5.07 HUMAN PAPILLOMAVIRUS 9-VALENT VACCINE Injection 0.5mL, pre-filled syringe Gardasil® 9, Seqirus

1 Purpose of Application

1.1 National Immunisation Program (NIP) listing for a 2-dose schedule of a 9-valent Human Papillomavirus (HPV) vaccine for vaccination of females and males aged 12-13 years for the prevention of HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58.

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

Component	Description
Population	Females and males aged 12-13 years
Intervention	2-dose, 9-valent HPV vaccine (types 6, 11, 16, 18, 31, 33, 45, 52, 58) (9vHPV)
Comparator	3-dose, quadrivalent HPV vaccine (types 6, 11, 16, 18) (4vHPV)
Outcomes	HPV 15/18/31/33/45/52/58-related cervical intraepithelial neoplasias (CIN2/3), adenocarcinoma in situ (AIS), invasive cervical carcinoma, vulval intraepithelial neoplasias (VIN 2/3), vaginal intraepithelial neoplasias (VaIN 2/3), vulval cancer, vaginal cancer, anal intraepithelial neoplasias (AIN 2/3) and anal cancer.
Clinical claim	A 2-dose schedule of 9vHPV compared with the current 3-dose schedule of 4-vHPV vaccine in girls and boys 9-14 years is: • Non-inferior with respect to efficacy against HPV 6/11/16/18 infection and disease. • Superior with respect to efficacy against HPV 31/33/45/52/58 infection and disease. • Non-inferior with respect to safety.

Source: p152-53 of the submission and compiled during the evaluation.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
HUMAN PAPILLOMAVIRUS 9-VALENT (TYPES 6, 11, 16, 18, 31, 33, 45, 52, 58) VACCINE Injection 0.5mL, pre-filled syringe	1	1	$[redacted]	Gardasil® 9 Seqirus

Category / Program:	National Immunisation Program
Indication:	2-dose schedule (0, 6 month or 0, 12 month) for females and males aged 12-13 years as part of school based program.

2.1 The submission sought listing of a 2-dose schedule of 9vHPV on the NIP on the basis of a cost-utility analysis comparing, in adolescent girls and boys aged 12-13 years:

- The 2-dose 9vHPV vaccine to the 3-dose 4vHPV vaccine; and
- The 3-dose 9vHPV vaccine to the 3-dose 4vHPV vaccine.

2.2 The submission requested a price of $[redacted] per dose for the requested 2-dose 9vHPV vaccine NIP schedule. The price was calculated based on the weighted requested prices of $[redacted] for females and $[redacted] for males, plus $[redacted] administration cost avoided by switching to a 2-dose regimen. The weighting is

based on the eligible population (female = 0.4888, male = 0.5112) and is the same weighting that was used to calculate the 4vHPV price, as set out in a letter from the Pharmaceutical Benefits Pricing Authority (PBPA) of 16 December 2011 to the sponsor. By comparison, the 4vHPV price per dose is $[redacted] ($[redacted] for females and $[redacted] for males).

2.3 The PSCR provided further details regarding the proposed risk sharing arrangement (RSA) for a fourth booster dose to maintain lifelong protection and a proposed price per dose if a third booster dose is required (see the *Financial Management – Risk Sharing Arrangements* section of this advice).

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

3 Background

3.1 The 9vHPV vaccine was TGA registered on 29 June 2015. The TGA approved indications are:

- Females aged 9 through 45 years for the prevention of cervical, vulvar, vaginal and anal cancer, precancerous or dysplastic lesions, genital warts, and infection caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 (which are included in the vaccine).
- Males 9 through 26 years of age for the prevention of anal cancer, precancerous or dysplastic lesions, external genital lesions and infection caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 (which are included in the vaccine).

3.2 When 9vHPV was first registered by the TGA, the recommended dose schedule in the TGA approved product information (PI) was for 3 doses (0, 2, 6 months) for females aged 9 to 45 years and males aged 9 to 26 years. The PI was subsequently amended in January 2017 to include a 2-dose schedule (0, 5-13 months) in females and males aged 9-14 years.

3.3 This was the first consideration of the 9vHPV vaccine by the PBAC.

3.4 The PBAC recommended the 4vHPV vaccine for listing on the NIP for females aged 12-13 years (plus a catch-up program for females up to 26 years) at its 22 November 2006 extraordinary meeting. The PBAC subsequently recommended the 4vHPV vaccine for listing on the NIP for males aged 12-13 years (plus a catch up program for Year 9 males) at its November 2011 meeting.

4 Population and disease

4.1 HPV is the most common sexually transmitted infection. Anogenital HPV infection is transmitted by skin-to-skin and mucosal contact, generally in the course of sexual contact. Under the Renewed National Cervical Screening Program (NCSP), the current projected incidence of cervical cancer and cervical intraepithelial neoplasia (CIN) 2/3 is 5.71 and 177.16 per 100,000 unvaccinated females, respectively.

Currently around 71.8% of cervical cancer cases are due to HPV types 16/18, followed by 14.7% due to HPV types 31/33/45/52/58.

4.2 The submission requested that 9vHPV vaccine be listed on the NIP as a 2-dose schedule (with the second dose to be given either 6 or 12 months following the first dose) for females and males aged 12-13 years as part of school based program.

4.3 The evaluation identified the following as issues regarding the number of doses:

- Reducing the number of doses potentially increases the vaccine course completion rate (the proportion of individuals who receive all doses). However, it also reduces the scope for catch-up amongst individuals who miss a dose – when an individual misses a dose they will still receive two doses with a 3-dose schedule, but they will only receive one dose with a 2-dose schedule (unless they obtain the missed dose privately). An increased course completion rate will increase the effectiveness of the 9vHPV vaccine in clinical practice, while reduced scope for catch-up will reduce the effectiveness in clinical practice. The PSCR (p2) acknowledged the public health importance of maintaining a high compliance with the proposed 2-dose 9vHPV vaccine schedule and noted that the sponsor supports initiatives to improve HPV vaccination uptake at a state and territory level.
- ATAGI recommended a 3-dose schedule for individuals older than 15 years, and for those who are immunocompromised (p9 of the ATAGI pre-submission advice).

4.4 The evaluation identified the following issues regarding the dosage interval:

- The immunogenicity results vary by the dosage interval; consequently, the ATAGI considered that 12 months should be the recommended schedule interval for use in the NIP for adolescents aged 9-14 years, although a minimum interval of 6 months between doses would be acceptable (p9 of the ATAGI pre-submission advice).
- ATAGI also considered it preferable for adolescents to compete the vaccine course as early as possible prior to sexual debut (p9 of the ATAGI pre-submission advice). Under the current 3-dose 4vHPV vaccine NIP schedule adolescents receive all doses by 6 months, but with a 12 month dosage interval some additional adolescents may experience sexual debut before receiving the second dose.
- A more flexible 2-dose schedule would create more flexibility around co-administering with other vaccines listed on the NIP, thus reducing the number of nurse visits per school. Similarly, a 2-dose schedule at 0 and 12 months may enable vaccinating two school year groups (e.g. Year 7s receiving the first dose and 8s receiving the second dose) in one session. The ATAGI stated that states and territories will need to take into consideration the logistics and potential vaccination uptake when considering the preferred timing of the 2nd

dose within an interval of 6 to 12 months to suit their implementation strategies (p9 of the ATAGI pre-submission advice).

- The PSCR stated that the sponsor will be guided by the PBAC and ATAGI regarding the timing of doses of the 9vHPV vaccine program.

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

5 Comparator

5.1 The submission nominated the 3-dose 4vHPV vaccine (which includes HPV types 6, 11, 16, 18) schedule in 12-13 year old females and males as the main comparator. The main argument provided in support of this nomination is that it is the NIP funded vaccine and dose schedule that would be replaced. The ESC considered this was an appropriate comparator.

5.2 The evaluation considered that for the requested population, 2-doses of the 4vHPV vaccine may also be a relevant intermediate comparator. In 2014, the World Health Organization revised its recommended HPV vaccination schedule for females younger than 15 years of age from three doses to two doses[1] and subsequently, many countries with a HPV vaccination program have adopted a 2-dose schedule[2] (p1 of the ATAGI pre-submission advice). Similarly, in November 2015, the PBAC considered a claim of non-inferiority in terms of comparative effectiveness between 2-doses and 3-doses of the 2vHPV vaccine (Cervarix®) to be adequately supported.[3] The PSCR noted that there is no provision for a 2-dose schedule in the 4vHPV vaccine PI and no data relating to a 2-dose schedule has been considered by PBAC or ATAGI. Nevertheless, the ESC agreed with the evaluation that a 2-dose 4vHPV vaccine was a relevant intermediate comparator as it could feasibly replace the current 3-dose 4vHPV schedule.

