**Attachment 1: Product information for AusPAR GARDASIL 9, Human Papillomavirus 9-Valent Vaccine. Merck Sharp & Dohme Australia Pty Ltd PM-2014-01099-1- Final 3 January 2017. This Product Information was approved at the time this AusPAR was published.**

**PRODUCT INFORMATION**

# GARDASIL®9

[Human Papillomavirus 9-valent (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) vaccine, Recombinant]

## DESCRIPTION

GARDASIL 9, Human Papillomavirus 9-valent Vaccine, Recombinant, is a non-infectious recombinant 9-valent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

The L1 proteins are produced by separate fermentations using recombinant yeast *Saccharomyces cerevisiae* and self-assembled into VLPs. The fermentation process involves growth of *S. cerevisiae* on chemically-defined fermentation media which include vitamins, amino acids, mineral salts, and carbohydrates. The VLPs are released from the yeast cells by cell disruption and purified by a series of chemical and physical methods. The purified VLPs are adsorbed on pre-formed aluminum-containing adjuvant (Amorphous Aluminum Hydroxyphosphate Sulfate or AAHS). The 9-valent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of the aluminum-containing adjuvant formulation and the final purification buffer.

GARDASIL 9 is a sterile preparation for intramuscular administration. Each 0.5-mL dose contains approximately 30 mcg of HPV 6 L1 protein, 40 mcg of HPV 11 L1 protein, 60 mcg of HPV 16 L1 protein, 40 mcg of HPV 18 L1 protein, 20 mcg of HPV 31 L1 protein, 20 mcg of HPV 33 L1 protein, 20 mcg of HPV 45 L1 protein, 20 mcg of HPV 52 L1 protein, and 20 mcg of HPV 58 L1 protein.

Each 0.5-mL dose of the vaccine contains approximately 500 mcg of aluminium (as amorphous aluminium 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 , residual traces (<7mcg/dose) of yeast protein and water for injection. The product does not contain a preservative or antibiotics.

## PHARMACOLOGY

GARDASIL 9 is a recombinant vaccine that protects against 9 genotypes of Human Papillomavirus (HPV). Each virus-like particle (VLP) is composed of a unique recombinant L1 major capsid protein for the respective HPV type. Because the virus-like particles contain no viral DNA, they cannot infect cells or reproduce. GARDASIL 9 contains the 4 HPV types (6, 11, 16, and 18) that are in GARDASIL plus an additional 5 HPV types (31, 33, 45, 52, and 58) absorbed on amorphous aluminum hydroxyphosphate adjuvant (AAHS).

HPV only infects humans. Animal studies with analogous animal papillomaviruses suggest that the efficacy of L1 VLP vaccines may involve the development of humoral immune responses. Humans develop a humoral immune response to the vaccine although the exact mechanism of protection is unknown.

## CLINICAL STUDIES

HPV infection is very common; in the absence of vaccination, the majority of sexually active individuals will become infected with HPV during their lifetime.

Most HPV infections clear without sequelae but some progress to HPV-related diseases including cervical cancers and their precursors (Cervical Intraepithelial Neoplasia or CIN grades 1, 2, and 3), anal, vulvar, vaginal, and penile cancers and their precursors (Anal Intraepithelial Neoplasia or AIN, Vulvar Intraepithelial Neoplasia or VIN, Vaginal Intraepithelial Neoplasia or VaIN and Penile Intraepithelial Neoplasia or PIN), genital warts, and lesions in the aerodigestive tract including oropharyngeal cancers and recurrent respiratory papillomatosis.

In female subjects, 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.

In male subjects, penile/perineal/perianal intraepithelial neoplasia (PIN) 1 (low grade) and PIN 3 (high grade) has been associated with HPV. HPV 16 is the most common type detected.

GARDASIL 9 is a recombinant vaccine with L1 proteins resembling 9 HPV types. GARDASIL 9 includes the same four HPV types contained in GARDASIL (HPV 6, 11, 16, 18) and five additional HPV types (31, 33, 45, 52, and 58).

### Efficacy Data for GARDASIL

GARDASIL was first licensed in 2006. Efficacy was assessed in 6 AAHS-controlled, double-blind, randomized Phase II and III clinical studies evaluating 28,413 individuals (20,541 girls and women 16 through 26 years of age, 4,055 boys and men 16 through 26 years of age. The median duration of follow up in these studies ranged from 2.9 through to 4.0 years, with a maximum follow up of 5 years.

GARDASIL was efficacious in reducing the incidence of CIN (any grade including CIN 2/3); AIS; genital warts; VIN (any grade); and VaIN (any grade) related to vaccine HPV types 6, 11, 16, or 18 in those girls and women who were PCR negative and seronegative at baseline (Table 1). In addition, girls and women who were already infected with one or more vaccine-related HPV types prior to vaccination were protected from precancerous cervical lesions and external genital lesions caused by the other vaccine HPV types. Individuals who had prior infection that had been resolved before vaccination (PCR negative and seropositive at baseline) were protected from reinfection or recurrence of infection leading to clinical disease with the same HPV type.

GARDASIL was efficacious in reducing the incidence of external genital lesions (Genital Warts and PIN grades 1/2/3) and persistent infection related to vaccine HPV types 6, 11, 16,

or 18 in boys and men who were PCR negative and seronegative at baseline (Table 1). 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 boys and men who were PCR negative and seronegative at baseline (Table 1).

**Table 1: Analysis of Efficacy of GARDASIL in the Per Protocol Efficacy (PPE)* Population for Vaccine HPV Types**

| Disease Endpoints | GARDASIL | | AAHS Control | | % Efficacy (95% CI) |
|---|---|---|---|---|---|
| | N | Number of cases | N | Number of cases | |
| **16- Through 26-Year-Old Girls and Women†** | | | | | |
| **HPV 16- or 18-related CIN 2/3 or AIS** | 8493 | 2 | 8464 | 112 | 98.2 (93.5, 99.8) |
| **HPV 16- or 18-related VIN 2/3** | 7772 | 0 | 7744 | 10 | 100.0 (55.5, 100.0) |
| **HPV 16- or 18-related VaIN 2/3** | 7772 | 0 | 7744 | 9 | 100.0 (49.5, 100.0) |
| **HPV 6-, 11-, 16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS** | 7864 | 9 | 7865 | 225 | 96.0 (92.3, 98.2) |
| **HPV 6-, 11-, 16-, or 18-related Genital Lesions (Genital Warts, VIN, VaIN, Vulvar Cancer, and Vaginal Cancer)** | 7900 | 2 | 7902 | 227 | 99.1 (96.8, 99.9) |
| **HPV 6- and 11-related Genital Warts** | 6932 | 2 | 6856 | 189 | 99.0 (96.2, 99.9) |
| **16- Through 26-Year-Old Boys and Men** | | | | | |
| **External Genital Lesions HPV 6-, 11-, 16-, or 18-related** | | | | | |
| **External Genital Lesions** | 1394 | 3 | 1404 | 32 | 90.6 (70.1, 98.2) |
| **Genital Warts** | 1394 | 3 | 1404 | 28 | 89.3 (65.3, 97.9) |
| **PIN 1/2/3** | 1394 | 0 | 1404 | 4 | 100.0 (<0.0, 100.0) |
| **HPV 6-, 11-, 16-, or 18-related Endpoint** | | | | | |
| **AIN 1/2/3** | 194 | 5 | 208 | 24 | 77.5 (39.6, 93.3) |
| **AIN 2/3** | 194 | 3 | 208 | 13 | 74.9 (8.8, 95.4) |
| **AIN 1** | 194 | 4 | 208 | 16 | 73.0 (16.3, 93.4) |

*The PPE 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).
†Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria.
N=Number of individuals with at least 1 follow-up visit after Month 7
CI=Confidence Interval
Note 1: Point estimates and confidence intervals are adjusted for person-time of follow-up.
Note 2: The first analysis in the table (i.e., HPV 16- or 18-related CIN 2/3, AIS or worse) was the primary endpoint of the vaccine development plan.
Note 3: Table 1 does not include cases due to non-vaccine HPV types.
AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

A minimum anti-HPV level that provides protection against HPV infection and disease has not been defined. Also, immune responses to vaccines are typically lower in older individuals compared to younger individuals. Therefore, to confirm the utility of GARDASIL to prevent cervical, vulvar, and vaginal cancers and related diseases caused by the types targeted by the vaccine in individuals up to and including age 45 years, an efficacy study was conducted.

