PUBLIC SUMMARY DOCUMENT
Product: Quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine, solution for injection, 0.5 mL, solution for injection pre-filled syringe single dose, Gardasil®
Sponsor: CSL Limited
Date of PBAC Consideration: November 2011

1. Purpose of Application

To seek an extension of the current listing on the National Immunisation Program (NIP) to include prevention of human papillomavirus (HPV) in males 12-13 years of age and a catch-up program over 2 years for Year 9 males.

2. Background

At the March 2011 meeting, the PBAC rejected a request to extend the NIP listing for Gardasil to include the prevention of HPV in males 12 to 13 years of age and a catch-up program over 2 years for Year 9 males because of unacceptably high and uncertain cost-effectiveness. This conclusion was reached despite a substantially lower proposed price because of insufficient evidence to demonstrate the claimed effects of the vaccine in reducing the rate of future HPV-associated cancers beyond the previously accepted effects on cervical cancer.

For further details refer to March 2011 Public Summary Document.

3. Registration Status

Gardasil was first registered on 22 June 2006 and is currently registered by the TGA for the following indications:

- Prevention of cervical, vulvar, vaginal and anal cancer, precancerous or dysplastic lesions, genital warts and infection caused by HPV types 6, 11, 16 and 18 (which are included in the vaccine) in females aged 9 to 45 years* ; and
- Prevention of anal cancer, precancerous or dysplastic lesions, external genital lesions and infection caused by HPV types 6, 11, 16 and 18 (which are included in the vaccine) in males aged 9 to 26 years.

*Immunogenicity studies have been conducted to link efficacy in females and males aged 16 to 26 years to the younger populations.

4. Listing Requested and PBAC's View

The requested listing was unchanged, refer to March 2011 Public Summary Document.

5. Clinical Place for the Proposed Therapy

Refer to March 2011 Public Summary Document.

6. Comparator

The resubmission did not explicitly state the primary comparator.

The results of the revised economic evaluation were presented in terms of the secondary comparator from the previous submission (current female HPV vaccination).

7. Clinical Trials

The re-submission presented an alternative analysis of the same trial data (Protocol 020) in the men who have sex with men (MSM) sub-group and prospective studies to support the claim of a link between anal intraepithelial neoplasia (AIN) and anal cancer.

8. Results of Trials

The submission presented efficacy results regarding the number of external genital lesions (EGLs) in the per-protocol efficacy population (PPE), generally HPV naive population (GHN), FAS (Full analysis set) and HNRT (Naïve to the Relevant-HPV-type) populations. Overall, the vaccine efficacy against HPV 6,11,16,18 related EGL in the PPE population was 90.6% (95% CI: 70.1 – 98.2).

The alternative analysis of efficacy against AIN in the MSM sub population in Protocol 020 included some cases of AIN which were re-assigned to non-vaccine HPV types. The reassignment resulted in increased estimates of the efficacy of the vaccine. The data highlight the sensitivity of the results of vaccine efficacy with respect to how cases are assigned as related to HPV 6, 11, 16 or 18. Overall, the vaccine efficacy against HPV 6, 11, 16, 18 related AIN any grade in the PPE population was 77.5% (95% CI: 39.6 – 93.3) in the original analysis and 91.1% (95% CI: 64.2 – 99.0) in the re-assigned cases analysis.

The re-submission presented further evidence to support the claim that the results for the MSM sub-group of protocol 020 can be generalised to the general male population (the proposed NIP population).

For PBAC's view on these results, see Recommendation and Reasons.

The re-submission presented new toxicity data, in terms of additional analyses of serious injection site reactions in Protocols 016, 018 and 020. The data from Protocol 020 indicated that most injection site reactions were judged to be of mild or moderate intensity, but severe injection site adverse events were reported by 2% (60 of 3003 subjects followed up for 5 days after any injection):

- 0.8% (25/3003) reported severe pain
- 0.8% (25/3003) reported severe swelling (>2 inches)
- 0.8% (23/3003) reported severe erythema (>2 inches).

9. Clinical Claim

The clinical claim in the March 2011 submission described GARDASIL as being therapeutically superior and having significant clinical advantages with greater toxicity than the main comparator, placebo. The PBAC previously accepted this claim regarding the use of the GARDASIL in adolescent and young adult males in a universal program.

