LOCAL PRODUCT CIRCULAR **LPC-GRD-I-012021a-Malaysia**

GARDASIL®
[Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine]
[Suspension for Injection]

I. THERAPEUTIC CLASS

GARDASIL® is a recombinant, quadrivalent vaccine that protects against Human Papillomavirus (HPV).

II. Active Ingredients

GARDASIL is a sterile preparation for intramuscular administration. Each 0.5-mL dose contains approximately 20 mcg of HPV 6 L1 protein, 40 mcg of HPV 11 L1 protein, 40 mcg of HPV 16 L1 protein, and 20 mcg of HPV 18 L1 protein.

III. Inactive Ingredients

Each 0.5-mL dose of the vaccine contains approximately 225 mcg of aluminum (as amorphous aluminum hydroxyphosphate sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, and water for injection. The product does not contain a preservative or antibiotics.

IV. CLINICAL PHARMACOLOGY

Disease Burden

Worldwide, over 490,000 cases of cervical cancer are diagnosed annually. Cervical cancer prevention focuses on repeat screening (e.g., Papanicolaou's [Pap] testing and/or Human Papillomavirus [HPV] testing) and early intervention. This strategy has reduced cancer rates by approximately 75% in the developed world but has shifted the burden from managing cervical cancer to monitoring and treating a large number of premalignant lesions.

Cervical cancer is caused by Human Papillomavirus (HPV) infection. HPV infection is necessary for the development of squamous cell cervical cancer (and its precursor lesions Cervical Intraepithelial Neoplasia [CIN] 1 and CIN 2/3) and cervical adenocarcinoma (and its precursor lesion adenocarcinoma *in situ* [AIS]). HPV also causes a subset of vulvar and vaginal cancers and their precursor lesions Vulvar Intraepithelial Neoplasia (VIN) and Vaginal Intraepithelial Neoplasia (VaIN).

HPV infection is very common. Most HPV infections clear without sequelae but some progress to cervical cancer and/or other HPV-related diseases. In the absence of vaccination, over 50% of sexually active individuals will become infected with HPV during their lifetime. Men play an important role in transmission of HPV to their sexual partners. Several prospective studies have shown a high level of HPV concordance between couples who recently became infected, indicating transmission of HPV between the couples (male to female, and female to male). These data consistently support the sexually transmitted nature of HPV and the role of men in infecting women, who subsequently can develop HPV-related anogenital cancers and warts. Based on these various lines of evidence it is expected that decreasing the risk of HPV infection in men

through vaccination should decrease the risk of infection in their sexual partners, thereby providing additional public health benefit.
Infection with HPV types 6, 11, 16, and 18 can cause abnormal Pap test results and low-grade dysplastic lesions (CIN 1, VIN 1, and VaIN 1). HPV 6- and HPV 11-related lesions are unlikely to progress to cancer but are clinically indistinguishable from premalignant lesions caused by HPV 16 and HPV 18.

Infection with HPV 6 and HPV 11 also causes genital warts (condyloma acuminata) which are growths of the cervicovaginal, vulvar, perianal and intra-anal mucosa and the external genitalia that rarely progress to cancer. The lifetime risk for acquisition of genital warts has been estimated to exceed 10%. The incidence of this lesion is generally comparable between men and women.

Recurrent Respiratory Papillomatosis (RRP), a disease of infants and adults, is also caused by HPV 6 and HPV 11. RRP is characterized by repeated growth of warts in the respiratory tract. In the U.S., 5,900 cases are diagnosed annually. Therapy requires repeated surgery.

HPV infection is strongly associated with anal cancer. The great majority of anal cancers are squamous cell carcinoma (SCC). Anal canal SCC are HPV positive in 80 to 90% of cases in men and women. HPV 16 (73%) and HPV 18 (5%) are the most common associated types. Approximately 100,000 new cases of anal cancer are estimated to occur annually around the world and the rate of anal cancer cases has been increasing. There are no routine screening tests for this cancer in healthy people.

HPV is accepted as a cause of head and neck cancer, and emerging data shows an increase over the past several decades in the proportion of head and neck cancers caused by HPV. The majority of HPV-related head and neck cancers occur in the oropharynx, specifically in the tonsillar area of Waldever's Ring. Of oropharyngeal cancers, 60-70% are caused by HPV, and of these, approximately 90% are associated with HPV 16. Overall, approximately 2/3 of these cases occur in men. Oral HPV infection and seropositivity for HPV 16 have been associated with a significantly elevated risk for development of head and neck cancer.

GARDASIL is a recombinant vaccine with L1 proteins resembling HPV types 6, 11, 16, and 18. HPV types 16 and 18 cause approximately:
- 70% of cervical cancer, AIS, and CIN 3 cases;
- 50% of CIN 2 cases;
- 70% of HPV-related vulvar and vaginal cancer, VIN 2/3, and VaIN 2/3 cases;
- 90% of HPV-related anal cancers and their precursor lesions;
- 70% of HPV-related AIN 2/3; and
- 60% of HPV-related penile cancers.

HPV types 6, 11, 16, and 18 cause approximately:
- 35 to 50% of all CIN 1, VIN 1, and VaIN 1 cases.

HPV types 6 and 11 cause approximately:
- 90% of genital wart and RRP cases; and
- 9 to 12% of CIN 1 cases.

HPV type 16 causes approximately:
- 90% of Oropharyngeal squamous cell carcinomas

The effects of GARDASIL have also been studied on HPV types 31, 33, 52, 56, 58 and 59. These types cause approximately:
- 11.6% of cervical cancer cases;

- 32.2% of CIN 1 cases;
- 39.3% of CIN 2 cases; and
- 24.3% of CIN 3 or AIS cases.

Mechanism of Action
GARDASIL contains L1 VLPs, which are proteins that resemble wild-type virions. Because the virus-like particles contain no viral DNA, they cannot infect cells or reproduce.

In preclinical studies, induction of anti-papillomavirus antibodies with L1 VLP vaccines resulted in protection against infection. Administration of serum from vaccinated to unvaccinated animals resulted in the transfer of protection against HPV to the unvaccinated animals. These data suggest that the efficacy of L1 VLP vaccines is mediated by the development of humoral immune responses.

Clinical Studies
In female individuals, CIN 2/3 and AIS are the immediate precursors of invasive squamous cell carcinoma and invasive adenocarcinoma of the cervix, respectively. Their detection and removal has been shown to prevent invasive cancer (secondary prevention); thus, their primary prevention through vaccination will prevent invasive cancer.

Invasive cervical cancer cannot be used as an endpoint for efficacy studies of HPV vaccines because of the importance of employing secondary prevention measures. Therefore, the immediate precursors, CIN 2 (moderate-grade cervical dysplasia), CIN 3 (high-grade cervical dysplasia including carcinoma *in situ*), and AIS are the most appropriate endpoints for the demonstration of the prevention of cervical cancer by HPV vaccines.

CIN 3 and AIS are classified as Stage 0 cervical cancers according to FIGO (International Federation of Obstetrics and Gynaecology). VIN 2/3 and VaIN 2/3 are the immediate precursors to HPV-related vulvar and vaginal cancer, respectively.

In men, up to 84% of penile/perineal/perianal intraepithelial neoplasia (PIN) 1 (low-grade) and over 90% of PIN 3 (high-grade) has been associated with HPV. HPV 16 is the most common type detected. Erythoplasia of Queyrat (EQ), Bowen's disease (BD), and bowenoid papulosis (BP) are clinical presentations of high-grade PIN. As high as 33% of BD and EQ have been associated with invasive cancer. BP rarely progresses to malignancy.