GARDASIL was highly efficacious in reducing the incidence of persistent infection; CIN (any grade); and external genital lesions (EGL) caused by HPV types 6, 11, 16, and 18. GARDASIL was also highly efficacious in reducing the incidence of a HPV 16/18-related Pap Test diagnosis of ASC-US (Atypical Squamous Cells of Undetermined Significance) positive for high-risk HPV. The primary analyses of efficacy, with respect to HPV types 6, 11, 16, and

18, were conducted in the per-protocol efficacy (PPE) population. Efficacy was measured starting after the Month 7 visit (Table 2).

On the basis of these efficacy findings, the efficacy of GARDASIL with respect to prevention of cervical, vulvar, and vaginal cancers and related diseases in individuals up to and including age 45 years can be inferred.

**Table 2 Analysis of Efficacy of GARDASIL in the PPE Population of 24- Through 45-Year-Old Women**

| Endpoint | GARDASIL | | Placebo | | % Efficacy (95% CI) |
|---|---|---|---|---|---|
| | n | Number of cases | n | Number of cases | |
| HPV 6-, 11-, 16-, or 18-related CIN (any grade), Persistent Infection, or EGL | 1,601 | 10* | 1,599 | 86 | 88.7 (78.1, 94.8) |
| HPV 16- or 18-related CIN (any grade), Persistent Infection, or EGL | 1,587 | 8 | 1,571 | 51 | 84.7 (67.5, 93.7) |
| HPV 6- or 11-related CIN (any grade), Persistent Infection, or EGL | 1,316 | 2 | 1,316 | 38 | 94.8 (79.9, 99.4) |
| HPV 16/18-related Pap Diagnosis of ASC-US Positive for High-risk HPV | 1,565 | 1 | 1,557 | 27 | 96.3 (77.7, 99.9) |

*There was 1 case of CIN 2 (HPV 16 and HPV 51 identified) in the PPE group. The CIN 2 case was positive for HPV types 16 and 51 at a Month 18 biopsy. The remaining 9 cases in the PPE group were persistent infection endpoints.
CI = Confidence Interval
ASC-US = Atypical Squamous Cells of Undetermined Significance

## Clinical Trials for GARDASIL 9

Efficacy and/or immunogenicity of GARDASIL 9 were assessed in six clinical studies. Clinical studies evaluating the efficacy of GARDASIL 9 against placebo were not acceptable because HPV vaccination represents the standard of care for protection against HPV infection and disease in many countries. Therefore, the pivotal clinical study (Protocol 001) evaluated the efficacy of GARDASIL 9 to prevent HPV-related cervical, vulvar, and vaginal disease using GARDASIL as a comparator.

Efficacy against HPV Types 6, 11, 16, and 18 was primarily assessed using a bridging strategy that demonstrates comparable immunogenicity (as measured by Geometric Mean Titers [GMT]) of GARDASIL 9 compared with GARDASIL (Protocols 001, 002, and 009).

The analysis of efficacy for GARDASIL 9 was evaluated in the PPE population of 16- through 26-year-old women, who were naïve to the relevant HPV type(s) prior to dose one and through 1 month Postdose 3 (Month 7). Overall, approximately 52% of subjects were negative to all vaccine HPV types by both PCR and serology at Day 1.

The primary analysis of efficacy against HPV Types 31, 33, 45, 52, and 58 is based on a combined endpoint of Cervical Intraepithelial Neoplasia (CIN) 2, CIN 3, Adenocarcinoma in situ (AIS), invasive cervical carcinoma, Vulvar Intraepithelial Neoplasia (VIN) 2/3, Vaginal Intraepithelial Neoplasia (VaIN) 2/3, vulvar cancer, or vaginal cancer. Other endpoints evaluated include cervical, vulvar , and vaginal disease of any grade; persistent infection; cytological abnormalities and invasive procedures. For all endpoints, the efficacy against the HPV Types in GARDASIL 9 (31, 33, 45, 52, and 58) was evaluated compared to GARDASIL.

The efficacy is further extended to 9- through 15-year-old adolescents, for all endpoints

studied, using immunological bridging. The immunogenicity bridging analyses were performed in the per-protocol immunogenicity (PPI) 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 (PCR negative and seronegative) to the relevant HPV type(s) prior to dose 1 and through Month 7.

Protocol 001 evaluated efficacy and immunogenicity of GARDASIL 9 to prevent infection and disease caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in 16- through 26-year-old girls and women (N = 14,204: 7,099 receiving GARDASIL 9; 7,105 receiving GARDASIL). Two immunological bridging studies evaluated HPV types 6, 11, 16 and 18 (Protocols 002 and 009) and HPV types 31, 33, 45, 52, and 58 (Protocol 002). Protocol 002 evaluated immunogenicity of GARDASIL 9 in girls and boys 9 through 15 years of age and women 16 through 26 years of age (N=3,066: 1,932 girls; 666 boys; and 468 women receiving GARDASIL 9). Protocol 009 evaluated immunogenicity in girls 9 through 15 years of age (N=600; 300 receiving GARDASIL 9 and 300 receiving GARDASIL).

Protocol 006 evaluated administration of GARDASIL 9 to girls and women 12 through 26 years of age previously vaccinated with GARDASIL (N=921; 615 receiving GARDASIL 9 and 306 receiving placebo). Protocols 005 and 007 evaluated GARDASIL 9 concomitantly administered with vaccines recommended routinely in girls and boys 11 through 15 years of age (N=2,295). Together, these six studies evaluated 13,360 individuals who received GARDASIL 9 (8,053 girls and women 16 through 26 years of age at enrollment with a mean age of 21.8 years; 3,498 girls 9 through 15 years of age at enrollment with a mean age of 12.0 years; and 1,809 boys 9 through 15 years of age at enrollment with a mean age of 12.1 years.

The totality of results from the clinical studies support that GARDASIL 9 was efficacious against HPV disease and persistent infection caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Therefore the efficacy for cervical, vulvar, vaginal, and anal diseases and persistent infection that was demonstrated in the original clinical studies for GARDASIL can be extended to GARDASIL 9. In clinical studies, protective efficacy has been shown to last at least 4 years in duration for GARDASIL 9 and 6 years in duration for GARDASIL.

**Comparison of Immune Responses Between GARDASIL 9 and GARDASIL for HPV Types 6, 11, 16, and 18 in the Clinical Studies for GARDASIL 9**

*Studies Supporting the Efficacy of GARDASIL 9 Against HPV Types 6, 11, 16, 18*

Because of the high efficacy of GARDASIL, there is no known immune correlate of protection. The minimal anti-HPV response associated with protection against HPV 6-, 11-, 16-, and 18-related infection and disease has not been established. In addition, the existence of HPV Types 6, 11, 16, and 18 antigens in both the formulations for GARDASIL 9 and the active comparator vaccine (GARDASIL) should result in no or few infection and disease endpoints associated with these HPV types. A low number of efficacy endpoints in both vaccination groups preclude a direct measurement of efficacy using disease endpoints associated with these HPV types.

GARDASIL 9 efficacy against HPV 6-, 11-, 16-, and 18-related infection and disease was inferred from comparative studies to a quadrivalent HPV vaccine, GARDASIL, in which GARDASIL 9 elicited immune responses as measured by GMT. These studies were designed to evaluate immunologic non-inferiority of GARDASIL 9 to GARDASIL. Therefore, the efficacy findings from the pivotal clinical studies for GARDASIL against HPV Type 6-, 11-, 16-, and 18-related disease were bridged to GARDASIL 9 by demonstrating that the

immune responses elicited by GARDASIL 9 were non-inferior to the immune responses elicited by GARDASIL.

