and previous vaccine exposure, and there was also a strong degree of selection bias. The ESC considered that results of these comparisons should be interpreted with caution.

Comparative effectiveness

6.7 Table 3 presents the results of Geometric Mean antibody concentrations in Pichichero 1997. Tables 4 to 6 present the results of naïve comparison.

Table 3: Results of Geometric Mean antibody concentrations after fourth dose in Pichichero 1997

		Tripacel (CLL-4F2/CLL-4F2)			Infanrix (SKB-3P/SKB3P)		
		N	GMT (95% CI)	% Protected [a]	N	GMT (95% CI)	% Protected[a]
PT	Pre	44	2.4 (1.9, 2.9)		41	6.0 (4.3, 8.2)	
	Post	44	43.3 (34.1, 54.9)	95.5%	41	92.9 (69.7, 124.0)	92.7%
FHA	Pre	44	2.9 (2.3, 3.7)		41	12.0 (8.0, 17.8)	
	Post	44	32.3 (25.6, 40.9)	84.1%	41	275.6 (214.1, 354.9)	95.1%
PRN	Pre	44	10.1 (7.8, 13.1)		41	21.5 (14.9, 31.0)	
	Post	44	182.4 (133.5, 249.3)[c]	95.5%	41	533.3 (394.7, 720.5)[c]	92.7%
FIM	Pre	43	13.4 (9.5, 19.0)		41	4.3 (2.7, 6.9)	
	Post	43	308.2 (223.1, 425.8)[c]	95.5%	41	3.8 (2.5, 5.7)	0.0%
T	Pre[d]	11	1.2 (0.6, 2.1)	100%	11	1.2 (0.4, 3.2)	100%
	Post	11	21.3 (18.8, 24.1)[c]	100%	11	20.0 (16.7, 24.0)[b]	100%
D	Pre	11	1.6 (0.8, 3.5)	100%	11	2.2 (0.6, 7.8)	82%
	Post	11	9.0 (7.2, 11.3)[c]	100%	11	10.2 (8.9, 11.6)	100%

Source: Table B.6-1, p36 of the submission.

Note: a Defined as a 4-fold increase for PT, FHA, PRN and FIM; diphtheria ≥ 0.1 IU; tetanus ≥ 0.01 IU; b P < 0.01; c P < 0.001; d: Pichichero 1997 reports (p785) that diphtheria and tetanus antibodies were measure only for a small number of children.

PT= Pertussis Toxoid; FHA= Filamentous Haemagglutinin ; PRN= Pertactin; FIM= Pertussis fimbriae ; D = diphtheria; T = tetanus; AGG = agglutinin; CHO = Chinese hamster ovary; GMT = Geometric Mean Titer; Pre= pre-booster; Post= post-booster.

Table 4: Summary of comparative benefits for 18 months DTaP booster vs. 18 months DTPa booster-derived from Pichichero 1997

Continuous Outcome I: Geometric Mean antibody concentrations; protection defined as a 4-fold increase for PT, FHA, PRN and FIM; diphtheria ≥ 0.1 IU; tetanus ≥ 0.01 IU					
	18 months DTaP booster		18 months DTaP booster		Mean difference*: 18 months DTaP booster vs. DTPa
	n	%protected	n	%protected	
PT	44	95.5%	41	92.7%	2.8%
FHA	44	84.1%	41	95.1%	-11%
PRN	44	95.5%	41	92.7%	2.8%
FIM	43	95.5%	41	0.0%	95.5%
T	11	100%	11	100%	0%
D	11	100%	11	100%	0%

Source: *Compiled during the evaluation*

6.8 Infanrix (DTPa) does not contain pertussis fimbriae and no vaccine-specific antibody response for pertussis fimbriae was detected. Higher antibody levels were measured against pertussis antigens, but the clinical benefit of these differences is unknown (particularly no accepted thresholds for antibody response to pertussis antigen that can be used as a surrogate for protection). The ESC noted the constraints in determining whether the antigenic difference produced any clinically meaningful difference between the two boosters.

6.9 On the basis of the head to head trials, DTaP appears to have the same immunogenicity as DTPa, although the ESC noted that no formal, clinically meaningful non-inferiority limit was nominated. The non-inferiority conclusion is consistent with the Cochrane review (Zhang, Axelsson and Halperin 20141) whereby multi-component (≥ three) acellular pertussis vaccines are effective and have an acceptable safety profile. The ESC considered that it was unclear whether the Pichichero trial was *a priori* powered for multiple comparisons, or subsequently corrected. While the ESC accepted that the DTaP and DTPa boosters were likely to confer similar % protected, it considered that differences between the vaccines were likely to be slightly underestimated due to the lack of adjustment for multiple comparisons.

