

## 6.09 Human Papillomavirus (HPV) types 16 18 vaccine injection, 0.5ml Cervarix®, GlaxoSmithKline Australia Pty Ltd

### 1 Purpose of Application

- 1.1 Amend the listing on the National Health (Immunisation Program – Designated Vaccines) Determination 2014 (No.1) for Cervarix as a vaccine against human papillomavirus types (HPV) 16 and 18 in females aged 12-13 years from a 3-dose regimen to a 2-dose regimen.

### 2 Requested listing

#### 2.1

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
IM 0.5 mL	2	0	\$ [REDACTED]/dose	Cervarix® GlaxoSmithKline Australia Pty Ltd

- 2.2 Cervarix is currently listed on the National Health (Immunisation Program – Designated Vaccines) Determination 2014 (No.1) as a 3-dose regimen for prophylactic vaccination of 12-13 year old girls against cervical cancer and precancerous lesions associated with HPV-16 and HPV-18. It is proposed that the new 2-dose regimen be added as an approved alternative to the current 3-dose schedule, for the same population of 12-13 year old girls.
- 2.3 The requested basis for listing is 1) cost-minimisation to Cervarix 3-dose and 2) cost-effectiveness compared with Gardasil 3-dose based on the coverage of HPV-6/11.

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

### 3 Background

- 3.1 TGA status at time of PBAC consideration: CERVARIX is registered and indicated in females from 10 to 45 years of age for the prevention of persistent infection, premalignant cervical lesions and cervical cancer caused by human papillomavirus types 16 and 18. Immunogenicity studies have been conducted in females aged 10 to 14 years and 26 to 45 years to link efficacy in females aged 15 to 25 years to other populations.

The ACPM considered CERVARIX suspension for injection, containing human papillomavirus vaccine with 20 µg each of types HPV-16 L1 and HPV-18 L1 as virus-like particles (VLPs) [recombinant, AS04 adjuvanted] to have an overall positive benefit–risk profile for the proposed 2-dose vaccine schedule in 10-14 years old girls (ACPM outcome 305).

- 3.2 Cervarix 2-dose has not been considered by the PBAC previously.

#### **4 Clinical place for the proposed therapy**

- 4.1 Cervarix is a vaccine against HPV types 16 and 18.
- 4.2 It is proposed that an alternative 2-dose schedule of Cervarix 2 x 0.5 mL (at 0 and 5-12 months), replaces the current 3-dose schedule Cervarix 3 x 0.5mL (at 0, 1 and 6 months).

#### **5 Comparator**

- 5.1 The submission nominated two relevant comparators:
- A 3-dose course of Cervarix, administered at 0, 1 and 6 months
  - A 3-dose course of Gardasil, administered at 0, 2 and 6 months

The comparators are appropriate. However the Australian Technical Advisory Group on Immunisation (ATAGI) advice states that Cervarix may only be appropriate on the National Immunisation Program (NIP) in the instance that Gardasil is not available. Under these circumstances, the 3-dose course of Cervarix may be considered the main comparator.

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

#### **6 PBAC consideration of the evidence**

##### **Sponsor hearing**

- 6.1 There was no hearing for this item.

##### **Consumer comments**

- 6.2 The PBAC noted that no consumer comments were received for this item.

##### **Clinical trials**

###### **6.3 Comparator 1: Cervarix 2-dose vs. Cervarix 3-dose.**

The submission was based on

- 2 randomised trials comparing Cervarix 3-dose to Cervarix 2-dose (HPV-048: n=960; HPV-070: n=1447).
- 2 supplementary randomised trials comparing Hepatitis A vaccine (HAV) vs. Cervarix 2-dose (HPV-008; HPV-009) including clinical efficacy outcomes

###### **Comparator 2: Cervarix 2-dose vs. Gardasil 3-dose.**

The submission was based on

- 1 randomised trial comparing Cervarix 2-dose to Gardasil 3-dose (HPV-071; n=1075)
- 1 supplementary randomised trial (HPV-010) comparing Cervarix 2-dose vs. Gardasil.