Comparison of GARDASIL 9 with GARDASIL efficacy with respect to HPV types 6, 11, 16, and 18 were conducted in a population of 16- through 26-year-old women from Protocol 001 and 9- through 15-year-old girls from Protocol 009. The primary analyses were conducted in the per-protocol immunogenicity population which included subjects who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were HPV-naïve (seronegative and among female subjects 16 through 26 years of age in Protocols 001 and 002, PCR negative in cervicovaginal specimens) to the relevant HPV type(s) prior to dose 1 and through Month 7.

A statistical analysis of non-inferiority was performed at Month 7 cLIA anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs between individuals administered GARDASIL 9 and individuals administered GARDASIL. Immune responses, measured by GMT, for GARDASIL 9 were non-inferior to immune responses for GARDASIL (Table 3). Therefore, efficacy for GARDASIL 9 against persistent infection and disease related to HPV Types 6, 11, 16, or 18 can be inferred to be comparable to that of GARDASIL.

**Table 3: Comparison of Immune Responses (Based on cLIA) Between GARDASIL 9 and GARDASIL for HPV Types 6, 11, 16, and 18 in the Per Protocol Immunogenicity (PPI)* Population of 9- Through 26-Year-Old Girls and Women**

| POPULATION | GARDASIL 9 | | | GARDASIL | | | GARDASIL 9/ GARDASIL | |
|---|---|---|---|---|---|---|---|---|
| | N[†] (n[‡]) | % Seropositive (95% CI) | GMT (95% CI) mMU[§]/mL | N[†] (n[‡]) | % Seropositive (95% CI) | GMT (95% CI) mMU[§]/mL | GMT Ratio | (95% CI) |
| **Anti-HPV 6** | | | | | | | | |
| 9- through15-year-old girls | 300 (273) | 100 (98.7, 100) | 1679.4 (1518.9, 1856.9) | 300 (261) | 100 (98.6, 100) | 1565.9 (1412.2, 1736.3) | 1.07 | (0.93, 1.23) |
| 16- through 26-year-old girls and women | 6792 (3993) | 99.8 (99.6, 99.9) | 893.1 (871.7, 915.1) | 6795 (3975) | 99.8 (99.7, 99.9) | 875.2 (854.2, 896.8) | 1.02 | (0.99, 1.06)[¶] |
| **Anti-HPV 11** | | | | | | | | |
| 9- through 15-year-old girls | 300 (273) | 100 (98.7, 100) | 1315.6 (1183.8, 1462.0) | 300 (261) | 100 (98.6, 100) | 1417.3 (1274.2, 1576.5) | 0.93 | (0.80, 1.08) |
| 16- through 26-year-old girls and women | 6792 (3995) | 100 (99.9, 100) | 666.3 (649.6, 683.4) | 6795 (3982) | 99.9 (99.8, 100) | 830.0 (809.2, 851.4) | 0.80 | (0.77, 0.83)[¶] |
| **Anti-HPV 16** | | | | | | | | |
| 9- through 15-year-old girls | 300 (276) | 100 (98.7, 100) | 6739.5 (6134.5, 7404.1) | 300 (270) | 100 (98.6, 100) | 6887.4 (6220.8, 7625.5) | 0.97 | (0.85, 1.11)[¶] |
| 16- through 26-year-old girls and women | 6792 (4032) | 100 (99.9, 100) | 3131.1 (3057.1, 3206.9) | 6795 (4062) | 100 (99.8, 100) | 3156.6 (3082.3, 3232.7) | 0.99 | (0.96, 1.03)[¶] |
| **Anti-HPV 18** | | | | | | | | |
| 9- through 15-year-old girls | 300 (276) | 100 (98.7, 100) | 1956.6 (1737.3, 2203.7) | 300 (269) | 100 (98.6, 100) | 1795.6 (1567.2, 2057.3) | 1.08 | (0.91, 1.29)[¶] |
| 16- through 26-year-old girls and women | 6792 (4539) | 99.8 (99.7, 99.9) | 804.6 (782.7, 827.1) | 6795 (4541) | 99.7 (99.5, 99.8) | 678.7 (660.2, 697.7) | 1.19 | (1.14, 1.23)[¶] |

*The PPI population consisted of individuals who received all 3 vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, 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).

†N=Number of individuals randomized to the respective vaccination group who received at least 1 injection

‡Number of individuals contributing to the analysis

§mMU=milli-Merck units

¶p-value <0.001

CI=Confidence Interval

GMT=Geometric Mean Titers

cLIA= Competitive Luminex Immunoassay

**Prophylactic Efficacy of GARDASIL 9 for HPV Types 31, 33, 45, 52, and 58 in Girls and Women 16 Through 26 Years of Age**

*Studies Supporting Efficacy of GARDASIL 9 Against HPV Types 31, 33, 45, 52, and 58*

The efficacy of GARDASIL 9 in 16- through 26- year-old women was assessed in an active comparator-controlled, double-blind, randomized clinical study (Protocol 001) that included a total of 14,204 women (GARDASIL 9 = 7,099; GARDASIL = 7,105), who were enrolled and vaccinated without pre-screening for the presence of HPV infection. Subjects were followed up to Month 54 with a median duration of follow-up of 40 months.

The primary efficacy is based on evaluation of a composite clinical endpoint of HPV 31-, 33-, 45-, 52-, and 58- related cervical cancer, vulvar cancer, vaginal cancer, CIN 2/3 or AIS, VIN 2/3, and VaIN 2/3. The efficacy is further supported by evaluation of HPV 31-, 33-, 45-, 52-, and 58-related cervical, vulvar, and vaginal disease of any grade, and persistent infection. In addition, the study also evaluated the impact of GARDASIL 9 on the rates of HPV 31-, 33-, 45-, 52-, and 58- related abnormal Pap tests, cervical and external genital procedures (i.e., biopsies) and cervical definitive therapy procedures.

Efficacy was evaluated in the PPE population of 16- through 26-year-old women, who were naïve to the relevant HPV type(s) prior to dose one and through Month 7. Efficacy was measured starting after the Month 7 visit. GARDASIL 9 was efficacious in preventing HPV 31-, 33-, 45-, 52-, and 58- related persistent infection and disease (Table 4). GARDASIL 9 also reduced the incidence of HPV 31-, 33-, 45-, 52-, and 58- related Pap test abnormalities, cervical and external genital procedures (i.e., biopsies), and cervical definitive therapy procedures (Table 4).

**Table 4: Analysis of Efficacy of GARDASIL 9 Against HPV Types 31, 33, 45, 52, and 58 in the PPE* Population 16- Through 26-Year-old Women**

| Disease Endpoint | GARDASIL 9 N†=7099 | | GARDASIL N†=7105 | | %Efficacy (95% CI) |
|---|---|---|---|---|---|
| | n‡ | Number of cases | n‡ | Number of cases | |
| **HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer** | 6016 | 1 | 6017 | 30 | 96.7 (80.9, 99.8) |
| **HPV 31-, 33-, 45-, 52-, 58-related CIN 1** | 5948 | 1 | 5943 | 69 | 98.6 (92.4, 99.9) |
| **HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3 or AIS** | 5948 | 1 | 5943 | 27 | 96.3 (79.5, 99.8) |
| **HPV 31-, 33-, 45-, 52-, 58-related Vulvar or Vaginal Disease** | 6009 | 1 | 6012 | 16 | 93.8 (61.5, 99.7) |
| **HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥6 Months§** | 5939 | 35 | 5953 | 810 | 96.0 (94.4, 97.2) |
| **HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥12 Months¶** | 5939 | 21 | 5953 | 544 | 96.3 (94.4, 97.7) |
| **HPV 31-, 33-, 45-, 52-, 58-related ASC-US HR-HPV Positive or Worse Pap# Abnormality** | 5881 | 35 | 5882 | 462 | 92.6 (89.7, 94.8) |
| **HPV 31-, 33-, 45-, 52-, 58-related Biopsy** | 6016 | 7 | 6017 | 222 | 96.9 (93.6, 98.6) |
| **HPV 31-, 33-, 45-, 52-, 58-related Definitive Therapy** | 6012 | 4 | 6014 | 32 | 87.5 (65.7, 96.0) |

*The PPE 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 31, 33, 45, 52, and 58) prior to dose 1 and through 1 month postdose 3 (Month 7).
†N=Number of individuals randomized to the respective vaccination group who received at least 1 injection
‡Number of individuals contributing to the analysis
§Persistent infection detected in samples from two or more consecutive visits 6 months (±1 month visit windows)

apart
¶Persistent infection detected in samples from two or more consecutive visits over 12 months or longer
#Papanicolaou test
CI=Confidence Interval
ASC-US=Atypical squamous cells of undetermined significance
HR=High Risk

### Evaluation of the Efficacy for GARDASIL 9 Against Overall HPV Disease Burden

The efficacy of GARDASIL 9 against the overall incidence of cervical, vulvar and vaginal diseases; Papanicolaou (Pap) test abnormalities; and invasive cervical and external genital procedures; regardless of HPV detection, results from a combination of prophylactic efficacy against vaccine HPV types, pre-existing disease caused by vaccine HPV types, disease caused by HPV types not contained in the vaccine, and disease not caused by HPV.