6.10 The naïve comparisons of effectiveness are presented below.

Table 5: Naïve comparison of GMT/GMC pertussis antigens (PT, FHA, and PRN)

	PT		FHA		PRN	
GMT (95% CI)	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
DTaP/Tripacel						
CANADA II	18.4 (15.8, 21.4)	137.7(122.5, 154.8)	9.6 (8.4, 11.0)	102.9 (93.5, 113.4)	11.5 (10.0, 13.4)	234.4 (208.3, 263.7)
Halperin 95	35.9(28.4,45.3)	107 (82.3, 139)	17.9 (12.5, 25.7)	91.8 (67.0, 126)	17.4 (11.1, 27.3)	282 (204, 389)
PHASE IIC	13.5 (5.8, 31.1)	121 (55.2, 267)	12.3 (9.09,16.7)	82.5 (21.4, 318)	16.6(5.87,46.9)	367(55.2, 2447)
Chatterjee	66.48 (NR)	98.05 (NR)	22.51 (NR)	46.79 (NR)	33.63 (NR)	157.46 (NR)
Guerra 2009	7.73 (7.0, 8.54)	168.5 (153.5, 184.9)	5.4 (4.8, 6.0)	64.0 (58.8, 69.7)	7.83 (6.97, 8.8)	186.1 (168.2, 205.9)
PERTB9301	8.12 (6.3,10.5)	115 (87, 151)	6.15 (4.0, 8.8)	64.4(48, 86.3)	9.34(6.1, 14.2)	226 (152, 335)
Halperin 94	3.1 (NR)	50.9 (NR)	1.6 (NR)	55.1 (NR)	2.5 (NR)	96.1 (NR)
DTPa/Infanrix						
Pichichero 1996	8 (6, 10)	67 (56, 80)	44 (32, 59)	642 (516, 799)	33 (25, 43)	671 (529, 850)
Schmitt 1998	39.3 (36.8, 41.9)	113.2(95.4, 134.3)	93.0 (86.8, 99.5)	744.0(642.5, 861.5)	102.7(94.8, 111.2)	735.7(604.5, 895.4)
Trofa 2011	NR	87.0 (NR)	NR	536.1 (NR)	NR	326.4 (NR)
NCT00289913	NR	69.2 (57.4, 83.5)	NR	253.8 (215.3, 299.2)	NR	333.5 (267.3, 416.1)
Schmitt 96	10.2 (NR)	115.0 (NR)	39.3 (NR)	514.0 (NR)	20.6 (NR)	633.0 (NR)

Source: Table B.6-19, p53 of the submission.

[1] Zhang, LI Prietsch SOM, I Axelsson, and SA. Halperin. 2014. "Acellular vaccines for preventing whooping cough in children (Review)." The Cochrane Library Issue 9 pp. 1-154.

Note: PT= Pertussis Toxoid; FHA= Filamentous Haemagglutinin ; PRN= Pertactin; GMT/GMC = Geometric Mean Titer/Geometric Mean Concentration; Pre= pre-booster; Post= post-booster; NR= not reported.

Table 6: Naïve comparison of 4-fold titres rises for pertussis antigens (PT, FHA, and PRN)

	PT	FHA	PRN
	4-fold rise	**4-fold rise**	**4-fold rise**
Tripacel			
CANADA II	71.1 (65.0, 76.5)	88.4 (84.0, 91.6)	95.8 (92.6, 97.7)
PHASE IIC	60.0 (14.7,94.7)	60.0 (14.7, 94.7)	80.0 (28.4,99.5)
Chatterjee 2012	92.2	73.5	94.9
Guerra 2009	97.1 (94.0, 98.8)	79.3 (73.7, 84.3)	98.3 (95.8,99.5)
PERTB9301	95.2 (76.2,99.9)	85.7 (63.7, 97.0)	95.2 (76.2, 99.9)
Halperin 1994	NR	NR	NR
Infanrix			
Pichichero 1996	87 (NR)	90 (NR)	90 (NR)

Source: Table B.6-20, p53 of the submission.
Note: PT= Pertussis Toxoid; FHA= Filamentous Haemagglutinin ; PRN= Pertactin; GMT = Geometric Mean Titer; Pre= pre-booster; Post= post-booster; NR= not reported.

