PUBLIC SUMMARY DOCUMENT

Product: Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) recombinant vaccine, injection, 0.5 mL, Gardasil®

Sponsor: CSL Limited

Date of PBAC Consideration: November 2006

1. Purpose of Application

The submission sought funding for Gardasil on the National Immunisation Program (NIP) for the prevention of human papillomavirus (HPV) infection in an ongoing group of 12 year old girls and for a catch-up program for all girls and women 13-26 years.

2. Background

This vaccine had not previously been considered by the PBAC.

3. Registration Status

Gardasil was registered on 16 June 2006 for use in females aged 9 to 26 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), and males aged 9 to 15 years for the prevention of infection caused by human papillomavirus (HPV) types 6, 11, 16 and 18 (which are included in the vaccine).

4. Listing Requested and PBAC's View

The following groups were proposed for funding under the National Immunisation Program (NIP):

1. Ongoing cohort in girls approximately 12 years of age. This cohort to be consistent with the current school-based hepatitis B vaccine program, typically in the first year of secondary school.
2. Catch-up cohort for all girls 13 – 18 years of age not captured in the routine annual schedule. This would largely be via a school-based catch-up program.
3. Catch-up cohort for all women up to the age of 26 who are no longer in school. For simplicity this is assumed to be all women 19 – 26 years of age.

5. Clinical Place for the Proposed Therapy

Human papillomavirus (HPV) infection is very common. Evidence indicates that infection with certain types of HPV is the principal cause of invasive cervical squamous cell and adenocarcinomas and their precursor lesions. HPV infection is generally asymptomatic and is not recognised until patients are diagnosed with cervical dysplasia, cancer or genital warts.

6. Comparator

The submission nominated current management involving screening for cervical cancer as the main comparator. The PBAC accepted that the appropriate comparator for this vaccine was standard medical management, which, in Australia, includes the operation of the National Cervical Screening Program (NCSP).

7. Clinical Trials

The submission presented six randomised trials comparing Gardasil and placebo. Efficacy analyses were based on combined analyses of four of the trials (Protocols 005, 007, 013, 015). The populations in these trials were 16 to 23 year-old women. The remaining two trials (Protocols 016, 018) included pre-adolescent and adolescent males and females and assessed immunogenicity outcomes. The following populations were used in the efficacy analyses:

- per protocol (PPE): seronegative and PCR-negative at Day 1 and at Month 7 to the relevant vaccine HPV types and received all 3 vaccinations, case counting from Month 7;

- modified intention-to-treat population 2 (MITT-2): seronegative and PCR-negative at Day 1 to the relevant vaccine HPV types and received at least 1 vaccination, case counting from Month 1;

- modified intention-to-treat population 2, restricted (RMITT-2): seronegative and PCR-negative at Day 1 to all four vaccine HPV types; normal Pap test results at Day 1 and received at least 1 vaccination, case counting from Month 1;

- modified intention-to-treat population 3 (MITT-3): subjects may have had infection on or prior to the first vaccination and received at least 1 vaccination, case counting from Month 1.

The trials used for efficacy analyses recruited female subjects 16 to 23 years of age, while the main on-going cohort proposed for NIP funding is girls approximately 12 years of age.

The primary outcome in the trials to assess prophylactic efficacy were:

- HPV 16- and 18-related intraepithelial neoplasias (CIN) 2/3 or adenocarcinoma in situ (AIS) – the immediate precursors of invasive squamous cell carcinoma and invasive adenocarcinoma of the cervix, respectively;
- HPV 6-, 11-, 16-, or 18-related CIN (CIN 1,CIN 2/3) or AIS;
- HPV 6-,11-,16-, or 18-related External Genital Lesions including genital warts, vulval intraepithelial neoplasias (VIN), vaginal intraepithelial neoplasias (VaIN) - VIN 2/3 and VaIN 2/3 are the immediate precursors to HPV-related vulvar and vaginal cancer, respectively.

Interim alanyses against disease caused by any HPV type were undertaken in the RMITT-2 and MITT-3 populations

All results were presented in terms of 'vaccine efficacy'.