An efficacy analysis against disease endpoints regardless of HPV detection was conducted in the All HPV naïve (All HN) population of 16- through 26-year-old women from Protocol 001. The All HN population represents a generally 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 adolescents and women plus women shortly after sexual debut. This population is a substitute for a truly HPV-naïve population and represents the majority of likely vaccine recipients.

Because Protocol 001 evaluated the efficacy of GARDASIL 9 using GARDASIL as an active comparator, a comprehensive estimate of efficacy regardless of HPV detection required that GARDASIL 9 be compared relative to historical GARDASIL and placebo cohorts from clinical studies that supported the initial licensure for GARDASIL. This estimated efficacy in the population of women in Protocol 001 was affected by HPV infection prevalence and risk of exposure in the populations at the time the studies were conducted.

GARDASIL 9 reduced the overall incidence of cervical, vulvar, and vaginal disease (Table 5).

**Table 5: Efficacy of GARDASIL 9 Against the Overall Incidence of Cervical, Vulvar, and Vaginal Disease Irrespective of HPV in the All HN* Population**

| Disease Endpoint | Protocol 001 | | | | Historical Cohorts† | | | | % Reduction of GARDASIL 9 vs. Historical Placebo (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| | GARDASIL 9 N‡=7099 | | GARDASIL N‡=7105 | | GARDASIL N‡=9075 | | Placebo N‡=9075 | | |
| | n§ | Number of cases | n§ | Number of cases | n§ | Number of cases | n§ | Number of cases | |
| CIN 1/2/3, AIS or Cervical Cancer | 2976 | 133 | 3009 | 178 | 4696 | 276 | 4759 | 400 | 47.1 (30.6, 59.7) |
| CIN 2 or Worse | 2976 | 26 | 3009 | 41 | 4696 | 77 | 4759 | 137 | 62.8 (34.8, 78.8) |
| Condyloma | 3032 | 10 | 3076 | 13 | 4771 | 29 | 4816 | 169 | 86.1 (66.0, 94.3) |
| VIN 2/3, VaIN 2/3 or Worse | 3032 | 0 | 3076 | 2 | 4771 | 8 | 4816 | 32 | 94.6 (-23.3, 99.8) |

*The All HN Population consisted of individuals who received at least 1 vaccination and who had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1 and were naïve to 14 common HPV types at Day 1. Case counting started at Day 1 following vaccination.
†Historical cohorts included GARDASIL and placebo groups from clinical studies that supported initial licensure of GARDASIL.
‡N=Number of individuals randomized to the respective vaccination group who received at least 1 injection
§Number of individuals contributing to the analysis
CI=Confidence Interval

The actual population benefit of GARDASIL 9 can vary widely depending on subject characteristics. The overall benefit will vary with the incidence of infection and disease against which GARDASIL 9 has shown protection and those infections against which GARDASIL 9 has not been shown to protect. GARDASIL 9 does not protect against genital disease not related to HPV.

GARDASIL 9 reduced the proportions of individuals who experienced a Pap test abnormality suggestive of CIN, colposcopy, cervical 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 (Table 6).

**Table 6: Impact of GARDASIL 9 on Pap* Test Abnormalities and External Genital or Cervical Procedures Irrespective of HPV in the All HN† Population**

| Disease Endpoint | Protocol 001 | | | | Historical Cohorts‡ | | | | % Reduction of GARDASIL 9 vs. Historical Placebo (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| | GARDASIL 9 N§=7099 | | GARDASIL N§=7105 | | GARDASIL N‡=9075 | | Placebo N‡=9075 | | |
| | n¶ | Number of cases | n¶ | Number of cases | n¶ | Number of cases | n¶ | Number of cases | |
| **Pap Test Abnormalities** | | | | | | | | | |
| ASC-US HR-HPV Positive or Worse | 2965 | 562 | 3002 | 617 | 4696 | 1021 | 4758 | 1226 | 23.3 (11.6, 33.4) |
| High Grade (ASC-H or Worse) | 2965 | 14 | 3002 | 25 | 4696 | 82 | 4758 | 132 | 63.8 (27.1, 82.1) |
| **External Genital or Cervical Procedures** | | | | | | | | | |
| Colposcopy | 2951 | 592 | 2985 | 654 | 4696 | 869 | 4759 | 1077 | 25.6 (14.2, 35.5) |
| External Genital Biopsy | 3032 | 69 | 3076 | 70 | 4771 | 144 | 4816 | 303 | 52.1 (29.5, 67.4) |
| Cervical Biopsy | 2976 | 490 | 3010 | 539 | 4696 | 741 | 4759 | 950 | 27.7 (15.6, 38.1) |
| External Genital Definitive Therapy | 3032 | 16 | 3076 | 15 | 4771 | 44 | 4816 | 89 | 45.4 (-19.2, 75.0) |
| Cervical Definitive Therapy | 2976 | 39 | 3010 | 44 | 4696 | 132 | 4759 | 230 | 47.2 (14.8, 67.3) |

*Papanicolaou test
†The All HN Population consisted of individuals who received at least 1 vaccination and who had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1 and were naïve to 14 common HPV types at Day 1. Case counting started at Day 1 following vaccination.
‡Historical cohorts included GARDASIL and placebo groups from clinical studies that supported initial licensure of GARDASIL.
§N=Number of individuals randomized to the respective vaccination group who received at least 1 injection
¶Number of individuals contributing to the analysis
CI=Confidence Interval
ASC-US=Atypical squamous cells of undetermined significance
HR=High Risk
LSIL=Low-grade squamous intraepithelial lesion
ASC-H=Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion

## Immunogenicity of GARDASIL 9

*Assays to Measure Immune Response*

The minimum anti-HPV titer that confers protective efficacy has not been determined.

Because there were few disease cases in individuals naïve (PCR negative and seronegative) to vaccine HPV types at baseline in the group that received GARDASIL 9 it has not been possible to establish minimum antibody levels that protect against clinical disease caused by vaccine HPV types.

Type-specific immunoassays with type-specific standards were used to assess immunogenicity to each vaccine HPV type. These assays measured antibodies against neutralizing epitopes for each HPV type. The scales for these assays are unique to each HPV type; thus, comparisons across types and to other assays are not appropriate.

*Immune Response to GARDASIL 9 at Month 7 Across All Clinical Studies*

The primary immunogenicity analyses were conducted in a per-protocol immunogenicity (PPI) population. This population consisted of individuals who were PCR negative in cervicovaginal specimens among female subjects 16 through 26 years of age in Protocols 001 and 002 and seronegative (Protocols 001, 002 and 009) to the relevant HPV type(s) at enrollment, remained HPV PCR negative to the relevant HPV type(s) through 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).

GARDASIL 9 induced robust anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 responses measured at Month 7 (Table 7). In clinical studies 99.6% to 100% who received GARDASIL 9 became seropositive for antibodies against all 9 vaccine types by Month 7 across all groups tested. GMTs were higher in girls and boys than in 16- through 26-year-old women and higher in boys than in girls and women.