The PBAC considered that the claim of a vaccine treatment effect on oropharyngeal (HPVOP) cancer was only weakly supported by the evidence presented in the re-submission. The PBAC noted that only HPV serotype 16 is associated with this form of cancer, the attributable fraction of oropharyngeal cancer due to HPV serotype 16 compared to other factors such as smoking and HIV infection is not clear and there is no evidence of any difference in oropharyngeal HPV infections or cancer precursers between vaccinated and unvaccinated populations.

10. Economic Analysis

An updated modelled economic evaluation was presented of the male+female vaccination program vs female vaccination only.

The model was a hybrid model, as previously, which comprised a Dynamic Infectious Disease Model and a Markov model.

The results of the economic evaluation produced a base case ICER of between $15,000 - $45,000/QALY.

The vaccine coverage for males was reduced by 10 % from the previous submission to a first dose coverage of 70 %, the catch-up program was included and the price was reduced.

The PBAC considered the removal of penile and perineal cancers from the economic evaluation appropriate given that the available data were insufficient to support a claim of a vaccine treatment effect on these types of cancer. The PBAC noted that HPVOP cancer remained in the economic evaluation, however, vaccine efficacy against HPVOP cancer was assumed to be between 0 % and 100 % of AIN vaccine efficacy (whereas previously it was 100 %).

The incidences of anal and HPVOP cancers were assumed to grow indefinitely into the future based on a multiplicative rather than an additive model and the ICER was highly sensitive to whether the incidence of anal and HPVOP cancers was assumed to grow indefinitely. When no growth of anal cancer and HPVOP cancer is assumed after 2014, the PBAC noted that the ICER increases to between $45,000 - $75,000/QALY.

Sensitivity analyses were conducted on both the Dynamic Infectious Disease model and Markov model.

The ICER was sensitive to vaccine efficacy against HPVOP and anal cancer in the Markov model (based on comparing the ICER assuming the upper and lower 95% confidence intervals for vaccine efficacy based on the GHN population). The ICER was also sensitive to the cost of administration, the incidence of genital warts, the proportion of the population who were MSM, and the proportion of anal cancers attributable to HPV 16/18. The ICER was largely insensitive to changes in the other parameters.

11. Estimated PBS Usage and Financial Implications

The likely number of patients/year was estimated by the submission to be greater than 200,000 in Year 1, consisting of 12 year old males, 12-year old females (who are already immunised under the existing GARDASIL programme), and 14-year old males under the proposed catch-up programme (which runs for the two years following listing).

The financial cost/year to the NIP was estimated by the submission to be between $5 – $30 million in Year 1.

12. Recommendation and Reasons

The PBAC recommended extension of the National Immunisation Program listing of quadrivalent human papillomavirus (HPV) (types 6, 11, 16, 18) recombinant vaccine, solution for injection 0.5 mL, to include ongoing administration to males approximately twelve to thirteen years of age in a school-based program and for two catch-up cohorts for all

males in the two year groups above the ongoing cohort, delivered over two years for Year 9 males, on the basis of acceptable cost effectiveness compared with female-only vaccination, which forms the basis of the revised economic evaluation in the re-submission.

The PBAC noted that no direct evidence was presented regarding HPV vaccine efficacy against anal or other cancers. The re-submission presented an alternative analysis of the same trial data (Protocol 020) in the men who have sex with men (MSM) sub-group and prospective studies to support the claim of a link between anal intraepithelial neoplasia (AIN) and anal cancer. The PBAC also noted the additional studies identified by ATAGI including Watson 2006 regarding the postulated link between AIN and anal cancer. The PBAC considered that quantifying the risk of progression to anal cancer from AIN remained uncertain, and that detecting and staging AIN was less consistent than has already been accepted with cervical intraepithelial neoplasia. However, on balance, that the evidence supported some association between AIN and progression to anal cancer, in particular for higher grade AIN (AIN-2 and AIN-3). The PBAC considered that uncertainty remained about the magnitude of the association between AIN and progression to anal cancer, the extent to which AIN and anal cancers are associated with HPV serotypes 16 and 18 compared with other strains of HPV, and the influence of other risk factors on the causal pathway to anal cancer.

The re-submission presented further evidence to support the claim that the results for the MSM sub-group of protocol 020 can be generalised to the general male population (the proposed NIP population). The PBAC noted the ATAGI advice and considered that, based on the available evidence, the development of HPV-related AIN and anal cancer are likely to be similar in nature across the MSM and the general male populations and hence that HPV vaccine efficacy is likely to be similar in relative terms across these populations. The PBAC noted it had previously accepted HPV vaccine efficacy against condyloma acuminata (genital warts) in females and males attributable to HP 6 or 11 and AIN in the MSM sub-group attributable to HPV 16 or 18.