The trials published at the time of the submission were:

Trial/First author	Protocol title	Publication citation
Protocol 005		
Koutsky, L. A, et al 2002	A controlled trial of a human papillomavirus type 16 vaccine.	New England Journal of Medicine, vol. 347, no. 21, pp. 1645-1651.
Mao, C, et al, 2006	Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia: a randomized controlled trial.	Obstetrics and gynecology, vol. 107, no. 1, pp. 18-27.
Protocol 007		

Trial/First author	Protocol title	Publication citation
Villa, L. L, 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 Oncology, vol. 6, no. 5, pp. 271-278.
Protocol 015		
Lehtinen, M, et al, 2006	Population-based enrolment of adolescents in a long-term follow-up trial of human papillomavirus vaccine efficacy.	International Journal of STD and AIDS, vol. 17, no. 4, pp. 237-246.

8. Results of Trials

The results of the primary analysis (Protocols 005, 007, 013, 015) demonstrated that Gardasil, including the monovalent vaccine in Protocol 005, is 100% effective in both the per protocol population (negative to the relevant HPV types at baseline and 7 months, case counting from month 7) and 98.2% – 100% effective in the modified intention-to-treat population 2 (MITT-2) population (negative to the relevant HPV types at baseline, case counting from Month 1) in protecting against HPV 16, 18 related CIN 2/3 and AIS.

The results of a combined analysis of the comparative randomised trials (Protocols 007, 013, 015) which calculated vaccine efficacy in the prevention of external genital lesions (EGL), including condyloma (genital warts), vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VaIN) demonstrated that Gardasil was 94.2% - 100% effective in preventing all the above in the MITT-2 population.

Analysis of the immunogenicity responses one month following the 3-dose vaccination regimen, for Protocols 007, 013, 015, 016 and 018 combined, demonstrated that seroconversion was ≥99.5%, with anti-HPV Geometric Mean Titres (GMTs) highest in 9-15 year-old boys, followed by 9-17 year-old girls and 18-26 year-old women.

The longest trial duration was 5 years, with available results demonstrating advantages for immunogenicity outcomes, HPV 6, 11, 16 or 18 related CIN and genital warts outcomes for vaccinated subjects.

9. Clinical Claim

The submission described Gardasil as significantly more effective than the main comparator of standard medical management, but with similar or greater toxicity. Based on the supporting data, the PBAC considered that the submission's description of the effectiveness of Gardasil was reasonable, but the magnitude and precision of the benefit were uncertain. *See Recommendations and Reasons.*

10. Economic Analysis

The submission did not provide a preliminary economic evaluation, as a strictly trial-based economic evaluation was not able to take into consideration the relevant costs and outcomes over the long term.

The submission presented nine modelled evaluations, one for the primary 12 year-old cohort, along with 8 additional models for the catch-up cohorts.

The main model used by the submission to estimate the cost-effectiveness of Gardasil was the 2006+ model.

The submission provided weighted incremental cost-effective ratios (ICERs) for all women from age 12 to 26 years, using a discount rate of 5% and Schedule fee costs.

The incremental cost-effectiveness ratios for the primary cohort was estimated in the submission to be $16,000 - $44,000 (overall base case), $15,000- $38,000 (overall base case) for the first catch-up cohort for a school-based program and $18,000 – $70,000 (overall base case) for the second catch-up cohort.

11. Estimated PBS Usage and Financial Implications

The estimated number of doses of Gardasil in the first four years of NIP funding is > 200,000 in all cohorts. No patient uptake would be expected in the 13-18 year old catch-up cohort by year 3, and by year 4 for the 19-26 year-old catch-up cohort.

The financial cost/year to the NIP was estimated to be up to > $100 million in Year 1 including the primary 12 year-old cohort and the two catch-up cohorts, decreasing to $30 – 60 million in Year 4 for only the 12 year-old cohort. The total cost of the vaccine program in the first four years of listing on the NIP was estimated to be > $100 million. Around 26% of this total cost relates to the primary cohort of 12 year-olds, the remaining costs relate to the two catch-up cohorts, with the 13 to 18 year-old cohort accounting for 35% and the 19 to 26 year-old cohort 38%.

