

6.02 PERTUSSIS VACCINE-ACELLULAR COMBINED WITH DIPHtherIA AND TETANUS TOXOIDS [ADSORBED], Vaccine 0.5 ml, Adacel[®], Sanofi Australia Pty Ltd.

1 Purpose of Application

- 1.1 The submission requested National Immunisation Program (NIP) listing for Adacel (a pertussis vaccine-acellular, combined with diphtheria and tetanus toxoids (adsorbed) (dTpa vaccine)) for maternal vaccination, in the third trimester of each pregnancy, primarily to reduce the risk of pertussis in newborn infants up to 2 months of age.

2 Requested listing

- 2.1 The submission sought the following addition (*in italics*) to Schedule 1 (Designated vaccines and circumstances in which vaccines may be provided) of National Health (Immunisation Program – Designated Vaccines Determination 2014 (No. 1):

Vaccine and the circumstances in which vaccine may be provided	Brand	Formulation	Active ingredient and strength	Number and timing of doses
Vaccine	Adacel	Injection (0.5mL)	Each of the following:	1 dose (booster)
Diphtheria, tetanus and pertussis (adult/adolescent)			(a) diphtheria toxoid — not less than 2 IU;	
Circumstances			(b) tetanus toxoid — not less than 20 IU;	
Vaccine may be provided to:			(c) PT — 2.5 µg;	
(a) a child who is at least 10 years but less than 18 years old; or			(d) FHA — 5 µg;	
(b) a pregnant woman during each pregnancy.			(e) PRN — 3 µg	
			(f) FIM 2+3 — 5 µg	

- 2.2 The submission sought listing on the basis of a cost-minimisation analysis of Adacel compared with Boostrix for vaccination of pregnant women in the third trimester of each pregnancy.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

3 Background

- 3.1 **TGA status at time of PBAC consideration:** Adacel was added to the Australian Register of Therapeutic Goods (ARTG) on 21 November 2005 for ‘active immunisation against tetanus, diphtheria and pertussis in persons aged 10 years and over as a booster following primary immunisation’.
- 3.2 The Product Information includes a precaution: “The effect of Adacel on the development of the embryo and foetus has not been assessed. Vaccination in pregnancy is not recommended unless there is a definite risk of acquiring pertussis. As the vaccine is detoxified, risk to the embryo or the foetus is highly improbable. The benefits versus the risks of administering Adacel in pregnancy should carefully be evaluated when there is a high probable risk of exposure to a household contact or during an outbreak in the community”. [REDACTED]
- 3.3 The Product Information for Boostrix (comparator vaccine) was updated on 17 January 2017 to state that use may be considered during pregnancy.
- 3.4 This is not the first consideration of dTpa by the PBAC. A submission for Boostrix for vaccination of both parents of newborn infants at or around the time of birth (known as the ‘cocooning’ strategy) was reviewed by PBAC in July 2011. A similar submission for Adacel for the cocooning strategy was made in November 2011. Due to uncertain clinical effectiveness and high and uncertain cost-effectiveness, both submissions were rejected.
- 3.5 At its July 2016 meeting, the PBAC recommended a change to the circumstances under which Boostrix (pre-filled syringe, 0.5 mL) is made available as a designated vaccine on the NIP to include vaccination of women during each pregnancy to reduce pertussis disease in infants (prior to being vaccinated) and in mothers on the basis of cost-effectiveness compared with no vaccination (6.01 Boostrix July 2016 Public Summary Document).
- 3.6 All states and territories have implemented jurisdictionally-funded antepartum pertussis vaccination programs. The vaccines currently used in the programs are either Boostrix only or Boostrix and Adacel (see Table 1).

Table 1: Pertussis immunisation programs in Australian States and Territories (information as of 31 May 2015)

