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

## 1. Purpose of Application

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

## 2. Background

This drug had not previously been considered by the PBAC for this indication in males.

Gardasil is available under the National Immunisation Program (NIP) for females aged 12–13 years for vaccination against human papillomavirus (HPV) types 6, 11, 16 and 18.

## 3. Registration Status

As of 8 November 2010, Gardasil was TGA registered for the following indications:

- Females aged 9 to 45 years* for the prevention of cervical, vulvar and vaginal cancer, precancerous or dysplastic lesions, genital warts and infection caused by human papillomavirus (HPV) types 6, 11, 16 and 18 (which are included in the vaccine). (TGA registered 22 June 2006 for females aged 9-26 years, extended in 2009 to include females to 45 years)
- Males aged 9 to 26 years of age for the prevention of external genital lesions and infection caused by human papillomavirus (HPV) types 6, 11, 16 and 18. (TGA registered 12 October 2010)

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

The TGA is currently considering an application (submitted October 2010) to extend the indication in males and females to include anal cancer and precancerous or dysplastic lesions caused by the HPV types in the vaccine.

## 4. Listing Requested and PBAC's View

The following cohorts were proposed for NIP funding:

- 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 such that the program is a gender neutral HPV vaccination program. As for the female vaccination program GARDASIL is intended as a prophylactic vaccine to be administered prior to exposure to HPV which occurs at the onset of sexual activity.

- Two catch-up cohort for all males in the two year groups above the ongoing cohort, ie. ~ 13 – 15 years of age and not captured in the routine annual schedule. This would be via a school-based catch-up program. This is intended to provide catch-up

coverage to cohorts still unexposed to HPV. The median age of sexual debut for males is 16 – 17 years (Rissel et al, 2003; Smith et al, Age at First Sex Appendix 6.H).

*For PBAC's view, see Recommendation and Reasons.*

## 5. Clinical Place for the Proposed Therapy

Human papilloma virus (HPV) is the most common sexually transmitted infection. The disease burden and natural history of genital HPV infection in males appears to be similar to what has been reported in females and is significantly associated with sexual behaviour including age at first intercourse and number of lifetime and recent partners. Among average risk male populations in the US the prevalence of any HPV infection ranged from 35 – 61%.

As in females, HPV infection in males is usually asymptomatic but can result in a number of anogenital diseases, including anogenital warts, the pre-cursor lesions for anal and penile cancer – intraepithelial neoplasia of the anus (AIN) and penis (PIN) and anal cancer and penile cancer. HPV causes infection and disease in the respiratory tract and is recognised as an important cause of oral cavity and oropharyngeal cancers.

The submission proposed that in addition to a direct benefit to males from HPV vaccination of males, there may be additional benefit to unvaccinated females through interruption of transmission.

## 6. Comparator

The submission nominated no vaccination (placebo) in males as the main comparator and nominated the current female only vaccination as a secondary comparator.

## 7. Clinical Trials

The submission presented three randomised trials, Protocols 016, 018 and 020, comparing Gardasil to placebo in healthy males.

Protocol 016 recruited healthy males aged 10 to 15 years and Protocol 018 recruited healthy males aged between 9 years and 0 days to 15 years and 364 days. The main inclusion criteria for both Protocol 016 and 018 was that the participants had not yet had coitarche and did not plan to become sexually active during the course of the study.

Protocol 020 compared Gardasil to placebo in heterosexual men (HM) aged 16 to 23 years inclusive and men who identified themselves as having sex with other men (MSM) aged 16 to 26 years inclusive.

The study reports presented in the submission are shown in the table below:

| Trial ID / First author | Protocol title / Publication title | Publication citation |
|---|---|---|
| **Direct randomised trials** | | |
| Protocol 016 | A Study to Demonstrate Immunogenicity and Tolerability of the Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine in Preadolescents and Adolescents, and to Determine End-Expiry Specifications for the Vaccine (P016V1) | Clinical Study Report |

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| Protocol 018 | A Safety and Immunogenicity Study of Quadrivalent HPV (Types 6, 11, 16, 18) L1 Virus-Like Particle (VLP) Vaccine in Preadolescents and Adolescents (P018V1) | Clinical Study Report |
| Protocol 020 | A Study to Evaluate the Efficacy of GARDASIL™ in Reducing the Incidence of HPV 6-, 11-, 16-, and 18 – Related External Genital Warts, PIN, Penile, Perianal and Perineal Cancer, and the Incidence of HPV 6-, 11-, 16-, and 18– Related Genital Infection in Young Men (P020V1 and P020) | Clinical Study Report |

## 8. Results of Trials

The efficacy results from Protocol 020, looked at the number of external genital lesions (EGLs) in the per-protocol efficacy population (PPE) and the generally HPV naïve population (GHN). 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) and 90.8% (95%CI: 70.7-98.2) against HPV 6,11,16,18 related EGL in the GHN population.

