

PUBLIC SUMMARY DOCUMENT

Product: Human papillomavirus (Types 16 and 18) recombinant, AS04 adjuvanted vaccine, injection, 0.5 ml vial and pre-filled syringe, Cervarix[®]

Sponsor: GlaxoSmithKline Australia Pty Ltd

Date of PBAC Consideration: July 2007

1. Purpose of Application

The submission sought funding for Cervarix on the National Immunisation Program (NIP) for prophylactic vaccination of 12 and 13 year old girls against cervical cancer and precancerous lesions associated with high risk human papillomavirus-types 16 and 18 with a two-year catch up program for girls and women aged 13-26.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

The vaccine was TGA registered on 18 May 2007 for the prevention of cervical cancer in females from 10 to 45 years by protecting against incident and persistent infections, cytological abnormalities including atypical squamous cells of undetermined significance (ASC-US) and cervical intraepithelial neoplasia (CIN), CIN 1 and pre-cancerous lesions (CIN 2 and CIN 3) caused by human papillomavirus (HPV) 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.

4. Listing Requested and PBAC's View

The requested NIP indication is:

For prophylactic vaccination of 12 and 13 year old girls (with a two-year catch up program for girls and women aged 13-26) against cervical cancer and precancerous lesions associated with HPV-16 and HPV-18.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Infection with human papillomavirus (HPV) has been clearly established as the central cause of cervical cancer. In Australia, HPV-16 and HPV-18 account for approximately 70% of all cervical cancers and up to 50% of high-grade pre-cancerous lesions. Therefore, an effective HPV-16/18 vaccine is expected to represent an important preventative, primary health care intervention against cervical cancer and pre-cancerous cervical lesions.

Cervarix is a human papillomavirus vaccine that protects against infection caused by HPV-types 16 and 18.

6. Comparator

Appropriately, the submission nominated the human papillomavirus types 6, 11, 16 and 18 vaccine (Gardasil) as the main comparator.

7. Clinical Trials

The submission presented an indirect comparison based on three randomised trials of Cervarix versus placebo and three randomised trials of Gardasil versus placebo.

The trials which had been published at the time of submission are as follows:

Trial/First author	Protocol title/Publication title	Publication citation
Cervarix		
HPV-001 Harper et al, 2004	Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial	Lancet 2004; 364: 1757-65
HPV-007 Harper et al, 2006	Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial	Lancet 2006; 367: 1247-55
HPV-001/007 – pooled analysis Harper et al, 2006	Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial	Lancet 2006; 367: 1247-55
Gardasil		
P-007		
Villa et al, 2006	Immunologic responses following administration of a vaccine targeting human papillomavirus Types 6, 11, 16, and 18	Vaccine 2006; 24:5571-83
Villa et al, 2005	Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial	Lancet Oncol 2005; 6:271-78
Villa et al, 2006	High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up.	Br J Cancer 2006; 95(11): 1459-66
P-013 Harper et al., 2005 (poster) Sattler et al., 2005 (poster)	Phase III randomised trial to assess efficacy of Gardasil in reducing HHPV-6/11/16/18 related CIN AIS or cervical cancer, genital warts, VI, ValN, vulva or vaginal cancer	
P-015 Skjeldestad et al.	Phase III randomised trial to assess efficacy of Gardasil in reducing incidence of Hpv-6/11/16/8 related CIN 2/3, AIS or invasive cervical cancer	43 rd annual meeting of IDSA 2005
Pooled analyses - combined efficacy analyses of P-005/007/013/015 and P-007/013/015		
Ault.	Late breaking Prophylactic use of quadrivalent human papillomavirus (HPV) (types 6, 11, 16, 18) L1 virus-like particle (VLP) vaccine reduces cervical intraepithelial neoplasia (CIN) 2/3 and adenocarcinoma in situ (AIS) risk	Eur J Cancer supplements 2005; 3(4)
Paavonen J.	Efficacy of a quadrivalent HPV (types 6/11/16/18) L1 virus-like particle (VLP) vaccine against vaginal and vulvar pre-cancerous lesions: a combined analysis	J Clin Oncology 2006; 24(18s):5011

8. Results of Trials

The submission did not provide a formal indirect comparison of Cervarix and Gardasil, it only provided the results of the two sets of trials.