	ACT	NSW	NT	QLD	South Australia	Tasmania	Victoria	Western Australia
Start	April 2015	April 2015	April 2015†	August 2014	March 2015	June 2015	June 2015	April 2015
Vaccine	Boostrix® and Adacel®	Boostrix®	Boostrix®	Adacel® - adol Boostrix®	Adacel® adol Boostrix®	Adacel® adol Boostrix®	Boostrix®	Boostrix® adol Adacel®
Target group	From 28 weeks gestation (recommended at 28 weeks)	From 28 weeks gestation (ideally 28–32 weeks)	From 28 weeks gestation in each pregnancy, or after delivery	From 28 weeks gestation, if have not had last 5 years†	From 28 weeks gestation (ideally 28–32 weeks)	From 28 weeks gestation (ideally 28–32 weeks)	From 28 weeks gestation (ideally 28–32 weeks) or after delivery	From 28 weeks gestation (ideally 28–32 weeks)
Cocoon Program	No	No	Yes	No	No	No	Yes	No
Providers	GPs, antenatal clinics	GPs, AMs, antenatal clinics	All providers	Mainly GPs, also antenatal clinics	Mainly GPs, also antenatal clinics and councils	GPs mainly, some in antenatal clinics	All providers	GPs, antenatal clinics and obs
Coverage Assessed	NR	Perinatal data collection	Northern Territory immunisation register	Perinatal data collection	Not in perinatal data collection	NR	Perinatal data collection	Annual survey

Adol = adolescents; NR = Not reported

Source. Compiled from <http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-cdi3903c.htm>

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

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 three scheduled childhood doses of pertussis vaccine at two, four and six months of age, and booster doses at 18 months, four years and 10-15 years. There are four diphtheria, tetanus and acellular pertussis vaccines used in Australia: Infanrix and Tripacel are used in children; Adacel and Boostrix are used in adults, adolescents and children aged ≥10 years.
- 4.2 The submission proposed to include Adacel on the NIP schedule for immunisation of women in the third trimester of every pregnancy. The submission did not specify the timing of the vaccination within the third trimester.
- 4.3 According to the Australian Immunisation Handbook (10th Edition) the optimal time for vaccination is early in the third trimester (between 28 and 32 weeks), however the vaccine can be given at any time during the third trimester up to delivery (Pertussis Chapter, 4.12, of the 10th Edition of the Australian Immunisation Handbook 2016).

- 4.4 The ESC noted that it would be advantageous to have a second supplier of a pertussis vaccine-acellular, combined with diphtheria and tetanus toxoids (adsorbed) (dTpa vaccine) in Australia.

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

5 Comparator

- 5.1 The submission nominated Boostrix as the main comparator. Boostrix was recommended at the July 2016 PBAC meeting for listing on the NIP as a single dose during each pregnancy. Boostrix is a combined diphtheria-tetanus-acellular pertussis (dTpa) vaccine containing diphtheria toxoid, tetanus toxoid and three purified antigens of *Bordetella pertussis*: pertussis toxoid (PT), pertussis filamentous haemagglutinin (FHA) and pertactin (PRN). The comparator is appropriate.

Table 2: Comparative characteristics of the vaccine products presented in the submission

Vaccine	Adacel	Boostrix
Diphtheria toxoid	≥2µg IU	≥2µg IU
Tetanus toxoid	≥20µg IU	≥20µg IU
PT	2.5µg	8µg
FHA	5µg	8µg
PRN	3µg	2.5µg
FIM 2+3	5µg	-
Aluminium phosphate	0.33mg	0.5mg

Source: Table A.6.1 p 30, of the submission for Adacel and Boostrix

Abbreviations: IU = international unit, PT = pertussis toxin, FHA = filamentous haemagglutinin, PRN = pertactin, FIM = fimbrial.

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 one individual via the Consumer Comments facility on the PBS website. The comment raised concerns about the effectiveness of maternal antibodies in protecting newborns against pertussis, and a perceived lack of data regarding the safety of maternal pertussis vaccination.

Clinical trials

- 6.3 The submission was based on three head-to-head RCTs:
- Blatter 2009: Comparing immunogenicity and safety for adults treated with Adacel (n=762) versus Boostrix (n=1522)