Table 7: Naïve comparison of GMT/GMC diphtheria and tetanus antigens

	DT		TT	
GMT (95% CI)	**Pre**	**Post**	**Pre**	**Post**
Tripacel				
CANADA II	0.11 (0.10, 0.13)	5.98 (5.30, 6.74)	0.19 (0.17, 0.21)	3.57 (3.32, 3.83)
Halperin 1995	0.69 (0.47, 1.02)	5.51 (3.73, 8.13)	0.20 (0.13, 0.28)	3.46 (2.66, 4.50)
PHASE IIC	0.12 (0.06, 0.26)	5.9 (1.91, 18.0)	0.27 (0.09, 0.85)	6.0 (3.95, 9.13)
Chatterjee 2012	0.32 (NR)	5.34 (NR)	0.97 (NR)	5.83 (NR)
Guerra 2009	0.57 (0.51, 0.64)	5.69 (5.11, 6.34)	0.50 (0.45, 0.54)	4.98 (4.61, 5.37)
PERTB9301	0.05 (0.03, 0.08)	3.0 (1.96, 4.70)	0.23 (0.15, 0.36)	5.7 (4.54, 7.28)
Halperin 1994	0.65 (NR)	17.61 (NR)	0.18 (NR)	5.15 (NR)
Infanrix				
Pichichero 1996	4.8 (3.4, 6.6)	12.7 (10.6, 15.2)	0.16 (0.1, 0.2)	4.9 (4.0, 5.9)
Schmitt 1998	1.08 (1.01, 1.17)	4.49 (3.73, 5.41)	1.27 (1.18, 1.37)	6.80 (5.86, 7.88)
Schmitt 1996	0.65 (NR)	17.61 (NR)	0.18 (NR)	5.15 (NR)

Source: Table B.6-21, p54 of the submission.
Note: PT= Pertussis Toxoid; FHA= Filamentous Haemagglutinin ; PRN= Pertactin; GMT/GMC = Geometric Mean Titer/Geometric Mean Concentration; Pre= pre-booster; Post= post-booster; NR= not reported.

6.11 The naïve comparisons of effectiveness suggest that DTaP is likely to confer similar immunogenicity outcomes to DTPa and therefore imply non-inferiority. The ESC considered, however, that, secondary to the limitations of trial exchangeability (described above), these results may imply non-inferiority only insofar that they do not explicitly contradict the results of the primary Pichichero study. The ESC suggested a formal indirect comparison across a smaller subset of the more contemporary and comparable trials may have been preferable to no formal indirect comparison, in terms of further corroborating the observation of non-inferior effectiveness.

Comparative harms

6.12 Tables below presented the reaction data in Pichichero 1997 and the results of the naïve comparison of reactogenicity.

6.13 The results suggest that DTaP has a similar safety profile, compared to DTPa.

Table 8: Summary of severe reaction data in Pichichero 1997

	Tripacel (CLL-4F2/CLL-4F2) (N=75)	Infanrix (SKB-3P/SKB-3P) (N=76)
Severe Irritability	1 (1.3%)	1 (1.3%)
Redness >50 mm	2 (2.7%)	3 (3.9%)
Swelling >50 mm	4 (5.3%)	5 (6.6%)
Severe Pain	1 (1.3%)	0

Source: Table B.6-12, p45 of the submission.

Table 9: Naïve comparison of reactogenicity (assumed %, not indicated in the submission)

	Fever	Redness	Swelling	Diarrhoea	Vomiting
Tripacel					
CANADA II	10.0	35.9	18.3	NR	NR
Halperin 1995	11	54	21	11	0
PHASE IIC	34.7	29.2	18.1	18.1	9.72
Chatterjee 2012	16.9	12.6	7.8	NR	8.0
Guerra 2009	8.7	18.2	11.6	16.5	3.9
PERTB9301	27.6	27.6	24.1	3.45	6.90
Halperin 1994	33	53	33	10	3
Infanrix					
Pichichero 1996	9.6	19.2	21.2	NR	NR
Nolan 2004	13.6	69.6	58.0	NR	NR
Schmitt 1998	24.6	34.8	26.1	10.1	1.4
Trofa 2011	22.0	36.5	27.0	NR	NR
Schmitt 1996	38.8	60.8	41.9	16.2	2.7

Source: Table B.6-22, p54 of the submission

Clinical claim

6.14 The submission described the 18-month DTaP booster as non-inferior in terms of comparative effectiveness and safety over 18 months DTPa booster. This claim appears adequately supported, though the claim of efficacy is based on surrogate immunogenicity outcomes and the primary data is both under-powered and likely not adjusted for multiple comparisons.

