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

ASSESSOR: [redacted]

COMPOUND: recombinant HPV vaccine [types 6, 11, 16, 18]

PRODUCT: Gardasil

DOSE FORM: 0.5mL vial, prefilled single use synringe

MOH FILE NUMBER: TT50-7571

STRENGTH: 20-40-40-20mcg of the L1 protein of HPV types 6-11-16-18

PROPOSED INDICATION(S): The prevention of

- cervical cancer, cervical intraepithelial neoplasia (CIN) grade 2 and 3, vaginal cancer, and vulvar cancer caused by HPV types 16 and 18
- HPV infection, CIN grade1, 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 or 18

PROPOSED DOSAGE: For children and adolescents 9 to 17 years of age, and women 18 to 26 years of age: intramuscular initial vaccination, with second dose at 2 months and third dose at 6 months.

BACKGROUND

HPV has been associated with about 99.7% of cervical cancers, 64-100% of vulvar cancers, and 33-73% of cervical abnormalities (CIN 1, 2 and 3). Cervical screening has contributed to reducing the number of cervical cancer cases. Procedures required to remove pre-cancerous cervical lesions may be debilitating, and may impact on fertility. A vaccination approach to prevention of cervical cancer and other disorders caused by HPV has not previously been available.

The HPV family consists of over 90 subtypes, of which only a subset are oncogenic. Of the oncogenic types, HPV 16 and 18 between them cause about 70% of cases of cervical cancer, which is the second most common cancer in women worldwide. The dysplastic subtypes HPV 6 and 11 cause over 90% of genital warts. The lifetime risk of genital warts is over 10% for males and females. By 5 years after sexual debut about 50% of women will have been infected by at least one HPV type that preferentially infect the genitals, probably with a similar pattern in men. Most HPV infections resolve without intervention.

To date there are no Gardasil marketing authorisations. Submitted documentation includes a TGA clinical evaluation report. The FDA Advisory Panel unanimously recommended approval on May 18th 2006, according to media coverage, and a decision from the FDA is

expected June 8th. A statistical review and evaluation of the clinical trial data by the FDA is available on http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222B2.pdf

PART III - PHARMACOTOXICOLOGICAL (PRECLINICAL) DATA

Gardasil is a recombinant yeast-expressed quadrivalent vaccine comprising the LI proteins of HPV types 6, 11, 16, and 18, these proteins being assembled as virus-like particles (VLP). There is no viral DNA present, so that the vaccine is incapable of causing infection. The vaccine adjuvant is aluminium hydroxyphosphate sulfate, which is present in several marketed vaccines.

A. Animal pharmacology

1. Pharmacodynamics

Five non-GLP primary pharmacodynamic studies were performed in 3 species of non-human primates to determine whether a HPV VLP specific immune response was elicited, whether it was changed when the VLP types were mixed together, and whether the adjuvant was needed for optimal immunogenicity. The immune response was assayed using monoclonals recognising each VLP type and binding to epitopes that have been shown to neutralise infection. Both IgG and IgA were induced. Protective efficacy could not be demonstrated as there are no HPV type 6, 16 and 18 animal models. In a HPV type 11 xenograft model, specific human sera titres correlated with the potential to neutralise HPV11 infection. IgG titres after dose 3 were substantially greater with the adjuvant present.

2. Animal pharmacokinetics

In line with EMEA guidelines, no ADME studies were performed for any of the VLPs. The adjuvant has an established safety profile.

