MEDICINES ASSESSMENT ADVISORY COMMITTEE (MAAC) REPORT ON THE EVALUATION OF THE PRECLINICAL AND CLINICAL DATA OF A NEW MEDICINE APPLICATION

Assessor: [redacted]

Compound: Gardsasil

Product: Quadrivalent Humanpapillomavirus (HPV) [Types 6, 11, 16, 18] Recombinant Vaccine

Dose Form: Injection

Strength: 20/40/40/20 µg L1 capsid viral like particles, in 0.5 ml

Proposed Indication:
Prevention of:

- Cervical cancer, cervical intraepithelial neoplasia (CIN) grade 2 and 3, vaginal cancer, and vulvar cancer caused by the HPV types 16 and 18
- HPV infection, CIN grade 1, external genital warts, perianal warts, vulvar intraepithelial neoplasia (VIN) grade 1, 2 and 3 and vaginal intraepithelial neoplasia (VaIN) grade 1, 2 and 3 caused by HPV types 6, 11, 16 and 18.

Proposed Dosage: One injection, 0.5 ml, followed by second dose at 2 months, third at 6 months (3 doses in 6 months).

MOH File Number: TT50- 7571

BACKGROUND:

Merck have applied under section 21 to register Gardasil to prevent cervical and related cancers due to four HPV types. They estimate there are 200 cases of cervical cancer in New Zealand annually. Current strategy is Papanicolaou's (Pap) test, and/or testing for HPV, with early intervention. CIN grade 1 occurs with infection with HPV. CIN grade 2 and 3 are the immediate precursors of cervical cancer, and are excised if detected, so are used as endpoints in the clinical trial program, since it is unethical to wait for invasive cancer development. Most cancer is squamous, but adenocarcinoma of the cervix also occurs, with adenocarcinoma in situ (AIS) its precursor lesion. CIN3 and AIS are defined as cervical cancer, FIGO Stage 0. VIN 2 and 3 and VaIN 2 and 3 are the immediate precursors of the less common vulval and vaginal cancers respectively. HPV is associated with 99.7% cervical, 64-100% vulval, 21-67% vaginal and 24-100% perianal cancers. Types 16 and 18 are most common, and most likely to cause CIN 2/3, while HPV 6 and 11 cause dysplasia but rarely cancer, but account for >90% genital warts and recurrent respiratory papillomatosis. HPV types 6,11,16,18 are associated with 33% of histologically confirmed CIN1, 51% CIN2, 73% CIN3.

Most HPV infection is acquired in the first 10 years after sexual debut, and takes up to 5 years to progress to CIN, and then up to 20 or more years to become invasive cancer. About half of all adults become infected with HPV in their lifetime. Vaccination needs to precede infection. Median age of sexual debut is 16 years in most countries, with 50% females acquiring at least one HPV subtype within 5 years. Trials therefore need to demonstrate development of immunity in 10-16 year-olds. Public health prevention is recommended to include young males and females.

The same submission has been made in the EU, US and Australia.

The NZ 2006 Immunisation Handbook states that HPV type 16 is associated with 60% cervical cancers, and type 18 with 10% with other types accounting for the rest. An Auckland colposcopy clinic recorded type 16 as 39% of the HPV types, with type 18 10%, type 31 10%, and all the rest less common. The NZ 2001 Youth Health Survey found that 17% of students aged 13 years reported sexual debut. There is one other vaccine under trial, bivalent HPV-16, 18, Cervarix, GlaxoSmithKline, which shows 100% seroconversion to type 16 and 99.7% to type 18.

PART III – PHARMACOTOXICOLOGICAL (PRECLINICAL) DATA

A. Animal pharmacology

1. Pharmacodynamics

Five non-GLP studies were carried out in primates, to demonstrate development of an immune response.

Six rhesus macaques received HPV 16 monovalent L1 VLP vaccine (MV-VLP), 3 with MAA and 3 not, as 3 doses at 0, 2 and 6 months. All showed rise in specific neutralizing antibodies, 16 fold greater at 2 weeks after dose 3 if with MAA.