- Southern 2005: Comparing reactogenicity and immunogenicity in adolescents treated with tetanus and diphtheria vaccine (n=79), Boostrix (n=79), Adacel (n=83), and Repevax (Adacel+Polio) (n=82)
 - Td516 2010: Comparing reactogenicity and immunogenicity in adolescents treated with Boostrix (n=321) versus Adacel (n=326)
- 6.4 The submission also presented five small RCTs or observational studies comparing Adacel (or Repevax (Adacel+Polio)) or Boostrix to no vaccination in pregnant women, and three observational studies comparing Adacel (or Repevax (Adacel+Polio)) versus Boostrix (or Boostrix-IPV (Boostrix+Polio)) in pregnant women. One of these studies, Amirthalingam 2016, was an extension of the 2014 study presented in the GSK Boostrix July 2016 PBAC submission. This analysis was possible because the pertussis containing vaccine offered to pregnant women in the UK was changed from Repevax (Adacel+Polio) to Boostrix-IPV (Boostrix+Polio) in July 2014. The study may be subject to bias due to the study design (unmeasured confounders), timing of vaccination (before and after a pertussis outbreak in the UK) and sample size.
- 6.5 No head-to-head RCTs comparing Adacel and Boostrix in pregnant women were identified.
- 6.6 Details of the head-to-head RCTs and the key observational study presented in the submission are provided in the table below.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Section B: Direct randomised trials – Vaccine efficacy and safety		
Blatter 2009 NCT00436073/ NCT00489970	Immunogenicity and safety of a tetanus toxoid, reduced diphtheria toxoid and three-component acellular pertussis vaccine in adults 19-64 years of age.	Vaccine 2009, 27:765-72
Td516 2010 NCT00319553	Descriptive, post-licensure, modified double-blind, multi-centre study evaluating safety and immunogenicity of Adacel and Boostrix vaccines among adolescents 11-18 years of age.	Clinical Study Report
Southern 2005	Immunogenicity and reactogenicity of combined acellular pertussis/tetanus/low dose diphtheria vaccines given as a booster to UK teenagers.	Vaccine 2005, 23: 3829-3835
Section C: Key observational Study – Vaccine effectiveness, efficacy and safety		
Amirthalingam 2016	Sustained effectiveness of the maternal pertussis immunisation programme in England three years following introduction	Clinical Infectious Diseases 2016, 63 (Suppl 4): S236-S243

Source: Table B.2.1, p36 of the submission.

- 6.7 The key features of the direct RCTs and the key observational study on vaccine efficacy are summarised in the table below.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Section B: Direct randomised trials – Vaccine efficacy and safety					
<i>Adacel versus Boostrix</i>					
Blatter 2009	2,337 Adacel (n=762) Boostrix (n=1522)	R, SB(O) 4 weeks + optional 1,3,5 and 10 year follow-up extension	High	Adults (aged 19 – 64 years) USA	Immunogeni city Safety
<i>Adacel versus Boostrix versus Repevax (Adacel+Polio) versus Tetanus diphtheria (control)</i>					
Southern 2005	323 Adacel (n=83) Boostrix (n=79) Repevax (Adacel+Polio) (n=82) Tetanus diphtheria (Td) (n=79)	R, SB (P), 6 weeks	High	Adolescents (aged 13 – 17 years) UK	Immunogeni city Safety
<i>Adacel versus Boostrix</i>					
Td516 2010	647 Adacel (n=326) Boostrix (n=321)	R, modified DB 4 weeks	Low	Adolescents (aged 11 – 18 years) USA	Immunogeni city Safety
Section C: Key observational Study – Vaccine effectiveness, efficacy and safety					
Amirthalingam 2016	243 Repevax (Adacel+Polio) (n=172) Boostrix-IPV (Boostrix+Polio) (n=71)	Observational, 3 years (1 October 2012 to 31 August 2015)	High	Pregnant women and infants (aged < 2 months) UK	Pertussis cases

Abbreviations: DB=double blind; SB (O) =single blind (observer (investigator and outcome assessor)); SB (P) =single blind (patient); R=randomised. Source: compiled during the evaluation

Comparative effectiveness

6.8 Table 5 presents the vaccine immunogenicity/efficacy results of Adacel versus Boostrix in the RCTs presented in Section B of the submission. Table 6 presents the vaccine effectiveness result of Repevax (Adacel+Polio) and Boostrix-IPV (Boostrix+Polio) in pregnant women from the observational study presented in Section C of the submission.

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Table 5: Results of vaccine efficacy across the direct randomised trials