12. Recommendation and Reasons

In summary, the PBAC considered the following main points in relation to the application.

- The magnitude of the per patient clinical benefit for this vaccine is small across the vaccinated population overall and in most cases, the overall benefits for cervical cancer prevention will take a long time (modelling occurs over a lifetime to 85 years of age) to be realised. The current cumulative lifetime risk of cervical cancer is 0.78%, which was predicted to reduce to 0.38% following immunisation and screening of 12 year old girls, to 0.43% for 14 year old girls and to 0.59% for 26 year old women.
- If the assumption of lifelong protection is proved not to be the case, there would need to be a mechanism, in the form of a registry, for identifying vaccinated females to deliver a booster dose to avoid a disproportionately unfavourable increase in the incremental cost-effectiveness ratios.
- The potential impact of herd immunity for HPV-16/18 types did not have a sufficient favourable impact to change the PBAC's conclusions based on the submission's incorporation of the results of the dynamic transmission model into the base case of the primary cohort.
- The utility claims were considered to be overestimated, especially for pre-cancerous health states.
- The National Cervical Screening Program (NCSP) is a highly effective program which has significantly reduced the risk of cervical cancer in Australia. There is a risk of unintended harmful consequences to patients if vaccinated females do not continue to participate in the NCSP, even though this would also tend to reduce overall costs of screening, including managing pre-cancerous health states. For instance if vaccination were to substitute for cervical screening, costs savings would

occur but the cervical cancer lifetime risk would increase from 0.78% lifetime risk (cervical screening only) to 1.173% (vaccination only).

- Implementation costs for education, communication or establishment of a register have not been factored into the incremental cost-effectiveness ratios. The PBAC noted the Australian Technical Advisory Group on Immunisation (ATAGI) advice that these would be essential components of any school-based vaccination program.
- The total cost of a HPV vaccination program is large.

Other relevant considerations included:

- HPV exposure is a strong treatment effect modifier and age is not an ideal proxy for identifying the target population. Ideally this population should be HPV naïve but ensuring vaccination in such patients only would not be practical and would not be likely to be cost-effective. The PBAC noted ATAGI advice, in not supporting NIP funding of a catch-up program for females 19 to 26 years of age, that for women who are already sexually active, the best use of population health resources at present would be to support the appropriate intervention for secondary prevention of cervical cancer ie Pap smears;
- The applicability of the trial population to the Australian community; and
- The incorporation of the genital warts model results into the base case did not have a sufficient impact to change the PBAC's conclusions based on the submission.

Thus, overall, the PBAC rejected the application for this population-based intervention (for both the primary cohort and both catch-up cohorts) based on unacceptable and uncertain cost-effectiveness at the price requested. In this context, the PBAC noted that the cost effectiveness of the vaccine should be compared to other population preventative interventions such as lipid-lowering and anti-hypertensive drugs rather than with treatment of patients with severe symptomatic disease such as late stage cancer.

Further Information

Further to the PBAC's consideration of this product at the 1-3 November 2006 meeting (at which the committee decided not to recommend that the product be subsidised), the PBAC was requested by the Minister to consider a minor resubmission on the basis of additional information provided by the sponsor.

The re-submission addressed the main matters of concern to the PBAC as follows:

- The price of the vaccine was reduced to improve the cost-effectiveness ratios.
- Further information to support the use of the QALY weights was provided and additional sensitivity analyses around them were undertaken.
- A more comprehensive risk-share arrangement around the possibility of a booster was provided.

In addition the sponsor committed to support a number of program enhancements including the establishment of an immunisation register that will enable subjects to be recalled if a booster is required in the future.

The submission also stated that as cervical cancer usually took a very long time to develop, and as lesions to more than one type of HPV can develop concurrently in the cervix, the low proportion of cancers where there are HPV types other than HPV 16/18 gave further

assurance that the expected population benefit of Gardasil would be realised. The submission acknowledged that surveillance post the introduction of a vaccination program with Gardasil was essential, as it was with any vaccination program.