The efficacy of GARDASIL was assessed in 6 placebo-controlled, double-blind, randomized Phase II and III clinical studies. The first Phase II study evaluated the HPV 16 component of GARDASIL (Protocol 005, N = 2,391 girls and women) and the second evaluated all components of GARDASIL (Protocol 007, N = 551 girls and women). Three Phase III studies, termed FUTURE (Females United To Unilaterally Reduce Endo/Ectocervical Disease), evaluated GARDASIL in 5,442 (FUTURE I), 12,157 (FUTURE II) and 3,817 (FUTURE III) girls and women. A fourth Phase III study, Protocol 020 evaluated GARDASIL in 4,055 boys and men, including a subset of 598 (GARDASIL = 299; placebo =299) men who self-identified as having sex with men (MSM population). Together, these studies evaluated 24,358 girls and women 16 through 45 years of age and 4,055 boys and men 16 through 26 years of age at enrollment. The median duration of follow-up was 4.0, 3.0, 3.0, 3.0, 2.2 and,2.9 years for Protocol 005, Protocol 007, FUTURE I, FUTURE II, FUTURE III and Protocol 20 base studies, respectively. Individuals received vaccine or placebo on the day of enrollment and 2 and 6 months thereafter. Efficacy was analyzed for each study individually and for all studies conducted in girls and women combined.

The studies did not have a screening phase. Thus, individuals who had been exposed to a vaccine HPV type prior to enrollment were included in the studies. Overall, 73% of 16- through 26 year old girls and women and 67% of 24- through 45-year old women were naïve to all 4 vaccine

HPV types at enrollment. Overall, 83% of 16- through 26-year-old boys and men were naïve to all 4 vaccine HPV types at enrollment. The naïve individuals continued to be at risk for infection and disease caused by all 4 vaccine HPV types. Among the 16- through 26-year-old boys and men, only 0.2% had been exposed to all 4 vaccine HPV types.

Prophylactic Efficacy – HPV Types 6, 11, 16, and 18 in 16- Through 26-Year-Old Girls and Women
GARDASIL was highly efficacious in reducing the incidence of cervical, vulvar, and vaginal cancers; CIN (any grade); AIS; non-invasive cervical cancer (CIN 3 and AIS); and external genital lesions, including condyloma acuminata, VIN (any grade) and VaIN (any grade) caused by HPV types 6, 11, 16, and 18. Based on a pre-specified analysis of lesions evident beginning 30 days Postdose 1, there was evidence that the vaccine was already efficacious during the course of the 3-dose vaccination regimen.

The primary analyses of efficacy, with respect to HPV types 6, 11, 16, and 18, were conducted in the per-protocol efficacy (PPE) population, consisting of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve to the relevant HPV type(s) prior to dose one and through 1 month Postdose 3 (Month 7). Efficacy was measured starting after the Month 7 visit.

The efficacy of GARDASIL against HPV 16- or 18-related CIN 2/3 or AIS was 98.2% (95% CI: 93.5%, 99.8%) in the combined protocols. Analyses of individual protocols demonstrated the following results: 100% (95% CI: 65.1%, 100.0%) in Protocol 005, 100% (95% CI: <0.0%, 100.0%) in Protocol 007, 100% (95% CI: 89.2%, 100.0%) in FUTURE I and 96.9% (95% CI: 88.2%, 99.6%) in FUTURE II. There were two cases of CIN 3 that occurred in the group that received GARDASIL. In the first case HPV 16 and HPV 52 were detected. This individual was chronically infected with HPV 52 (infection at Day 1, and Months 32.5 and 33.6) in 8 of 11 specimens, including tissue that was excised during LEEP (Loop Electro-excision Procedure). HPV 16 was found in 1 of 11 specimens at Month 32.5. HPV 16 was not detected in tissue that was excised during LEEP. In the second case HPV 16, HPV 51, and HPV 56 were detected. This individual was infected with HPV 51 (infection detected by PCR at Day 1) in 2 of 9 specimens. HPV 56 was detected (in tissue excised during LEEP) in 3 of 9 specimens at Month 52. HPV 16 was detected in 1 of 9 specimens at a Month 51 biopsy. Given that these cases occurred in the context of mixed infection, with the dominant type being the non-vaccine HPV type, it is likely that the relevant vaccine HPV type was not the causal HPV type. Based on this assessment, it can be inferred that vaccine efficacy against HPV 16/18-related CIN 2/3 or AIS was 100%.

The efficacy of GARDASIL against HPV 16-related CIN 2/3 or AIS was 97.9% (95% CI: 92.3%, 99.8%) in the combined protocols. The efficacy of GARDASIL against HPV 18-related CIN 2/3 or AIS was 100.0% (95% CI: 86.6%, 100.0%) in the combined protocols.

The efficacy of GARDASIL against HPV 16- or 18-related VIN 2/3 was 100% (95% CI: 55.5%, 100.0%) in the combined protocols. Analyses of individual protocols demonstrated the following results: 100% (95% CI: 14.4%, 100.0%) in FUTURE I and 100% (95% CI: <0.0%, 100%) in FUTURE II.

The efficacy of GARDASIL against HPV 16- or 18-related VaIN 2/3 was 100% (95% CI: 49.5%, 100.0%) in the combined protocols. Analyses of individual protocols demonstrated the following results: 100% (95% CI: <0.0%, 100.0%) in FUTURE I and 100% (95% CI: <0.0%, 100%) in FUTURE II.

The efficacy of GARDASIL against HPV 6-, 11-, 16- or 18-related CIN (CIN 1, CIN 2/3) or AIS was 96.0% (95% CI: 92.3%, 98.2%) in the combined protocols. Analyses of individual protocols

demonstrated the following results: 100% (95% CI: <0.0%, 100.0%) in Protocol 007, 100% (95% CI: 95.1%, 100.0%) in FUTURE I, and 93.8% (95% CI: 88.0%, 97.2%) in FUTURE II.

The efficacy of GARDASIL against HPV 6-, 11-, 16-, or 18-related genital lesions (genital warts, VIN, VaIN, Vulvar Cancer, and Vaginal Cancer) was 99.1% (95% CI: 96.8%, 99.9%) in the combined protocols. Analyses of individual protocols demonstrated the following results:
100% (95% CI: <0.0%, 100.0%) in Protocol 007, 100% (95% CI: 94.9%, 100.0%) in FUTURE I and 98.7% (95% CI: 95.2%, 99.8%) in FUTURE II.

The efficacy of GARDASIL against HPV 6- or 11-related genital warts was 99.0% (95% CI: 96.2%, 99.9%) in the combined protocols.

In the long-term extension study of FUTURE II, 2,536 women 16-23 years old during vaccination with GARDASIL in the base study were followed. In the PPE population, no cases of HPV diseases (HPV types 6/11/16/18 related high grade CIN) were observed up to approximately 14 years (median follow-up of 11.9 years). In this study, a durable protection was statistically demonstrated to approximately 12 years.

Supplemental Analysis of Efficacy for Cancer Endpoints in 16-Through 26-Year-Old Girls and Women
In a supplemental analysis, the efficacy of GARDASIL was evaluated against HPV 16/18-related FIGO Stage 0 cervical cancer (CIN 3 and AIS) and for the immediate precursors to vulvar and vaginal cancer (VIN 2/3 or VaIN 2/3) in the PPE population and a modified intention to treat-2 (MITT-2) population. The MITT-2 population consisted of individuals who were naïve to the relevant HPV types(s) (types 6, 11, 16, and 18) prior to dose 1, received at least one dose of vaccine or placebo, and had at least one follow-up visit post-Day 30. The MITT-2 population differs from the PPE population in that it includes individuals with major protocol violations and who became infected with a vaccine HPV type during the vaccination period. Efficacy was measured starting 30 days Postdose 1 for the MITT-2 population.