Six chimps received type 16 MV-VLP, 4 with MAA, with 5 developing antibodies, 3-fold greater with MAA.

Four African green monkeys received type 18 MV-VLP, and showed immune response. Thirty-four African green monkeys received type 6, types 11, type 16 or type 18 MV-VLP with MAA, or Quadrivalent L1 VLP (QV-VLP) vaccine with MAA, given at 0, 2 and 6 months. Specific immune titres developed in all, slightly higher for monovalent, declining after dose 3 but still detectable after one year. Sera from vaccinated monkeys inhibited VLP entry into C33A cells, an HPV negative cervical cancer cell line.

Ten rhesus macaques received QV-VLP, 5 with MAA, and all developed antibodies, 1-2 log higher with MAA. Response was predominantly T helper type 2, with high IgG1 and IgG4, and low IgG2. High IgA was also seen, which may help mucosal immunity.

There is only one animal model to demonstrate protective efficiency, an HPV type 11 xenograft neutralization model, in which sera from humans immunized with HPV type 11 were used to neutralize infection of epithelial tissue with HPV type 11 virions.

2. Animal pharmacokinetics

The vaccine is made in yeast using expression vectors which are recombinant major capsid (L1) protein of the 4 HPV types, each type made separately, then combined. The Virus Like Particles (VLPs) are adsorbed onto Merck Aluminum adjuvant (MAA) to form monovalent bulk adsorbed product (MBAP). Types 6, 11, 16 need disassembly and reassembly for stability, while type 18 VLPs are inherently stable. These are then combined in the proportions 1:2:2:1 by weight to form quadrivalent product (QBAP). MBAP and QBAP are stable for at least 36 months at 2-8^{0}C, but sensitive to UV light so needs protection. Gardasil marketed formulation contains 20 µg HPV type 6 LI VLP, 40 µg type 11, 40 µg type 16, and 20 µg type 18, together with 225 µg aluminum MAA. The 4 types have been extensively tested by monoclonal antibodies to different parts of the L1 protein, and confirmed.

Studies of ADME have not been done for the VLPs because it is not needed for vaccines, while MAA already has been widely used and is safe.

B. Toxicology

Five GLP studies are presented.

Single doses of Gardasil were studied IM in mice and rats, using doses 1200 and 300 fold excess over the equivalent for a 75 kg human. There were no adverse effects.

Three repeat doses were given IM to mice, doses 1450-fold human doses, with no toxicity but demonstration of lymph node hyperplasia.

Carcinogenicity is not required for vaccines. (CPMP, WHO).

Reproductive and developmental toxicity was rats and showed no effects other than antibody production, with dose 300-fold human.

Local tolerance in rabbits showed slight reaction, similar to MAA alone.

Two non-GLP studies showed that immune response occurred in the rats to be used for reproductive toxicity.

C. Summary of the pharmacotoxicological data

Generally less presented than for a chemical entity, but fulfills requirements for a vaccine. No concerns. The TGA report (seen after I prepared my report) states that there

are "no non-clinical objections to the registration of Gardasil for the proposed indication".

PART IV – CLINICAL DATA

A. Clinical Pharmacology

1. Pharmacodynamics

Dose finding was carried out in 3 studies of monovalent vaccination. Study 001 (140 people) used doses of 10-100μg HPV type 11, study 002 (109 people) doses of 10-80 μg HPV type 16, and study 004 (480 people) doses of 10-80 μg HPV type 16 with each determining the specific antibody response by competitive RIA. Essentially these studies showed that levels attained were not improved by doses higher than in Gardasil (20/40/40/20 μg for HPV types 6/11/16/18).

Study 007 entered 1158 into 4 arms, with Quadrivalent vaccine, at doses of 20/40/40/20, 40/40/40/40, 80/80/40/80, or placebo, with follow-up 3 years, and primary endpoints subclinical infections with the 4 types, CINs, AIS and cancers.