No new clinical data were presented.

The PBAC recommended to the Minister that a school-based program (for 12 to 18 year-old girls) be implemented under the National Immunisation Program on the basis of a high, but acceptable cost-effectiveness ratio resulting from a price reduction. The PBAC judged that the decrease in the price improved the cost effectiveness of the vaccine in the primary cohort and the initial catch-up cohort sufficiently to make a positive recommendation. The PBAC also noted that some areas of uncertainty had been resolved. Residual areas of uncertainty which will need to be dealt with in relation to the implementation of the PBAC's recommendation related to the need to:

- educate those eligible for the vaccine to maintain their rates of participation in the National Cervical Screening Program, because vaccination is effective against only a certain percentage of cervical cancer-causing HPV strains. Prevention of cervical cancer caused by HPV strains other than 16/18 can only be detected and managed through the current Pap screening program;
- establish and maintain a register of those who are vaccinated, primarily to facilitate booster management should this be required, in the event that there is an unacceptable waning of vaccine effectiveness in the future;
- establish and maintain sentinel HPV type surveillance to detect any changes in the HPV genotypes causing cervical disease; and
- ensure successful delivery of a complete 3-dose program, preferably within each school year.

The recommended school-based program should comprise on-going primary cohorts of 12 and 13 year-old girls and a catch-up program over two years to cover 13 to 18 year-old girls when the first two primary cohorts are being vaccinated. Given that some otherwise eligible girls may have left school before commencing or completing their vaccination course, these may need to be vaccinated by GPs in a related program under the National Immunisation Program. The PBAC also advised that there would be no objection to initiating the program at a younger age for the Aboriginal and Torres Strait Islander population to ensure maximum possible coverage.

In summary, the PBAC considered that the reduced price resulting in a more favourable incremental cost-effectiveness ratio was an important factor in its decision. The new proposals in relation to a vaccination registry and the new pricing arrangements in the event that a booster is needed were also relevant and were more favourable for a recommendation for NIP funding than in the previous submission. The Committee concluded that the additional information in relation to the utility estimates supported its previous conclusion to rely on the incremental cost per extra life-year gained ratios rather than the cost-utility ratios. Also relevant to the decision to recommend the vaccine (but influential to a lesser extent), the Committee also recalled that the modelled economic evaluation relied on implicit assumptions in relation to the natural history of non-HPV 16/18 cervical disease in Gardasil vaccinated women (which remained uncertain), but that the modelled economic evaluation did not favour Gardasil in relation to a series of other assumptions which had been listed in the pre-PBAC response associated with the previous submission.

Following further negotiations, the PBAC subsequently recommended funding of the 18-26 year cohort on the NIP, as a catchup program for a period of 2 years based on a price reduction additional to that proposed for the second catch up group. As a consequence of this price reduction, the incremental cost per life year gained was now of a similar magnitude as that for the primary cohort (12 and 13 year olds). The Committee considered that the decrease in price improved the cost effectiveness ratio sufficiently to support a recommendation to include the 18-26 year old cohort in the NIP catch-up for a period of 2 years. In making this recommendation, the Committee stated the need for educational messages directed at both health professionals and consumers in regard to the need to maintain participation in the national cervical screening program given that the vaccine will not protect against disease caused by prior or existing infections (whether the vaccine types or non-vaccine HPV types) or by new infections with non-vaccine HPV types.

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 recommended Gardasil for inclusion in the National Immunisation Program following a second submission. However, CSL does not agree with the PBAC decision to reject the initial application for funding based on unacceptable and uncertain cost-effectiveness at the price requested, particularly related to the non-acceptance of quality of life offsets for cervical cancer and precancer, and the non-acceptance of herd immunity benefits. CSL also has concerns that the PBAC position to not consider a lower discount rate and to require a lower cost-effectiveness threshold for preventative vaccination programs, has the potential to disadvantage such programs compared to pharmaceuticals. CSL will continue to work with the PBAC and Government on these issues.