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 that if 9vHPV

[1] World Health Organization. Human papillomavirus vaccines: WHO position paper, October 2014. *Weekly Epidemiological Record* 2014;89:465-92.

[2] Brotherton JM, Zuber PL, Bloem PJ. Primary prevention of HPV through vaccination: update on the current global status. *Current Obstetrics and Gynecology Reports* 2016;5:210-24.

[3] PBAC Public Summary Document: Human Papillomavirus (HPV) types 16 and 18, vaccine injection, 0.5ml, Cervarix®, GlaxoSmithKline Australia Pty Ltd, November 2015 PBAC meeting

is not recommended for listing, Australians will have to continue to use a potentially less effective vaccine.

Clinical trials

6.3 There were no head-to-head RCTs comparing the proposed 2-dose 9vHPV vaccine with the 3-dose 4vHPV vaccine in adolescents.

6.4 The submission was based on one efficacy trial:

- Protocol V503-001: Double blinded RCT comparing:
    - 9vHPV 3-dose (0, 2, 6 Month) in women 16-26 years (Part B: N=7106)
    - 4vHPV 3-dose (0, 2, 6 Month) in women 16-26 years (Part B: N=7109)

6.5 The submission also presented the following immunobridging trials:

- Protocol V503-010: Open label, partially randomised, controlled trial comparing:
    - 9vHPV 2-dose regimens (0, 6 month) in boys 9-14 years (N=301)
    - 9vHPV 2-dose regimens (0, 6 month) in girls 9-14 years (N=301)
    - 9vHPV 2-dose regimens (0, 12 month) in boys/girls 9-14 years (N=300)
    - 9vHPV 3-dose (0, 2, 6 month) in women 16-26 years (N=314)
    - 9vHPV 3-dose (0, 2, 6 month) in girls 9-14 years (N=300)
- Protocol V503-009: Double blinded RCT comparing:
    - 9vHPV 3-dose (0, 2, 6 month) in girls 9-15 years (N=300)
    - 4vHPV 3-dose (0, 2, 6 month) in girls 9-15 years (N=300)
- Protocol V503-002: Open label, partially randomised, controlled trial comparing:
    - 9vHPV 3-dose (0, 2, 6 month) in women 16-26 years (N=470)
    - 9vHPV 3-dose (0, 2, 6 month) in boys 9-14 years (N=669)
    - 9vHPV 3-dose (0, 2, 6 month) in girls 9-14 years (N=648)

6.6 The submission also presented safety data from the integrated safety population for six studies, protocols V503-001, -002, -005, -006, -007 and -009.

6.7 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Randomised trials		
Protocol V503-001	A Randomized, International, Double-Blinded (With In-House Blinding), Controlled With GARDASIL™, Dose-Ranging, Tolerability, Immunogenicity, and Efficacy Study of a Multivalent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine Administered to 16- to 26-Year-Old Women (Visit cut-off for primary efficacy and immunogenicity analyses 10 April 2013)	CSR - 2013
	Joura EA, Giuliano AR, Iversen O-E, et al (2015) A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women.	New Engl J Med; 372(8):711-723
	Luxembourg A, Brown D, Bouchard C, et al (2015) Phase II Studies to Select the Formulation of a Multivalent HPV L1 Virus-Like Particle (VLP) Vaccine.	Hum Vaccines Immunother 11:1313-1322
Protocol V503-010	A Phase III Clinical Trial to Study the Tolerability and Immunogenicity of a 2-dose regimen of V503, a Multivalent Human Papillomavirus (HPV) L1 Virus-Like Particle (VLP) Vaccine, administered in Preadolescents and Adolescents (9 to 14 year olds) with a Comparison to Young Women (16 to 26 year olds)	CSR- 2015
	Iversen OE, Miranda MJ, Ulied A, et al (2016) Immunogenicity of the 9-Valent HPV Vaccine Using 2-Dose Regimens in Girls and Boys Vs a 3-Dose Regimen in Women.	JAMA 316:2411-2421
Protocol V503-009	A Randomized, Double-Blinded, Controlled with GARDASIL® (Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed)), Phase III Clinical Trial to Study the Immunogenicity and Tolerability of V503 (9-Valent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) in Preadolescent and Adolescent Girls (9- to 15-year-olds)	CSR - 2012
	Vesikari T, Brodszki N, Van Damme P, et al (2015) A Randomized, Double-Blind, Phase III Study of the Immunogenicity and Safety of a 9-Valent Human Papillomavirus L1 Virus-Like Particle Vaccine (V503) Versus Gardasil® in 9-15-Year-Old Girls.	Pediatr Infect Dis J 34:992-998
Protocol V503-002	A Phase III Clinical Trial to Study the Immunogenicity, Tolerability, and Manufacturing Consistency of V503 (A Multivalent Human Papillomavirus [HPV] L1 Virus-Like Particle [VLP] Vaccine) in Preadolescents and Adolescents (9 to 15 year olds) with a Comparison to Young Women (16 to 26 year olds)	CSR - 2011
	Van Damme P, Olsson SE, Block S, et al (2015) Immunogenicity and Safety of a 9-Valent HPV Vaccine.	Pediatrics 136:e28-e39
	Luxembourg A, Moreira ED, Samakoses R, Kim KH, Sun X, Maansson R, Moeller E, Christiano S and Chen J (2015) Phase III, Randomized Controlled Trial in Girls 9-15 Years Old to Evaluate Lot Consistency of a Novel Nine-Valent Human Papillomavirus L1 Virus-Like Particle Vaccine.	Hum Vaccines Immunother 11:1306-1312

CSR= Clinical Study Report
Source: Table B.2.3, p48of the submission

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

Table 3: Key features of the included evidence, 2-dose and 3-dose 9vHPV vs. 3-dose 4vHPV

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
V503-001 Part A (dose ranging) (0, 2, 6 Month) Part B clinical efficacy and immunogenicity 9vHPV 3-dose (0, 2, 6 Month) 4vHPV 3-dose (0, 2, 6 Month)	1,240 7,106 7,109	R, DB, MC, PG Part A: 7 months Part B: 42 months	Low	Women, aged 16-26 years	Immunogenicity Serum samples for analysis of anti-HPV 6/11/16/18/31/33/45/52/58 responses by HPV-9 cLIA. Results reported as GMTs and seroconversion rates. Efficacy CIN2/3, AIS, cervical cancer, VIN2/3, VaIN2/3, vaginal cancer, vulval cancer. HPV-related persistent infection. Safety	Yes
V503-010 9vHPV (0,6) (girls) 9vHPV (0,6) (boys) 9vHPV (0,12) (girls/boys) 9vHPV (0,2,6) (women) 9vHPV (0,2,6) (girls)	 301 301 300 314 300	R, OL, MC, PG 36 mths	Low	Girls and boys, aged 9-14 years, and women aged 16-26 years	Immunogenicity Serum samples at 4 weeks following the last dose of the assigned regimen of the 9vHPV vaccine (Month 7 or Month 13) for anti-HPV 6/11/16/18/31/33/45/52/58 responses by HPV-9 cLIA. Results reported as GMTs and seroconversion rates. Safety	No
V503-009 9vHPV (0,2,6) 4vHPV (0,2,6)	 300 300	R, DB, MC, PG 7 mths	Low	Adolescent females aged 9-15 years	Immunogenicity Anti-HPV 16 and 18 at four weeks post dose three by cLIA. Results reported as GMTs and seroconversion rates. Safety	No
V503-002 9vHPV (0,2,6) (women) 9vHPV (0,2,6) (girls) 9vHPV (0,2,6) (boys)	 470 648 669	R, OL, MC, PG 12 mths	Low	Adolescent females and males aged 9-15 years and females aged 16-26 years	Immunogenicity Serum samples at four weeks post dose three (Month 7) for anti-HPV 6/11/16/18/31/33/45/52/58 responses by HPV-9 cLIA. Results reported as GMTs and seroconversion rates. Safety	No

cLIA = Competitive Luminex immunoassay; DB=double blind; GMT = Geometric mean titre; HPV = Human papillomavirus; MC=multi-centre; PG=parallel group; OL=open label; R=randomised.