One interaction study was done with hepatitis B immunization since the 2 vaccines are most conveniently given together. There was no detectable interaction.

Efficacy and safety has not been studied in children less than 9 years of age, nor in pregnancy or immune-suppression.

2. Pharmacokinetics

See under clinical pharmacodynamics

B. Clinical experience

1. Clinical studies

These were divided into efficacy studies and immunogenicity studies. The FDA and CPMP pre-agreed criteria for efficacy. They agreed to vaccine-specific prevention of CIN 2/3 in baseline negative women, and similarly for VaIN 2/3 and VIN 2/3. More than 3,000 9-17 years-olds were specified for safety; and immunogenicity in 9-15 year-olds, including males, had to be not inferior to the 16-26 year-olds.

Efficacy (prophylaxis):

There are 4 efficacy studies, 005, 007, 013 and 015. Since early lesions cannot be left to evolve to cancer, endpoints are the immediate precursors of cancer, especially CIN 2/3 and AIS, as well as cancers. HPV 16/18 related CIN1 has a low risk of evolving to cancer, while HPV 16/18 related CIN 2/3 or AIS has a high risk of evolving to cancer.

An algorithm was used for results of Pap smears. CIN 2/3, AIS or repeat CIN1 results were referred for colposcopy. High grade squamous epithelial lesions (HSIL) and unsatisfactory colposcopies were managed by excision. If Pap showed atypical cells of uncertain significance, HPV was determined and if detected, colposcopy was preformed. All 4 studies were GCP, entered women aged 16-26 years, mostly HPV negative, but regardless of baseline HPV status and Pap smear, and excluded those with greater than 4 or 5 sexual partners. Studies 007, 013, and 015 included formal examination of the entire vagina and perineum, so assessed extragenital lesions. A Central Lab was used for Pap smears, a Central Pathology Panel of Gynaecological Pathologists for histology, while HPV testing was by PCR, blinded by Merck. Pregnant women were excluded.

Pap smears at day 1 were negative for SIL in 88%. The 12% with SIL were made up of ASC-US in 5.0%, ASC-H (cannot exclude HSIL) in 0.3%, LSIL (low grade squamous epithelial lesion) in 5.9%, HSIL (high grade SIL) in 0.6%, atypical glandular cells, 0.0% (n=10), adenocarcinoma in situ (AIS) 0% (n=1). They were all included as they reflect the population in which vaccination will be used. For HPV types, 80.3% were negative to all 4 by serology, 85.2% by PCR and 72.0% both. Positivity to one or more HPV type occurred in 19.7% by serology, 14.8% PCR and 27.0% both.

Study 005 used monovalent HPV type 16 vaccine, in 2,409 females aged 16-23 years. The primary endpoint was HPV infection with type 16. Follow-up is now 4 years.

Study 007 is mentioned above, and didn't use Gardasil. 1158 women aged 16-23 years were randomized to 3 doses of quadrivalent vaccine or placebo.

Study 013 was called FUTURE I, and randomized 5,455 females aged 16-23 years to Gardasil as 3 doses, 0, 2, and 6 months, or placebo. Primary endpoints were CINs (including CIN1), AIS, cancer. Pap smears are done every 6 months. Follow-up is now between 2 and 3 years, and is ongoing.

Study 015, called FUTURE II randomized 12,167 females aged 16-26 years to Gardasil or placebo, with Pap smears every 12 months. Follow-up for efficacy is ongoing, and especially for 10 extra years in Scandinavia to decide when booster immunization might be needed. Primary endpoints are CIN2/3, AIS, cancer.