**Table 7: Summary of Month 7 Anti-HPV cLIA Geometric Mean Titers in the PPI* Population**

| Population | N† | n‡ | % Seropositive (95% CI) | GMT (95% CI) mMU§/mL |
|---|---|---|---|---|
| **Anti-HPV 6** | | | | |
| 9- through 15-year-old girls | 2805 | 2349 | 99.7 (99.4, 99.9) | 1744.6 (1684.7, 1806.7) |
| 9- through 15-year-old boys | 1239 | 1055 | 99.9 (99.5, 100) | 2085.3 (1984.2, 2191.6) |
| 16- through 26-year-old women | 7260 | 4321 | 99.8 (99.6, 99.9) | 893.7 (873.5, 914.3) |
| **Anti-HPV 11** | | | | |
| 9- through 15-year-old girls | 2805 | 2350 | 99.9 (99.7, 100) | 1289.7 (1244.3, 1336.8) |
| 9- through 15-year-old boys | 1239 | 1055 | 100 (99.7, 100) | 1469.2 (1397.7, 1544.4) |
| 16- through 26-year-old women | 7260 | 4327 | 100 (99.9, 100) | 669.3 (653.6, 685.4) |
| **Anti-HPV 16** | | | | |
| 9- through 15-year-old girls | 2805 | 2405 | 99.9 (99.7, 100) | 7159.9 (6919.7, 7408.5) |
| 9- through 15-year-old boys | 1239 | 1076 | 100 (99.7, 100) | 8444.9 (8054.2, 8854.5) |
| 16- through 26-year-old women | 7260 | 4361 | 100 (99.9, 100) | 3159.0 (3088.6, 3231.1) |
| **Anti-HPV 18** | | | | |
| 9- through 15-year-old girls | 2805 | 2420 | 99.9 (99.6, 100) | 2085.5 (2002.2, 2172.3) |
| 9- through 15-year-old boys | 1239 | 1074 | 100 (99.7, 100) | 2620.4 (2474.3, 2775.2) |
| 16- through 26-year-old women | 7260 | 4884 | 99.8 (99.7, 99.9) | 809.9 (789.2, 831.1) |
| **Anti-HPV 31** | | | | |
| 9- through 15-year-old girls | 2805 | 2397 | 100 (99.8, 100) | 1883.3 (1811.3, 1958.1) |
| 9- through 15-year-old boys | 1239 | 1069 | 100 (99.7, 100) | 2173.5 (2057.0, 2296.6) |
| 16- through 26-year-old women | 7260 | 4806 | 99.8 (99.6, 99.9) | 664.8 (647.4, 682.6) |
| **Anti-HPV 33** | | | | |
| 9- through 15-year-old girls | 2805 | 2418 | 99.9 (99.7, 100) | 960.6 (927.5, 994.9) |
| 9- through 15-year-old boys | 1239 | 1076 | 100 (99.7, 100) | 1178.6 (1120.9, 1239.4) |
| 16- through 26-year-old women | 7260 | 5056 | 99.7 (99.5, 99.8) | 419.2 (409.6, 429.1) |
| **Anti-HPV 45** | | | | |
| 9- through 15-year-old girls | 2805 | 2430 | 99.8 (99.6, 100) | 728.7 (697.6, 761.2) |
| 9- through 15-year-old boys | 1239 | 1079 | 100 (99.7, 100) | 841.7 (790.0, 896.7) |
| 16- through 26-year-old women | 7260 | 5160 | 99.6 (99.4, 99.7) | 254.1 (247.0, 261.5) |
| **Anti-HPV 52** | | | | |
| 9- through 15-year-old girls | 2805 | 2426 | 99.9 (99.7, 100) | 978.2 (942.8, 1015.0) |
| 9- through 15-year-old boys | 1239 | 1077 | 100 (99.7, 100) | 1062.2 (1007.2, 1120.2) |
| 16- through 26-year-old women | 7260 | 4792 | 99.8 (99.6, 99.9) | 382.4 (373.0, 392.0) |
| **Anti-HPV 58** | | | | |
| 9- through 15-year-old girls | 2805 | 2397 | 99.9 (99.7, 100) | 1306.0 (1259.8, 1354.0) |
| 9- through 15-year-old boys | 1239 | 1072 | 100 (99.7, 100) | 1545.8 (1470.6, 1624.8) |
| 16- through 26-year-old women | 7260 | 4818 | 99.8 (99.6, 99.9) | 489.2 (477.5, 501.2) |

*The PPI population consisted of individuals who received all 3 vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, 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).
†Number of individuals randomized to the respective vaccination group who received at least 1 injection
‡Number of individuals contributing to the analysis
§mMU=milli-Merck Units
cLIA=Competitive Luminex Immunoassay
CI=Confidence Interval
GMT=Geometric Mean Titers

Table 7 displays the Month 7 immunogenicity data for girls and women and boys. Anti-HPV responses at Month 7 among 9- through 15-year-old girls were comparable to anti-HPV responses in 16- through 26-year-old women in the combined database of immunogenicity studies for GARDASIL 9. Anti-HPV responses at Month 7 among 9- through 15-year-old

boys were comparable to anti-HPV responses in both 16- through 26-year-women and 9- through 15-year-old girls.

On the basis of this immunogenicity bridging, the efficacy of GARDASIL 9 in 9- through 15-year-old girls and boys is inferred.

A formal immunogenicity bridging has not been conducted in 16- through 26-year-old men or in 27- through 45-year-old women. Efficacy of GARDASIL 9 in these groups is inferred based on high efficacy of GARDASIL in these groups and comparable immunogenicity of GARDASIL 9 and GARDASIL in other age groups.

*Variation in Dosing Regimen in 16-Through 26-Year-Old Women*

All individuals evaluated for efficacy in the PPE population of Protocol 001 received all 3 vaccinations 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 9 (see DOSAGE AND ADMINISTRATION*, Administration of GARDASIL 9 in Individuals Who Have Been Previously Vaccinated with GARDASIL).*

*Persistence of Immune Response to GARDASIL 9*

The duration of immunity following a complete schedule of vaccination with GARDASIL 9 has not been established. Persistence of immunity has been demonstrated through Month 24. Individuals who were seropositive to the relevant HPV type at baseline had substantially higher GMTs at Month 7, 12, and 24 than those who were seronegative to the same vaccine HPV type(s) at Day 1. In addition, persistence of efficacy has been demonstrated through Month 54 as evident by a low incidence of HPV-related disease and persistent infection in Protocol 001.

*Administration of GARDASIL 9 to Individuals Previously Vaccinated with GARDASIL*

Protocol 006 evaluated the immunogenicity of GARDASIL 9 in 921 girls and women (12 through 26 years of age) who had previously been vaccinated with GARDASIL. Prior to enrollment in the study, over 99% of subjects had received 3 injections of GARDASIL within a one year period. The time interval between the last injection of GARDASIL and the first injection of GARDASIL 9 ranged from approximately 12 to 36 months.

Seropositivity to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in the per protocol population ranged from 98.3 to 100% by Month 7 in individuals who received GARDASIL 9. The GMTs to HPV Types 31, 33, 45, 52, and 58 were lower than in the population who had not previously received GARDASIL in Protocols 001, 002, 005, 007 and 009. Efficacy of GARDASIL 9 in preventing infection and disease related to HPV Types 31, 33, 45, 52, and 58 in individuals previously vaccinated with GARDASIL has not been assessed.

**Concomitant Use Of GARDASIL 9 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)]*

In Protocol 005, the safety and immunogenicity of co-administration of GARDASIL 9 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 study of 1,237 boys and girls 11 through 15 years of age at enrollment.

One group received GARDASIL 9 in one limb and both Menactra and Adacel, as separate injections, in the opposite limb concomitantly on Day 1 (n = 619). The second group received the first dose of GARDASIL 9 on Day 1 in one limb then Menactra and Adacel, as separate injections, at Month 1 in the opposite limb (n = 618). Subjects in both vaccination groups received the second dose of GARDASIL 9 at Month 2 and the third dose at Month 6. Immunogenicity was assessed for all vaccines 1 month post completion of the vaccination series (1 dose for Menactra and Adacel and 3 doses for GARDASIL 9).