Source: Compiled during the evaluation, Attachment 1.B, Protocol V503-001-End-of-Study Report, Table 1; Attachment 1.D, Protocol V503-010 CSR, Section 10.1; Attachment 1.E, Protocol V503-009 CSR, Section 10.1; Attachment 1.F, Protocol V503-002 CSR, Section 10.1

Comparative effectiveness

6.8 Tables 4 and 5 summarise the key efficacy and immunobridging results, respectively.

6.9 Vaccine efficacy: The observed vaccine efficacy against HPV 31/33/45/52/58-related CIN2/3, AIS, cervical cancer, VIN2/3, VaIN2/3, vaginal cancer, vulval cancer was 96.7% for 3-dose 9vHPV compared with 3-dose 4vHPV in Protocol V503-001. The submission argued that the lower bound of the 95% CI (of 80.9%), met the pre-specified criterion for superiority of >25%.

6.10 There was limited incidence of high-grade cervical, vaginal and vulval disease due to the short follow-up period in Protocol V503-001 (42 months). The short follow-up period increased the uncertainty in the estimated vaccine efficacy and meant that there is limited evidence regarding the duration of vaccine protection.

6.11 Vaccine efficacy by the number of doses received was not available in Protocol V503-001 due to the high level of vaccine coverage (number of patients receiving all three doses) and the low frequency of cases.

6.12 Immunogenicity: The observed competitive Luminex Immunoassay (cLIA) geometric mean titers (GMTs) and the seroconversion rates for HPV types 6, 11, 16 and 18 with 3-dose 9vHPV compared with 3-dose 4vHPV were similar, and met the statistical criterion for non-inferiority in Protocol V503-001.

6.13 The cLIA GMTs and seropositivity rates declined over time in both treatment groups in Protocol V503-001. However, it is difficult to interpret this data in terms of the duration of vaccine-conferred immunity given that the submission acknowledged that minimum anti-HPV levels associated with protection from acquisition of HPV infection (i.e. an immune correlate of protection) remain to be determined.

6.14 Non-inferiority of the cLIA GMTs four weeks after the last dose in each of the three 2-dose regimen cohorts, compared with the 3-dose regimen in women aged 16-26 years, in Protocol V503-010 was demonstrated.

6.15 For each of the three 2-dose regimen cohorts, non-inferiority of seroconversion rates versus the cohort of women 16-26 years receiving 3 doses for each of 9 vaccine HPV types was demonstrated successfully in Protocol V503-010 (p-values <0.001 for each of the 9 HPV type-specific tests).

6.16 Immunogenicity varied by number of doses for HPV type 45 in Protocol 503-010. The GMTs for HPV types 31, 45 and 52 were lower in the 2-dose group (girls 0, 6) compared with the 3-dose group (girls 0, 2, 6) at 4 weeks after the last dose. The estimated fold-difference between the treatment groups was 0.54 (0.45, 0.65) for HPV type 45 and 0.64 (0.55, 0.75) for HPV type 52 (Table 11-16, p181 of Protocol V503-010 CSR). Thus the non-inferiority criterion was not met for HPV 45 and 52 (non-inferiority was demonstrated if the lower limit of the 95% CI for the fold-difference is greater than 0.67). Furthermore, the GMTs for HPV type 45 was lower in the 2-dose group (girls 0, 12) compared to the 3-dose group (girls 0, 2, 6) at 4 weeks after the last dose in Protocol V503-010. The estimated fold-difference between these treatment groups was 0.66 (0.53, 0.84) (Table 11-17, p 182 of Protocol V503-010 CSR) which also did not meet the non-inferiority criterion. The PSCR (p2) reiterated that in the absence of an immune correlate of protection, the correlation between GMTs and effectiveness is unknown.

6.17 Immunogenicity varied with the dosage interval in Protocol 503-010. GMTs and seroconversion rates were higher for all 9vHPV types group using the 2-dose (0, 12) regimen compared with the 2-dose (0, 6) regimen.

6.18 ATAGI considered that a 12-month dose interval is optimal, although a minimum interval of 6 months between doses is acceptable based on its non-inferiority compared with 3 doses of 9vHPV in women (16-26 years) (p9 of the ATAGI pre-submission advice).

Table 4: Results of efficacy against HPV 31/33/45/52/58-related high-grade cervical, vaginal and vulval disease in the PPE population of Protocol V503-001

Trial ID	9vHPV (N = 7,099)				4vHPV (N = 7,105)				Observed vaccine efficacy[3] % (95% CI)
V503-001 (PPE population)	n	No. of cases	Person-years at risk	Incidence/ 100 person-years at risk	n	No. of cases	Person- years at risk	Incidence/ 100 person-years at risk	
HPV 31/33/45/52/58-related CIN2/3, AIS, cervical cancer, VIN2/3, VaIN2/3, vaginal cancer, vulval cancer	6,016	1	19,005.1	0.0	6,017	30	18,976.6	0.2	96.7 (80.9, 99.8) (p <0.0001)[2]
By HPV type:									
HPV 31-related	5,308	0	16,744.4	0.0	5,252	7	16,560.7	0.0	100 (40.1, 100)
HPV 33-related	5,624	0	17,771.4	0.0	5,628	7	17,803.0	0.0	100 (39.3, 100)
HPV 45-related	5,724	0	18,102.7	0.0	5,724	2	18,079.2	0.0	100 (-246.8, 100)
HPV 52-related	5,320	0	16,777.1	0.0	5,216	11	16,473.6	0.1	100 (67.3, 100)
HPV 58-related	5,361	1	16,902.7	0.0	5,340	6	16,842.4	0.0	83.4 (-23.6, 99.3)
By lesion type:									
CIN 2 or worse	5,948	1	17,407.0	0.0	5,943	27	17,427.2	0.2	96.3 (79.5, 99.8)
CIN2	5,948	1	17,407.0	0.0	5,943	23	17,430.9	0.1	95.6 (76.3, 99.8)
CIN3	5,948	0	17,407.0	0.0	5,943	5	17,438.1	0.0	100 (-0.2, 100)
AIS	5,948	0	17,407.0	0.0	5,943	0	17,441.7	0.0	NA
Cervical cancer	5,948	0	17,407.0	0.0	5,943	0	17,441.7	0.0	NA
VIN2/3 or VaIN2/3 or worse	6,009	0	18,976.0	0.0	6,012	3	18,988.0	0.0	100 (-71.5, 100)
VIN2/3 or worse	6,009	0	18,976.0	0.0	6,012	0	18,988.0	0.0	NA
VaIN2/3 or worse	6,009	0	18,976.0	0.0	6,012	3	18,988.0	0.0	100 (-71.5, 100)
Vaginal cancer	6,009	0	18,976.0	0.0	6,012	0	18,988.0	0.0	NA

N = number of subjects randomised to the respective vaccination group who received at least 1 injection; n = number of subjects in the given population who have at least one follow-up visit after Month 7 in the per-protocol population; after Day 1 in all other analysis populations; AIS = Adenocarcinoma in situ; CI = Confidence interval; CIN = Cervical intraepithelial neoplasia; HPV = Human papillomavirus; VaIN = Vaginal intraepithelial neoplasia; VIN = Vulval intraepithelial Neoplasia; POP = population; PPE = per protocol efficacy.

NB: Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.

[1] In addition to meeting all the criteria for becoming a primary efficacy endpoint case (ie. HPV 31/33/45/52/58-related high grade cervical, vulval or vaginal disease endpoint case), subjects are also required to be PCR-positive to the same HPV type on a study visit immediately before or immediately after the study visit when the subject became a primary efficacy endpoint case.

[2] P-value calculated for the lower bound of the two sided 95% CI for the vaccine efficacy being greater than 25%.