The results of these 4 studies are integrated, although the smallest (007) did not use Gardasil itself. A total of 20,887 females were randomized, from 22 countries, including 748 from the Asia-Pacific region, with 20,845 receiving at least one dose of vaccine or placebo. At database lock, 92.7% were still evaluable. As noted, at day 1, 12% had CIN1 and 27% were either seropositive (past infection) or PCR-positive (current infection) to one of the 4 vaccine serotypes. Median follow-up is 2 years overall, 4, 3, 2.4 and 2 years for studies 005, 007, 013 and 015. Several study populations were identified with respect to prior exposure to any of the four HPV subtypes, determined from baseline serology and Pap smears, with colposcopy when indicated. In the 4 trials, 26.7% were smokers, 8.4% ex-smokers, 15.2% had one pregnancy, 4.6% two, and 0.4% three. Hormonal contraception was used by 57.8% and barrier by 29.2%.

Per-protocol efficacy (PPE) assessed women 30 days after last of the 3 vaccinations, given over 6 months. They had to be seronegative on day 1 to the HPV type, PCR-negative at 7 months, and get all 3 doses. Efficacy for HPV 16 or 18 related CIN2/3 or worse (i.e. cancer) was 100% in each study and overall (CI 92.9-100%). There were no cases in those vaccinated (8,487) but 53 cases in placebo (8,460). For HPVs 6,11,16 and 18- related CIN efficacy was 95.2% (CI 87.2-98.7%) with 4 cases (7,858 vaccinated) Gardasil compared with 83 (7,861) placebo, for the 3 studies combined. (This excluded study 005 which only had HPV type 16). For HPV 6,11,16, and 18 related genital warts, VIN, VaIN, vulvar and vaginal cancers, efficacy was 99.1% (CI 95.0-100%), combined, excluding 005, with 1 case (from 7,897 vaccinated) Gardasil compared with 113 (from 7,899) placebo.

The MITT2 analysis included women seronegative and PCR- negative at day1, but assessed from 30 days after the first dose. The MITT2 data were very similar to the PPE population so it is inferred that protective efficacy of vaccination begins during the vaccination period of 6 months. HPV 16 or 18 related CIN 2/3 or worse was 1 of 9,342 Gardasil, compared with 81 of 9,400 placebo, efficacy 98.8% (92.9-100%).

For cancer related endpoints, Gardasil was associated with no HPV 16 or 18 CIN3/AIS compared with 32 placebo, PPE, or 52 placebo, MITT2. Similar data were seen for HPV 16 or 18 related VIN2/3 or VaIN 2/3, with no cases in vaccinees but 10 in placebo, PPE and 24 on MITT2 analysis.

The MITT3 analysis assessed vaccination in the presence of infection of one or more of the subtypes in the vaccine. Efficacy was much lower. For HPV 16 or 18 related CIN 2/3 or worse, efficacy was 39% overall (CI 23.3-51.7%); for CIN related to the 4 subtypes, 46.4% (CI 35.2-55.7%); for genital warts, VIN, VaIN, vulvar and vaginal cancer related to the 4 subtypes 70.4% (CI 61-77.7%). If analysed by HPV 6,11,16,18 related CIN 1 or worse, and for extragenital lesions, against time, the combined placebo arm showed steady increase, while the vaccinated arms increased at a slower rate, both significant at p=0.001. Thus vaccination slowed development of HPV- related changes, and reduced the risk of CIN changes after infection.

In placebo patients the risk of CIN was 0.8/100 subject-years-at-risk if naïve at day 1, 6.4 if PCR+ day1, 9.2 if PCR+ and sero+ at day1, and 0.2 if sero+ alone at day1. Over the median 2 year follow-up, the pooled placebo arms showed 31.8% with Pap smears suggesting CIN, 21.3% having colposcopy for CIN, 8.9% diagnosed with CIN, 4.4% treated for CIN, and 3.4% were diagnosed with HPV extragenital lesions, "much" by HPV types 6,11,16 and 18. The association with HPV 16 or 18 was 11.2% for no SIL, 21.9% for CIN 1, 46.5% for CIN 2 and 64.6% for CIN 3. The association with HPV 6 or 11 was 1.5% for no SIL, 7.0% fro CIN 1, 3.1% for CIN 2, and 1.3% for CIN 3.