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

**Table 1: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Key trials</b>		
<b>Cervarix 2-dose versus Cervarix 3-dose</b>		
HPV-048 GSK  Romanowski, B  Romanowski, B  Additional reports: HPV-048 CTRS (M60)	Annex 5 Clinical Study Report for Study 110659 (HPV-048 PRI) Development Phase I/I Romanowski B, Schwarz T, Ferguson LM . Immunogenicity and safety of the HPV-16/18 AS04- adjuvanted vaccine administered as a 2-dose schedule compared to the licensed 3-dose schedule Romanowski B, Schwarz T, Ferguson LM. Immune response to the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose or 3-dose schedule up to 4 years after vaccination	HPV-048 CSR (M48)  <i>Human Vaccines</i> , 2011: 7:12, 1374-1386  <i>Human Vaccines &amp; Immunotherapeutics</i> , 2014: 10:5, 1155-1165
HPV-070 GSK	Final (Month 7) Clinical Study Report for Study 114700 (HPV-070PRI)  Annex 1 Clinical Study Report for Study 114700 (HPV- 070 PRI)	2013: HPV-070 CSR (M7);  2014: HPV-070 CSR (M12/13)
<b>Cervarix 2-dose versus Gardasil 3-dose</b>		
HPV-071 GSK	Clinical Study Report for Study 115411 (HPV-071 PRI)	2014: HPV-071 CSR (M7)
<b>Supportive trials</b>		
HPV-008 GSK  Apter, D  Additional reports: (Paavonen, et al., 2009); (Wheeler, et al., 2012) (Lehtinen, et al., 2012); (Szarewski, et al., 2013)	Clinical Study Report for Study 580299/008 (HPV-008) for the end-of-study analyses of efficacy, safety and immunogenicity analyses at end of study (Month 48)  Apter D, Wheeler CM, Paavonen J et al. Efficacy of Human Papillomavirus 16 and 18 (HPV-16/18) AS04-Adjuvanted Vaccine against Cervical Infection and Precancer in Young Women: Final Event-Driven Analysis of the Randomized, Double- Blind PATRICIA Trial	2013: HPV-008 CSR (M48)  <i>Clinical and Vaccine Immunology</i> 2015: 22:4
HPV-009 GSK  Hildesheim, A  Additional reports: (Herrero, et al., 2011); (Kreimer, et	Clinical Study Report for Study 580299/009 (HPV-009)  Hildesheim A, Wacholder S, Catteau G, et al. . Efficacy of the HPV-16/18 vaccine: Final according to protocol results from the blinded phase of the randomized Costa Rica HPV-16/18 vaccine trial	2012: HPV-009 CSR (M48)  2014: <i>Vaccine</i> : 32:, 5087-5097

Trial ID	Protocol title/ Publication title	Publication citation
al., 2011);		
HPV-010 GSK  Einstein,M          Additional reports: (Einstein, et al., 2009); (Einstein, et al., 2011); (Einstein, et al., 2014)	Clinical Study Report for Study 108933 (HPV-010) (Active Phase: Month 0 - 7) Einstein MH, Takacs P, Chatterjee A, et al. Comparison of long-term immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine in healthy women aged 18-45 years: End-of-study analysis of a Phase III randomized trial,	HPV-010 CSR (M7); HPV-010 CSR (M60) [Human Vaccines & Immunotherapeutics, 2014:10:12, 3435-3445

Source: developed as part of the evaluation.

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

**Table 2: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Cervarix 2-dose vs. Cervarix 3-dose</b>						
HPV-048	960	R, PB 6 mths	Low	Treatment naive <sup>1</sup>	Antibodies (GMT),safety	Used in Cost min
HPV-070	1447	R, OL 6 mths	Low	Treatment naive <sup>1</sup>	Antibodies (GMT),safety	Used in Cost min
<b>Cervarix 2-dose vs Gardasil 3-dose</b>						
HPV-071	1075	R, OB 6 mths	Low	Treatment naive <sup>1</sup>	Serum neutralising antibodies, safety	Used in econ evaluation. (Outcome EGL)

DB=double blind; OL=open label; PB=Partial blind; OB: Observer blind; R=randomised.; GMT=Geometric Mean Titre; EGL =external genital lesions Source: compiled during the evaluation. <sup>1</sup>Some participants were not seronegative. These were not assessed in primary outcomes.