[3] 100%*(1-risk of becoming a case in the intervention group/risk of becoming a case in the comparator group)

Source: Table B.6.1, p90 of the submission and Table B.6.3 p95 of the submission

Table 5: Anti-HPV GMTs by vaccination cohort: girls and boys 9-14 years versus women 16-26 years in the PPI population1 of Protocol V503-010 in Protocol V503-010

Assay (cLIA)	Timepoint2	Girls 9-14 years (0, 6) N = 301		Boys 9-14 years (0, 6) N = 301		Girls & boys 9-14 years (0, 12) N = 300		Girls 9-14 years (0, 2, 6) N = 300		Women 16-26 years (0, 2, 6) N = 314	
		n	GMT (95% CI) (mMU/mL)	n	GMT (95% CI) (mMU/mL)	n	GMT (95% CI) (mMU/mL)	n	GMT (95% CI) (mMU/mL)	n	GMT (95% CI) (mMU/mL)
HPV 6	Day 1	258	<16 (<16, <16)	263	<16 (<16, <16)	257	<16 (<16, <16)	254	<16 (<16, <16)	238	<16 (<16, <16)
	Month 7/13	258	1,658 (1,480, 1,858)	263	1,557 (1,392, 1,743)	257	2,679 (2,390, 3,002)	254	1,496 (1,334, 1,678)	238	771 (685, 868)
HPV 11	Day 1	258	<6 (<6, <6)	264	<6 (<6, <6)	257	<6 (<6, <6)	254	<6 (<6, <6)	238	<6 (<6, <6)
	Month 7/13	258	1,389 (1,240, 1,555)	264	1,424 (1,273, 1,592)	257	2,942 (2,627, 3,295)	254	1,306 (1,166, 1,464)	238	581 (516, 653)
HPV 16	Day 1	272	<12 (<12, <12)	273	<12 (<12, <12)	264	<12 (<12, <12)	269	<12 (<12, <12)	249	<12 (<12, <12)
	Month 7/13	272	8,005 (7,161, 8,949)	273	8,475 (7,582, 9,472)	264	14,329 (12,796, 16,046)	269	6,996 (6,254, 7,826)	249	3,154 (2,807, 3,544)
HPV 18	Day 1	272	<8 (<8, <8)	272	<8 (<8, <8)	266	<8 (<8, <8)	270	<8 (<8, <8)	267	<8 (<8, <8)
	Month 7/13	272	1,873 (1,652, 2,124)	272	1,861 (1,641, 2,110)	266	2,810 (2,475, 3,191)	270	2,049 (1,806, 2,325)	267	762 (671, 865)
HPV 31	Day 1	272	<4 (<4, <4)	271	<4 (<4, <4)	268	<4 (<4, <4)	271	<4 (<4, <4)	264	<4 (<4, <4)
	Month 7/13	272	**1,436 (1,272, 1,622)**	271	**1,**498 (1,327, 1,692)	268	2,118 (1,874, 2,393)	271	**1,748 (1,548, 1,975)**	264	572 (506, 647)
HPV 33	Day 1	273	<4 (<4, <4)	271	<4 (<4, <4)	269	<4 (<4, <4)	275	<4 (<4, <4)	279	<4 (<4, <4)
	Month 7/13	273	1,030 (920, 1,153)	271	1,040 (929, 1,164)	269	2,198 (1,962, 2,461)	275	796 (712, 891)	279	348 (312, 389)
HPV 45	Day 1	274	<3 (<3, <3)	273	<3 (<3, <3)	268	<3 (<3, <3)	275	<3 (<3, <3)	280	<3 (<3, <3)
	Month 7/13	274	**358 (314, 408)**	273	352 (309, 402)	268	**418 (366, 477)**	275	**662 (581, 754)**	280	214 (188, 243)
HPV 52	Day 1	272	<3 (<3, <3)	273	<3 (<3, <3)	268	<3 (<3, <3)	275	<3 (<3, <3)	271	<3 (<3, <3)
	Month 7/13	272	**581 (522, 647)**	273	640 (575, 713)	268	1,123 (1,008, 1,252)	275	**910 (818, 1,013)**	271	364 (327, 406)
HPV 58	Day 1	270	<4 (<4, <4)	270	<4 (<4, <4)	265	<4 (<4, <4)	273	<4 (<4, <4)	261	<4 (<4, <4)
	Month 7/13	270	1,251 (1,120, 1,398)	270	1,326 (1,186, 1,482)	265	2,445 (2,185, 2,735)	273	1,229 (1,101, 1,373)	261	491 (439, 550)

CI = Confidence interval; HPV = Human papillomavirus; PPI = per protocol immunogenicity; GMT = Geometric mean titre; mMU = Milli Merck units; cLIA = 9 valent Competitive Luminex immunoassay; N = Number of subjects randomised to the respective vaccination group who received at least one injection; n = Number of subjects contributing to the analysis; m = Number of subjects seropositive to the relevant HPV type(s).
1 Includes all subjects who: (1) received all planned vaccinations within acceptable day ranges; (2) had four weeks post last dose serum sample collected within an acceptable day range; (3) were seronegative at Day 1 for the relevant HPV type(s); and (4) had no other protocol violations that could interfere with the evaluation of immune response.
2 The second timepoint was four weeks post the last vaccine dose, ie. Month 7 for 0, 6 and 0, 2, 6 regimens and Month 13 for 0, 12 regimens.
Source: Table B.6.17, p118 of the submission. Attachment 1.D, Protocol V503 010 CSR, Table 11-1, p134-136

Comparative harms

6.19 Table 6 summarises the main safety results from the randomised trials.

Table 6: Summary of key adverse events in the randomised trials

Adverse event	Protocol V503-001		Integrated V503-001, -002, -005, -006, -007, -009
	9vHPV n (%)*	4vHPV n (%)*	9vHPV n (%)
	N = 7,071	N = 7,078	N = 13,307
Days 1-15 after any vaccination visit			
≥1 AE	6,640 (93.9)	6,419 (90.7)	12,231 (91.9)
Injection-site related	6,423 (90.8)	6,023 (85.1)	11,751 (88.3)
Non injection-site related	3,948 (55.8)	3,883 (54.9)	7,138 (53.6)
Vaccine-related AE	6,519 (92.2)	6,200 (87.6)	11,956 (89.8)
Injection-site related	6,422 (90.8)	6,023 (85.1)	11,750 (88.3)
Non injection-site related	2,086 (29.5)	1,929 (27.3)	3,736 (28.1)
SAE	25 (0.4)	17 (0.2)	48 (0.4)
Vaccine-related SAE	2 (0.0)	1 (0.0)	5 (0.0)
Death	1 (0.0)	1 (0.0)	1 (0.0)
Discontinued due to an AE	7 (0.1)	3 (0.0)	14 (0.1)
Discontinued due to a vaccine-related AE	5 (0.1)	3 (0.0)	11 (0.1)
Discontinued due to a SAE	2 (0.0)	0 (0.0)	4 (0.0)
Discontinued due to a vaccine-related SAE	1 (0.0)	0 (0.0)	2 (0.0)
Day 1 after vaccination to final visit**			
≥1 AE	6,661 (94.2)	6,444 (91.0)	12,270 (92.2)
Injection-site related	6,423 (90.8)	6,024 (85.1)	11,753 (88.3)
Non injection-site related	4,052 (57.3)	3, 957 (55.9)	7,324 (55.0)
Vaccine-related AE	6,519 (92.2)	6,202 (87.6)	11,958 (89.9)
Injection-site related	6,422 (90.8)	6,024 (85.1)	11,752 (88.3)
Non injection-site related	2,088 (29.5)	1,930 (27.3)	3,742 (28.1)
SAE	233 (3.3)	183 (2.6)	305 (2.3)
Vaccine-related SAE	2 (0.0)	2 (0.0)	5 (0.0)
Death	5 (0.1)	5 (0.1)	5 (0.0)
Discontinued due to an AE	8 (0.1)	4 (0.1)	15 (0.1)
Discontinued due to a vaccine-related AE	5 (0.1)	3 (0.0)	11 (0.1)
Discontinued due to a SAE	3 (0.0)	1 (0.0)	5 (0.0)
Discontinued due to a vaccine-related SAE	1 (0.0)	0 (0.0)	2 (0.0)

*Number of subjects experiencing adverse events

**180 days post the third dose.

AE = adverse event; SAE = serious adverse event

Source: Table B.6.26 of the submission, Attachment 1.A, Protocol V503-001 CSR, Table 12-3 and 12-4, p749-750; Attachment 1.I, 9vHPV Vaccine – Summary of Clinical Safety, Table 2.7.4: 12/13, p72-73.

6.20 9vHPV vaccine was associated with an increase in injection-site vaccine-related adverse events (AEs) within 15 days of any dose compared with 4vHPV vaccine (RR = 1.067, 95% CI: 1.054, 1.081), with most injection-site AEs being mild or moderate in intensity and few subjects reporting severe injection-site AEs. In particular, there was a slightly raised risk of erythema, pain and swelling.

Benefits and harms

6.21 A summary of the comparative benefits and harms for the 2-dose 9vHPV vaccine versus the 3-dose 4vHPV vaccine is presented in Table 7 below.