The efficacy of GARDASIL against HPV 16/18-related disease was 96.9% (95% CI: 88.4%, 99.6%), 100% (95% CI: 30.6%, 100.0%), and 100% (95% CI: 78.6%, 100.0%) for CIN 3, AIS, and VIN 2/3 or VaIN 2/3, respectively, in the PPE population. Efficacy against HPV 16/18-related disease was 96.7% (95% CI: 90.2%, 99.3%), 100.0% (95% CI: 60.0%, 100.0%), and 97.0% (95% CI: 82.4%, 99.9%) for CIN 3, AIS, and VIN 2/3 or VaIN 2/3, respectively, in the MITT-2 population.

Prophylactic efficacy against overall persistent infection or disease in an extension phase of Protocol 007, that included data through Month 60, was 95.8% (95% CI: 83.8%, 99.5%). In the group that received GARDASIL, no cases due to waning immunity were observed.

GARDASIL was equally efficacious against HPV disease caused by HPV types 6, 11, 16, and 18.

Efficacy in 16- Through 26-Year-Old Girls and Women with Current or Prior Infection with HPV Types 6, 11, 16, or 18
Individuals who were already infected with one or more vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the remaining vaccine HPV types.

Individuals with evidence of a prior infection that had resolved by vaccination onset were protected from reacquisition or recurrence of infection leading to clinical disease.

Individuals who received GARDASIL, but had ongoing HPV infection at the time of vaccination had a 21.6% (95% CI: <0.0%, 42.1%) lower incidence of CIN (CIN 1 or CIN 2/3) or AIS resulting from this infection as compared with placebo. Ongoing infection was defined as infection with a vaccine HPV type at enrollment, but no evidence of immune response to it.

Prophylactic Efficacy in a Generally HPV-naïve Population and the General Study Population – HPV Types 31, 33, 45, 52, 56, 58 and 59 in 16- Through 26-Year-Old Girls and Women
The cross-protective efficacy of GARDASIL was evaluated in the combined database of the FUTURE I and FUTURE II trials (N = 17,599). The primary endpoint of this analysis was the combined incidence of HPV 31- and HPV 45-related CIN (grades 1, 2, 3) or AIS. The secondary endpoint of this analysis was the combined incidence of HPV 31-, 33-, 45-, 52-, and 58-related CIN (grades 1, 2, 3) or AIS. Analyses were also conducted to evaluate efficacy with respect to CIN (grades 1, 2, 3) or AIS caused by non-vaccine HPV types individually. In individuals who were naïve to the relevant vaccine HPV types at Day 1 (MITT-2 population, n = 16,895 for the 31/45 composite endpoint and n = 16,969 for the 31/33/45/52/58 composite endpoint), a trend towards a reduction in the incidence of HPV 31- and 45-related and HPV 31-, 33-, 45-, 52-, and 58-related CIN (grades 1, 2, 3) or AIS was observed. Administration of GARDASIL reduced the incidence of HPV 31- and HPV 45-related CIN (grades 1, 2, 3) by 37.3% (95% CI: 17.0%, 52.8%) compared with placebo. Administration of GARDASIL reduced the incidence of HPV 31-, 33-, 45-, 52-, and 58-related CIN (grades 1, 2, 3) or AIS by 26.4% (95% CI: 12.9%, 37.8%) compared with placebo. Efficacy was driven by reductions in HPV 31-, 33-, 52-, and 58-related endpoints. There was no clear evidence of efficacy for HPV 45. In a post-hoc analysis, prophylactic administration of GARDASIL also reduced the incidence of HPV 56-related and HPV 59-related CIN (grades 1, 2, 3) or AIS, compared with placebo in this population.

Further post-hoc analyses considered efficacy in 2 clinically relevant populations: (1) an HPV-naïve population (negative to 14 common HPV types and had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1), approximating a population of sexually-naïve individuals plus individuals shortly after sexual debut; and (2) the general study population of individuals regardless of baseline HPV status, some of whom had HPV-related disease at vaccination onset. Administration of GARDASIL to HPV-naïve individuals reduced the incidences of HPV 31-, 33-, 52-, and 58-related CIN (grades 1, 2, 3) or AIS, HPV 56-related CIN (grades 1, 2, 3) or AIS, and HPV 59-related CIN (grades 1, 2, 3) or AIS. Reductions in the rates of these diseases were also observed in the general study population (which included HPV-naïve and HPV-infected individuals).

In the HPV-naïve population (n = 9,296), GARDASIL reduced the incidence of CIN (any grade) or AIS by 43.6% (95% CI: 12.9%, 64.1%) for HPV 31/45; 29.2% (95% CI: 8.3%, 45.5%) for HPV 31/33/45/52/58; 33.8% (95% CI: 13.4%, 49.6%) for HPV 31/33/52/58; 27.6% (95% CI: <0.0%, 49.3%) for HPV 56; and 22.3% (95% CI: <0.0%, 58.9%) for HPV 59.

In the general study population (n = 17,151), GARDASIL reduced the incidence of CIN (any grade) or AIS by 23.2% (95% CI: 5.6%, 37.7%) for HPV 31/45; 19.6% (95% CI: 8.2%, 29.6%) for HPV 31/33/45/52/58; 21.2% (95% CI: 9.6%, 31.3%) for HPV 31/33/52/58, 16.8% (95% CI: <0.0%, 32.8%) for HPV 56; and 39.2% (95% CI: 8.1%, 60.3%) for HPV 59 .

Cross-protection efficacy analyses demonstrate that prophylactic administration of GARDASIL to individuals reduces the risk of acquiring CIN 1, CIN 2/3, and AIS caused by HPV types 31, 33, 52, 56, 58, and 59.

Protection Against the Overall Burden of Cervical, Vulvar, and Vaginal HPV Disease in 16-Through 26- Year-Old Girls and Women
The impact of GARDASIL against the overall risk for cervical, vulvar, and vaginal HPV disease (i.e., disease caused by any HPV type) was evaluated in a pre-specified analysis of 17,599 individuals enrolled in FUTURE I and FUTURE II. Among individuals who were naïve to at least one of 14 common HPV types and/or had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1 (MITT-2 population), administration of GARDASIL reduced the

incidence of CIN 2/3 or AIS caused by vaccine- or non-vaccine HPV types by 33.8% (95% CI: 20.7%, 44.8%).

Further efficacy analyses were conducted in 2 clinically relevant populations: (1) an HPV-naïve population (negative to 14 common HPV types and had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1), approximating a population of sexually-naïve individuals plus individuals shortly after sexual debut; and (2) the general study population of individuals regardless of baseline HPV status, some of whom had HPV-related disease at vaccination onset.

Among HPV-naïve individuals and among the general study population (including individuals with HPV infection at vaccination onset) GARDASIL reduced the overall incidence of CIN 2/3 or AIS; of VIN 2/3 or VaIN 2/3; of CIN (any grade) or AIS; and of Genital Warts. These reductions were primarily due to reductions in lesions caused by HPV types 6, 11, 16, and 18. Among HPV-naïve individuals and the general study population, the benefit of the vaccine with respect to the overall incidence of CIN 2/3 or AIS (caused by any HPV type) became more apparent over time. This is because GARDASIL does not impact the course of infections that are present at vaccination onset. Such infected individuals may already have CIN 2/3 or AIS at vaccination onset and some will develop CIN 2/3 or AIS during follow-up. GARDASIL reduces the incidence of CIN 2/3 or AIS caused by infections with HPV types 6, 11, 16, 18, 31, 33, 52, 56, 58 and 59 that occur after vaccination onset.

GARDASIL has not been shown to protect against the diseases caused by every HPV type, and will not treat existing disease. The overall efficacy of GARDASIL will vary with the baseline prevalence of HPV infection and disease, the incidence of infections against which GARDASIL has shown protection, and those infections against which GARDASIL has not been shown to protect.