Blatter 2009	Time point	Adacel (dTpa5v)			Boostrix (dTpa 3v)								
		n	GMC/BR	95% CI	n	GMC/BR	95% CI						
PT													
GMC (EU/mL)	Pre	722	8.1	7.5, 8.8	1435	7.3	6.9, 7.7						
	Post	722	32.2	29.6, 35.1	1431	63.6	60.1, 67.4						
BR (%)	Post	717	47.1	43.4, 50.9	1419	77.2	74.9, 79.3						
FHA													
GMC (EU/mL)	Pre	717	34.8	32.0, 37.8	1438	31.6	29.9, 33.5						
	Post	724	368.4	344.3, 394.2	1443	624.4	593.9, 656.6						
BR (%)	Post	714	94.0	92.0, 95.6	1433	96.9	95.8, 97.7						
PRN													
GMC (EU/mL)	Pre	727	14.3	12.9, 15.7	1445	13.4	12.5, 14.3						
	Post	726	351.9	315.7, 392.2	1444	401.0	368.5, 436.3						
BR (%)	Post	725	91.7	89.5, 93.6	1441	93.2	91.8, 94.4						
Southern 2005	Time point	Adacel (dTpa5v)			Boostrix (dTpa 3v)			Repevax (Adacel+Polio)			Placebo (Td)		
		n	GMT/GMFR	95% CI	n	GMT/GMFR	95% CI	n	GMT/GMFR	95% CI	n	GMT/GMFR	95% CI
PT													
GMT	Pre	83	857	633, 1160	79	1077	756, 1536	82	848	632, 1138	79	995	699, 1416
	Post		2998	2288, 3925		8792	6689, 11556		3812	2947, 4931		984	701, 1382
GMFR	Post		3.51	2.90, 4.23		8.16	6.30, 10.57		4.50	3.61, 5.61		0.99	0.93, 1.04
FHA													
GMT	Pre	83	2450	1930, 3111	79	2659	2042, 3462	82	2299	1845, 2865	79	2858	2214, 3691
	Post		17360	14058, 21439		36367	30736, 43029		12597	10509, 15100		2882	2246, 3699
GMFR	Post		7.08	5.40, 9.30		13.68	10.16, 18.41		5.48	4.48, 6.69		1.00	0.97, 1.05
PRN													
GMT	Pre	83	1859	1384, 2497	79	2782	1942, 3984	82	1735	1264, 2381	79	2524	1819, 3502
	Post		36406	27778, 47715		81177	61344, 107424		66438	52843, 83531		2534	1840, 3491
GMFR	Post		19.44	13.40, 28.21		29.18	21.46, 39.67		38.33	28.05, 52.37		1.00	0.96, 1.05
FIM													
GMT	Pre	83	3630	2635, 5001	79	3654	2489, 5364	82	3558	2455, 5157	79	4082	2634, 6328
	Post		58225	44204, 76694		4355	3087, 6144		45704	34466, 60608		4224	2752, 6484
GMFR	Post		16.03	10.25, 25.06		1.19	1.10, 1.29		12.84	8.87, 18.58		1.03	0.98, 1.09

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Blatter 2009	Time point	Adacel (dTpa5v)			Boostrix (dTpa 3v)		
		n	GMC/BR	95% CI	n	GMC/BR	95% CI
PT							
GMC (EU/mL)	Pre	722	8.1	7.5, 8.8	1435	7.3	6.9, 7.7
	Post	722	32.2	29.6, 35.1	1431	63.6	60.1, 67.4
BR (%)	Post	717	47.1	43.4, 50.9	1419	77.2	74.9, 79.3
FHA							
GMC (EU/mL)	Pre	717	34.8	32.0, 37.8	1438	31.6	29.9, 33.5
	Post	724	368.4	344.3, 394.2	1443	624.4	593.9, 656.6
BR (%)	Post	714	94.0	92.0, 95.6	1433	96.9	95.8, 97.7
PRN							
GMC (EU/mL)	Pre	727	14.3	12.9, 15.7	1445	13.4	12.5, 14.3
	Post	726	351.9	315.7, 392.2	1444	401.0	368.5, 436.3
BR (%)	Post	725	91.7	89.5, 93.6	1441	93.2	91.8, 94.4
Td516 2010	Time point	Adacel (dTpa5v)			Boostrix (dTpa 3v)		
		n	GMC	95% CI	n	GMC	95% CI
PT							
GMC	Pre	300	14.4	12.5, 16.6	296	13.5	11.6, 15.8
	Post	296	86.7	78.8, 95.4	304	135.9	122.9, 150.2
FHA							
GMC	Pre	304	26.1	22.7, 30.0	300	28.2	24.5, 32.4
	Post	305	240.7	217.7, 266.1	304	402.9	365.5, 444.2
PRN							
GMC	Pre	305	12.4	10.6, 14.6	304	13.1	11.2, 15.5
	Post	305	322.7	279.7, 372.4	304	463.3	395.4, 542.9
FIM							
GMC	Pre	297	13.9	12.0, 16.2	297	14.5	12.2, 17.2
	Post	305	1203	1004, 1442	301	26.6	22.2, 31.8