Table 7: Summary of assumed comparative benefits and harms for the 2-dose 9vHPV vaccine and the 3-dose 4vHPV vaccine*

Benefits						
HPV 31/33/45/52/58-related CIN2/3, AIS, cervical cancer, VIN2/3, VaIN2/3, vaginal cancer, vulval cancer						
Trial	**Incidence / person-years at risk**		**Vaccine efficacy*** (95% CI)**	**Incidence / 10,000 person-years at risk ****		
	2-dose 9vHPV vaccine	**3-dose 4vHPV vaccine**		**2-dose 9vHPV vaccine**	**3-dose 4vHPV vaccine**	***RD***
V503-001	1 / 19,005.1	30 / 18976.6	96.7 (80.9, 99.8)	0.5	15.8	-15.3
Harms						
Injection-site vaccine- related adverse events (AEs) within 15 days of any dose						
Trial	**Subjects experiencing an AE**		**RR (95% CI)**	**Subjects experiencing an AE / 100 patients**		
	2-dose 9vHPV vaccine	**3-dose 4vHPV vaccine**		**2-dose 9vHPV vaccine**	**3-dose 4vHPV vaccine**	**RD**
V503-001	6,423 / 7,071	6,023 / 7,078	1.067 (1.054, 1.081)	90.8	85.1	5.7

* Assuming vaccine efficacy with 2-dose 9vHPV vaccine is non-inferior to 3-dose 9vHPV vaccine and that results for adult females are applicable to adolescents.
** Maximum duration of follow-up: 42 months
*** 100% x (1-risk of becoming a case in the intervention group/risk of becoming a case in the comparator group)
AIS = Adenocarcinoma in situ; CI = Confidence interval; CIN = Cervical intraepithelial neoplasia; HPV = Human papillomavirus; VaIN = Vaginal intraepithelial neoplasia; VIN = Vulval intraepithelial Neoplasia; RD = risk difference; RR = relative risk.
Source: Calculated during the evaluation based on Table B.6.1, p90 of the submission and Table B.6.3, p95 of the submission, and table B.6.26 of the submission

6.22 On the basis of the evidence presented by the submission (i.e. based on a trial comparing 9vHPV 3-dose and 4vHPV 3-dose in women 16-26 years with a maximum duration of follow-up of 42 months and assuming vaccine efficacy with 2-dose 9vHPV vaccine is non-inferior to 3-dose 9vHPV vaccine and that results for adult females are applicable to adolescents), for every 10,000 patients treated with the 2-dose 9vHPV vaccine in comparison to the 3-dose 4vHPV vaccine approximately 15 fewer patients per year would experience HPV 31/33/45/52/58-related CIN2/3, AIS, cervical cancer, VIN2/3, VaIN2/3, vaginal cancer or vulval cancer.

6.23 On the basis of the evidence presented by the submission, for every 100 patients receiving a dose of 9vHPV vaccine in comparison to a dose of 4vHPV vaccine, approximately 6 additional patients would experience injection-site vaccine-related AEs. The pre-PBAC response (p3) noted, however, that the increase in injection-site reactions per dose would be more than offset by the overall reduction in these AEs due to a reduction in doses from three of the 4vHPV vaccine to two of the 9vHPV vaccine.

Clinical claim

6.24 Largely on the basis of the vaccine efficacy trial (Protocol V503-001), the submission described the 3-dose 9vHPV vaccine compared with the 3-dose 4vHPV vaccine in females 16-26 years as:

- Non-inferior in terms of efficacy against HPV 6/11/16/18 infection and disease.
- Superior in terms of efficacy against HPV 31/33/45/52/58 infection and disease.
- Non-inferior in terms of comparative safety.

6.25 On the basis of the immunobridging trials (especially Protocol V503-010), the submission described the 2-dose 9vHPV vaccine in females and males 9-14 years compared with the 3-dose 9vHPV vaccine in females 16-26 years as:

- Non-inferior with respect to efficacy against HPV 6/11/16/18/31/33/45/52/58 infection and disease.
- Non-inferior with respect to safety.

6.26 The submission therefore described the 2-dose 9vHPV compared with the 3-dose 4vHPV vaccine in females and males 9-14 years as:

- Non-inferior with respect to efficacy against HPV 6/11/16/18 infection and disease.
- Superior with respect to efficacy against HPV 31/33/45/52/58 infection and disease.
- Non-inferior with respect to safety.

6.27 The evaluation considered that the claims regarding efficacy were uncertain due to the following issues:

- There is no head-to-head RCT of the 3-dose 9vHPV vaccine versus the 2-dose 4vHPV vaccine in adolescents (the proposed NIP population). The clinical claims are dependent on an efficacy trial in adults and immunobridging trials, which introduces significant uncertainty. Furthermore, in Protocol 503-010, immunogenicity results were poorer for HPV type 45 if 2-doses were administered (compared with 3-doses), and for all HPV types if the dosage interval was 6 months, rather than 12 months.
    - However, the ATAGI considered the 2-dose 9vHPV vaccine compared with 4vHPV is likely to provide non-inferior clinical protection against disease associated with 4vHPV types and superior clinical protection against disease associated with 9v-non4vHPV types (p5 of the ATAGI pre-submission advice). ATAGI also considered the immunogenicity of 2-dose 9vHPV vaccine in adolescent boys and girls (aged 9–15 years) to be non-inferior to that provided by 3-doses 9vHPV vaccine in women (aged 16–26 years) (p6 of the ATAGI pre-submission advice).
    - The PSCR noted the HPV vaccines are intended to be prophylactic and targeted at young cohorts prior to sexual debut and that due to practical considerations relating to follow-up time and ethical concerns, efficacy

studies are conducted in the sexually active populations at risk of HPV infection and disease.

- The ESC acknowledged that these issues were considered by the PBAC in its recommendation of 4vHPV vaccine and that ATAGI considered the efficacy claims to be reasonable.

- The follow-up period in the 9vHPV vaccine trials is short.
  - The PSCR (p2) noted that the follow-up period in the pivotal trial is comparable to that in the pivotal 4vHPV trials that were previously considered by the PBAC.
  - ATAGI noted there are no data on the duration of protection with a 2-dose schedule of 9vHPV, and that a review of immunogenicity in 2-dose schedules of 2vHPV and 4vHPV shows that antibody levels decrease over time and become inferior to a 3-dose schedule 24 and 18 months, respectively, after the first dose (p11 of the ATAGI pre-submission advice).
  - The ESC raised concerns regarding the decreasing antibody levels at a time when adolescents may start to become sexually active.
  - The PSCR (p3) proposed that a third dose of the 9vHPV vaccine be recommended in the event of waning vaccine efficacy.

6.28 The ESC considered the claims regarding safety were reasonable. ATAGI considered that, although 9vHPV appears to be associated with a greater frequency of transient injection-site reactions than 4vHPV, it does not have any significant concerns regarding the safety of 9vHPV (p9 of the ATAGI pre-submission advice).

6.29 The PBAC considered that the efficacy claims regarding the 2-dose 9vHPV vaccine schedule compared with the 3-dose 4vHPV vaccine schedule of (i) non-inferiority against HPV 6/11/16/18 infection and disease and (ii) superiority against HPV 31/33/45/52/58 infection and disease were reasonable. However, the PBAC considered the duration of vaccine protection of the 2-dose 9vHPV schedule was uncertain.

6.30 The PBAC noted the increase in injection site reactions following a dose of the 9vHPV vaccine, compared with a dose of the 4vHPV vaccine. However, taking into account the overall reduction in harm from the 2-dose course of 9vHPV, compared with a 3-dose course of the 4vHPV, the PBAC considered the increase in site reactions was not of significant concern and accepted the claim of non-inferior comparative safety.

Economic analysis

6.31 The submission presented a modelled cost-utility analysis comparing:

- A 9vHPV vaccine 2-dose program to the current 4vHPV vaccine 3-dose program.
- A 9vHPV vaccine 3-dose program to the current 4vHPV vaccine 3-dose program.

6.32 The ESC considered that a comparison of 2-dose 9vHPV to 2-dose 4vHPV was also informative because 2-dose 4vHPV is likely to be cost-effective compared with 3-dose 4vHPV and so provides an intermediary strategy between 3-dose 4vHPV and 3- or 2-dose 9vHPV. In this regard, the ESC noted the move internationally towards 2-dose HPV vaccine schedules and considered that a comparison to a 2-dose 4vHPV strategy would reduce the uncertainty regarding the cost effectiveness of various dosing frequencies.

6.33 The submission did not include a within-trial analysis step followed by extrapolation of trial outcomes using pre-modelling studies to a longer time frame in the economic model.

6.34 The economic model captured the incremental clinical benefit of the 9vHPV vaccine compared with the 4vHPV vaccine in preventing HPV disease attributable to HPV 31/33/45/52/58. The model also captured the cost-saving impact of implementing a 2-dose rather than a 3-dose vaccination schedule. The submission assumed that there would be no clinical impact of implementing a 2-dose 9vHPV vaccination schedule, compared with a 3-dose 9vHPV vaccination schedule.