The efficacy results from the MSM substudy of Protocol 020, looked at the number of AIN and anal cancer cases in the PPE and GHN populations. Overall, the vaccine efficacy against HPV 6,11,16,18 related AIN and anal cancer in the PPE population was 77.5% (95.1% CI: 39.6 – 93.3) and 89.6% (95% CI: 57.2 – 98.9) against HPV 6,11,16,18 related AIN and anal cancer in the GHN population.

The PBAC noted that condyloma was a significant driver of the EGL clinical analysis and considered that there was little information on cancers (PIN) to inform decisions.

The efficacy results against HPV 6,11,16,18 and lesion type-related EGL in the naïve to the relevant-HPV-type (HNRT) and full analysis set (FAS) populations indicated that the magnitude of the benefit decreases with both populations, compared to the PPE population. Again condyloma was a significant driver of the results and there was little information on cancers (PIN).

The efficacy results against HPV 6,11,16,18 related AIN and anal cancer in the HNRT population of the MSM substudy were similar to results in the PPE population. The magnitude of the benefit decreased in the FAS population, compared to the PPE population.

A larger proportion of subjects who received Gardasil (74%) reported an adverse event (AE) compared with subjects who received placebo (64%). All injection site AEs were considered to be vaccine related. A larger number of serious adverse events (SAE) were reported in the Gardasil group (nine subjects) versus one subject in the placebo group. None of the severe adverse events were determined by the clinical investigator to be vaccine-related.

*For PBAC's view, see Recommendation and Reasons.*

## 9. Clinical Claim

The submission described Gardasil as being therapeutically superior and having significant clinical advantages with greater toxicity than the main comparator, placebo.

Based on the supporting data, the PBAC accepted this claim regarding the use of the Gardasil in adolescent and young adult males in a universal program.

## 10. Economic Analysis

The submission presented a stepped economic evaluation.

A Markov model was used to examine the cost-effectiveness of the primary comparator (males vs placebo).

The model assumed that the effectiveness of Gardasil did not taper over time and provided lifetime protection in vaccinated males and females.

A hybrid model, which comprises a Dynamic Infectious Disease Model and a Markov model, was used to examine the cost-effectiveness of the secondary comparator (male+female vaccination vs females only vaccination).

The results of the economic evaluation produced a base case ICER for all diseases of less than $15,000 in male+female vs female only, with herd immunity.

The PBAC considered that the presented base case was overly optimistic for the following reasons;

- The use of the PPE population overestimates the efficacy of the vaccine in the Australian population.
- The comparison assumes efficacy against only the included vaccine serotypes rather than all HPV serotypes, which implicitly assumes no change in prevalence of other HPV serotypes.
- The data are more robust for condyloma, but condyloma is not driving the benefits seen in the model.
- The quantified association between HPV and AIN/PIN is uncertain.
- The lifetime risks of cancer seem implausibly high.
- The disutilities for cancer appear not to take into account earlier stages of cancer.

The submission presented limited sensitivity analyses on the Markov model.

A more detailed sensitivity analysis was conducted as part of the evaluation which found:

- The incremental cost-effectiveness ratio (ICER) is highly sensitive to the duration of vaccine efficacy. The PBAC noted there is a possibility of waning of the vaccine efficacy over time, which is becoming most pronounced for serotype 18 after three years.
- The ICER is sensitive to which diseases are included in the model (i.e. in line with TGA license or all diseases) and whether only the benefits in males (the recipients of the vaccine) are included.
- In terms of vaccine efficacy in vaccinated individuals (not including the herd immunity benefits), the ICER is only slightly sensitive to the use of the PPE population vaccine efficacy estimates (as suggested by ATAGI) compared to the GHN population estimates. However the ICER is sensitive to individual estimates of vaccine efficacy against HPV type 16 and 18-related oropharyngeal cancer (HPVOP) and anal cancer.
- The ICER is somewhat sensitive to the herd immunity estimates generated by the Dynamic Infectious Disease model, as indicated when male+female herd immunity

benefits are set to female only herd immunity benefits (i.e. there is no additional herd immunity benefits).