B. Toxicology

Single dose i.m. toxicity studies were performed in rats and mice, a repeat dose i.m. toxicity study in mice, development and reproductive study in rats, and a local tolerance study in rabbits. These studies fulfil the requirements of the applicable EMEA guidelines for pharmacological and toxicological testing of vaccines. Administered doses were 0.1mL for mice and 0.2mL for rats of LI VLPs at concentrations of 160/160/80/160mcg/mL of HPV types 6/11/16/18, representing for mice approximately 1450-fold excess by body weight compared with human doses. There was no evidence of adjuvant-induced systemic toxicity. Treatment-related inflammation at the muscle injection sites was seen at necropsy, and treatment-related hyperplasia was present in inguinal and iliac lymph nodes. Genotoxicity and carcinogenicity were not evaluated. The rat strain used for reproductive and developmental toxicity mounts an immune response to the vaccine. A full human dose of Gardasil 0.5mL of 40/80/80/40mcg/mL VLPs was employed, one group of female rats receiving 4 immunisations prior to fertilisation, and the other group receiving 2 vaccinations on gestation day 6 and lactation day 7, with appropriate control groups. There were no treatment-related effects on the rats or their offspring. There was passive transfer of antibodies to the offspring. Local tolerance for a number of different VLP formulations in rabbit was similar to that of the adjuvant-alone control group.

C. Summary of the pharmacotoxicological data

A robust immune response against the VLP types present in the vaccine administered was demonstrated in non-human primates. The adjuvant increased the level of immune

response. The only treatment-related toxicological findings were indicative of the expected immune response.

PART IV - CLINICAL DATA

Since there is a lead time of some 20 years from acquisition of infection to the development of invasive cervical cancer, the development of this prophylactic vaccine has focused on earlier lesions. CIN 2 and 3 and AIS (adenocarcinoma in situ) are the immediate and obligate precursors of invasive cervical cancer, and were used as the best available surrogate markers for the cervical cancer prophylaxis clinical efficacy studies. Studies with primary endpoints including CIN1 were used to assess the impact of the vaccine on cervical HPV disease, as CIN1 is also caused by low-risk HPV subtypes such as HPV 6 and 11.

A. Clinical Pharmacology

No clinical pharmacology studies were performed. The bioavailability of the vaccine is confirmed by the development of serum anti-HPV responses to the component L1 VLP types.

B. Clinical experience

1. Clinical studies

Efficacy was assessed in four randomised double blind placebo-controlled phase 2 and 3 studies. Protocol 005 (n=2391) was a phase 2 study employing the HPV16 component, and protocol 007 (n=551) the 20/40/40/20 quadrivalent vaccine. The placebo was adjuvant without VLPs. Two additional formulations with different proportions of VLPs were also evaluated in protocol 007. The two placebo-controlled phase 3 studies evaluating the quadrivalent vaccine were protocol 013 FUTURE1 (n=5,746) and protocol 015 FUTURE2 (n=12,157) which used the final manufacturing process Gardasil formulation. These four named studies randomised 20,887 women aged 16-26 years, and overall 19,321 (92.7% of subjects who received at least one dose of the study vaccine) continued in the study from enrollment until the time of database close. About 12% of the study population had a Pap result compatible with the presence of CIN at day 1, and 27% of the combined study population was either seropositive (suggesting prior infection) or PCR positive (suggesting ongoing infection) to a vaccine HPV type.

The main efficacy analyses were performed in subjects who were naïve to the vaccine HPV types at baseline, as Gardasil is intended as a prophylactic vaccine. The primary analysis was the per-protocol efficacy (PPE) population, who received all 3 doses of vaccine at Day 1 month 2 and month 6, were negative to the vaccine HPV types up to month 7, and with efficacy evaluation starting after 7 months. A secondary analysis was the modified intent to treat (MITT-2), which included those seronegative and PCR negative to vaccine HPV types at Day 1 and for whom efficacy evaluation started at day 30. A restricted MITT-2 also had Day 1 Pap negative for SIL. MITT-3 included all subjects who received at least one dose of vaccine without regard to whether or not they were infected with one or more vaccine HPV types at baseline, and started counting cases for the efficacy analyses at day 30.