Abbreviations: dTPa- diphtheria, tetanus and pertussis; dTpa 3v- Boostrix; dTpa 5v-Adacel; BR-Booster Response; GMC- Geometric Mean Concentration; GMT- Geometric Mean Titre; GMFR- Geometric Mean Fold Rises; EU/ml - ELISA Units per millilitre; PT- Pertussis Toxoid; FHA- Filamentous Hemagglutinin; PRN = Pertactin; FIM = Fimbriae types 2 and 3; 95%CI- 95% Confidence Interval
Source: Table B.6.1 p55 of the submission, Table B.6.3 p57 of the submission, Table B.6.4-7 p58 of the submission

Table 6: Results of vaccine efficacy in the key observational study

Infant age/vaccination timing	Pertussis cases vaccinated / total n/N (%)	Matched coverage (%) / Vaccinated controls n/N (%)	VE: % (95% CI)
Amirthalingam 2016 : Screening Method			
Maternal pertussis VE by vaccine product ^			
Repevax (Adacel+Polio)	35/243 (14.4%) (*Should be 20/172 (11.6%))	64.8% (*Should be 63.1%)	91% (88, 94) (*Should be 93% (89, 95))
Boostrix-IPV (Boostrix+Polio)	31/192 (16.1%) (*Should be 15/71 (21.1%))	64.3% (*Should be 69.3%)	90% (86, 93) (*Should be 88% (79, 93))

Source: Table C.2.7, p104-105 of the submission, and compiled during evaluation based on Amirthalingam 2016 p21.^ Pertussis vaccines recorded as administered after 28 weeks of gestation and between 300 days prior to a birth and up to 8 weeks after birth *Submission incorrectly entered figures from Amirthalingam 2016 Table 2, p.20 rather than Amirthalingam 2016 Table 4, p21 into Table C.2.7 in the submission."

- 6.9 On the basis of direct RCT evidence presented in Table 5, the comparison of Adacel and Boostrix resulted in:
- Post-vaccination geometric mean titres (GMTs) and geometric mean concentrations (GMCs) of pertussis antigens that were lower in the Adacel group compared to the Boostrix group for all antigens components, except FIM which is not present in Boostrix.
- 6.10 On the basis of Amirthalingam 2016, presented by the submission in Table 6, the comparison of Repevax (Adacel+Polio) and Boostrix-IPV (Boostrix+Polio) resulted in:
- A maternal vaccine effectiveness (VE) for Repevax (Adacel+Polio) of 93% (95% CI: 89%, 95%) and VE for Boostrix-IPV of 88% (95%CI: 79%, 93%)

Comparative harms

- 6.11 The key patient-relevant harms were injection site pain, headache, and fever. A summary of relevant harms reported in the direct RCTs are found in Table 7 below.

Table 7: Summary of key adverse events in the direct randomised trials of Adacel and Boostrix

Trial ID	Adacel n with event (%)	Boostrix n with event (%)	p-Value
Blatter 2009, 15-day follow-up booster	(N=741)	(N=1480)	
Injection site reactions			
Pain	513 (69.2)	903 (61.0)	0.000
Redness	201 (27.1)	313 (21.1)	0.002
Swelling	190 (25.6)	260 (17.6)	0.000
Any systematic symptom			
- Fatigue	214 (28.9)	416 (28.1)	0.704
- Fever (>= 37.5)	59 (8.0)	82 (5.5)	0.027
- Gastrointestinal	130 (17.5)	235 (15.9)	0.318
- Headache	230 (31.0)	445 (30.1)	0.639
Td516	(N=323)	(N=321)	
Immediate unsolicited adverse event	1 (0.3)	2 (0.6)	-
Immediate unsolicited reaction	0	2 (0.6)	-
Solicited reaction	285 (89.1)	279 (88.0)	-
Solicited injection site reaction	273 (85.3)	257 (81.1)	-
Solicited systemic reaction	216 (67.5)	205 (64.7)	-
Unsolicited adverse event	90 (27.9)	88 (27.4)	-
Unsolicited reaction	37 (11.5)	25 (7.8)	-
Unsolicited injection site reaction	11 (3.4)	10 (3.1)	-
Unsolicited systemic reaction	27 (8.4)	18 (5.6)	-
Adverse event & discontinuation	0	0	-
Serious adverse event	0	0	-
Death	0	0	-
Southern 2005	(N=74)	(N=68)	
Local reactions and temperature			
- Redness >= 2.5cm	15 (20.3)	7 (10.1)	-
- Swelling >= 2.5cm	18 (24.3)	11 (16.2)	-
- Pain Tenderness >= 3 days	45 (60.8)	40 (58.0)	-
- Oral Temperature >= 38c	5 (6.8)	2 (2.9)	-
Systemic symptom episodes			
- Dizziness/feeling faint 1-10 days	3 (4.1)	3 (4.4)	-
- Fatigue/malaise/drowsy 1-10 days	12 (16.2)	9 (13.2)	-
- Gastrointestinal problem 1-10 days	4 (5.4)	2 (2.9)	-
- Headache 1-10 days	23 (31.1)	24 (35.3)	-
- Nausea/vomiting 1-10 days	9 (12.2)	5 (6.9)	-
- URTI symptoms 1-10 days	11 (14.9)	12 (16.7)	-