6.15 The ESC also noted that there were differences between the recommended NIP schedule and the trials presented as supporting evidence, including variable co-administration of Hib/IPV/HepB, use of a 7-valent pneumococcal vaccine, a mixture of oral and inactivated polio vaccine and the absence of influenza or meningococcal vaccine in the presented trials. Overall, the ESC did not consider this would significantly influence the therapeutic relativity of DTaP and DTPa.

Economic analysis

6.16 The economic evaluation was a cost-minimisation analysis.

6.17 The equi-effective doses were estimated as 1 x 0.5 mL dose of DTaP for 1 x 0.5 mL dose of DTPa.

6.18 The submission claimed that the proposed NIP price of DTPa is not publically available. Thus the submission assumed a price of $[redacted]. The ESC noted the actual prices of the two vaccines would be established through a subsequent national tender.

Drug cost/patient:

6.19 The proposed treatment consists of a single additional booster dose of DTaP at 18 months, with a medication cost of $[redacted] (assumed price).

Estimated PBS usage & financial implications

6.20 This submission was not considered by DUSC.

6.21 The submission:

- assumed there will be no market growth for 18-month DTaP containing vaccines;
- excluded administration costs and the cost of adverse events (likely cost underestimate). The ESC noted the Pre-Sub-Committee Response argued that these costs would be no different whether DTaP or DTPa were used, however considered that there was no data to either support or refute this claim; and
- assumed the uptake for DTaP will be [redacted]%.

Table 10: Estimated use and financial implications

Parameter	Year 1 2016	Year 2 2017	Year 3 2018	Year 4 2019	Year 5 2020
Cost to NIP					
Total (Tripacel)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Change (Infanrix)	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net total cost	$0	$0	$0	$0	$0

Source: Table E.4-1, p69 of the submission.

6.22 The redacted table above shows that the assumption of market uptake will have little impact on the overall cost estimates. The net cost to the NIP was estimated to be nil as the submission assumed that DTaP will be a direct substitute for DTPa.

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

7 PBAC Outcome

7.1 The PBAC recommended including the 18-month booster of the Pertussis Vaccine-Acellular, combined with Diphtheria and Tetanus Toxoids (Adsorbed) (Tripacel, DTaP) vaccine on the National Immunisation Program (NIP) for the prevention of pertussis on the basis of cost-minimisation to the 18-month booster of the combined diphtheria, tetanus and acellular pertussis (Infanrix, DTPa) vaccine recommended at the November 2014 PBAC meeting for inclusion on the NIP. One dose of 0.5mL Tripacel is equi-effective to one 0.5mL dose of Infanrix.

7.2 The PBAC noted that this would be the second pertussis-containing vaccine recommended at the 18-month time point for inclusion on the NIP. The PBAC agreed with the Australian Technical Advisory Group on Immunisation that the reintroduction of an 18-month DTPa booster onto the NIP is necessary from a public health perspective, as an additional measure to improve control of pertussis in Australia.

7.3 The PBAC accepted the nominated comparator of DTPa (Infanrix) vaccine, as it was recommended at the November 2014 PBAC meeting.

7.4 The PBAC noted that the advice from ESC raised a number of issues:

- the differences in antigenic composition between the DTaP and the DTPa.
- the head to head trial (Pichichero, Deloria, et al. 1997) was both likely under-powered and likely not adjusted for multiple comparisons,
- no formal indirect comparison of the heterogeneous supportive trials,
- no accepted thresholds for antibody response to pertussis antigen as a correlate of for protection

Overall, the PBAC considered, though the clinical benefit of the differences in the vaccines was unknown, it was reasonable to conclude that the two vaccines were likely to confer similar immunogenicity and likely similar efficacy and safety.

7.5 The PBAC noted the availability of the second vaccine at the 18-month time point would likely have no additional financial impact to the Commonwealth.

Outcome:
Recommended

Recommended listing

8.1 List the Diphtheria and Tetanus Toxoids (Adsorbed) (Tripacel) vaccine on the NIP for infants aged approximately 18 months.

8 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.

9 Sponsor's Comment

The sponsor had no comment.