Concomitant administration of GARDASIL 9 with Menactra and Adacel did not interfere with the antibody response to any of the vaccine antigens when GARDASIL 9 was given concomitantly with Menactra and Adacel or separately (see INTERACTIONS WITH OTHER MEDICINES, *Use with Other Vaccines*).

*Repevax [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content) (dTAP-IPV)]*

In Protocol 007, 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) (dTAP-IPV)] (same visit, injections at separate sites) were evaluated in a study of 1,053 boys and girls 11 through 15 years of age at enrollment.

One group received GARDASIL 9 in one limb and Repevax in the opposite limb concomitantly on Day 1 (n = 525). The second group received the first dose of GARDASIL 9 on Day 1 in one limb then Repevax at Month 1 in the opposite limb (n = 528). Subjects in both vaccination groups received the second dose of e 9 at Month 2 and the third dose at Month 6. Immunogenicity was assessed for all vaccines 1 month post completion of the vaccination series (1 dose for Repevax and 3 doses for GARDASIL 9).

Concomitant administration of GARDASIL 9 with Repevax did not interfere with the antibody response to any of the vaccine antigens when GARDASIL 9 was given concomitantly with Repevax or separately (see INTERACTIONS WITH OTHER MEDICINES, *Use with Other Vaccines*).

## INDICATIONS

GARDASIL 9 is indicated in females aged 9 through 45 years* for the prevention of cervical, vulvar, vaginal and anal cancer, precancerous or dysplastic lesions, genital warts, and infection caused by Human Papillomavirus (HPV) Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 (which are included in the vaccine).

GARDASIL 9 is indicated in males 9 through 26 years of age for the prevention of anal cancer, precancerous or dysplastic lesions, external genital lesions and infection caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 (which are included in the vaccine).

* Evidence of vaccine efficacy is based on core efficacy population of females 16 to 26 years of age. Immunogenicity studies have been conducted to link efficacy to younger populations (females and males 9 to 15 years of age). Currently there are no data from studies of GARDASIL 9 relating to females over 26 years of age (see CLINICAL TRIALS Clinical

Studies for GARDASIL 9 *Immune Response to GARDASIL 9 at Month 7 Across All Clinical Studies*).

## CONTRAINDICATIONS

Hypersensitivity to the active substances of GARDASIL 9 or GARDASIL or to any of the inactive ingredients of either vaccine (see DESCRIPTION).

Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of GARDASIL 9 or GARDASIL should not receive further doses of GARDASIL 9.

## PRECAUTIONS

### General

As for any vaccine, vaccination with GARDASIL 9 may not result in protection in all vaccine recipients.

This 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 will not protect against diseases that are not caused by HPV or non-vaccine genotypes.

Routine cervical screening and detection and removal of cervical lesions should be continued in individuals who receive the vaccine.

Syncope (fainting) may follow any vaccination, especially in adolescents and young adults. Syncope, sometimes associated with falling, has occurred after HPV vaccination. Therefore, vaccinees should be carefully observed for approximately 15 minutes after administration of GARDASIL 9 (see ADVERSE EFFECTS).

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.

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 INTERACTIONS WITH OTHER MEDICINES).

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.

### Effects on Fertility

*Non-clinical studies: Animal Toxicology*

GARDASIL 9 administered to female rats at a dose approximately 240 times the human dose (mg/kg basis) had no effects on mating performance, fertility, or embryonic/foetal survival.

GARDASIL 9 administered to female rats at a dose approximately 160 times the human dose (mg/kg basis) had no effects on development, behavior, reproductive performance or fertility of the offspring.

A repeat dose toxicity study has been performed in rats at a dose approximately 250 times the human dose (mg/kg basis) and revealed no special hazards to humans.

**Use in Pregnancy (Category B2)**

*Studies in Female Rats*
Reproduction studies have been performed in female rats at a dose approximately 240 times the human dose (mg/kg basis) and have revealed no evidence of impaired female fertility or harm to the foetus due to GARDASIL 9 vaccination prior to mating and at gestational day 6.

An evaluation of the effect of GARDASIL 9 vaccination prior to mating, at gestational day 6 and on lactational day 7 on embryo-foetal, pre- and postweaning development was conducted in studies using rats. No adverse effects on mating, fertility, pregnancy, parturition, lactation, embryo-foetal or pre- and postweaning development were observed. There were no vaccine-related foetal malformations or other evidence of teratogenesis noted. In addition, there were no treatment-related effects on developmental signs, behaviour, reproductive performance, or fertility of the offspring. GARDASIL 9 induced a specific antibody response against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in pregnant rats following one or multiple intramuscular injections. Antibodies against all 9 HPV types were transferred to the offspring during gestation and possibly during lactation.

*Clinical Studies in Humans*
There are 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 9.

In clinical studies, women underwent serum or urine pregnancy testing prior to administration of GARDASIL 9. Women who were found to be pregnant before completion of a 3-dose regimen of GARDASIL 9 were instructed to defer completion of their vaccination regimen until resolution of the pregnancy.

The overall proportion of pregnancies occurring at any time during the studies that resulted in an adverse outcome defined as the combined numbers of spontaneous abortion, late foetal death and congenital anomaly cases out of the total number of pregnancy outcomes for which an outcome was known (and excluding elective terminations), was 14.1% (145/1,028) in women who received GARDASIL 9 and 17.0% (168/991) in women who received GARDASIL. The proportions of adverse outcomes observed were consistent with pregnancy outcomes observed in the general population.

Further sub-analyses were conducted to evaluate pregnancies with estimated onset within 30 days or more than 30 days from administration of a dose of GARDASIL 9 or GARDASIL. For pregnancies with estimated onset within 30 days of vaccination, no cases of congenital anomaly were observed in women who have received GARDASIL 9 or GARDASIL. In pregnancies with onset more than 30 days following vaccination, 20 and 21 cases of congenital anomaly were observed in women who have received GARDASIL 9 and GARDASIL, respectively. The types of anomalies observed were consistent (regardless of

when pregnancy occurred in relation to vaccination) with those generally observed in pregnancies in the general population.

Thus, there is no evidence to suggest that administration of GARDASIL 9 adversely affects fertility, pregnancy, or infant outcomes.

**Use in Lactation**

*Studies in Female Rats*
GARDASIL 9 administered to female rats at a dose approximately 160 times the human dose (mg/kg basis) vaccination prior to mating and at gestational day 6 had no effects on development, behavior, reproductive performance or fertility of the offspring. Antibodies against all 9 HPV types were transferred to the offspring during gestation and lactation.

*Clinical Studies in Humans*

GARDASIL 9 may be administered to lactating women.

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

A total of 86 women were breast feeding during the vaccination period of the clinical studies for GARDASIL 9. In these studies, the adverse experience profile for nursing women was comparable to that of the women in the overall safety population. There were no serious adverse experiences reported in infants who were nursing during the vaccination period. In addition, vaccine immunogenicity was comparable between nursing women and women who did not nurse.

**Paediatric Use**

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

**Use in the Elderly**

The safety and efficacy of GARDASIL 9 have not been evaluated in individuals aged 65 years and over.

**Genotoxicity**

GARDASIL 9 has not been evaluated for genotoxic potential.

**Carcinogenicity**

GARDASIL 9 has not been evaluated for carcinogenic potential.

**Use in Immunocompromised Individuals**

The immunologic response to GARDASIL 9 may be diminished in immunocompromised individuals (see INTERACTIONS WITH OTHER MEDICINES, *Use with Steroids*).

## INTERACTIONS WITH OTHER MEDICINES

### Use with Other Vaccines

Results from clinical studies indicate that GARDASIL 9 may be administered concomitantly (at a separate injection site) with 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)] (dTap-IPV) (see CLINICAL TRIALS, *Concomitant Use of GARDASIL 9 With Other Vaccines*).

### Use with Hormonal Contraceptives

In 7,269 women (16 through 26 years of age), 60.2% used hormonal contraceptives during the vaccination period of the clinical studies. Use of hormonal contraceptives did not appear to affect the immune responses to GARDASIL 9.