Impact on the Rates of Pap Test Abnormalities and Cervical, Vulvar, and Vaginal Procedures in 16-Through 26-Year-Old Girls and Women

The impact of GARDASIL on rates of abnormal Pap tests and cervical procedures (colposcopic biopsy, definitive therapy) regardless of causal HPV types was evaluated in 18,150 individuals enrolled in Protocol 007, FUTURE I and FUTURE II. The impact of GARDASIL on rates of genital excisional procedures to treat lesions caused by any HPV type was evaluated in 5,442 individuals enrolled in FUTURE I. Two populations were considered: (1) an HPV-naïve population (negative to 14 common HPV types and had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1), approximating a population of sexually-naïve individuals plus individuals shortly after sexual debut; and (2) the general study population of individuals regardless of baseline HPV status, some of whom had HPV-related disease at vaccination onset.

In both populations, GARDASIL reduced the proportions of individuals who experienced a Pap test abnormality suggestive of CIN, a colposcopic biopsy, a definitive cervical therapy procedure (Loop Electro-Excision Procedure or Cold-Knife Conization), a vulvar or vaginal biopsy, or a definitive excisional procedure of the vagina or vulva.

In addition, administration of GARDASIL to a generally HPV-naïve population of 16- through 26-year-old individuals reduced the incidence of HPV 16-related and HPV 18-related Pap abnormalities (ASC-US HR positive, LSIL, or worse) by 92.4% (95% CI: 83.7%, 97.0%) and 96.9% (95% CI: 81.6%, 99.9%) in the FUTURE I study.

Prophylactic Efficacy – HPV Types 6, 11, 16, and 18 in 24- Through 45-Year-Old Women

The efficacy of GARDASIL in 24- through 45-year-old women was assessed in 1 placebo-controlled, double-blind, randomized Phase III clinical study (Protocol 019, FUTURE III) including a

total of 3,817 women, who were enrolled and vaccinated without pre-screening for the presence of HPV infection.

The primary efficacy endpoints included the combined incidence of HPV 6-, 11-, 16- or 18-related and the combined incidence of HPV 16- or HPV 18-related persistent infection (6 month definition), genital warts, vulvar and vaginal lesions, CIN of any grade, AIS, and cervical cancers. The median duration of follow-up for this study was 4.0 years.

In the long-term extension study of FUTURE III, 685 women 24-45 years old during vaccination with GARDASIL in the base study were followed. In the PPE population, no cases of HPV diseases (HPV types 6/11/16/18 related CIN any grade and Genital Warts) were observed through 10.1 years (median follow-up of 8.7 years).

Efficacy in women naïve to the relevant vaccine HPV type(s)

The primary analyses of efficacy were conducted in the per-protocol efficacy (PPE) population (i.e. all 3 vaccinations within 1 year of enrollment, no major protocol deviations and naïve to the relevant HPV type(s) prior to dose 1 and through 1 month Postdose 3 (Month 7)). Efficacy was measured starting after the Month 7 visit. Overall, 67% of individuals were naïve (PCR negative and seronegative) to all 4 HPV types at enrollment.

The efficacy of GARDASIL against HPV 6-, 11-, 16-, or 18-related persistent infection, CIN of any grade, or EGL was 88.7% (95% CI: 78.1%, 94.8%).

The efficacy of GARDASIL against HPV 16- or 18-related persistent infection, CIN of any grade, or EGL was 84.7% (95% CI: 67.5%, 93.7%).

Efficacy in women with and without prior infection or disease due to HPV 6, 11, 16, or 18

The Full Analysis Set population (also known as the ITT population) included women regardless of baseline HPV status at Day 1, who received at least one vaccination and in whom case counting started at Day 1. This population approximates to the general population of women with respect to prevalence of HPV infection or disease at enrollment.

The efficacy of GARDASIL against the combined incidence of HPV 6-, 11-, 16-, or 18-related persistent infection, genital warts, vulvar and vaginal lesions, CIN of any grade, AIS, and cervical cancers was 47.2% (95% CI: 33.5, 58.2).

The efficacy of GARDASIL against the combined incidence of HPV 16-, or 18-related persistent infection, genital warts, vulvar and vaginal lesions, CIN of any grade, AIS, and cervical cancers was 41.6% (95% CI: 24.3, 55.2).

Efficacy in women (16 to 45 years) with evidence of a prior infection with a vaccine HPV type (seropositive) that was no longer detectable at vaccination onset (PCR negative)

In post hoc analyses of individuals (who received at least one vaccination) with evidence of a prior infection with a vaccine HPV type (seropositive) no longer detectable (PCR negative) at vaccination onset, the efficacy of GARDASIL to prevent conditions due to recurrence of the same HPV type was 100% (95% CI: 62.8,100.0; 0 vs. 12 cases [n = 2572 from pooled studies in young women]) against HPV 6-, 11-, 16- and 18-related CIN 2/3, VIN 2/3, VaIN 2/3, and genital warts in women 16 to 26 years. Efficacy was 68.2% (95% CI: 17.9, 89.5; 6 vs. 20 cases [n = 832 from studies in young and adult women combined]) against HPV 16- and 18- related persistent infection in women 16 to 45 years.

Prophylactic Efficacy – HPV Types 6, 11, 16, and 18 in 16- Through 26-Year-Old Boys and Men
In clinical studies in boys and men, efficacy was evaluated using the following endpoints: external genital warts; penile/perineal/perianal intraepithelial neoplasia (PIN) grades 1/2/3 or

penile/perineal/perianal cancer; and persistent infection. High grade PIN is associated with certain types of penile/perineal/perianal cancers. Persistent infection is a predictor of clinical disease.

The primary analyses of efficacy were conducted in the PPE population. This population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month Postdose 3 (month 7). Efficacy was measured starting after the Month 7 visit.

GARDASIL was efficacious in reducing the incidence of external genital lesions (Condyloma and PIN grades 1/2/3) and persistent infection related to vaccine HPV types 6, 11, 16, or 18 in those who were PCR negative and seronegative at baseline.

The efficacy of GARDASIL against HPV 6-, 11-, 16-, or 18-related external genital lesions (Condyloma and PIN grades 1/2/3) was 90.6% (95% CI: 70.1%, 98.2%). Analyses of individual components of the endpoint demonstrated the following results: 89.3% (95% CI: 65.3%, 97.9%) for Condyloma and 100.0% (95% CI: <0.0%, 100.0%) for PIN grades 1/2/3.

The efficacy of GARDASIL against HPV 6-, 11-, 16-, or 18-related persistent infection was 85.5% (95% CI: 77.0%, 91.3%). Analyses of individual HPV serotype-related persistent infection demonstrated the following results: 90.1% (95% CI: 75.3%, 96.9%), 94.4% (95% CI: 64.7%, 99.9%), 79.3% (95% CI: 61.9%, 89.6%), and 93.9% (95% CI: 76.3%, 99.3%), for HPV 6-, 11-, 16- and 18-related persistent infection, respectively.

Prophylactic Efficacy – Anal Disease Caused by HPV Types 6, 11, 16, and 18 in Boys and Men 16 Through 26 Years of Age in the MSM Sub-study

A sub-study of Protocol 020 evaluated the efficacy of GARDASIL against anal disease (anal intraepithelial neoplasia and anal cancer) in a population of 598 MSM. In this sub-study, cases of AIN 2/3 were the efficacy endpoints used to assess prevention of HPV-related anal cancer. The primary analyses of efficacy were conducted in the PPE population of Protocol 020.

GARDASIL was efficacious in reducing the incidence of anal intraepithelial neoplasia (AIN) grades 1 (both condyloma and non-acuminate), 2, and 3 related to vaccine HPV types 6, 11, 16, and 18 in those boys and men who were PCR negative and seronegative at baseline.