The primary outcomes in the Cervarix trials included incident cervical infection with HPV 16/18 and CIN2+ associated with HPV-16 or 18. In the Gardasil trials, the primary outcomes

were HPV-6/11/16/18-related persistent infection, external genital lesions, cervical intraepithelial neoplasia (CIN), adenocarcinoma in situ (AIS) or cervical cancer, and combined incidence of HPV-16 or 18-related CIN2, CIN3, AIS or cervical cancer.

These results were presented in terms of ‘vaccine efficacy’, which was defined as $100\% \times (1 - \text{attack rate in the vaccinated group} / \text{attack rate in the placebo group})$.

Both Cervarix and Gardasil demonstrated statistically significantly greater efficacy than placebo against the primary outcomes of the trials.

The PBAC agreed that the evidence presented indicates that Cervarix and Gardasil offer broadly equivalent prophylactic efficacy against persistent infection and cervical lesions associated with the two most prevalent HPV types (16 and 18).

Although Cervarix is a bivalent vaccine, designed to provide protection against HPV-16 and HPV-18 and Gardasil is a quadrivalent vaccine, efficacious against HPV-6/11/16/18, the submission claimed it was constructed on the premise that the rationale and value of HPV vaccination is prevention of cervical cancer and that any comparison between available vaccines should be made on the basis of their likely efficacy against cervical cancer. The submission also stated that the “overwhelming value” of HPV vaccination lies in its ability to prevent cervical cancer, and in contrast, the ability to prevent genital warts (caused by HPV types 6 and 11 in 90% of cases) should be regarded as providing a marginal and incidental benefit of the program, in both clinical and economic terms. The PBAC did not accept this argument.

The submission claimed that Cervarix has shown promising signals of providing efficacy against virological outcomes associated with non-vaccine included HPV-types which are phylogenetically related to either HPV-16 or HPV-18 in particular HPV-31 and HPV-45. However, the PBAC noted that the outcomes for HPV types 45 and 31 need to be regarded with caution for a number of reasons.

The sponsor also claimed that Cervarix may have an advantage in terms of duration of protection over Gardasil because, although the protection for HPV 16 after 5 years is similar, for HPV 18 geometric mean titres (GMTs) of Gardasil appear to revert to levels approximately the same as for natural infection after 5 years. The PBAC concluded that there is considerable uncertainty around this claim which will only be resolved with further evidence.

The submission presented toxicity results for Cervarix based on number of doses and results for Gardasil based on number of patients. The submission concluded that even though the safety results for Cervarix and Gardasil cannot be directly compared, the safety profile indicated that there is no significant difference between Cervarix and Gardasil in safety outcomes. The PBAC partially accepted this claim.

For further PBAC comments on these results, see Recommendation and Reasons.

9. Clinical Claim

The submission described Cervarix as non-inferior to Gardasil in terms of both comparative efficacy and safety.

The PBAC partially accepted this claim, *see Recommendations and Reasons*.

10. Economic Analysis

The submission presented a cost-minimisation analysis, and stated that Cervarix is proposed for inclusion on the NIP for the same population, and at the same price as Gardasil. The submission assumed that there will be no incremental costs associated with management of adverse vaccine reactions. The proposed equi-effective doses in the context of cost-minimisation were 3 doses of Cervarix are equal to 3 doses of Gardasil.

The PBAC concluded it could not accept the sponsor's claim of cost-minimisation and was therefore unable to determine a cost-effective price for Cervarix.

The submission also presented an "alternative scenario" assessing the impact of differences in the supplementary benefits of the two vaccines (broader protection against infection associated with non-vaccine oncogenic HPV types 31 and 45 for Cervarix and protection against infection and disease associated with HPV-6/11, specifically genital warts and low grade lesions, for Gardasil). The submission presented a cost-utility analysis, with the results of a cervical cancer model and a genital warts model combined to provide an overall estimate of cost-effectiveness. A supplementary cost-benefit analysis using willingness-to-pay was also presented.

The cervical cancer model presented by the submission compares vaccination in addition to cervical cancer screening with screening alone. The HPV types included in the model are HPV-16/18/31/45/52 and other high-risk and low-risk types. The model used vaccine efficacy based on 6 month persistent infection in the clinical trials. Vaccine efficacy for Gardasil in the cervical cancer model was derived from Gardasil vaccine efficacy against HPV-6/11/16/18.