- Finally the ICER is sensitive to growth rates in anal and HPVOP cancer incidence (which are assumed to increase forever, which may be optimistic), the cost of administration, and the age-related utilities in the well state.

In the pre-PBAC response, the submission presented a revised base case and sensitivity analyses including PPE vaccine efficacy, unchanged HPV attributable fractions, unchanged cancer incidence, modified duration of genital warts and utility weights for well state.

*For PBAC's view, see Recommendation and Reasons.*

## 11. Estimated PBS Usage and Financial Implications

The submission presented a weighted vaccine cost between males and females reflecting the different costs and the different gender populations.

The submission estimated the financial cost/year to the NIP would be in the range of $5 – $30 million per year in Yr 5 of listing.

## 12. Recommendation and Reasons

The PBAC accepted a clear immunogenic effect of the vaccine had been demonstrated and reaffirmed its acceptance of benefit of the vaccine as currently administered to girls to reduce the rate of cervical cancer in women. The effect of the vaccine on reducing the rate of condyloma acuminata (genital warts) in both females and males was also accepted.
There were two main sources of clinical uncertainty in relation to the claims for the benefit of the vaccine with uncertainty increasing from anal cancer, through penile, perianal and perineal cancers to greatest uncertainty with oropharyngeal cancer. Of these, anal and oropharyngeal cancers account for relatively large incremental QALY gains in the modelled economic evaluation.

The first main clinical uncertainty relates to the demonstration of any treatment effect in males beyond condyloma. The claim for a treatment effect on anal cancer relies on a subgroup of Protocol 20 of men who have sex with men, and so the submission relies on an inference that the treatment effect in this subgroup can be generalised to the Australian male population on the basis of a constant relative treatment effect (i.e., "vaccine efficacy" in the subgroup applies to all Australian males). The demonstrated effect was on anal intraepithelial neoplasia (AIN) rather than directly on anal cancers. The PBAC noted that the claim of a vaccine treatment effect on anal lesions is the subject of a concurrent application to TGA, which is still under consideration (and no claim for reducing any other cancer is being considered by a regulatory agency). The claim for a treatment effect on penile, perianal and perineal cancers relies on assuming that the treatment effect on the composite outcome of external genital lesions can also be applied to each component of the composite outcome. The demonstrated effect was assessed with reference to penile, perianal and perineal intraepithelial neoplasia (PIN) rather than directly on penile, perianal and perineal cancers. PBAC noted that the composite outcome was driven by condylomata, and the trial was underpowered to conclude any effect on PIN independent of other external genital lesions. The claim of a vaccine treatment effect on oropharyngeal cancer was not supported with reference to any clinical data. PBAC noted that no surrogate outcome evidence was provided

even of an effect on HPV-related infection, let alone persistent infection or intraepithelial neoplasia.

The second main clinical uncertainty relates to the translation of any vaccine effect on AIN or PIN to subsequent rates of related cancers. The evidence relating persistent HPV infection to either AIN or PIN and then to anal cancer or penile, perianal and perineal cancers is based on retrospective data, which is in contrast to, and much weaker than, the prospective data accepted by PBAC previously relating persistent HPV infection to cervical intraepithelial neoplasia (CIN) and then to cervical cancer. Further, the grading of CIN as 1, 2 or 3 is much more robust than similar attempts to grade AIN or PIN. In contrast to cervical cancer, there is also uncertainty about the fraction of anal and other cancers attributable to HPV since the presence of HPV in a lesion does not necessarily mean it is causally related to development of cancer as coincidental infections are common. There is also doubt over whether persistent HPV infection is sufficient alone to translate into subsequent anal cancer, or whether co-infection with HIV (or other factors) is a necessary in some cases. Interpretation of Australian epidemiological data, which is influenced by the high incidence of anal cancer in men who have sex with men (more than 30 times greater than in heterosexual men according to estimates in the ATAGI advice), may also be influenced by this uncertainty, which also affects the assumptions of lead time to this cancer in the modelled economic evaluation.