Vaccination after cleared infection of a subtype with the same subtype prevented new infections of that subtype. The risk of HPV 6, 11, 16 and 18 related CIN increased with follow-up, but more rapidly for placebo than vaccinated, with similar protection for

extragenital lesions. For the MITT3 analysis the reduction in CIN2/3 or AIS was 12.2%, reduction in CIN or AIS 13.7%, VIN2/3 or VaIN 2/3 48.7%, and for warts/VIN/VaIN 39.8%. If analysis is further restricted to MITT2 where all have to be sero-negative and PCR-negative to all 4 subtypes at day 1, and Pap smear clear, reduction in CIN2/3 or AIS is 37.9%, CIN or AIS 21.9%, VIN 2/3 or VaIN 2/3 81.3%, and extragenital lesions 65.7%. The data for the subgroups are interpreted as therapeutic efficacy only for very early HPV infection with the HPV type.

Vaccination may uncover undetected disease caused by less aggressive subtypes which would have been removed during therapy of the aggressive subtypes 16 and 18. There is no impact evident but longer follow-up will be required.

The only factor to predict efficacy was infection with a vaccine HPV subtype at onset of vaccination, and this only affected protection from that subtype. Duration of efficacy is uncertain, with median follow-up in the combined 4 trials 2 years from end of dosing. Efficacy was not affected by variations in dosing schedule, peak level of anti-HPV antibodies, subsequent pregnancy, breast feeding, contraceptives, new partners or non-HPV STD's. Efficacy has not yet been demonstrated in males, but is expected from the immunogenicity data.

Immunogenicity:
Five phase I/IIa studies in 3160 subjects aged 16-26 years treated with monovalent vaccine or placebo, showed high immunogenicity with responses for > 3.5 years. Anti-HPV was determined by Luminex-based immunoassay.

Studies 007, 011, 012, 013, 015, 016 and 018 analysed immunogenicity.

Study 007 was dose-finding and study 011 assessed any interference from concomitant Hepatitis B vaccination (See above)

Study 012 randomized 3882 subjects to Gardasil, monovalent HPV 16 vaccine, or placebo, to bridge monovalent and quadrivalent vaccine.

Study 013 and 015 included immunogenicity and continue follow-up.

Study 018 treated 939 females aged 9-15 years, and 842 males 9-16 years, and is ongoing.

There were a total of 12,344 subjects in phase III trials of immunogenicity with Gardasil or placebo, aged 9-26 years and males 9-15 years. Of the 18-26 year-old women, 27% were either sero- or PCR-positive for one of the 4 HPV types. At 1 month after the third dose 99.5% had developed anti-HPV antibodies to subtypes to which they were not previously exposed. The titres fell by about 0.75-1.0 log-fold by 2 years, but then stabilize. Longest follow-up is 3.5 years to date. (For Hepatitis B, immunity persists even if antibody has become not detectable.) If subjects were sero-positive to an HPV type before dosing, the antibody titres were higher to that type than if naïve, and response to

other HPV types were not diminished. This suggests an anmnestic response associated with memory B cells. Variations in timing of vaccination within the 6 months did not affect titres.

Study 016 included 10-15 year-old males and females, and showed that levels of anti-HPV antibodies in previously unexposed subjects were at least as high in the young girls, and the young boys, as older girls, justifying bridging efficacy from the 16-26 year-old females to younger females and males. There was trend to lower antibody titres post-vaccination with increasing age at vaccination. The post dose 2 levels of anti-HPV in all active groups of study 016 were higher than in the persistence phase of the combined efficacy trials, supporting onset of protection during the 6 month vaccination period.