Source: Blatter 2009 Table 5, p. 771; Td516 CSR Table 5.1, p. 60; and Southern 2005 p. 3832-3833

- 6.12 There were similar safety results for subjects vaccinated with Adacel and Boostrix, with injection site reactions reported more frequently in the Adacel group.

Clinical claim

- 6.13 The submission described Adacel as non-inferior in terms of comparative efficacy and non-inferior in terms of comparative safety to Boostrix. The claim regarding comparative safety was adequately supported. The ESC noted:
- There were no head-to-head RCTs measuring the vaccine efficacy of Adacel versus Boostrix in the target population of pregnant women.

- The RCTs did not report cases of pertussis prevented, they only reported immunogenicity results. The three head-to-head RCTs presented by the submission report different antibody level responses between Adacel and Boostrix. However, as there are currently no accepted thresholds for antibody response to pertussis antigen that can be used as a surrogate for protection, the clinical benefit of the antibody response is unknown. In addition, Adacel contains pertussis fimbriae types 2 and 3 (FIM) (5 µg) antigens; Boostrix does not contain these components.
- The trials were not powered to show a difference between Boostrix and Adacel and there were no formal statistical comparisons of immunogenicity between Boostrix and Adacel.
- The risk of bias in the estimates reported in Amirthalingam 2016 is high due to the study design (unmeasured confounders), timing of vaccination (before or after a pertussis outbreak in the UK) and sample size.

- 6.14 In the PSCR, the sponsor argued that
- The submission provides a large body of evidence to support the clinical claim.
 - Amirthalingam (2014) has previously been considered by the PBAC and the PBAC previously considered Adacel (or Repevax) and Boostrix equivalent on the basis of this evidence (Boostrix PSD, July 2016).
 - Amirthalingam (2016) reaffirm the results of Amirthalingam (2014).
 - The Tripacel submission (recommended by the PBAC in July 2015) faced many of the same issues of comparability and heterogeneity outlined in the Adacel commentary. (see above)
- 6.15 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.16 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.17 The submission presented a cost minimisation analysis of Adacel compared to Boostrix.
- 6.18 The equi-effective doses were estimated as Adacel 1 x 0.5 mL dose and Boostrix 1 x 0.5 mL dose. Given that 1 dose of Adacel would directly substitute for 1 dose of Boostrix and there are no claims of superior efficacy, the PBAC considered that this approach is appropriate.
- 6.19 The two vaccines have different presentations: Adacel (vial) and Boostrix (pre-filled syringe, 0.5 mL). There may be different non-drug related cost (administration and consumables) associated with the different presentations. The ESC noted that GP surgeries are experienced in vaccinating people with vaccines in both presentations.

Drug cost/patient: \$ [REDACTED]

6.20 Based on the current price of Adacel under the state- and territory-based maternal vaccination programs, a proposed price of \$ [REDACTED] per dose was applied.

Estimated PBS usage & financial implications

6.21 This submission was not considered by DUSC. The submission used a market share approach. The NIP cost was calculated based on the number of pregnant women, projected coverage and vaccine unit costs. Based on the assumed price in the submission, the substitution of Adacel for Boostrix at the same unit price results in no change to overall costs to the NIP.