6.35 The model differed from previous HPV submissions in that a static Markov cohort model was used rather than a dynamic transmission model. The impact on herd immunity was estimated using a separate dynamic transmission model (see Table 8).

Table 8: Summary of model structure and rationale

Component	Summary
Time horizon	Lifetime. Patients were followed beginning at the age of vaccination, followed until age 100 years. In comparison, the maximum duration of follow-up in Protocol V503-001 was 42 months.
Outcomes	QALYs for the following HPV-related disease states were estimated: CIN2/3, cervical, vulval, vaginal and anal cancers.
Methods used to generate results	Markov cohort model. The model did not include the costs of cervical screening and downstream costs resulting from imperfect compliance and test specificity and sensitivity.
Health states	7 health states: Well; CIN2/3; cervical cancer; vulval cancer; vaginal cancer, anal cancers; death (health outcomes for females only). The model excluded genital warts, low-grade cervical disease (i.e. CIN1), VIN, VAIN, AIN, and HPV-related oropharyngeal (HPVOP) cancers. AEs due to the vaccine were not considered. Health benefits in males were also not modelled, although the incremental cost impact of 9vHPV vaccine in males was included.
Utilities	Utilities for full health were age-dependent. Utilities for CIN2/3 = 0.99; cervical cancer = 0.71; vulval cancer = 0.639; vaginal cancer = 0.585; anal cancer = 0.57. Utilities were based on the literature and were used in previous PBAC submissions for the 4vHPV vaccine (except for CIN2/3). There were previously some concerns regarding the vignettes developed for vulval, vaginal and anal cancer standard gamble questionnaire, which may bias results in favour of intervention due to question framing. The utility estimates were applied proportionally to the age-dependent full health utilities (i.e. utility for full health * utility for cervical cancer). *The ESC noted that these utilities were applied to all stages of the specified cancers.*
Cycle length	1 year
Transition probabilities	Vaccine efficacy was obtained from the following sources: - HPV 31/33/45/52/58-related CIN2/3 and cervical, vulval and vaginal cancer from the PPE population from Protocol V503-001; - HPV 16/18-related CIN2/3 and cervical cancer from the pivotal 4vHPV trials in females (FUTURE I (Protocol V501-013), FUTURE II (Protocol V501-015), Protocol 005, Protocol 007), - HPV 16/18-related vulval and vaginal cancer from the pivotal 4vHPV trials in females (Protocols 007, 013 and 015); and - HPV 31/33/45/52/58-related anal cancer was based on vaccine efficacy against HPV 6/11/16/18-related AIN from the GHN population of Protocol 020 (the pivotal 4vHPV trial in males). Lifetime duration of protection assumed. No cross-protection provided by the 4vHPV vaccine to HPV 31/33/45/52/58 was assumed. Herd immunity was based on a separate Dynamic Infectious Disease model (Regan-Philp model, presented in the 2011 PBAC submission for the 4vHPV vaccine for boys). Background CIN and cervical cancer age-specific incidences for an unvaccinated population were taken from the dynamic Policy1-Cervix model. The incidence of the other cancers was based on data from the AIHW. Transition probabilities between health states were age dependent, reflecting the age dependent incidence of CIN2/3 and cervical, anal, vulval and vaginal cancers. The proportion of CIN and cancers attributable to HPV types 31/33/45/52/58 were based on Australian and international sources. Cancer deaths were based on data from the AIHW. Probabilities of death from other causes were based on the rate of all cause death in females, obtained from Australian Life Tables, 2013-2015

Source: p229-246 of the submission and compiled during the evaluation.

6.36 ATAGI considered that, in the absence of data that definitely predict the duration of protection from a 2-dose schedule of 9vHPV, the same baseline assumption of lifelong protection as used in the evaluation for 4vHPV was acceptable (p7 of the ATAGI pre-submission advice). However, ATAGI also noted that there is "insufficient data to draw a firm conclusion on whether this impacts duration of protection" and that there is potential for the antibody titre with a 2-dose schedule to wane faster than with a 3-dose schedule (p14). The overall duration of protection is also governed by coverage; ATAGI noted that widening the interval between doses reduced the scope for catch-up amongst those who missed one vaccination (p14). ATAGI therefore recommended that sensitivity analysis should consider the potential impact if waning occurs earlier with the 2-dose schedule than with the 3-dose (p7).

6.37 Despite the ATAGI advice, the submission did not conduct a sensitivity analysis of the economic model on the duration of protection. Univariate sensitivity analysis was conducted on the time horizon of the model by the submission and the evaluation; however, a dynamic transmission model was needed to undertake a more accurate sensitivity analysis of the duration of protection.

- The PSCR (p3) stated that the relatively straightforward cohort model used in the submission precluded the ability to evaluate durations of vaccine protection less than lifelong in the economic evaluation. The PSCR argued that the sensitivity analyses presented in the evaluation examining the shorter time horizons on the incremental cost effectiveness ratio (ICER) was not a surrogate analysis for a shorter duration of vaccine protection.
- The PSCR (p3) further stated that "if the effectiveness of a 2-dose schedule was found to wane faster than a 3-dose schedule, it is anticipated that a third dose of 9vHPV vaccine would be recommended to complete the 3-dose schedule".
- The ESC noted the ATAGI advice that "caution needs to be used in estimating herd protection with 9vHPV vaccine using data from the 4vHPV program because the rapid herd protection initially seen in Australia was accelerated by the large catch-up program which provided rapid high level coverage" [and] "that herd protection estimates for 9v-non4vHPV types need to be estimated using dynamic transmission models with explicit assumptions regarding coverage and single cohort assumptions rather than catch-up for these types.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Vaccination schedule	Costs avoided from adoption a 2- versus 3-dose vaccination schedule.	High. Favours 9vHPV vaccine.
Vaccine efficacy	The model applied vaccine efficacy from Protocol V503-001, the pivotal 4vHPV trials in females, and Protocol 020 in males.	High. Inclusion of vaccine efficacy against CIN2/3, cervical, vulval and vaginal cancer favours 9vHPV vaccine. Varying vaccine efficacy rates has a lesser impact.
Herd immunity	Herd immunity was based on a separate Dynamic Infectious Disease model (Regan-Philp model, presented in the 2011 PBAC submission for the 4vHPV vaccine for boys).	Moderate. Inclusion of herd immunity favours 9vHPV. Varying different herd immunity rates has a lesser impact.
Duration of protection	Assumed lifelong protection.	Unknown impact. Favours the 9vHPV vaccine.

Source: compiled during the evaluation

6.38 The submission estimated that the 2-dose 9vHPV vaccine schedule would result in more QALYs and lower costs than the current 3-dose 4vHPV vaccine schedule.

6.39 The submission also estimated the ICER of a 9vHPV 3-dose vaccine schedule versus the current 4vHPV 3-dose vaccine schedule was $15,000/QALY - $45,000 QALY gained.

6.40 An additional scenario which compared a hypothetical 2-dose 4vHPV vaccine schedule with a 2-dose with 9vHPV vaccine schedule was conducted during the evaluation which resulted in an ICER of $15,000/QALY - $45,000 QALY gained. This scenario was based on an assumption of non-inferiority but accounting for differences in coverage with a 2-dose versus 3-dose schedule and assumed the same price per dose of 4vHPV for a 2-dose schedule as for the 3-dose schedule (of $[redacted]/dose). The PSCR (p3) considered that this ICER was uncertain as there is no agreed price per dose of 4vHPV for a 2-dose schedule. The PSCR presented an alternative sensitivity analysis of 2-dose 9vHPV vaccine compared with 2-dose 4vHPV vaccine which assumed a cost per dose of $[redacted], resulting in an ICER of less than $15,000 per QALY gained

Table 10: Results of the economic evaluation

Component	9vHPV	4vHPV	Increment
9vHPV vaccine 2-dose NIP versus the current 4vHPV vaccine 3-dose NIP			
Costs	$	$	-$
QALYs	16.550134	16.549669	0.000465
Incremental cost/QALY gained			Dominates
9vHPV vaccine 3-dose NIP versus the current 4vHPV vaccine 3-dose NIP			
Costs	$	$	$
QALYs	16.550198	16.549669	0.000529
Incremental cost/QALY gained			$
9vHPV vaccine 2-dose NIP versus 4vHPV vaccine 2-dose NIP (evaluation assumed price of $ /dose)*			
Costs	$	$	$
QALYs	16.550134	16.549609	0.000526
Incremental cost/QALY gained			$
9vHPV vaccine 2-dose NIP versus 4vHPV vaccine 2-dose NIP (sponsor assumed price of $ /dose)			
Costs	$	$	$
QALYs	16.550134	16.549609	0.000526
Incremental cost/QALY gained			$

Source: Table D.5.16 and D.5.17, p. 269 of the submission, constructed during the evaluation, and the pre-PBAC response.
*This scenario was constructed during the evaluation, assuming the same price per dose for 4vHPV as for the 3-dose schedule.