6.6 There are no head to head trials comparing a 2-dose schedule with a 3-dose schedule among the target population (9-14 years olds). Not all trials were blinded. However, the overall risk is low.

### Comparative effectiveness

6.7 Non-inferiority margins:

The upper limit of the 95% CI for the difference in seroconversion rates < 5%;  
and the lower limit of the 95% CI for the GMT ratio being > 0.5 (GMT ratio 2/3 doses)

**Table 3: Results of GMTs across the direct randomised trials (by dosing administration schedule and Age)**

Antigen	N	GMT	N	GMT	GMT ratio of 2 dose to 3 dose (95%CI)
HPV-048 Non inferiority of 2 dose vs. 3 dose (ATP cohort, S-subjects)					
	<b>Cervarix (0,6)</b>		<b>Cervarix (0,1,6)</b>		
HPV-16	178	8,093	178	13,165	0.61 (0.51; 0.74)
HPV-18	178	4639	178	5,089	0.91 (0.75, 1.11)
	<b>Cervarix (0,6) [9-14]</b>		<b>Cervarix (0,1,6) [15-25]</b>		
HPV-070 Non inferiority of 2 dose vs. 3 dose in age-strata (ATP cohort, S-subjects)					
HPV-16					
HPV-18					
	<b>Cervarix (0,6) [9-14]</b>		<b>Gardasil (0,1,6) [15-25]</b>		
HPV-071 Non inferiority of GMTs at month 7 (ATP cohort, S-subjects)					
HPV-16	330	8,244.1	322	4,807.4	1.71 (1.54; 1.92)
HPV-18	334	5,277.4	333	1,653.5	3.39 (2.78; 3.70)

Source: comparison of 2 dose to 3 dose, based on Table B.6.1.1, Table B.6.1.4, Table B.6.1.10 of the commentary.

**Table 4: Results of Seroconversion across the direct randomised trials (HPV-070, HPV-071)**

Seroconversion was not reported for HPV-048 as a primary outcome.

Antigen	N	%	N	%	difference
	<b>Cervarix (0,6)</b>		<b>Cervarix (0,1,6)</b>		
HPV-070 Non inferiority Seroconversion rates at month 7 (ATP cohort, S subjects)					
HPV-16					
HPV-18					
	<b>Cervarix 2-dose</b>		<b>Gardasil 2-dose</b>		
HPV-071 Non inferiority Seroconversion rates at month 7 (ATP cohort, S subjects)					
HPV-16	330	100	327	100	0.0 (-1.16; 1.15)
HPV-18	334	100	331	100	0.0 (-1.15; 1.14)

Source: Table B.6.1.4, Table 6.1.8, Section B, p 19 and p 20 of the commentary respectively. S subjects: Initially Sero-negative subjects

- 6.8 Comparison 1 Cervarix 2-dose vs Cervarix 3-dose  
 Trial HPV-048 and HPV-070 supports non-inferiority of 2-doses of Cervarix in girls aged 9-14 when compared to 3 doses of Cervarix in girls aged 9-14 years or women aged 15-25 years at month 7 (1 month after last vaccination).
- 6.9 The magnitude of the vaccine response is influenced by the age at the first dose with younger females (9-14 years) having a greater response.
- 6.10 The interval between the first and the second dose is important. Trial HPV-048 shows a 6-month interval resulted in higher antibody GMTs compared with the 2-month interval in all age groups in the study (9–14, 15–19, 20–25 years). This is consistent with the proposed listing, allowing flexibility of administration.
- 6.11 Follow-up in the trials is limited to 4 years. Non-inferiority is largely supported at each time point. Immunogenicity data suggests similar waning effects for Cervarix 2-doses (9-14 years) when compared to Cervarix 3-doses (15-25 years), although GMTs are marginally higher at 60 months for 3-doses (Table B.6.1.2). ATAGI notes there is uncertainty regarding whether the stability of antibody levels is similar beyond this time period and that modelling scenarios should consider the potential impact if waning occurs earlier with 2 doses than with 3 doses. The impact of waning could not

be tested in the current model structure. The ESC provided further advice on this waning issue under the “Economic analysis” sub-heading.