The PBAC noted other clinical uncertainties which may not be as great as those already noted above. One uncertainty related to the net impact of parallel herd immunity effects, first of vaccinating girls on male outcomes and second of vaccinating boys on female outcomes. The PBAC accepted that the dynamic model was a necessary basis to predict the future rates of HPV infections in the context of female-only vaccination before examining the incremental effect of adding male vaccination. However, assumptions of herd immunity impacts are influenced by uncertain assumptions relating to extent of vaccine coverage (which is high in Australia, but not as high as assumed in the model, and which is likely to be lower in boys). These assumptions favour the vaccine in the modelled economic evaluation to the extent that herd immunity benefits in the female-only vaccinated population are underestimated and herd immunity benefits in the additional male vaccinated population are overestimated. Another uncertainty related to the projected increasing rates of anal, penile, perianal and perineal cancers in the future, which is likely influenced by diagnostic changes and by the extent of HIV co-infection in the population. A third uncertainty related to the possibility of a waning vaccine efficacy over time, which is becoming most pronounced for serotype 18 after three years. The PBAC noted that a similar uncertainty relating to a waning effect on cervical cancer had been addressed in the existing agreement between the Department and the applicant and considered that a similar arrangement would be appropriate for the current request, but reflecting a greater overall uncertainty (with substantial effects on the modelled economic evaluation, and with the sensitivity analysis of a booster dose not including all relevant costs of introducing a booster dose such as the costs of case finding). A fourth uncertainty relates to the rate of acute adverse effects related to vaccine injection (with 2% of recipients reporting severe intensity injection site reactions), noting that the rate of events for placebo may be increased because its aluminium content may be irritant. The PBAC noted that the choice of the trial population as the basis for the vaccine efficacy analysis was a lesser source of uncertainty, and that the per protocol efficacy analysis overestimated vaccine effectiveness for the requested population of boys prior to sexual debut, but who may not complete a full course of three injections. Despite this, the modelled economic evaluation used more favourable estimates of vaccine efficacy. A fifth uncertainty relates to the 80%

estimated uptake of HPV vaccine by boys, which is higher than the current rate in girls, of whom 80% commence but only 70% complete a course of HPV vaccine.

The PBAC observed that all the clinical uncertainties flowed into the modelled economic evaluation, but that the sensitivity analyses provided did not permit a full assessment of the impact of the clinical uncertainties. This was particularly a concern given the reliance on a complex and non-transparent model. An additional important uncertainty was the increasing rate of non-cervical cancers claimed in the model, for the reasons already noted about the less developed understanding of the role of HPV in causing these cancers and the associated lead times. The applicant's pre-PBAC base case was rejected as favouring the vaccine. Noting the importance of assessing multiple uncertainties simultaneously, the PBAC considered that a more likely incremental ratio might be in the range of $15,000- $45,000 per extra QALY gained, which excludes penile cancer and HPV-related oropharyngeal cancer and a more acceptable lower rate of growth in the incidence of anal cancer. However, this likely still favours the vaccine because it does not adequately examine the uncertainty of translating any vaccine effect on anal cancer.

Also in relation to the modelled economic evaluation, the PBAC noted that the utilities of the cancer health states favoured the vaccine to an extent in the incremental analysis of greater prevention because the utilities reflected the end stages of these cancers rather than reflecting any progression of severity of these conditions. In contrast, the utility in the well state remained at the maximum of 1 rather than accounting for the utility of a normal population, which also tends to overestimate the utility impact of the incremental clinical gains with the vaccine. The PBAC also noted that the measure of reduction in incidence of HPV infection is taken at equilibrium (2080) and this value is applied in the modelled economic evaluation to cohorts of 12 year-olds vaccinated from 2013 onwards, an assumption which is more favourable to the vaccine than applying the actual predicted reduction in incidence of HPV infection over time beginning in 2013.

Insufficient data was provided to assess the impact of including the requested catch-up program, which may be more likely to include some boys who are already sexually active and thus already exposed to HPV infection.

In deciding not to recommend the extension of the NIP listing as requested, the PBAC also noted its concern with the equity issues of not providing funded access to males as well as females. However this concern was not sufficient to outweigh the other reasons to reject the submission.

The PBAC thus rejected the requested extension of NIP listing of quadrivalent human papillomavirus recombinant vaccine to include boys 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.

***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

CSL believes extending HPV vaccination to males is an important public health initiative and is committed to working with the PBAC to secure a positive recommendation for the NIP.