6.41 Both univariate and multivariate sensitivity analyses were conducted by the submission. However, as noted in paragraph 6.38, the submission did not conduct sensitivity analysis on the duration of protection which was contrary to the advice from ATAGI.

- Sensitivity analyses indicated that the 2-dose 9vHPV vaccine schedule dominated the 3-dose 4vHPV vaccine schedule NIP comparator across a range of scenarios. The robustness of this result reflects the cost saving of adopting a 2-dose versus 3-dose schedule, despite the higher requested cost per dose of 9vHPV, compared with 4vHPV.

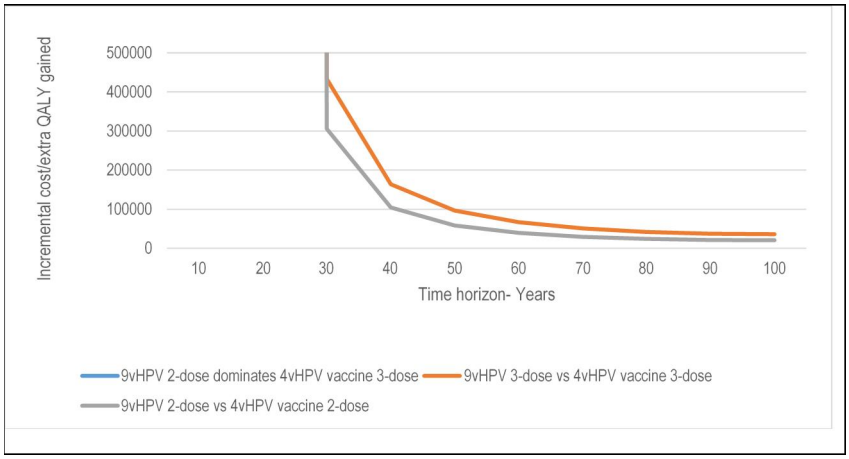
- Sensitivity analyses comparing the 3-dose 9vHPV vaccine schedule to the current 3-dose 4vHPV vaccine schedule indicated that the model results were robust to changes in all of the parameters tested, including coverage rates, vaccine efficacy, the proportion attributable to different HPV-types, the inclusion of the cross-protective efficacy of the 4vHPV vaccine against HPV 31, and the inclusion of herd immunity.

6.42 The ESC considered that the sensitivity analyses performed by the submission for the 3-dose 9vHPV versus 3-dose 4vHPV comparison could have encompassed a larger range of possible values. For example, the ESC considered that given the simplicity of the model structure and the single utilities used to represent each cancer regardless of stage of disease, the cost estimates applied in the model were inherently uncertain. While the ESC noted that the submission varied costs by +/ 10% in sensitivity analyses, it considered that this should have been extended to at least +/- 25%. Similarly, the ESC considered sensitivity analyses on a wider range of utility values would have been informative. While proportions of cancers attributable to the types of HPV included in the 9vHPV vaccine, vaccine efficacy and herd immunity

analyses demonstrated moderate individual effect, the ESC noted that two-way analysis on vaccine efficacy and herd immunity increased the ICER to $15,000/QALY - $45,000/QALY gained (from $15,000/QALY - $45,000/QALY gained). The ESC considered that applying feasible values for the full range of uncertain parameters through multivariate sensitivity analyses would increase the ICERs substantially for the 3-dose 9vHPV and 3-dose 4vHPV comparison, and the evaluation's 2-dose 9vHPV and 2-dose 4vHPV comparison.

6.43 An additional analysis was conducted during the evaluation which investigated the impact of the time horizon on the ICER. The 2-dose 9vHPV vaccine dominated the 3-dose 4vHPV vaccine for all years (10-100). However, the 2- and 3-dose comparisons only fell to around $45,000/QALY – $75,000/QALY gained after 60-70 years; this reflected the time for adolescent girls to become sexually active and develop cancer.

Figure 1: ICER by time horizon



Note: Blue line not shown in figure because it is always dominant.
Source: Compiled during evaluation

Drug cost/patient/course: $[redacted]

6.44 Assuming 1.92 doses (1.93 doses per female and 1.91 doses per male) and a cost per dose of $[redacted], the vaccine cost per patient per 2-dose course is $[redacted].

Estimated NIP usage & financial implications

6.45 This submission was not considered by DUSC. The extent of use and financial implications were estimated using a market share approach based on Australian population projections of girls and boys aged 12 years. The submission assumed that the 2-dose 9vHPV will directly substitute the 3-dose 4vHPV, although consideration was given to potential differences in vaccination uptake.

6.46 Table 11 presents the estimated use and financial implications. At year 6, the estimated number of doses administered was over 200,000 per year and the net save to the NIP would be less than $10 million per year. The submission included

administration costs in the estimates; these were removed during the evaluation as they are not incurred by the Australian Government.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of doses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of the 9vHPV vaccine (excluding administration cost)						
Cost to NIP	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for 4vHPV vaccine (excluding administration cost)						
Cost to NIP	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net financial implications						
Net cost to NIP	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to NIP (excluding administration costs)	**-$**[redacted]	**-$**[redacted]	**-$**[redacted]	**-$**[redacted]	**-$**[redacted]	**-$**[redacted]

Source: Table E.4.1 p283 of the submission.

6.47 The evaluation and the ESC noted there is a potential for the net financial cost to differ from that estimated due to uncertainties regarding vaccine coverage.

Quality Use of Medicines

6.48 The submission outlined the ATAGI recommendations regarding the need to monitor population level HPV prevalence and HPV-related diseases and cancers.

6.49 The submission noted that there are several relevant systems already in place, including the National Cancer Screening Register, the Renewed NCSP, and the National HPV Vaccination Program Register. Linkage of these systems will enable estimation of the HPV vaccine effectiveness. Cohorts vaccinated with the 2-dose 9vHPV vaccine (aged 12-13 years) will not enter the Renewed NCSP for 12-13 years; lower uptake of the Renewed NCSP may affect the reliability of the results.

Financial Management – Risk Sharing Arrangements

6.50 The submission noted that the current 4vHPV vaccine RSA covers the potential of a fourth booster dose being needed to maintain lifelong protection. The submission stated that the sponsor had no objection to these same provisions for a fourth booster dose continuing for the 9vHPV vaccine.

6.51 The evaluation noted that it was unclear whether the proposed RSA would also cover a third booster dose to address the risk that the efficacy of a 2-dose 9vHPV vaccine schedule may wane more quickly than a 3-dose 9vHPV vaccine schedule, in addition to the current RSA for a fourth booster dose. The PSCR (p3) stated that if the effectiveness of 9vHPV 2-dose was found to wane faster than 3-dose 4vHPV vaccine, the sponsor anticipates that "a third dose of 9vHPV vaccine would be recommended to complete the 3-dose schedule". The PSCR (p4) proposed a pricing schedule for a 3-dose 9vHPV vaccine schedule and RSA for a fourth booster dose should it be required (see Tables 12 and 13). The PSCR stated that the 3-dose 9vHPV

schedule was "highly cost-effective compared to 3-dose 4vHPV vaccine" (with an ICER of $15,000/QALY - $45,000/QALY gained, see Table 10). The ESC noted that the financial implications of a 3-dose 9vHPV vaccine were not presented in the submission.

Table 12: Pricing of 9vHPV proposed in the PSCR

Recommended Schedule	9vHPV price per dose				Total cost
	Dose 1	Dose 2	Dose 3	Booster dose	
2-dose	$[redacted]	$[redacted]	-	-	$[redacted]
2-dose + 3rd dose to complete schedule	$[redacted]	$[redacted]	$[redacted]	-	$[redacted]
3-dose	$[redacted]	$[redacted]	$[redacted]	-	$[redacted]
3-dose + 4th dose booster	$[redacted]	$[redacted]	$[redacted]	see Table 13	$[redacted] + cost of 4th dose booster

Table 13: Risk sharing arrangement for the fourth dose booster proposed in the PSCR

Timing of 4th dose booster (if required) following the 3-dose course	Price per 4th booster dose[1]	
	Males	Females
0 to <5 years	At no cost	$[redacted][2] less [redacted]%
5 to <10 years	At no cost	$[redacted] less [redacted]%
10 to <15 years	At no cost	$[redacted] less [redacted]%
15 to 20 years	At no cost	$[redacted] less [redacted]%

[1] Final price calculated using the formula determined by the PBPA as set out in the PBPA letter 16 December 2011.
[2] $[redacted] is the proposed price per dose of the 9vHPV for females in a 3-dose program (see paragraph 2.2).