The principal clinical endpoint used in protocol 015 was the combined incidence of HPV 16/18-related CIN 2/3 and AIS (and invasive cervical cancer, if any detected). In protocol 005 a similar endpoint limited to HPV 16 was used. Such lesions would normally be treated by excision. The interval between HPV infection and the development of CIN2/3

and AIS is 6 months to 5 years. The main endpoint used in protocols 007 and 013 was the combined incidence of HPV 6,11,16,18 related CIN, AIS or cervical cancer to reflect the overall burden of disease caused by vaccine HPV types. All subjects underwent Pap testing and cervicovaginal sampling for HPV detection at routine visits (every 6 months in protocols 005, 007 and 013, and yearly in protocol 015), using ThinPrep cytology. Referral for colposcopy in protocols 007 and 013 was based on Pap test diagnosis of ASCUS with positive Digene Hybrid Capture HPV low-risk probe or worse. In protocol 015 6-month retesting was performed with ASCUS and LSIL, with colposcopy for higher grades, with a similar approach in protocol 005 but with colposcopy with LSIL or with ASCUS and a positive high risk Hybrid Capture HPV probe. HPV type was determined by PCR in tissue sample from biopsy or cervicovaginal swab. A substantial quality control system was put in place.

Of the 20,541 subjects randomised in protocols 005, 007, 013 and 015 (vaccine 10,268, placebo 10,273), for the HPV-16 PPE analysis 7,393 active vaccine subjects had post-7 month follow up and 7,200 placebo. For HPV-18 the corresponding numbers were 7,376 and 7,312. The majority of subjects were aged 16 to 23 years at enrolment (very few were older), and 94.1% were not virgins. Some 22% had been pregnant. 88% were negative for SIL on baseline Pap test, and 73% were negative for HPV 6,11,16,18 by both serology and PCR .

In protocol 013 Pap testing and cervicovaginal sampling were performed on Day 1 and months 7, 12, 18, 24, 30, 36 and 48. In the PPE analysis there were no cases of HPV 6,11,16 or 18 related CIN in the Gardasil group (n=2240) compared with 37 cases in the placebo group (n=2258), and no cases of EGL versus 40 in the placebo group. Vaccine efficacy was defined as 100(1-r), where r is the risk of becoming a case in the Gardasil group divided by the risk of becoming a case in the placebo group. For the primary analysis vaccine efficacy against HPV 6, 11, 16, 18-related CIN or worse was 100%, with 97.5%CI (87.4, 100), supporting the conclusion that Gardasil is effective in preventing these lesions. In secondary analysis limited to CIN2 lesions or worse, there were no cases in the Gardasil group and 19 in the placebo, giving 100% efficacy with 95%CI (78.5, 100). For EGL the PPE analysis also gave efficacy 100% with 97.5%CI (88.4, 100). Secondary analysis using cases of EGL due to any HPV type gave 25 cases in the Gardasil and 66 in the placebo group, an efficacy of 62.3% with 95%CI (39.4, 77.2).

Protocol 015 assessed efficacy at Day 1, months 7, 12, 24, 36, 48 with Pap tests and follow up according to triage as described above. In the primary PPE efficacy analysis there were no cases of HPV16/18-related CIN 2/3 or worse in the Gardasil group (n=5301) and 21 cases in the placebo group (n=5258). Vaccine efficacy for this endpoint was 100% with 97.96%CI (75.6, 100) used to control for multiple analyses and interim analysis. Results of exploratory analyses of HPV 1/11/16/18-related CIN and EGLs were consistent with the primary efficacy results.

In Protocol 007 PPE analysis there were 4 cases of HPV 6/11/16/18-related disease in the 20/40/40/20 vaccine treatment group (n=235) and 36 in the placebo (n=233), giving vaccine efficacy of 89.5% with 95%CI (70.7, 97.3). Of the 4 vaccine group cases, 3 had relevant HPV type DNA detected before the subjects were lost to follow up. In PPE analysis of protocol 005 there were no cases of persistent HPV16 infection in the vaccine

group (n=753) and 41 in the placebo group, giving vaccine efficacy 100% with 95%CI (90.9, 100).