Table 8: Estimated use and financial implications

	Current 2016	Year 1 2017	Year 2 2018	Year 3 2019	Year 4 2020	Year 5 2021
Eligible population						
Pregnant women in 3rd trimester	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Vaccine coverage (%)	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %
Number vaccinated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
NIP market share						
Adacel	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %
Boostrix	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %
Predicted utilisation						
Adacel patients	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Adacel doses	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Vaccine cost assumptions						
Adacel per dose	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Boostrix per dose	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated total cost of Adacel	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Change in cost of Boostrix	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net cost to NIP		\$0	\$0	\$0	\$0	\$0

Source: Table E-1.1, p 125 and Table E-2.1, p126, of the submission.

The redacted table shows that at year 5, the predicted utilisation is between 100,000 – 200,000 patients.

6.22 The estimates of vaccine coverage are uncertain due to the variation in the estimates available. The estimates of market share are uncertain and no justification was provided by the submission. However, as the costs of Adacel are directly offset by an equivalent value in reduced Boostrix procurement costs, the net cost to the NIP is zero.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

7 PBAC Outcome

7.1 The PBAC recommended a change to the circumstances under which dTpa, Adacel, is made available as a designated vaccine for the NIP to include vaccination of

women during each pregnancy to reduce pertussis disease in infants (prior to being vaccinated) and in mothers. The PBAC's recommendation was based on, among other matters, its assessment, as described above, that the cost-effectiveness of dTpa, Adacel would be acceptable if it was cost-minimised against dTpa, Boostrix.

- 7.2 The PBAC accepted that dTpa, Boostrix, is the appropriate comparator, and that the equi-effective doses are Adacel 1 x 0.5 mL dose and Boostrix 1 x 0.5 mL dose.
- 7.3 The PBAC noted the differences in the antigenic compositions of Adacel and Boostrix. In the post-submission advice, ATAGI considered that any of the presently available 3- [Boostrix] or 5-component [Adacel] pertussis vaccines is a suitable alternative for the prevention of pertussis in Australia.
- 7.4 The PBAC noted the limitations of the clinical evidence raised in the evaluation of the submission, including that the direct head-to-head randomised trials reported only immunogenicity outcomes which do not correlate with protection. The observational study from the UK assessing the effectiveness of the maternal dTpa vaccination program in infants with the Repevax and then Boostrix-IPV vaccines (Amirthalingam 2016) was most informative for the consideration of comparative efficacy. The PBAC agreed with the ATAGI that it is reasonable to assume comparable efficacy for Adacel and Boostrix on the basis of this post-licensure vaccine effectiveness data.
- 7.5 The PBAC noted that the rates of adverse events was similar between the two types of dTpa vaccine and were reasonable in the context of vaccination.
- 7.6 The PBAC noted that a positive recommendation for Adacel would provide a potential second supplier of dTpa vaccine in Australia. The PBAC noted that Adacel and Boostrix are used in Pertussis immunisation programs in the States and Territories.
- 7.7 The PBAC recalled in their consideration of Boostrix at the July 2016 meeting that the optimal timing of dTpa vaccination in pregnancy is an issue for further consideration, and that there is an emerging body of evidence supporting second trimester immunisation. Accordingly, the PBAC recommendation at the July meeting was for vaccination during each pregnancy, without restriction to the third trimester. The PBAC reiterated that the optimal timing of dTpa vaccination in pregnancy should be based on clinical evidence and informed by ATAGI.
- 7.8 The PBAC noted the availability of the second vaccine would likely have no additional financial impact to the Commonwealth.
- 7.9 The PBAC noted that this submission is not eligible for an Independent Review, as the PBAC has made a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Addition to Schedule 1 (Designated vaccines and circumstances in which vaccines may be provided) of National Health (Immunisation Program – Designated Vaccines Determination 2014 (No. 1):

Vaccine and the circumstances in which vaccine may be provided	Brand	Formulation	Active ingredient and strength	Number and timing of doses
Vaccine	Adacel	Injection (0.5mL)	Each of the following:	1 dose (booster)
Diphtheria, tetanus and pertussis (adult/adolescent)			(a) diphtheria toxoid — not less than 2 IU;	
Circumstances			(b) tetanus toxoid — not less than 20 IU;	
Vaccine may be provided to:			(c) PT — 2.5 µg;	
(c) a child who is at least 10 years but less than 18 years old; or			(d) FHA — 5 µg;	
(d) a pregnant woman during each pregnancy.			(e) PRN — 3 µg	
			(f) FIM 2+3 — 5 µg	

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 welcomes the PBAC's recommendation to list Adacel® on the National Immunisation Program for the protection of newborn infants and their mothers against pertussis.