The efficacy of GARDASIL against HPV 6-, 11-, 16-, or 18-related AIN 1/2/3 was 77.5% (95% CI: 39.6%, 93.3%). Analyses of individual components of the endpoint demonstrated the following results: 74.9% (95% CI: 8.8%, 95.4%) for AIN grades 2/3 and 73.0% (95% CI: 16.3%, 93.4%) for AIN grade 1 (condyloma and non-acuminate).

The duration of protection against anal cancer is currently unknown. In the long-term extension study of Protocol 020, 917 men 16-26 years old during vaccination with GARDASIL in the base study were followed. In the PPE population, no cases of HPV types 6/11 related genital warts, HPV 6/11/16/18 related external genital lesions or HPV 6/11/16/18 related high grade AIN in MSM were observed through 11.5 years (median follow-up of 9.5 years).

Immunogenicity

Assays to Measure Immune Response

Type-specific assays with type-specific standards were used to assess immunogenicity to each vaccine HPV type. These multiplexed competitive Luminex immunoassays (cLIA) measured antibodies against neutralizing epitopes for each HPV type, rather than the total antibodies directed at the VLPs in the vaccine. The scales for these assays are unique to each HPV type; thus, comparisons across types and to other assays are not meaningful. The assays used to

measure the immune responses to GARDASIL were demonstrated to correlate with the capacity to neutralize live HPV virions.

Because of the very high efficacy of GARDASIL in clinical trials, it has not been possible to establish minimum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 antibody levels that protect against clinical HPV disease.

The immunogenicity of GARDASIL was assessed in 23,951 9- through 45-year old girls and women (GARDASIL N = 12,634; placebo N = 11,317) and 5,417 9- through 26-year-old boys and men (GARDASIL N = 3,109; placebo N = 2,308).

The primary immunogenicity analyses were conducted in a per-protocol immunogenicity (PPI) population. This population consisted of individuals who were seronegative and Polymerase Chain Reaction (PCR) negative to the relevant HPV type(s) at enrollment, remained HPV PCR negative to the relevant HPV type(s) through 1 month Postdose 3 (Month 7), received all 3 vaccinations, and did not deviate from the study protocol in ways that could interfere with the effects of the vaccine.

Immunogenicity was measured by (1) the percentage of individuals who were seropositive for antibodies against the relevant vaccine HPV type, and (2) the Geometric Mean Titer (GMT).

Immune Response to GARDASIL at Month 7 in 9- Through 45-Year-Old Girls and Women (Time Point Approximating Peak Immunogenicity)
In the PPI population of 9- through 45-year-olds, seropositivity at Month 7 ranged from 96.4% to 99.9% across all 4 vaccine types and across populations defined by age range. Anti-HPV GMTs for all types decreased with age. This finding is expected, as the immune responses to vaccines generally decrease with age at vaccination. The efficacy of GARDASIL remained high despite the observed age-related decrease in anti-HPV GMTs.

Immune Response to GARDASIL at Month 7 in 9- Through 26-Year-Old Boys and Men (Time Point Approximating Peak Immunogenicity)
In the PPI population of 9- through 26-year-olds, seropositivity at Month 7 ranged from 97.4% to 99.9% across all 4 vaccine types and across populations defined by age range. Anti-HPV GMTs for all types decreased with age. This finding is expected, as the immune responses to vaccines generally decrease with age at vaccination. The efficacy of GARDASIL remained high despite the observed age-related decrease in anti-HPV GMTs.

Bridging the Efficacy of GARDASIL from Adults to Adolescents
A clinical study compared anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses in 10- through 15-year-old adolescent girls with responses in 16- through 23-year-old girls and women. Among the girls and women who received GARDASIL, 99.1% to 100% became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive by 1 month Postdose 3. Anti-HPV responses in 10- through 15-year-old adolescent girls were significantly superior to those observed in 16- through 23-year-old girls and women.

Similar outcomes were observed in a comparison of the anti-HPV responses 1 month Postdose 3 among 9- through 15-year-old adolescent girls with anti-HPV responses in 16- through 26-year-old girls and women in the combined database of immunogenicity studies for GARDASIL.

Anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses (GMTs) were compared between 9- through 15-year-old adolescent boys and 16- through 26-year-old boys and men. Among individuals who received GARDASIL, 97.4% to 99.9% became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive by 1 month Postdose 3. Anti-HPV responses in 9-

through 15-year-old adolescent boys were significantly superior to those observed in 16- through 26-year-old boys and men.

On the basis of this immunogenicity bridging, the efficacy of GARDASIL in 9- through 15-year-old adolescent girls is comparable to the efficacy of GARDASIL observed in 16- through 26-year-old girls and women. Additionally, the efficacy of GARDASIL in 9- through 15-year-old adolescent boys is comparable to the efficacy of GARDASIL observed in studies in 16- through 26-year-old boys and men.

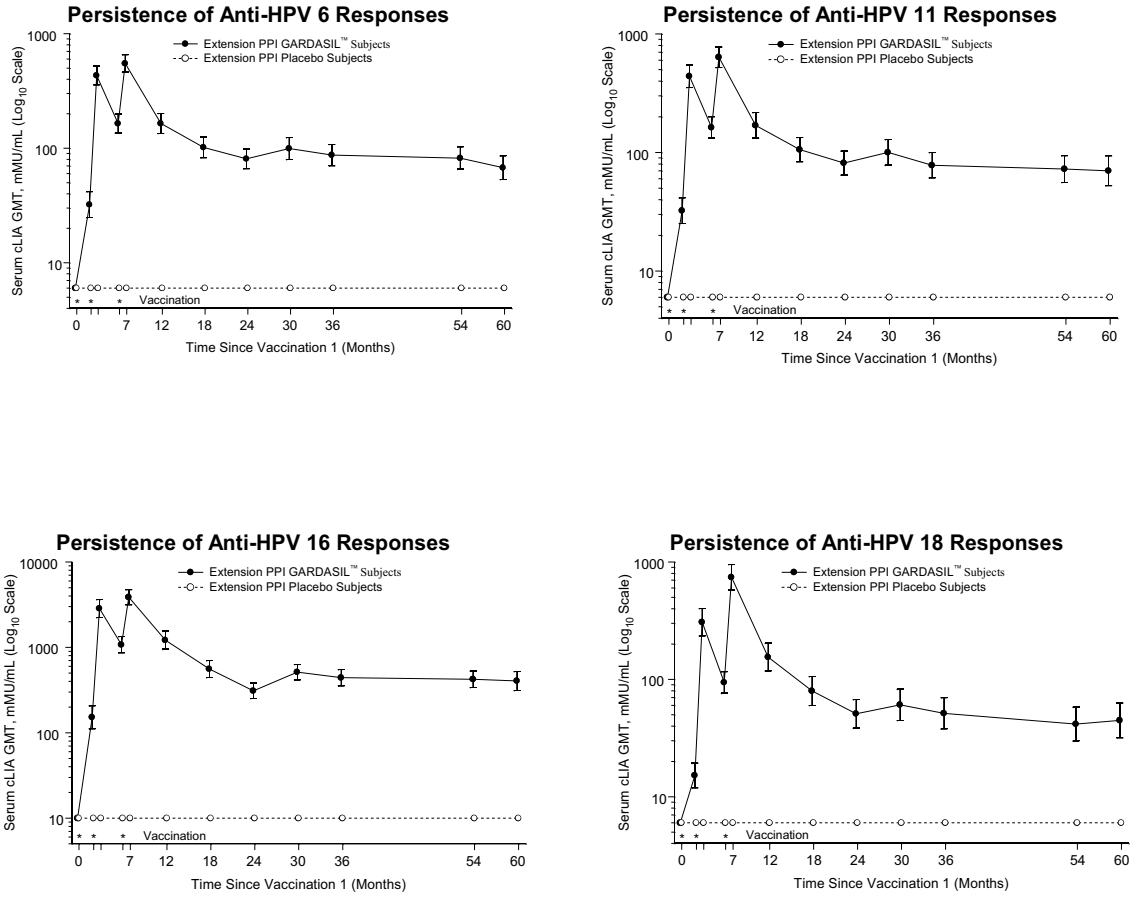
In the long-term extension study of Protocol 018, 369 girls and 326 boys 9-15 years old during vaccination with GARDASIL in the base study were followed. In the PPE population:

- in girls, no cases of HPV diseases (HPV types 6/11/16/18 related CIN any grade and Genital Warts) were observed through 10.7 years (median follow-up of 10 years).
- in boys, no cases of HPV disease (HPV types 6/11/16/18 related External Genital Lesions) were observed through 10.6 years (median follow-up of 9.9 years).