- 6.12 Comparison 1 Cervarix 2-dose vs Gardasil 3-dose  
Trial HPV-071 supports that Cervarix is at least non-inferior for 2-doses in girls aged 9-14 when compared to 2 doses Gardasil in girls aged 9-14 or 3 doses Gardasil in girls aged 9-14 years for HPV 16 and HPV 18 strains.
- 6.13 These data support inferiority of Cervarix compared to Gardasil for HPV 6 and HPV 11 strains.
- 6.14 There is some evidence of a cross-protective effect from Cervarix against other HPV strains and this effect is superior to Gardasil against strains HPV 33 and 44. ATAGI considers it “reasonable to assume that Cervarix in a 2-dose schedule would likely have superior cross-protective effect against disease associated with these HPV 16- and HPV 18-related types. However, it is not possible to determine accurately the differential clinical efficacy for various HPV-related disease outcomes from cross-protection against vaccine-related HPV types from a 2-dose schedule of Cervarix in adolescent girls compared to that from a 3-dose schedule of either Cervarix or Gardasil vaccine” (ATAGI pre-submission advice p 10).
- 6.15 In terms of immunogenicity persistence, there is evidence of higher immunogenicity following Cervarix compared to Gardasil in supportive studies (HPV-010). While uncertain due to the timeframe of follow-up, ATAGI suggests that these results could flow through into a modelled immune persistence that is greater for Cervarix.
- 6.16 Data on clinical outcomes from the supportive trials (HPV-008, HPV-009, HPV-010) support non-inferiority in both comparators, in strains HPV-16 and HPV-18.
- 6.17 There are limited data from HIV-infected or immune-compromised individuals receiving a 3-dose schedule and, no data from HIV-infected individuals receiving a 2-dose schedule. Although the immunogenicity and efficacy of HPV vaccines may be reduced in HIV-infected females, the potential benefit of vaccination in this group is particularly great owing to their increased risk of HPV-related disease, including cervical cancer.
- 6.18 If vaccination coverage of boys is sufficient, the herd immunity from coverage of HPV strains 6/11 elicited by Gardasil would be expected to contribute to overall protection.

## Comparative harms

**Table 5: Summary of key adverse events in the direct randomised trials**

Trial ID	Proposed drug n with event/N (%)		Main comparator n with event/N (%)	RR (95% CI)	
Trial HPV-048 Pain Redness Swelling Any SAEs At least one MSC	Cervarix 2 dose [REDACTED]		Cervarix 3 dose [REDACTED]	[REDACTED]	
Trial HPV-070 Pain Redness Swelling Treatment related SAEs At least one MSC	Cervarix (0,12) [REDACTED]	Cervarix (0,6) [REDACTED]	Cervarix 3 dose [REDACTED]	[REDACTED]	[REDACTED]
Trial HPV-071 Pain Redness Swelling Treatment related SAEs At least one MSC	Cervarix 2-dose 329/359(91.6%) 191/359(53.2%) 163/359(45.4%) [REDACTED]		Gardasil 3- dose 295/356(82.9%) 157/356(44.1%) 118/356(33.1%) [REDACTED]	1.11(1.04,1.17) 1.20(1.04,1.4) 1.37(1.14,1.65) [REDACTED]	

MSC: Medically significant conditions; SAE: Serious adverse event. Source: developed as part of the evaluation.