The PBAC noted that there are wide confidence intervals around the vaccine efficacy values used for types HPV-31 (68.1%; 95% CI: -27.6, 94.5) and HPV-45 (51.3%; 95% CI: -239.6, 95.6), therefore the value of the cross-protection for HPV-31/45 offered by Cervarix is uncertain.

The genital warts model assumed no vaccine efficacy for Cervarix against HPV-6/11. Vaccine efficacy for Gardasil was derived from Gardasil vaccine efficacy against HPV-6/11/16/18. The PBAC noted that, for the cervical cancer model the submission had not justified the use of a combined estimate of vaccine efficacy when vaccine efficacy results are available for HPV-6 and 11 alone. The values chosen by the submission bias against Gardasil.

The PBAC noted that essentially, there appeared to be little difference between Cervarix and Gardasil, as evident from the small incremental difference in cost and the small incremental difference in QALYs and life years. However, these results were dependent on the assumption of a benefit for Cervarix due to vaccine efficacy against HPV-31 and 45. The evidence supporting a clinical advantage for Cervarix in an Australian population in terms of protection against HPV-31 and 45 was inconclusive.

The PBAC also noted that if the vaccine efficacy for HPV-31 and 45 was assumed to be 0% for Cervarix, the results of the modelled evaluation demonstrate that Cervarix was dominated

by Gardasil ie being both more costly and less effective. The results also depend on the assumption – valid at the time the submission was lodged – that Gardasil offered no cross-protection against these HPV types.

The PBAC did not accept the validity of the ‘alternate scenario’ analysis.

11. Estimated PBS Usage and Financial Implications

The financial cost/year to the NIP was based on an equivalent price to Gardasil, the submission assumed no incremental costs associate with the inclusion of Cervarix on the NIP. However, the PBAC noted that given that Cervarix does not provide protection against genital warts, there are likely to be increased costs for government health budgets associated with genital warts treatment.

12. Recommendation and Reasons

The PBAC noted the application requests listing on the NIP on a cost-minimisation basis against the currently funded quadrivalent HPV vaccine, Gardasil[®]. The application also provides a cost-effectiveness analysis to assess the impact of the known, or potential, differences in the two vaccines in terms of protection against other HPV strains including HPV types 6, 11, 31 and 45, and in duration of protection.

The Committee noted that the inclusion of a second HPV vaccine on the NIP provides the potential for competition for state and territory supply tenders, along with strengthened supply arrangements. Availability of a second vaccine is an appropriate risk mitigation strategy should supply problems with one vaccine eventuate. However, the decision to introduce a second product onto the NIP is not the same as the decision to introduce the vaccination initially. Decisions about a product for the NIP cannot be made on the same basis as decisions about two competing drugs because individual patients cannot choose one or the other product, and because in this case more than one outcome of vaccination (ie protection against cervical cancer and genital warts) might arise for the same patient from the same administration. Further, there are potential issues regarding the mobility of females between jurisdictions if both vaccines are available to state programs, creating a level of complexity that does not exist in the NIP at present.

The PBAC agreed that quadrivalent human papillomavirus types 16, 18, 6, 11 vaccine (Gardasil) is the appropriate comparator for this product.

The PBAC further agreed that Cervarix is effective in preventing persistent infection due to HPV types 16 and 18, and in preventing cervical cancer precursors caused by these HPV types. The PBAC further agreed with the submission’s conclusion that Cervarix has demonstrated equivalent protection to Gardasil for cervical cancer and precancerous lesions associated with human papillomavirus (HPV) types 16 and 18.

The Committee noted that Cervarix does not provide protection against HPV types 6 and 11 and that, in this respect it differs from Gardasil which does offer this protection. A decision to treat Gardasil and Cervarix as equivalent for the purpose of conducting a cost-minimisation analysis would ignore a benefit provided by Gardasil which arises for the same patient from the same administration.