Persistence of the Immune Response to GARDASIL
The duration of immunity following a complete schedule of immunization with GARDASIL has not been established.

In Protocol 007, peak anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs were observed at Month 7. The GMTs decreased through Month 24 and then generally stabilized until at least Month 60 (see Figure 1).

Figure 1
Persistence of Anti-HPV Responses Following a 3-Dose Regimen of GARDASIL



A subset of individuals enrolled in the Phase III studies was followed up for a long-term period for safety, immunogenicity and effectiveness. Total IgG Luminex Immunoassay (IgG LIA) was used to assess the persistence of immune response in addition to cLIA.

In all populations (women 9 – 45 years, men 9 – 26 years), peak anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs cLIA were observed at Month 7. Afterwards, the GMTs declined through Month 24 - 48 and then generally stabilized. The exact duration of immunity following a 3-dose series has been observed for up to 14 years post-vaccination.

Girls and boys vaccinated with GARDASIL at 9-15 years of age in the Protocol 018 base study were followed up in an extension study. Depending on HPV type, 60-96% and 78-98% of subjects were seropositive by cLIA and IgG LIA respectively 10 years after vaccination.

Women vaccinated with GARDASIL at 16-23 years of age in the FUTURE II base study were followed up in an extension study. Fourteen years after vaccination, 91%, 91%, 98% and 52% were anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 seropositive in the cLIA, respectively, and 98%, 98%, 100% and 94% were anti-HPV6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 seropositive in the IgG LIA, respectively.

Women vaccinated with GARDASIL at 24-45 years of age in the FUTURE III base study were followed up in an extension study. Ten years after vaccination, 79%, 85%, 94% and 36% were anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 seropositive in the cLIA, respectively, and 86%, 79%, 100% and 83% were anti-HPV6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 seropositive in the IgG LIA, respectively.

Men vaccinated with GARDASIL at 16-26 years of age in the Protocol 020 base study were followed up in an extension study. Ten years after vaccination, 79%, 80%, 95% and 40% were anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 seropositive in the cLIA, respectively, and 92%, 92%, 100% and 92% were anti-HPV6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 seropositive in the IgG LIA, respectively.

In these studies, individuals who were seronegative for anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 in the cLIA were still protected against clinical disease after a follow-up of 14 years for 16-23 year-old women, 10 years for 24-45 year-old women, and 10 years for 16-26 year-old men.

Evidence of Anamnestic (Immune Memory) Response
Evidence of an anamnestic response was seen in vaccinated individuals who were seropositive to relevant HPV type(s) prior to vaccination.

In a study to evaluate the capacity to induce immune memory, individuals who received a 3-dose primary series of vaccine were given a challenge dose of GARDASIL 5 years after the onset of vaccination. These individuals exhibited a rapid and strong anamnestic response that exceeded the anti-HPV GMTs observed 1 month Postdose 3 (Month 7). The GMTs 1 week post-challenge dose were 0.9-, 2.2-, 1.2-, and 1.4-fold higher than the Postdose 3 GMTs for types 6, 11, 16, and 18, respectively. The GMTs 1 month post-challenge dose were 1.3-, 4.2-, 1.5-, and 1.7-fold higher than the Postdose 3 GMTs for types 6, 11, 16, and 18, respectively. At 1 week post-challenge dose, 87.2%, 94.9%, 86.4% and 95.2% of individuals had anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs higher than those detected at Month 60.

In addition, a subset of individuals that received a 3-dose primary series of vaccine became nominally anti-HPV 18 seronegative by Month 60. Although these individuals were nominally anti-HPV 18 seronegative, no cases of HPV 18-related disease were detected among these individuals. They also showed immune memory: when these individuals were given a challenge dose of GARDASIL (at Month 60), 93% and 97% became anti-HPV 18 seropositive by 1 week and 1 month post-challenge, respectively; 73% had anti-HPV 18 levels at 1 month post-challenge that were higher than their Month 7 (1 month Postdose 3) anti-HPV 18 level.

Schedule Flexibility
All individuals evaluated in the PPE populations of the Phase II and III studies received the 3-dose regimen of GARDASIL within a 1-year period, regardless of the interval between doses. An analysis of immune response data suggests that flexibility of ±1 month for Dose 2 (i.e., Month 1 to Month 3 in the vaccination regimen) and flexibility of ±2 months for Dose 3 (i.e., Month 4 to Month 8 in the vaccination regimen) do not substantially impact the immune responses to GARDASIL (see DOSAGE AND ADMINISTRATION).

Immune Responses to GARDASIL Using a 2-dose Schedule
A clinical trial showed that, at Month 7, the immune response in girls aged 9-13 years (n=259) who received 2 doses of GARDASIL (at 0, 6 months) was not inferior to the immune response in women aged 16-26 years (n=310) who received 3 doses of GARDASIL (at 0, 2, 6 months).

At 36 month follow-up, the GMT in girls (2 doses) remained non-inferior to the GMT in women (3 doses) for all 4 HPV types.

The duration of immunity following a 2-dose schedule has been observed for up to 10 years post-vaccination. At 120 month follow-up, the GMT in girls (2 doses, n = 35) remained non-inferior to the GMT in women (3 doses, n = 30) for all 4 HPV types. Among the girls receiving 2 doses of the vaccine, seropositivity rates were >95% for HPV6, 11, and 16, and >80% for HPV 18, in the cLIA.

Studies with Other Vaccines
HBvaxPRO [hepatitis B vaccine (recombinant)]
The safety and immunogenicity of co-administration of GARDASIL with HBvaxPRO [hepatitis B vaccine (recombinant)] (same visit, injections at separate sites) were evaluated in a randomized study of 1,871 women aged 16 through 24 years at enrollment. Immune response and safety profile to both HBvaxPRO [hepatitis B vaccine (recombinant)] and GARDASIL were similar whether they were administered at the same visit or at a different visit.

Repevax [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content)]
The safety and immunogenicity of co-administration of GARDASIL with Repevax [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content)] (same visit, injections at separate sites) were evaluated in a randomized study of 843 boys and girls 11 through 17 years of age at enrollment. Concomitant administration of GARDASIL with Repevax [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content)] does not interfere with the antibody response to any of the components of either vaccine. In addition, the safety profile was generally similar (see SIDE EFFECTS, *Concomitant Administration with Other Vaccines).*

Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)]
The safety and immunogenicity of co-administration of GARDASIL with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] (same visit, injections at separate sites) were evaluated in a randomized study of 1040 boys and girls 11 through 17 years of age at enrollment. Concomitant administration of GARDASIL with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] does not interfere with the antibody response to any of the components of any of the vaccines. In addition, the safety profile was generally similar (see SIDE EFFECTS, *Concomitant Administration with Other Vaccines).*

V. INDICATIONS

GARDASIL is a vaccine indicated in girls and women 9-45 years of age for the prevention of cervical, vulvar, vaginal cancer; precancerous or dysplastic lesions and genital warts caused by Human Papillomavirus (HPV). GARDASIL also provides protection in girls and women 9-26 years against anal cancer.