- 6.19 The Who Global Advisory Committee for Vaccine Safety (GACVS) has reviewed the safety of HPV vaccines on several occasions (2007, 2008, 2009 and 2013). The most recent safety update concludes “The Committee continues to be reassured by the safety profile of the available products. Anaphylaxis and syncope, outcomes previously identified as concerns, have been addressed through further studies and appropriate revisions were made to the products labelling. Serious adverse events that have been reported as potential signals have been investigated in more detail, including Guillain-Barre Syndrome, seizures, stroke, venous thromboembolism, anaphylaxis, and other allergic reactions. Surveillance of pregnancy outcomes among women inadvertently vaccinated during pregnancy through spontaneous reports and registries have not detected any adverse outcomes above expected rates”.
- 6.20 ATAGI is of the view that there are no specific safety concerns for a 2-dose schedule of Cervarix compared to a 3-dose schedule of either Cervarix or Gardasil vaccines, including in settings that have already adopted that schedule. ATAGI noted head-to-head data indicate that Cervarix is more locally and systematically reactogenic than Gardasil (more injection site pain, redness and swelling and more myalgia and fatigue), but considers it reasonable to assume that there would be greater acceptability by adolescent girls of a vaccine course that contains one less dose (ATAGI pre-submission advice p7).

### Clinical claim

- 6.21 The PBAC considered that the claim of non-inferiority in terms of comparative effectiveness and non-inferiority in terms of comparative safety of 2-dose Cervarix over 3-dose Cervarix was adequately supported.
- 6.22 The PBAC considered that the claim of non-inferiority in terms of comparative effectiveness and non-inferiority in terms of comparative safety of 2-dose Cervarix over 3-dose Gardasil was adequately supported in HPV-16 and HPV-18 strains.
- 6.23 The PBAC considered that the claim of inferiority in terms of comparative effectiveness and non-inferiority in terms of comparative safety of 2-dose Cervarix over 3-dose Gardasil was adequately supported in HPV-6 and HPV-11 strains.

### Economic analysis

- 6.24 The submission presented two separate economic evaluations.
- A cost-minimisation analysis comparing 2-dose Cervarix with 3-dose Cervarix under the assumption of non-inferiority.
  - A partial cost-effectiveness analysis comparing Cervarix 2-dose and Gardasil 3-dose, with the clinical claim of non-inferiority with respect to effectiveness of HPV-16 and HPV-18 strains and inferiority with respect to HPV-6 and HPV-11 strains. The cost effectiveness model is a simplified version of the economic evaluation seen previously by the PBAC in the November 2007 meeting. The changes made to the economic evaluation are summarised in Table 6 below.
- 6.25 The equi-effective doses were estimated as Cervarix 2 x 0.5 mL (at 0 and 5-12 months) and Cervarix 3 x 0.5mL (at 0, 1 and 6 months). The course cost proposed in the submission is \$ [REDACTED] per 2-dose vaccination course.
- 6.26 The cost-minimisation analysis included vaccine costs only (excluding administration costs and adverse events), which is conservative. The ESC noted that one important potential consideration for the cost-minimisation analysis was the possibility of earlier waning with a 2-dose Cervarix schedule when compared with 3 doses of Cervarix (see ATAGI pre-submission advice, p6). This could not be tested in the analysis, but if this did occur, it could potentially lead to fewer prevented health outcomes and reduce the cost savings when compared with a 3-dose Cervarix schedule. In the pre-PBAC response, the Sponsor disagreed with this proposition, stating it should not influence the cost minimisation assessment.
- 6.27 Table 6 presents the key drivers of the cost-effectiveness model

**Table 6: Key drivers of the cost-effectiveness model**

Description	Method/Value	Impact
Incidence	Pirootta (2009) Australian study from the BEACH and NHM databases- based on the incidence of EGL in Australia in the absence of vaccination.	High, favours Gardasil
Time horizon	20 years; assumed from 4 years trial duration	Moderate, favours Cervarix
Disutility	0.04 (0.06-0.1) in the literature	High, favours Cervarix
Waning	No Waning, 1% at 5 years for Gardasil only in previous models.	Moderate, favours Gardasil

Source: compiled during the evaluation

- 6.28 The ESC noted that the model assumed no waning but appears to use a shorter time horizon (20 years compared to 88 years in the 2007 submission). As a way of truncating the impact of the vaccine, the ESC noted that it was a simple approach that seems reasonable. The ESC considered that a question remains about what is a reasonable time horizon to balance effects of waning and the longer term effects of EGL.
- 6.29 Table 7 presents the results of the economic evaluation. Note: The ICER is reported by the submission as cost savings for QALYs lost.