### Use with Systemic Immunosuppressive Medications

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune responses to vaccines (see PRECAUTIONS, *Use in Immunocompromised Individuals*).

## ADVERSE EFFECTS

### Clinical Trials Experience with GARDASIL 9 and GARDASIL

The safety and tolerability of GARDASIL was assessed in clinical trials in females 9 through 45 years of age and males 9 through 26 years of age. The safety profile of GARDASIL 9 is generally comparable to that of GARDASIL in the groups studied (women 16 through 26 years of age and girls and boys 9 through 15 years of age).

The safety of GARDASIL 9 was evaluated in 6 clinical studies (Protocols 001, 002, 005, 006, 007, 009) that included 13,307 individuals who received at least one dose of GARDASIL 9 and had safety follow-up. Protocol 001 and Protocol 009 included 7,378 individuals who received at least one dose of GARDASIL and had safety follow-up. The vaccines were administered on the day of enrollment and the subsequent doses administered approximately 2 and 6 months thereafter. Safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of GARDASIL 9 or GARDASIL.

The individuals who were monitored using VRC-aided surveillance included 8,027 women 16 through 26 years of age and 5,280 girls and boys 9 through 15 years of age (3,481 girls and 1,799 boys) at enrollment who received GARDASIL 9 and 7,078 women 16 through 26 years of age and 300 girls 9 through 15 years of age at enrollment who received GARDASIL.

### Systemic and Injection-Site Adverse Reactions in Clinical Trials of GARDASIL 9

The vaccine-related adverse experiences that were observed among recipients of either GARDASIL 9 or GARDASIL at a frequency of at least 1% are shown in Tables 8 and 9. Few individuals (GARDASIL 9 = 0.1% vs. GARDASIL <0.1%) discontinued due to adverse experiences after receiving either vaccine. The safety profile was similar between GARDASIL 9 and GARDASIL in women and girls and boys.

**Attachment 1: Product information for AusPAR GARDASIL 9, Human Papillomavirus 9-Valent Vaccine. Merck Sharp & Dohme Australia Pty Ltd PM-2014-01099-1- Final 3 January 2017. This Product Information was approved at the time this AusPAR was published.**

**Table 8: Injection-Site and Vaccine-Related Systemic Adverse Reactions Reported at a Frequency of ≥1% in Individuals Who Received GARDASIL 9 from All Clinical Studies***

| Adverse Reaction | Women 16 Through 26 Years of Age | Girls and Boys 9 Through 15 Years of Age |
|---|---|---|
| | GARDASIL 9 (N=8027) % | GARDASIL 9 (N=5280) % |
| **Injection-Site Adverse Reactions (1 to 5 Days Postvaccination)** | | |
| Pain† | 89.6 | 78.8 |
| Swelling† | 40.2 | 33.8 |
| Erythema† | 34.3 | 28.0 |
| Pruritus | 5.6 | 2.6 |
| Bruising | 1.7 | 0.0 |
| Hematoma | 1.3 | 2.0 |
| Mass | 1.2 | 0.2 |
| Hemorrhage | 0.9 | 1.0 |
| Induration | 0.7 | 1.1 |
| **Systemic Adverse Reactions (1 to 15 Days Postvaccination)** | | |
| Headache | 14.7 | 12.7 |
| Pyrexia | 5.1 | 8.9 |
| Nausea | 4.2 | 2.2 |
| Dizziness | 2.9 | 1.6 |
| Fatigue | 2.3 | 1.3 |
| Diarrhea | 1.2 | 0.5 |
| Oropharyngeal pain | 1.0 | 0.8 |
| Abdominal pain upper | 0.7 | 1.3 |

*Data from Protocols 001,002, 005, 006, 007, 009
†Designates a solicited adverse reaction
N=number of subjects vaccinated

**Table 9: Injection-Site and Vaccine-Related Systemic Adverse Reactions Reported at a Frequency of ≥1% for GARDASIL 9 Compared with GARDASIL from Two Clinical Studies***

| Adverse Reaction | Women 16 Through 26 Years of Age | | Girls 9 Through 15 Years of Age | |
|---|---|---|---|---|
| | GARDASIL 9 (N=7071) % | GARDASIL (N=7078) % | GARDASIL 9 (N=299) % | GARDASIL (N=300) % |
| **Injection-Site Adverse Reactions (1 to 5 Days Postvaccination)** | | | | |
| Pain† | 89.9 | 83.5 | 89.3 | 88.3 |
| Swelling† | 40.0 | 28.8 | 47.8 | 36.0 |
| Erythema† | 34.0 | 25.6 | 34.1 | 29.3 |
| Pruritus | 5.5 | 4.0 | 4.0 | 2.7 |
| Bruising | 1.9 | 1.9 | ‡ | ‡ |
| Mass | 1.3 | 0.6 | ‡ | ‡ |
| Hemorrhage | 1.0 | 0.7 | 1.0 | 2.0 |
| Hematoma | 0.9 | 0.6 | 3.7 | 4.7 |
| Warmth | 0.8 | 0.5 | 0.7 | 1.7 |
| Induration | 0.8 | 0.2 | 2.0 | 1.0 |
| Reaction | 0.6 | 0.6 | 0.3 | 1.0 |
| **Systemic Adverse Reactions (1 to 15 Days Postvaccination)** | | | | |
| Headache | 14.6 | 13.7 | 11.4 | 11.3 |
| Pyrexia | 5.0 | 4.3 | 5.0 | 2.7 |
| Nausea | 4.4 | 3.7 | 3.0 | 3.7 |
| Dizziness | 3.0 | 2.8 | 0.7 | 0.7 |
| Fatigue | 2.3 | 2.1 | 0.0 | 2.7 |
| Diarrhea | 1.2 | 1.0 | 0.3 | 0.0 |
| Myalgia | 1.0 | 0.7 | 0.7 | 0.7 |
| Oropharyngeal pain | 1.0 | 0.6 | 2.7 | 0.7 |
| Abdominal pain upper | 0.7 | 0.8 | 1.7 | 1.3 |
| Upper respiratory tract infection | 0.1 | 0.1 | 0.3 | 1.0 |

*The data for women are from Protocol 001 and data for girls are from Protocol 009.
†Designates a solicited adverse reaction

‡There are no reports of injection-site bruising or mass for girls.
N=number of subjects vaccinated

### Solicited Systemic and Injection-Site Adverse Reactions in Clinical Trials of GARDASIL 9

Temperature and injection-site pain, swelling, and erythema were solicited using VRC-aided surveillance for 5 days after each injection of GARDASIL 9 during the clinical studies. The incidence and severity of solicited adverse reactions that occurred within 5 days following each dose of GARDASIL 9 are shown in Table 10.

**Table 10: Postdose Evaluation of Solicited Systemic and Injection-Site Adverse Reactions by Incidence and Severity from All Clinical Studies* (1 to 5 Days Postvaccination)**

| Solicited Systemic Adverse Reaction | Severity | Dose 1 N=12,875 % | Dose 2 N=12,619 % | Dose 3 N=12,447 % | Any Dose N=12,925 % |
|---|---|---|---|---|---|
| Temperature | < 37.8 °C (100.0 °F) | 96.9 | 97.3 | 96.7 | 92.0 |
| | ≥ 37.8 °C (100.0 °F) < 38.9 °C (102.0 °F) | 2.7 | 2.3 | 2.7 | 6.6 |
| | ≥ 38.9 °C (102.0 °F) < 39.9 °C (103.8 °F) | 0.4 | 0.3 | 0.5 | 1.2 |
| | ≥ 39.9 °C (103.8 °F) < 40.9 °C (105.6 °F) | 0.1 | 0.1 | 0.1 | 0.2 |
| | ≥ 40.9 °C (105.6 °F) | 0.0 | 0.0 | 0.0 | 0.0 |
| **Solicited Injection-site Adverse Reaction** | **Severity** | **Dose 1 N=13,304** | **Dose 2 N=13,142** | **Dose 3 N=13,005** | **Any Dose N=13,307** |
| Pain | Mild | 53.5 | 47.6 | 45.3 | 51.1 |
| | Moderate | 11.5 | 16.3 | 17.8 | 30.3 |
| | Severe | 0.7 | 1.6 | 2.3 | 3.9 |
| Swelling† | Mild | 9.6 | 15.3 | 18.5 | 25.4 |
| | Moderate | 1.8 | 3.9 | 4.9 | 7.8 |
| | Severe | 0.8 | 1.7 | 2.7 | 4.3 |
| Erythema† | Mild | 8.6 | 14.0 | 16.6 | 25.3 |
| | Moderate | 0.9 | 2.0 | 2.7 | 4.6 |
| | Severe | 0.2 | 0.5 | 1.2 | 1.7 |