GARDASIL is indicated to prevent the following diseases

- Cervical vulvar and vaginal, and anal cancer caused by HPV types 16 and 18
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

and the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16 and 18:

- Cervical intraepithelial neoplasia (CIN) grade 2/3 and Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 1
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

GARDASIL is indicated in boys and men 9 through 26 years of age for the prevention of the following diseases caused by HPV types included in the vaccine:

- Anal cancer caused by HPV types 16 and 18
- Genital warts (condyloma acuminate) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16 and 18:

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

VI. DOSAGE AND ADMINISTRATION

Dosage
GARDASIL should be administered intramuscularly as 3 separate 0.5-mL doses according to the following schedule:

First dose: at elected date
Second dose: 2 months after the first dose
Third dose: 6 months after the first dose

Individuals are encouraged to adhere to the 0, 2, and 6 months vaccination schedule. However, in clinical studies, efficacy has been demonstrated in individuals who have received all 3 doses within a 1-year period. The second dose should be administered at least 1 month after the first dose, and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period.

Alternatively, in individuals 9 through 13 years of age, GARDASIL can be administered according to a 2-dose (0, 6 months) schedule.

The use of GARDASIL should be in accordance with official recommendations.

It is recommended that individuals who receive a first dose of GARDASIL complete the vaccination course with GARDASIL.

The need for a booster dose has not been established.

Method of Administration
GARDASIL should be administered intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

GARDASIL must not be injected intravascularly. Neither subcutaneous nor intradermal administration has been studied. These methods of administration are not recommended.

The prefilled syringe is for single use only and should not be used for more than one individual. For single-use vials a separate sterile syringe and needle must be used for each individual.

The vaccine should be used as supplied; no dilution or reconstitution is necessary. The full recommended dose of the vaccine should be used.

Shake well before use. Thorough agitation immediately before administration is necessary to maintain suspension of the vaccine.

After thorough agitation, GARDASIL is a white, cloudy liquid. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the product if particulates are present or if it appears discolored.

Single-dose Vial Use
Withdraw the 0.5-mL dose of vaccine from the single-dose vial using a sterile needle and syringe free of preservatives, antiseptics, and detergents. Once the single-dose vial has been penetrated, the withdrawn vaccine should be used promptly, and the vial must be discarded.

Prefilled Syringe Use
Inject the entire contents of the syringe.

VII. CONTRAINDICATIONS

Hypersensitivity to the active substances or to any of the excipients of the vaccine.

Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of GARDASIL should not receive further doses of GARDASIL.

VIII. PRECAUTIONS

General
The health care provider should inform the patient, parent, or guardian that vaccination does not substitute for routine cervical cancer screening. Women who receive GARDASIL should continue to undergo cervical cancer screening per standard of care.

GARDASIL has not been demonstrated to provide protection against disease from vaccine and non-vaccine HPV types to which a woman has previously been exposed through sexual activity.

The decision to vaccinate an individual should take into account the risk for previous HPV exposure and potential benefit from vaccination.

As for any vaccine, vaccination with GARDASIL may not result in protection in all vaccine recipients.

GARDASIL is for prophylactic use only and has no effect on active HPV infections or established clinical disease. GARDASIL has not been shown to have a therapeutic effect. The vaccine is not intended to be used for treatment of active external genital lesions; cervical, vulvar, vaginal, or anal cancers; CIN, VIN, VaIN, or AIN.

This vaccine has not been definitively shown to protect against disease caused by HPV types that are not included in the vaccine.

Not all vulvar and vaginal cancers are caused by HPV and GARDASIL protects only against those vulvar and vaginal cancers caused by HPV 16 and 18.

This vaccine will not protect against diseases that are not caused by HPV.

As with all injectable vaccines, appropriate medical treatment should always be readily available in case of rare anaphylactic reactions following the administration of the vaccine.

Syncope (fainting) may follow any vaccination, especially in adolescents and young adults. Syncope, sometimes associated with falling, has occurred after vaccination with GARDASIL. Therefore, vaccinees should be carefully observed for approximately 15 minutes after administration of GARDASIL (See SIDE EFFECTS, *Post-Marketing Reports*).

The decision to administer or delay vaccination because of a current or recent febrile illness depends largely on the severity of the symptoms and their etiology. Low-grade fever itself and mild upper respiratory infection are not generally contraindications to vaccination.

Individuals with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, Human Immunodeficiency Virus (HIV) infection, or other causes, may have reduced antibody response to active immunization (see DRUG INTERACTIONS).

This vaccine should be given with caution to individuals with thrombocytopenia or any coagulation disorder because bleeding may occur following an intramuscular administration in these individuals.

IX. PREGNANCY

Studies in Female Rats
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development. GARDASIL induced a specific antibody response against HPV types 6, 11, 16, and 18 in pregnant rats following one or multiple intramuscular injections. Antibodies against all 4 HPV types were transferred to the offspring during gestation and possibly during lactation.

Clinical Studies in Humans
There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, pregnancy should be avoided during the vaccination regimen for GARDASIL.

In clinical studies, women underwent urine pregnancy testing prior to administration of each dose of GARDASIL. Women who were found to be pregnant before completion of a 3-dose regimen of GARDASIL were instructed to defer completion of their vaccination regimen until resolution of the pregnancy. Such non-standard regimens resulted in Postdose 3 anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses that were comparable to those observed in women who received a standard 0, 2, and 6 month vaccination regimen (see DOSAGE AND ADMINISTRATION).

During clinical trials, 3,819 women (vaccine N = 1,894 vs. placebo N = 1,925) reported at least one pregnancy. The overall proportions of pregnancies that resulted in an adverse outcome defined as the combined numbers of spontaneous abortion, late fetal death and congenital anomaly cases out of the total number of pregnancy outcomes for which an outcome was known (and excluding elective terminations), were 22.6% (446/1,973) in individuals who received GARDASIL and 23.1% (460/1,994) in individuals who received placebo.

Further sub-analyses were done to evaluate pregnancies with estimated onset within 30 days or more than 30 days from administration of a dose of GARDASIL or placebo. For pregnancies with estimated onset within 30 days of vaccination, 5 cases of congenital anomaly were observed in the group that received GARDASIL compared to 1 case of congenital anomaly in the group that

received placebo. Conversely, in pregnancies with onset more than 30 days following vaccination, 40 cases of congenital anomaly were observed in the group that received GARDASIL compared with 33 cases of congenital anomaly in the group that received placebo. The types of anomalies observed were consistent (regardless of when pregnancy occurred in relation to vaccination) with those generally observed in pregnancies in women aged 16 through 45 years.

Thus, there is no evidence to suggest that administration of GARDASIL adversely affects fertility, pregnancy, or infant outcomes.

X. NURSING MOTHERS

It is not known whether vaccine antigens or antibodies induced by the vaccine are excreted in human milk.

GARDASIL may be administered to lactating women.

GARDASIL or placebo were given to a total of 1,133 women who were breast feeding at any time during the relevant Phase III clinical studies. In these studies, the rates of adverse experiences in the mother and the nursing infant were comparable between vaccination groups. In addition, vaccine immunogenicity was comparable among nursing mothers and women who did not nurse during the vaccine administration.

XI. PEDIATRIC USE

The safety and efficacy of GARDASIL have not been evaluated in children younger than 9 years.

XII. USE IN ELDERLY

The efficacy of GARDASIL has not been evaluated in adults above the age of 45 years.