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

7 PBAC Outcome

7.1 The PBAC recommended that human papillomavirus 9-valent vaccine (Gardasil® 9) be made available as a designated vaccine for the purpose of funding through the NIP as a 2-dose schedule for 12-13 year olds as part of a school based immunisation program for the prevention of HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58. The recommendation was made on the basis of cost effectiveness compared with a 3-dose schedule of 4vHPV vaccine.

7.2 The PBAC recommended the 2-dose 9vHPV vaccine schedule on the provision that it replace the current 3-dose 4vHPV vaccine schedule that is currently provided through schools and funded through the NIP.

7.3 The PBAC noted that ATAGI recommended a 3-dose schedule of 9vHPV for individuals older than 15 years and for those who are immunocompromised (p9 of the ATAGI pre-submission advice). The PBAC noted that the submission did not request a 3-dose schedule for these populations, nor did it request a catch-up program for previous recipients of the 3-dose 4vHPV vaccine schedule.

7.4 The PBAC noted the advice from ATAGI that a 12-month interval between the two doses would be optimal but that a minimum interval of 6 months between doses would be acceptable. Accordingly, the PBAC recommended that the designated

vaccines list state that the second dose of Gardasil® 9 be administered between 6 and 12 months (inclusive) following the first dose. The PBAC advised that states and territories should take into consideration ATAGI's recommended interval of 12 months, as well as logistics and potential vaccination uptake, when considering their preferred timing within this range.

7.5 The PBAC accepted that the 3-dose 4vHPV vaccine schedule was the appropriate main comparator. The PBAC considered that it was also appropriate to consider the intermediate vaccine schedule comparisons of 3-dose 9vHPV versus 3-dose 4vHPV and 2-dose 9vHPV versus 2-dose 4vHPV.

7.6 The PBAC noted limitations in the clinical evidence including the lack of head-to-head randomised controlled trials comparing the 2-dose 9vHPV vaccine schedule to the 3-dose 4vHPV vaccine schedule in the population of interest. The submission relied on a vaccine efficacy trial in adult females and immunobridging trials, which introduced uncertainty. However, the PBAC further noted efficacy studies for HPV vaccines are conducted in the sexually active populations at risk of HPV infection and disease due to practical considerations relating to follow-up time and ethical concerns. The PBAC further noted that ATAGI considered the efficacy claims made by the submission to be reasonable.

7.7 The PBAC noted the immunogenicity results were numerically poorer for HPV type 45 if 2 doses of the 9vHPV vaccine were administered instead of 3 doses, and for all HPV types in a 2-dose schedule if the dosage interval was 6 months rather than 12 months. However, the PBAC noted that there are currently no known correlates of protection between antibody titres achieved through natural infection and disease outcomes, and hence between antibody titres achieved through vaccination and disease outcomes. The PBAC therefore considered that the consequences of the lower antibody titres for HPV type 45 and for a dosage interval of 6 months on long-term effectiveness of the vaccine were unknown.

7.8 The PBAC noted that a 2-dose schedule may increase the number of patients who receive only one dose, due to the reduced scope for catch up, and that reducing the number of doses may reduce the vaccine effectiveness. However, the PBAC noted that the economic model presented in the submission assumed no vaccine effectiveness in those patients receiving one dose of vaccine and that the sponsor stated it supports state and territory initiatives to increase vaccine uptake.

7.9 Overall, the PBAC accepted that the 2-dose 9vHPV vaccine schedule is likely to provide non-inferior clinical protection against disease associated with 4vHPV types (6/11/16/18) and superior clinical protection against disease associated with 9v-non4vHPV types (31/33/45/52/58), compared with the 3-dose 4vHPV vaccine schedule. In this regard, the PBAC noted that currently 71.8% of cervical cancer cases are due to HPV types 16/18 and an additional 14.7% are due to the 9v-non4vHPV types 31/33/45/52/58. However, the PBAC noted the follow-up period in the trials

were short and that the duration of vaccine protection of the 2-dose 9vHPV vaccine schedule was uncertain.

7.10 The PBAC accepted the submission's claim of non-inferiority with regard to safety compared with the 3-dose 4vHPV vaccine schedule.

7.11 The PBAC noted that the base case economic comparison of the 2-dose 9vHPV vaccine schedule and the current 3-dose 4vHPV vaccine schedule resulted in additional QALYs and lower costs and that this result was robust across a range of assumptions. However, the PBAC noted that the submission did not conduct sensitivity analysis of the economic model on the duration of vaccine protection, which the PBAC considered was the main uncertainty regarding the clinical evidence. In this context, the PBAC considered that the estimate of cost effectiveness of the 3-dose 9vHPV versus 3-dose 4vHPV vaccine schedules in the event that a third booster dose may be required to address waning vaccine effectiveness was informative.

7.12 The PBAC considered that that the base case ICER for the 3-dose 9vHPV versus 3-dose 4vHPV vaccine schedules comparison of $15,000/QALY - $45,000/QALY was acceptable. However, the PBAC considered that the sensitivity analyses performed by the submission should have encompassed a larger range of possible values and that applying feasible values for the full range of uncertain parameters through multivariate sensitivity analyses would likely have increased the ICER for this comparison substantially. The PBAC noted that this scenario is only relevant in the event that the efficacy of the vaccine wanes earlier than assumed such that a third vaccine dose is required. [redacted].

7.13 As per the current arrangements for the 3-dose 4vHPV schedule, the PBAC advised that there would need to be a mechanism, in the form of a registry, for identifying vaccinated persons to deliver a booster dose if the assumption of lifelong protection is proved not to be the case for 2-dose 9vHPV. The PBAC noted that there are several relevant systems already in place, including the National Cancer Screening Register, the Renewed NCSP, and the National HPV Vaccination Program Register and that linkage of these systems will enable estimation of the effectiveness of the HPV vaccine.

7.14 The PBAC further considered that a fourth booster dose of vaccine would have diminished cost effectiveness, as the booster would likely be administered at an age at which vaccination is not as effective as a greater proportion of people would already have been exposed to HPV or would be less likely to be exposed in the future. However, the PBAC considered that the risk that a fourth booster dose would

be required due to waning of vaccine effectiveness after 3 doses was sufficiently low that arrangements covering this risk are not warranted.

7.15 The PBAC noted that a 2-dose 4vHPV vaccine schedule could have feasibly replaced the current 3-dose 4vHPV vaccine schedule and therefore considered that the additional scenario comparing the 2-dose 9vHPV vaccine schedule with a hypothetical 2-dose 4vHPV vaccine schedule conducted during the evaluation was informative. The PBAC noted there is no agreed price per dose for a 2-dose 4vHPV vaccine and therefore considered that the cost effectiveness was acceptable on the basis of the range of ICERs calculated by the evaluation (of $15,000/QALY - $45,000/QALY gained, assuming the same price per dose for 4vHPV as for the 3-dose schedule) and the sponsor (of $[redacted] per QALY gained assuming a higher price per dose).

7.16 The PBAC accepted the utilisation and financial estimates provided in the submission and noted the overall cost saving to the Australian Government of a 2-dose 9vHPV vaccine schedule, compared with the current 3-dose 4vHPV vaccine schedule. [redacted]

7.17 The PBAC noted that this submission is not eligible for an Independent Review as the request is for listing on the National Immunisation Program and the PBAC made a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item to the National Health (Immunisation Program – Designated Vaccines) Determination 2014 (No.1) as follows:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
HUMAN PAPILLOMAVIRUS 9-VALENT (TYPES 6, 11, 16, 18, 31, 33, 45, 52, 58) VACCINE			Gardasil® 9	Seqirus
Injection 0.5mL, pre-filled syringe	1	1		

Category / Program:	National Immunisation Program
Circumstances:	2-dose schedule (second dose administered between 6 and 12 months following the first dose) for 12-13 year olds as part of school based program.

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

Seqirus welcomes the PBAC decision to recommend the NIP listing of Gardasil®9 as a 2-dose schedule for 12-13 year olds.