Safety:

The safety population of recipients of vaccine includes 16,014 subjects, 2,146 from monovalent trials, 11,792 from Gardasil trials, 2,026 from quadrivalent vaccine trials at higher (552) and lower (1,524) doses. The 7 trials of quadrivalent vaccines entered and randomized 21,514 subjects, of whom 21,480 got dose 1, 20,813 got dose 3, with 11,792 receiving at least one dose of Gardasil, and detailed safety data is available for 10,224 of them. The number of recipients below the age of 16 years is relatively low, approximately 400 for each age between 12 and 14 years. There were some imbalances, especially for smoking, with 21.5% Gardasil smokers, 25.4% placebo, but 18.7% Gardasil unknown vs. 6.2% placebo unknown smoking history. In all but one study a vaccination report card was used, with temperature measured for the first 5 days, and recordings for 14 days.

In the entire study, there was an 80% chance of 1 SAE when the true incidence was 0.01%, and in the detailed safety population, an 80% chance of 1 SAE when the true incidence was 0.03%. Two died within 15 days of vaccination, one Gardasil, one placebo. There were a total of 14 deaths, 0.07% and 0.06% from Gardasil and placebo. Causes were pancreas cancer, injury, traffic accident (2), overdose, DVT/PE (2) and arrhythmia for Gardasil, compared with ARDS, traffic accident (2), DVT/PE, suicide and asphyxia for placebo. Vaccination was stopped in 17 cases for ADRs, 11 Gardasil and 6 placebo. Injection site events were most common, affecting 82.9% Gardasil and 77.4% placebo. Systemic events occurred in 59.2% Gardasil and 60.4% placebo, fever (>37°C) in 11.4% Gardasil and 9.6% placebo. Thus there were no significant safety issues from the vaccine itself to date.

Pregnancy occurred after vaccination in 1901 subjects, with 2074 pregnancies, 78.1% with a known outcome. There was no evidence of a significant effect from the vaccination, and no impact on lactation.

2. Post-marketing experience

Post marketing surveillance of approximately 35,000 vaccinees is planned, together with recording exposure during pregnancy in the Nordic cancer Registry study, which is the ongoing part of study 015.

C. Summary of clinical data

There is evidence that Gardasil induces an antibody response in women aged 16-26 years, which is associated with almost complete protection from new lesions in the cervix, vagina or vulva, attributed to infection with 4 types in the vaccine. (But how many HPV infections proceed to cancer?) This includes protection from the immediate cancer precursors. "Almost complete" reflects the median follow-up of 2 years. Boys and girls aged 9-16 years have clinically similar antibody responses to vaccination, and are expected to have similar efficacy. There are no completed efficacy studies in males. There are no concerning adverse effects of the vaccine itself. The duration of protection from the three dose vaccination is uncertain, and will hopefully be determined during ongoing follow-up. Vaccination must occur before exposure to the HPV types. Brief review of the literature reveals uncertainty over how vaccination will be provided on a population basis. Parental concerns exist, especially with respect to possible sexual behaviour if "protected".

Other HPV types will not be protected, and cervical cancer may simply be delayed until after infection with other types. However this concern can only be resolved on follow-up over decades. It would have been helpful to have an analysis relevant to NZ and epidemiology of HPV types in CIN, VIN and VaIN. Warts although not life-threatening, are significantly symptomatic, and it is reasonable to include the HPV types associated with them.

The TGA report is now to hand. Essentially similar issues were raised, but they have suggested solutions.
1). They state that HPV infection is not a surrogate for non-invasive or invasive cervical cancer and most HPV infections resolve.
2). The efficacy in children 9-16 years in preventing HPV infection is untested, and should be part of further trials or post-marketing surveillance.
3). The exclusion criteria of the FUTURE trials are not proposed in the data-sheet, and more exposed women may have less efficacy; therefore there is a need for ongoing Pap smears in vaccinated women and long-term post-marketing efficacy.
4). The vaccine is highly effective against HPV 16/18 related CIN 2/3 and AIS if no prior exposure to the vaccine types, supporting this indication.
5). There is no therapeutic effect to a current infection, and some protection from acquisition of the other types in the vaccine, but efficacy beyond 24 months is uncertain.
6). The children aged 9-16 years were not screened for HPV infection at entry, so vaccine efficacy is unknown; the datasheet should state "ability to prevent HPV infection and cervical disease in pre-adolescent children has not been evaluated".
7). There was high efficacy in prevention of HPV 6,11,16 and 18 related VIN 2/3, VaIN 2/3 and extragenital disease. Warts, VIN 1 and VaIN 1 cannot be used as surrogate markers for invasive cancer.
8). The minimum protective antibody levels associated with protection from HPV infection and disease is unknown. Thus efficacy cannot be predicted from antibody