*Data from Protocols 001, 002, 005, 006, 007, 009
†Intensity of swelling and erythema was measured by size (inches): Mild = 0 to ≤1; Moderate = >1 to ≤2; Severe = >2.
N=Number of individuals with follow-up

### Serious Adverse Events in Clinical Trials of GARDASIL 9

Serious adverse events were collected throughout the entire study period for the six integrated clinical studies for GARDASIL 9. Out of the 13,309 individuals who were administered GARDASIL 9 and had safety follow-up, 305 reported a serious adverse event; representing 2.3% of the population. Five individuals administered GARDASIL 9 reported at least one serious adverse event that was determined to be vaccine-related. The vaccine-related serious adverse events were pyrexia, allergy to vaccine, asthmatic crisis, headache, and tonsillitis. An additional two vaccine-related serious adverse events that occurred after the study period were reported in GARDASIL 9 recipients including one case of postural orthostatic tachycardia syndrome and one case of hypersomnia.

### Clinical Trials Experience for GARDASIL 9 In Individuals Who Have Been Previously Vaccinated With GARDASIL

A clinical study (Protocol 006) evaluated the safety of GARDASIL 9 in 12- through 26-year-old girls and women who had previously been vaccinated with 3 doses of GARDASIL. The

time interval between the last injection of GARDASIL and the first injection of GARDASIL 9 ranged from approximately 12 to 36 months. Individuals were administered GARDASIL 9 or saline placebo and safety was evaluated using VRC-aided surveillance for 14 days after each injection of GARDASIL 9 or saline placebo in these individuals. The individuals who were monitored included 608 individuals who received GARDASIL 9 and 305 individuals who received saline placebo. Few (0.5%) individuals who received GARDASIL 9 discontinued due to adverse reactions. The vaccine-related adverse experiences that were observed among recipients of GARDASIL 9 at a frequency of at least 1.0% and also at a greater frequency than that observed among saline placebo recipients are shown in Table 11. Overall, the safety profile was similar between individuals vaccinated with GARDASIL 9 who were previously vaccinated with GARDASIL and those who were naïve to HPV vaccination.

**Table 11: Injection-Site and Vaccine-Related Systemic Adverse Reactions Reported at a Frequency of ≥ 1% and Greater Than Saline Placebo for GARDASIL 9 in 12- Through 26-year-old Girls and Women Who Have Been Previously Vaccinated with GARDASIL***

| Adverse Reaction | GARDASIL 9 (N=608) % | SALINE PLACEBO (N=305) % |
|---|---|---|
| **Injection-Site Adverse Reactions (1 to 5 Days Postvaccination)** | | |
| Pain† | 90.3 | 38.0 |
| Swelling† | 49.0 | 5.9 |
| Erythema† | 42.3 | 8.5 |
| Pruritus | 7.7 | 1.3 |
| Hematoma | 4.8 | 2.3 |
| Reaction | 1.3 | 0.3 |
| Mass | 1.2 | 0.7 |
| **Systemic Adverse Reactions (1 to 15 Days Postvaccination)** | | |
| Headache | 19.6 | 18.0 |
| Pyrexia | 5.1 | 1.6 |
| Nausea | 3.9 | 2.0 |
| Dizziness | 3.0 | 1.6 |
| Abdominal pain upper | 1.5 | 0.7 |
| Influenza | 1.2 | 1.0 |

*The data for GARDASIL 9 and Placebo are from Protocol 006.
†Designates a solicited adverse reaction
N=number of subjects vaccinated

### Clinical Trials Experience for Concomitant Administration of GARDASIL 9 with Other Vaccines

The safety of GARDASIL 9 when administered concomitantly with other vaccines was evaluated in clinical studies.

There was an increase in injection-site swelling reported at the injection site for GARDASIL 9 when GARDASIL 9 was administered concomitantly with Repevax [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content) (dTap-IPV)] or Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] and Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] as compared to non-concomitant vaccination. The majority of injection-site swelling seen with concomitant administration with other vaccines was 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 and may also be seen in post-marketing experience with GARDASIL 9.

The post-marketing safety experience with GARDASIL is relevant to GARDASIL 9 since the vaccines are similar in composition and contain L1 HPV proteins 4 of the same HPV types. 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.

## DOSAGE AND ADMINISTRATION

### Dosage

GARDASIL 9 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. If an alternate vaccination schedule is necessary, 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.

### Administration of GARDASIL 9 in Individuals Who Have Been Previously Vaccinated with GARDASIL

Studies using a mixed regimen (interchangeability) of HPV vaccines were not performed for GARDASIL 9.

For information regarding administration of GARDASIL 9 after receipt of GARDASIL, see CLINICAL TRIALS *Administration of GARDASIL 9 to Individuals Previously Vaccinated with GARDASIL*.

**Method of Administration**

Syncope (fainting) may follow any vaccination, especially in adolescents and young adults. Syncope, sometimes associated with falling, has occurred after vaccination with GARDASIL 9. Therefore, vaccinees should be carefully observed for approximately 15 minutes after administration of GARDASIL 9.

GARDASIL 9 should be administered intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

GARDASIL 9 must not be injected intravascularly. Neither subcutaneous nor intradermal administration has been studied. These methods of administration are not recommended.

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. Prior to agitation, GARDASIL 9 may appear as a clear liquid with a white precipitate. After thorough agitation, GARDASIL 9 is a white, cloudy liquid. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. Discard the product if particulates are present or if it appears discoloured.

Prefilled Syringe Use
Inject the entire contents of the syringe.
The prefilled syringe is for single use only and should not be used for more than one individual.

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.

For single-use vials a separate sterile syringe and needle must be used for each individual.
NOTE: When choosing a needle, it should fit securely on the syringe.

## OVERDOSAGE

There have been no reports of administration of higher than recommended doses of GARDASIL 9. For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) or 0800 764 766 (New Zealand).

## PRESENTATION & STORAGE CONDITIONS

**Presentation**

GARDASIL 9 is a suspension for intramuscular administration available in 0.5-mL single-dose vials and prefilled syringes. GARDASIL 9 is a sterile cloudy white liquid.

GARDASIL 9 may be supplied as

- a single-dose pre-filled syringe of vaccine
- a box of ten single-dose pre-filled syringes of vaccine

- a single-dose vial of vaccine*
- a box of ten single-dose vials of vaccine*

**not currently available in Australia*

The prefilled syringe is not supplied with a needle; the single-use vial is not supplied with a needle or syringe.

**Storage**

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

GARDASIL 9 should be administered as soon as possible after being removed from refrigeration. GARDASIL 9 can be administered provided total cumulative time out of refrigeration (at temperatures between 0°C and 25°C) does not exceed 72 hours. These are not, however, recommendations for storage.

Discard the product if it is frozen, particulates are present, or if it appears discolored.

## NAME AND ADDRESS OF SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A,
26 Talavera Road
Macquarie Park NSW 2113

## DISTRIBUTOR

bioCSL Pty Ltd
63 Poplar Road
Parkville VIC 3052

## POISONS SCHEDULE

Schedule 4 – Prescription Medicine

## DATE OF FIRST INCLUSION ON THE AUSTRALIAN REGISTER OF THERAPUETIC GOODS

This Product Information was approved by the Therapeutic Goods Administration on xx xxxx 2015.

## DATE OF MOST RECENT AMENDMENT

No amendments have been made to this Product Information.