The PBAC noted that an updated economic evaluation was presented. The PBAC considered the removal of penile and perineal cancers from the economic evaluation appropriate given that the available data are insufficient to support a claim of a vaccine treatment effect on these types of cancer. The PBAC also considered that the claim of a vaccine treatment effect on oropharyngeal (HPVOP) cancer was only weakly supported by the evidence presented in the submission, noting that only HPV serotype 16 is associated with this form of cancer, the attributable fraction of oropharyngeal cancer due to HPV serotype 16 compared to other factors such as smoking and HIV infection is not clear and there is no evidence of any difference in oropharyngeal HPV infections or cancer precursors between vaccinated and unvaccinated populations. The PBAC noted that although HPVOP cancer remained in the economic evaluation, vaccine efficacy against HPVOP cancer was assumed to be between 0 % and 100 % of AIN vaccine efficacy (whereas previously it was 100 %). The PBAC did not accept the sponsor's base case (percentage of vaccine efficacy against HPVOP set to 100 % of AIN vaccine efficacy), but did accept that, where the percent of vaccine efficacy against HPVOP is set to zero, this preferred base case would not include any reduction in HPVOP. The PBAC therefore accepted a base case ICER of between $15,000 - $45,000/QALY (varying depending on whether the 95 % or 99 % lower bound of the confidence interval of the annual percentage change in the incidence of anal and HPVOP cancers is used in the model). The PBAC noted that there were likely to be other oncogenes

against which future vaccines could be targeted, which conflicts with any acceptance of the claimed 100 % of AIN vaccine efficacy.

The vaccine coverage for males was reduced by 10 % from the previous submission to a first dose coverage of 70 %, which the PBAC considered was reasonable. The PBAC also noted that the catch-up program was included in the economic evaluation in the re-submission and that the price was reduced from the previous submission.

The incidence of both anal and HPVOP cancers was assumed to grow indefinitely into the future based on a multiplicative rather than an additive model and the PBAC considered both assumptions to be improbable. The PBAC also noted that the ICER was highly sensitive to whether the incidence of anal and HPVOP cancers is assumed to grow indefinitely. When no growth of anal cancer and HPVOP cancer is assumed after 2014, the PBAC noted that the ICER increases to between $45,000 – $75,000/QALY.

The PBAC considered the assumed lifetime efficacy of HPV vaccine in the economic evaluation to be uncertain and noted the ATAGI advice that the clinical relevance of waning of antibodies to HPV 18 remains unknown.

The PBAC noted that the sponsor proposed a price weighted by gender uptake, with the price adjusted based on actual uptake. The PBAC recommended that the weighted price be based on the eligible population rather than the existing female HPV vaccine register population, as the register was set-up specifically to monitor the female HPV vaccination program and to allow assessment of HPV vaccine effectiveness in preventing cervical abnormalities and cervical cancer.

The PBAC recommended that a register of males who are vaccinated, similar to that implemented for the female program, should be established and maintained. The register would need to have the capacity to identify and recall adolescents who have had an incomplete vaccination course or to receive a booster dose in the event that a booster dose is required. In addition, sentinel HPV type surveillance should be established and maintained to detect HPV genotypes causing anal, oropharyngeal, penile and perineal cancers. The PBAC noted that the vaccine sponsor had financially supported a register and sentinel surveillance program for funded use of the vaccine by girls, and advised that this support should extend to cover funded use of the vaccine by boys. Similarly, the PBAC noted that the vaccine sponsor had provided financial and “in kind” support for the promotion of a successful delivery of a complete 3-dose program, including for the recruitment and training of immunisation providers and the development of educational materials.

In making this recommendation the PBAC noted the consumer comments on this item.

Recommendation:
To extend beyond the cohorts in the current NIP program for females as follows:

- Ongoing cohort of males approximately 12 – 13 years of age in a school-based program. This cohort to be consistent with the current school-based HPV vaccine program for females.
- Two catch-up cohorts for all males in the two year groups above the ongoing cohort – delivered as a catch-up program over two years for Year 9 males.

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

CSL welcomes the PBAC decision to recommend the extension of the National Immunisation Program listing of the quadrivalent HPV (types 6, 11, 16, 18) vaccine to include males.