**Table 7: Results of the economic evaluation**

	Discounted	Undiscounted
Costs	-\$ [REDACTED]	-\$ [REDACTED]
ELG Cases	[REDACTED]	[REDACTED]
QALYs	[REDACTED]	[REDACTED]
ICER/EGL avoided	\$ [REDACTED]	\$ [REDACTED]
Incremental saving per QALY lost	\$ [REDACTED]	\$ [REDACTED]

Source: Table D.5, Section D, p 81 of the submission.

*The redacted table above shows an incremental saving per QALY foregone of \$105,000/QALY - \$200,000/QALY (discounted) and \$45,000/QALY - \$75,000/QALY (undiscounted).*

**Drug cost/patient/course: \$ [REDACTED]**

- 6.30 The current approved NIP price per dose of Cervarix is \$ [REDACTED] (\$ [REDACTED]/ course) and this price of Gardasil is assumed to be \$ [REDACTED]/dose in the context of the immunisation of females.

**Estimated NIP usage & financial implications**

- 6.31 This submission was not considered by DUSC. The submission used an epidemiological approach to generate utilisation and financial estimates for NIP funding of 2-dose Cervarix (replacing Gardasil 3-dose in females). These estimates were based on the Australian female population aged 12-13 years, vaccine coverage and the incidence of EGL in Australia in the absence of a vaccination program. This approach is appropriate under the assumption that Cervarix 2-dose will replace Gardasil 3-dose in females.

**Table 8: Estimated use and financial implications in the submission and revised during the evaluation.**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Number treated					
Overall Net Cost to NIP	-\$	-\$	-\$	-\$	-\$
Net Cost to Government for MBS	\$	\$	\$	\$	\$
<b>Revised Net Cost to Government for MBS/PBS/NIP</b>	\$	\$	\$	\$	\$
Net Cost to State & Territory Govts	\$	\$	\$	\$	\$
Overall Net cost to Combined Government Health Budgets	-\$	-\$	-\$	-\$	-\$
<b>Revised Overall Net cost to Combined Government Health Budgets</b>	-\$	-\$	-\$	-\$	-\$

Abbreviations: Govts: Governments; MBS: Medicare Benefit Scheme; NIP: National Immunisation Program. Table E.8.9 Section E, p 92 of the submission. Revised estimate are included for EGL treatment costs.

*The redacted table above shows that the number of patients treated for genital warts is estimated to be less than 10,000 per year at a net saving to MBS/PBS/NIP of more than \$10 million per year.*

- 6.32 The estimates of EGL under 2-doses of Cervarix are based the incidence of EGL prior to the introduction of the NIP HPV program in 2007, although the extent to which this reduction would be maintained if a switch was made to Cervarix in females is uncertain. This assumption is likely to be conservative and also applies to the cost-effectiveness analysis.
- 6.33 There is potential for the annual number of additional cases of EGL per cohort under 2-doses of Cervarix to be lower than predicted as:
- There is evidence of a reduction in the incidence of HPV since the introduction of HPV vaccination (Osborne SL et al, Vaccine 2015;33:201-8), which may partly continue if Gardasil is temporality replaced (e.g. in a supply shortage).
  - There is an expected herd immunity of HPV strains 6/11 elicited by Gardasil in boys. This would increase overall cost savings under 2-doses of Cervarix in females.
- 6.34 The submission did not include any costs associated with the management of EGL. Specifically, the costs associated with medication or specialist referrals were not included. This underestimates the cost to MBS. Revised estimates of EGL management costs were calculated during the evaluation. The overall cost savings were reduced (Table 8).
- 6.35 In addition, the ESC noted an error in the financial estimates of the cohort of females at risk of EGL if Cervarix 2-dose completely replaced Gardasil 3-dose for an extended period of time. The submission estimated a single cohort at risk in each of the 5 years. The ESC considered that this population would accumulate year-on-year. By year 5, there would 5 cohorts of young females at higher risk of EGL in a scenario where Cervarix is used and the potential savings would be less than