levels, e.g. the pre-adolescent group, and would they still be protected at commencement of sexual activity?
9). Safety data are limited in ages less than 15 years, especially males, and this should be further evaluated.

DATA SHEET

Generally informative. Table 1 needs to clearly define what the PPE population, and spell it out clearly in the heading, and also state the duration of follow-up. On page 6, considering persistence of immunity, Figure 1 shows levels and the time goes out to 48 months, but there is no statement that duration is not yet established.

The TGA recommends confirmation of the recommended dose with a 20% lower dose also mentioned. The efficacy studies used the full dose.

There were 3 (not 4) placebo-controlled clinical trials, since the fourth evaluated only HPV 16 vaccination.

Remove cervical, vulvar and vaginal cancer from the list of indications, but add statement that CIN 2/3, AIS, VIN 2/3 and VaIN may in some individuals progress to invasive cancer, since only long term studies will determine whether vaccination prevents cancer.

Cancer may occur even in vaccinated women especially when the duration of protection is unknown.

State that efficacy in preventing HPV infection, CIN, VIN, VaIN and genital warts has not been established in children.

Add precaution that cervical screening (Pap smears) should continue in vaccinated women.

Where it states that "this vaccine is not intended to be used for the treatment of active genital warts, cervical, vulvar or vaginal cancers, CIN, VIN, or VaIN" add "related to HPV vaccine or non-vaccine serotypes".

MEDICINE CLASSIFICATION

Administration on recommendation by appropriate public health authorities, doctors and specialists, or as usual for vaccines

OVERALL SUMMARY/DISCUSSION

Gardasil clearly induces high levels of antibodies to the L1 capsid protein of HPV types included in it, i.e. 6, 11, 16 and 18. In women aged 16-26 years, this was associated with very high level protection from cancer precursor lesions in the cervix, vagina, vulva and anal area, in women who had no prior exposure to HPV. In those previously exposed to at

least one type, there was protection from infection with the other types in the vaccine. The studies did not exclude women with prior exposure (except those with expected very high exposure through multiple partners) since this was the real situation and is therefore more relevant. Population efficacy depends on vaccination before sexual debut, and there is adequate evidence of seroconversion in males and females aged 9-16 years, with the applicants creating the bridge that protection will also occur in these younger people. This however remains to be demonstrated. It is not feasible to answer whether the incidence of cervical and the other cancers will be decreased by vaccination until after many years of use. There were no concerning safety issues for the vaccine itself, but public application may bring up psychosocial and other issues.

This reviewer would value comment from the vaccine subcommittee, and a specialist in treating CIN/AIS, but would support approval.

OUTSTANDING ISSUES

Does Gardasil reduce cancer, despite predictions from current understanding of HPV infections?

Consideration of the proportion of HPV-infected people who actually develop CIN 2/3 or AIS, and hence the extent of the benefit from vaccination on an individual basis. What is the risk per person of CIN 2/3, which can then progress to cancer? Is there data about this from any country or study?

Concern about reassurance from vaccination and decreased compliance with cervical screening (still necessary since 30% cervical cancers due to other causes or HPV types)

Efficacy in young people aged 9-16 years

Defining age group and gender for vaccination, which may fall outside scope of registration. Currently data sheet states women 18-26 years and children and adolescents 9-17 years.

Duration of efficacy

Defining guidelines for vaccination in New Zealand, which again probably falls outside scope of registration.