Combining all the protocols, in PPE analysis the vaccine efficacy against HPV-16/18-related CIN 2/3 or worse was 100% with 95%CI (92.9,100), against HPV 6/11/16/18-related CIN was 95.2% (87.2,98.7) and EGL 99.1% (95.0, 100). In MITT-2 analysis vaccine efficacy for these endpoints was over 90% for all studies, and 98.8% against HPV 16/18 CIN 2/3 or worse. Since cases started at 30 days in MITT-2 analysis and the efficacy was comparable to the PPE measured efficacy, protection appears to start during the 3-dose vaccination period.

In the broader MITT-3 population, reflecting the general population as subjects that were infected at baseline were included, a reduced impact of Gardasil was observed, with added cases in active and control groups mainly occurring in subjects infected with HPV types at Day 1. In the combined protocols there were 122 cases of HPV 16/18-related CIN 2/3 or worse in the Gardasil groups (n=9831) compared with 201 in the placebo (n=9896), giving vaccine efficacy 39% (23.3, 51.7). For HPV 6/11/16/18-related CIN the vaccine efficacy was 46.4%, and EGLs 70.4% in the combined MITT-3 analyses. With each screening round in the MITT-3 population, the vaccine efficacy against CIN/AIS related to vaccine HPV types increased, with early benefit of the vaccine small (ns) for women already infected at Day 1. In analysis limited to women infected at Day 1 by PCR but seronegative there was a trend towards reduction in CIN or AIS with the vaccine, with efficacy around 27% but not excluding 0% in the 95%CI. In the subgroup HPV positive at Day 1 by both PCR and seropositive the rate of CIN2/3 cases was numerically but not statistically different for those receiving Gardasil vs. placebo

There were a number of substudies addressing immunogenicity, including duration of antibody response. Durable antibodies to vaccine HPV subtypes were demonstrated to 2.5 years in protocol 007, and 1.5 years in the phase 3 studies. At 2.5 years geometric mean titres were above those of participants receiving placebo who were seropositive and PCR negative at baseline i.e. with naturally acquired previous infection. However, the minimum levels of antibody associated with protection from HPV infection are not known. Since the collection of specimens for HPV is not possible in children, protocol 016 evaluated antibody response to Gardasil in 10-15 year old males and females, and 16-23 year old females. For the participants receiving all three vaccinations, month 7 geometric mean titres vs vaccine HPV types were non-inferior (or superior) for females (n=426-9, numbers varying with HPV subtype measurements) and for males (n=430-2) compared with the 16-23 year old females (n=320-340). A fourth booster dose has not been formally evaluated. An ongoing safety study 018 in 9-15 year old subjects has demonstrated an antibody response in 98% of boys and girls (the Gardasil data package included a total of 237 nine-year olds). Overall, the antibody response was highest at month 7 and then declined, such that about a quarter of all subjects were anti-HPV negative at month 24 or later (whether there is residual prophylactic efficacy is not known). For subjects seropositive at baseline, anti-HPV titres were sustained at all time points.

Safety

The general safety analysis included 11,792 subjects who received Gardasil and 9,688 who received placebo. The detailed safety population included 10,224 subjects who also used VRC (vaccine report cards). VRC were used for subjects (or guardians) to record adverse

events, temperatures daily for 5 days, injection site reactions and systemic events up to 15 days. Any adverse events thought to be vaccine related were followed to resolution, and all adverse events leading to discontinuation were recorded.