estimated during the evaluation. The pre-PBAC response discussed that impact of this error would be marginal.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the current listing on the National Health (Immunisation Program – Designated Vaccines) Determination 2014 (No.1) for Human papillomavirus (HPV) Vaccine (Cervarix) for the vaccination of a female who is at least 12 years old but less than 14 years of age to be changed from three doses to two doses.
- 7.2 The PBAC noted that the equi-effective doses were estimated as Cervarix 2 x 0.5 mL (at 0 and 5-12 months) and Cervarix 3 x 0.5mL (at 0, 1 and 6 months), while the course cost proposed in the submission was \$ [REDACTED] per 2-dose vaccination course.
- 7.3 The PBAC noted the view of the Australian Technical Advisory Group on Immunisation (ATAGI):
  - "Cervarix vaccine in a 2-dose schedule is NOT suitable for implementation under the National Immunisation Program (NIP) at this time. This is based on two key factors: i) Cervarix vaccine does not provide significant protection against diseases caused by HPV types 6 and 11, notably anogenital warts and recurrent respiratory papillomatosis, which the Gardasil vaccine used in females and males under the NIP does (protection against HPV-related cancers and diseases is a stated aim of the national HPV vaccination program); and ii) Cervarix vaccine is not currently registered in Australia for use in males and the use of two different HPV vaccines, with different dosing schedules, in the gender neutral school-based program would have major implementation issues.
  - Cervarix vaccine in a 2-dose schedule is suitable for inclusion on the Determination as potentially eligible for use under the NIP in adolescent girls aged 10–14 years. This is based on a comparison with the currently accepted 3-dose Cervarix vaccine schedule in females and provides opportunity for future use of 2-dose Cervarix vaccine under the NIP, should it be deemed appropriate (e.g. if there are supply issues with Gardasil vaccine)".
- 7.4 The PBAC noted that proposed comparators were a 3-dose course of Cervarix, administered at 0, 1 and 6 months and a 3-dose course of Gardasil, administered at 0, 2 and 6 months. While both are appropriate comparators, in the context that the ATAGI advice states that Cervarix may only be appropriate on the NIP in the instance that Gardasil is not available, the PBAC considered that the 3-dose course of Cervarix was the main comparator.
- 7.5 The PBAC considered that the claim of non-inferiority in terms of comparative effectiveness and non-inferiority in terms of comparative safety of 2-dose Cervarix over 3-dose Cervarix was adequately supported.
- 7.6 The PBAC considered that comparison of 3-dose Gardasil was informative in the context of HPV vaccination in Australia, and noted that

- the claim of non-inferiority in terms of comparative effectiveness and non-inferiority in terms of comparative safety of 2-dose Cervarix over 3-dose Gardasil was adequately supported in HPV-16 and HPV-18 strains.
- that the claim of inferiority in terms of comparative effectiveness and non-inferiority in terms of comparative safety of 2-dose Cervarix over 3-dose Gardasil was adequately supported in HPV-6 and HPV-11 strains.
- that partial cost-effectiveness analysis comparing Cervarix 2-dose and Gardasil 3-dose presented a discounted incremental saving of \$ [REDACTED] per QALY lost.

7.7 The PBAC noted that financial implication to the NIP was difficult to estimate as it would be dependent on the circumstances in which Gardasil was not available throughout Australia.

**Outcome:**

Recommended

## **8 Recommended listing**

Amend the existing listing in the National Health (Immunisation Program – Designated Vaccines) Determination 2014 (No.1) as follows:

Vaccine

Human papillomavirus (HPV)

Circumstances

Vaccine may be provided to:

a female who is at least 12 years old but less than 14 years of age.

Cervarix

Injection (0.5mL)

Each of the following:

(a) HPV 16 L1 protein - 20µg;

(b) HPV 18 L1 protein - 20µg

**2 doses**

## **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**

The sponsor had no comment.