The PBAC disagreed with the sponsor's contention that the only relevant indication for the purposes of decision-making for this product was the prevention of cervical cancer. It is incorrect that the genital warts benefits were not considered relevant in the decision to approve Gardasil, even if they were secondary to the key benefit of prevention of cervical cancer. The PBAC noted the Australian Technical Advisory Group on Immunisation's (ATAGI) advice regarding the importance of genital warts as a disease in Australia. HPV types 6 and 11 are known to cause 90% of genital warts in Australia. Further, regardless of whether the decision to approve Gardasil would have been made without the genital warts benefit, now that Gardasil is approved on the NIP, this benefit is accepted and so is relevant to any future decision making.

The PBAC noted the sponsor's claim that Cervarix provides cross protection against infection caused by HPV types 31 and 45 (as per the TGA approved statement in the registered Product Information sheet for Cervarix), but concluded that the evidence presented does not provide a convincing case in support of an advantage for Cervarix over placebo for HPV types 31 and 45 infection and disease, particularly given the wide confidence intervals that include negative values. The PBAC accepts that it is probable that some clinical efficacy cross-protection is afforded by Cervarix. However, it is very difficult to judge at this point in time whether the cross-protection from Cervarix is the same, better or worse than the cross-protection that may be available from Gardasil.

The PBAC also noted the sponsor's claim that Cervarix may have an advantage in terms of duration of protection over Gardasil. The evidence presented to support this claim shows the GMTs for Gardasil against HPV type 18 appear to revert to the same level as seen following natural infection after five years, whereas for Cervarix the GMTs for HPV type 18 at 5 years were higher than those seen following natural infection. However the GMTs for both Cervarix and Gardasil against HPV type 16 were considerably higher than those seen following natural infection after 5 years of follow-up. The submission furthermore acknowledges that the argument for a greater duration of protection remains theoretical. The Committee concluded that there is considerable uncertainty around this claim which will only be resolved with further evidence.

The PBAC concluded that the safety of both vaccines was similar, with local reactions common and similar in incidence. Both vaccines had similar rates of serious adverse reactions. The reporting rates of new onset of autoimmune disease were low and no cluster of events has been detected in any treatment group. The low frequency of autoimmune diseases constitutes a limitation of their assessment in the clinical program. Therefore, they will be further evaluated in ongoing studies and the planned post-licensure activities.

The Committee also noted that ATAGI disagrees with the sponsor's contention that leakage of subsidised vaccine into non-eligible patients is no more likely with Cervarix than Gardasil. Given that Cervarix is licensed for use in women up to the age of 45 years, whereas Gardasil is not, the PBAC noted it is more likely that Cervarix may be inappropriately administered to women outside of the NIP target group seeking vaccination than Gardasil.

On the basis of these considerations, the PBAC concluded it could not accept the sponsor's claim of cost-minimisation. Although the pre-PBAC response offered to reimburse the Government for the incremental net cost of treating genital warts, the submission did not provide a full economic appraisal to enable the Committee to assess the impact of the health

foregone when Cervarix is used in place of Gardasil. The PBAC was therefore unable to determine a cost-effective price for Cervarix (ie. how much less the Government should pay for Cervarix compared with Gardasil to offset the loss of benefit against genital warts, in terms of the cost of treating the disease, the loss of public health benefit of protection against genital warts, and the disutility of suffering genital warts).

Therefore the PBAC rejected the application on the basis of uncertain cost-effectiveness against the comparator, noting the following:

- Cervarix is as effective as Gardasil in protection against the cancer-causing HPV types 16 and 18;
- There is uncertainty about the efficacy of the two vaccines in terms of cross protection against other cancer-causing HPV types; and
- Gardasil offers protection against genital warts.

Recommendation

Reject

13. 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.

14. Sponsor's Comment

GSK is extremely disappointed by the PBAC's decision. We believe the PBAC has significantly undervalued the evidence of some cross-protection by *Cervarix* against infection caused by HPV-31 and HPV-45, and significantly overvalued the clinical and economic importance of the protection offered by *Gardasil* against genital warts. GSK notes that there is nothing in the public domain to indicate that PBAC has evaluated any clinical efficacy cross protection data to support Gardasil. Irrespective of these comments, we are committed to working with the PBAC to find a way to ensure *Cervarix* can be listed on the National Vaccination Schedule, thus providing important competition for state and territory tenders and strengthened supply arrangements.