A total of 1,017 subjects discontinued study participation, 776 during the vaccination period and 241 during follow up. Drop-out rates during follow up were similar in the Gardasil (129/10,382 or 1.2%) and placebo (112/9387 or 1.2%) groups. Serious adverse events were uncommon, with 17 subjects in each group reporting SAE leading to discontinuation. Adverse experiences were common, with 88.2% of subjects reporting at least one AE. 63.8% of Gardasil recipients (3874/6160) reported injection site reactions 1-5 days following vaccination, compared with 33.6% (196/594) of placebo (non-aluminium) and 60.6% (2068/3470) of the placebo (aluminium) groups. This suggests that the adjuvant is the main agent responsible for injection site reactions. Injection site reactions tended to increase in the Gardasil group with subsequent vaccinations and not placebo, suggesting development of an immune reaction to the VLP antigens. A severe injection site reaction was reported by 4.5% of Gardasil group compared with 1.9% of placebo. The commonest systemic adverse experiences considered by the investigator to be vaccine related were headache (26%), pyrexia (12.9%) and nausea (6.1%) with little difference between the vaccination groups and occurring more commonly after dose 1 than dose 2 or 3. Pyrexia was low grade and no subject discontinued because of fever. 14 subjects died e.g. following trauma, but no cases were considered trial drug or procedure related. There were four subjects with SAE thought to be possibly related to the vaccine; following Gardasil bronchospasm on Day 1, gastroenteritis on Day 5, headache Day 1 and following placebo pyrexia Day 1. SAE considered probably related after Gardasil included injection site movement impairment Day 1, vaginal haemorrhage Day 26. One Gardasil recipient had headache and hypertension on Day 1 that was thought definitely related to study medication. Amongst the 9 to 15 year old males injection site adverse experiences were 76.9% in the Gardasil group and 55.4% in the placebo (non-aluminium), but with similar rates of systemic AEs. During the phase 3 trials 1901 women experience 2074 pregnancies (Gardasil 1031, placebo 1043), with outcomes known for 1619 pregnancies at the time of data cut off. The rates of spontaneous or elective termination were similar in the two groups, as were rates of congenital abnormality (diverse in morphology) amongst infants born. The spontaneous termination and congenital abnormality rates were in line with expected population rates.

2. Post-marketing experience
None yet available.

C. Summary of the clinical data

The prophylactic efficacy of Gardasil for CIN 2/3 and AIS, for CIN and for EGL related to vaccine HPV types has been clearly demonstrated for 16-23 year old women using a Day 1, month 2 and month 6 vaccination regimen. Duration of antibody response above that seen with naturally acquired infection is at least 2.5 years after the third vaccination, although minimum protective titres are not currently established. The HPV type specific serological response in 10-15 year old subjects of both sexes following vaccination is not inferior to that seen in 16-23 year old women. In 16-23 year old women with evidence of a vaccine HPV-type infection at baseline, Gardasil reduces the burden of clinical disease caused by other vaccine HPV types. For the vaccine HPV type carried at Day 1 the early CIN HPV type-related benefit of the vaccine was small (ns) and increasing over time. Injection site

reactions were common, with 4.5% of Gardasil recipients reporting a severe reaction vs. 1.9% with placebo. Injection site reactions overall were of similar frequency to those with the aluminium containing placebo (already in use with other marketed vaccines). Systemic reactions such as fever were generally mild, and rarely led to discontinuation.

DATA SHEET [OR SUMMARY OF PRODUCT CHARACTERISTICS]
Clear and comprehensive.

The TGA assessor notes that there were 3 main trials of quadrivalent vaccine, not 4 as on page three of the draft Data Sheet, since protocol 005 was a univalent (HPV16) vaccine. A similar modification for correctness is needed in the Adverse Reactions introduction section on page 10. For the indication, the prevention of cervical cancer has not strictly been demonstrated, nor practically could it have been in prospective clinical trials.

MEDICINE CLASSIFICATION
Prescription – at present. Might not need prescription status if wider safety profile is established? Exposure to the protein is already common as part of HPV infection.

OVERALL SUMMARY/DISCUSSION
Substantial clinical trial data package supporting a favourable risk/benefit profile in the prophylaxis of HPV 6, 11, 16 and 18-related gynaecological disease. Probably a significant medical advance.

OUTSTANDING ISSUES
1. Review of indication. Accept prevention of cervical cancer? Possibly "Gardasil is a prophylactic vaccine for 9-26 year old...."?
2. Post-marketing epidemiology and follow up
3. Potential rising immunogenicity with each Gardasil vaccination
4. Need for booster doses?