XIII. USE IN OTHER SPECIAL POPULATIONS

The safety, immunogenicity, and efficacy of GARDASIL have not been fully evaluated in HIV-infected individuals.

XIV. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no data to suggest that GARDASIL affects the ability to drive or operate machinery.

XV. DRUG INTERACTIONS

Use with Other Vaccines
Results from clinical studies indicate that GARDASIL may be administered concomitantly (at a separate injection site) with HBvaxPRO® [hepatitis B vaccine (recombinant)], Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine], Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)], and Repevax [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content)].

Use with Common Medications
In clinical studies for girls and women (aged 16 to 26 years), 11.9%, 9.5%, 6.9%, and 4.3% of individuals used analgesics, anti-inflammatory drugs, antibiotics, and vitamin preparations,

respectively. In a clinical study in women (aged 24 to 45 years), 30.6%, 20.2%, 11.6%, and 7.5% of individuals used analgesics, anti-inflammatory drugs, antibiotics, and vitamin preparations, respectively. Conversely in a clinical study in boys and men (aged 16 to 26 years), 10.3%, 7.8%, 6.8%, 3.4% and 2.6% of individuals used analgesics, anti-inflammatory drugs, antibiotics, antihistamines, and vitamin preparations, respectively. The efficacy, immunogenicity, and safety of the vaccine were not impacted by the use of these medications.

Use with Hormonal Contraceptives
In clinical studies, 50.2% of women (aged 16 to 45 years) who received GARDASIL used hormonal contraceptives. Use of hormonal contraceptives did not appear to affect the immune responses to GARDASIL.

Use with Steroids
In clinical studies for girls and women (aged 16 to 26 years), 1.7% (n = 158), 0.6% (n = 56), and 1.0% (n = 89) of individuals used inhaled, topical, and parenteral immunosuppressants, respectively. In a clinical study in women (aged 24 to 45 years), 1.4% (n = 27) used corticosteroids for systemic use. In a clinical study in boys and men (aged 16 to 26 years), 1.0% (n = 21) used corticosteroids for systemic use. The corticosteroids for all individuals were administered close to the time of administration of a dose of GARDASIL. These medicines did not appear to affect the immune responses to GARDASIL. Very few individuals in the clinical studies were taking steroids, and the amount of immunosuppression is presumed to have been low.

Use with Systemic Immunosuppressive Medications
There are no data on the concomitant use of potent immunosuppressants with GARDASIL. Individuals receiving therapy with immunosuppressive agents (systemic doses of corticosteroids, antimetabolites, alkylating agents, cytotoxic agents) may not respond optimally to active immunization (see PRECAUTIONS, *General*).

XVI. SIDE EFFECTS

Clinical Trials
In 7 clinical trials (6 placebo-controlled), individuals were administered GARDASIL or placebo on the day of enrollment and approximately 2 and 6 months thereafter. GARDASIL demonstrated a favorable safety profile when compared with placebo (aluminum or non-aluminum containing). Few individuals (0.2%) discontinued due to adverse experiences. In all except one of the clinical trials, safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of GARDASIL or placebo. The individuals who were monitored using VRC-aided surveillance included 10,088 individuals (6,995 girls and women 9 through 45 years of age and 3,093 boys 9 through 26 years of age at enrollment) who received GARDASIL and 7,995 individuals who received placebo.

The vaccine-related adverse experiences that were observed among recipients of GARDASIL at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients are listed according to frequency and system organ class.

The frequency classifications are as follows:
Very Common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1,000, <1/100); Rare (≥1/10,000, <1/1,000); Very Rare (<1/10,000)

Vaccine-Related Clinical Adverse Experiences in 9- Through 45-Year-Old Girls and Women

Nervous system disorders
Very Common: *headache*

Common: *dizziness*

Gastrointestinal disorders
Common: *nausea*

Musculoskeletal and connective tissue disorders
Common: *pain in extremity*

General disorders and administration site conditions
Very Common: *pyrexia*

The following injection-site reactions occurred at a greater incidence in the group that received GARDASIL compared with either the amorphous aluminum hydroxyphosphate sulfate adjuvant-containing or the saline placebo group: Very common*: erythema, pain and swelling*. Common: pruritus and hematoma.

Most injection-site reactions were mild to moderate.

In addition, bronchospasm was reported very rarely as a serious adverse experience.

Vaccine-Related Clinical Adverse Experiences in 9- Through 26-Year-Old Boys and Men

Nervous system disorders
Common: *headache*

General disorders and administration site conditions
Common: *pyrexia*

The following injection-site reactions occurred at a greater incidence in the group that received GARDASIL compared with either the amorphous aluminum hydroxyphosphate sulfate adjuvant-containing or the saline placebo group: Very common: erythema, pain and swelling

The following injection-site reaction occurred at a greater incidence in the group that received GARDASIL compared with the amorphous aluminum hydroxyphosphate sulfate adjuvant-containing placebo group: Common: *hematoma*

Most injection-site reactions were mild to moderate.

Concomitant Administration with Other Vaccines
The safety of GARDASIL when administered concomitantly with other vaccines was evaluated in clinical studies.

The frequency of adverse experiences observed with concomitant administration with hepatitis B vaccine (recombinant) was similar to the frequency when GARDASIL was administered alone.

There was an increase in headache and injection-site swelling when GARDASIL was given concomitantly with Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content).

There was an increase in injection-site swelling when GARDASIL was given concomitantly with Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine and Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap).

The majority of these adverse experiences seen with concomitant administration with other vaccines were reported as being mild to moderate in intensity.

Post- Marketing Reports
The following adverse experiences have been spontaneously reported during post-approval use of GARDASIL. Because these experiences were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish a causal relationship to vaccine exposure.

Infections and infestations: cellulitis

Blood and lymphatic system disorders: idiopathic thrombocytopenic purpura, lymphadenopathy

Nervous system disorders: acute disseminated encephalomyelitis, dizziness, Guillain-Barré syndrome, headache, syncope sometimes accompanied by tonic-clonic movements.

Gastrointestinal disorders: nausea, vomiting.

Musculoskeletal and connective tissue disorders: arthralgia, myalgia.

General disorders and administration site conditions: asthenia, chills, fatigue, malaise.

Immune system disorders: Hypersensitivity reactions including anaphylactic/anaphylactoid reactions, bronchospasm, and urticaria.

XVII. OVERDOSAGE

There have been reports of administration of higher than recommended doses of GARDASIL.
In general, the adverse event profile reported with overdose was comparable to recommended single doses of GARDASIL.

XVIII. APPEARANCE AND AVAILABILITY

Sterile, white, cloudy, liquid suspension.
Packed in 0.5mL single dose vials (1s and 10s) and syringes (1s and 10s).

XIX. STORAGE

Store refrigerated at 2 to 8°C (36 to 46°F). Do not freeze. Protect from light.

GARDASIL should be administered as soon as possible after being removed from refrigeration. GARDASIL can be out of refrigeration (at temperatures at or below 25°C (77°F), for a total time of not more than 72 hours.

XX. SHELF LIFE

Please refer to expiry date on the outer carton.

XXI. MANUFACTURER

MERCK SHARP & DOHME LLC
Sumneytown Pike

West Point, PA 19486, U.S.A.

XXII. REPACKER AND RELEASER

MERCK SHARP & DOHME BV
Waarderweg 39, Haarlem,
2031 BN, Netherlands.

XXIII. PRODUCT REGISTRATION HOLDER

MERCK SHARP & DOHME (MALAYSIA) SDN. BHD.
Lot No. B-22-1 & B-22-2, Level 22
The Ascent, Paradigm No. 1
Jalan SS 7/26A, Kelana Jaya
47301 Petaling Jaya
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