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PRODUCT CIRCULAR RCN000027167-TH

GARDASIL 9
[Human Papillomavirus 9-valent Vaccine, Recombinant]
[Suspension for Injection]

I. THERAPEUTIC CLASS

GARDASIL 9 is a recombinant vaccine that protects against 9 genotypes of Human Papillomavirus (HPV).

II. NAME AND STRENGTH OF ACTIVE INGREDIENT(S)

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.

III. PRODUCT DESCRIPTION

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

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.

IV. PHARMACODYNAMIC/PHARMACOKINETICS

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Viral Vaccine
ATC code: J07BM03

Mechanism of Action

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

CLINICAL STUDIES

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). In clinical studies conducted in girls and women, GARDASIL reduced the incidence of CIN (any grade including CIN 2/3); AIS; genital warts; VIN 2/3; and VaIN 2/3 related to vaccine HPV types 6, 11, 16, or 18.

Clinical Trials for GARDASIL 9

Efficacy and/or immunogenicity of the 3-dose regimen of GARDASIL 9 were assessed in nine 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, 009 and 020).

In the pivotal study 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).

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 003 evaluated immunogenicity of GARDASIL 9 in boys and men 16 through 26 years of age and in girls and women 16 through 26 years of age (N=2,515: 1,103 Heterosexual Men [HM]; 313 Men Who Have Sex with Men [MSM]; and 1,099 women receiving GARDASIL 9).

Protocol 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).

Protocol 006 evaluated administration of GARDASIL 9 to girls and women 12 through 26 years of age previously vaccinated with GARDASIL vaccine (N=921; 615 receiving GARDASIL 9 and 306 receiving placebo).

Protocol 009 evaluated immunogenicity of GARDASIL 9 in girls 9 through 15 years of age (N=600; 300 receiving GARDASIL 9 and 300 receiving GARDASIL).

Two additional immunological bridging studies were conducted. Protocol 020 evaluated immunogenicity of GARDASIL 9 compared to GARDASIL in boys and men 16 through 26 years of age (N=500: 249 receiving GARDASIL 9 and 251 receiving GARDASIL). Protocol 004 evaluated immunogenicity of GARDASIL 9 in girls and women 16 through 26 years of age compared to women 27 through 45 years of age (N=1,210: 640 women 27 through 45 years and 570 girls and women 16 through 26 years).

One clinical trial (Protocol 010) assessed the 2-dose regimen of GARDASIL 9. Protocol 010 evaluated the immunogenicity of 2 doses of GARDASIL 9 in girls and boys 9 through 14 years of age and 3 doses of GARDASIL 9 in girls 9 through 14 years of age and girls and women 16 through 26 years of age (N=1,516; 751 girls; 451 boys and 314 women). The mean age for the girls and boys 9 through 14 years of age was 11.5 years; the mean age for girls and women 16 through 26 years of age was 21.0 years.

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

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

Comparison of GARDASIL 9 with GARDASIL immunogenicity 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, 9- through 15-year-old girls from Protocol 009 and 16- through 26-year-old boys and men from Protocol 020. The primary analyses were conducted in the per-protocol immunogenicity population which included subjects who received all 3 vaccinations within pre-defined day ranges, met pre-defined criteria for the interval between the Month 6 and Month 7 visit, did not have major deviations from the study protocol, and were naïve [PCR negative (in girls and women 16 through 26 years of age; Protocol 001) and seronegative (Protocols 001, 009 and 020) prior to dose one] to the relevant HPV type(s) and who remained PCR-negative (in girls and women 16 through 26 years of age; Protocol 001) to the relevant HPV type(s) through Month 7.

A statistical analysis of non-inferiority was performed based on 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 1). 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 1: 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 and 16- through 26-Year-Old Boys and Men

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- through 15-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)¶
16- through 26-year-old boys and men	249 (228)	98.2 (95.6, 99.5)	758.3 (665.9, 863.4)	251 (226)	98.7 (96.2, 99.7)	618.4 (554.0, 690.3)	1.23	(1.04, 1.45)¶
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)¶
16- through 26-year-old boys and men	249 (228)	100 (98.4, 100)	681.7 (608.9, 763.4)	251 (226)	100 (98.4, 100)	769.1 (683.5, 865.3)	0.89	(0.76, 1.04)¶
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)¶
16- through 26-year-old boys and men	249 (234)	100 (98.4, 100)	3924.1 (3513.8, 4382.3)	251 (237)	100 (98.5, 100)	3787.9 (3378.4, 4247.0)	1.04	(0.89, 1.21)¶
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)¶
16- through 26-year-old boys and men	249 (234)	99.6 (97.6, 100)	884.3 (766.4, 1020.4)	251 (236)	99.6 (97.7, 100)	790.9 (683.0, 915.7)	1.12	(0.91, 1.37)¶

*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, were naïve (PCR negative [among 16- through 26-year-old girls and women] and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1 and among 16- through 26-year-old girls and women, were PCR negative to the relevant HPV type(s) through 1 month Postdose 3 (Month 7). The data for 16- through 26-year-old girls and women are from Protocol 001, and the data for 9- through 15-year-old girls are from Protocol 009. The data for 16- through 26-year-old boys and men are from Protocol 020.

†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

Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67

CI=Confidence Interval

GMT=Geometric Mean Titers

cLIA= Competitive Luminex Immunoassay

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 67 months postdose 3, with a median duration of 43 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 2). GARDASIL 9 also reduced the incidence of HPV 31-, 33-, 45-, 52-, and

58- related Pap test abnormalities, cervical procedures (i.e., biopsies), and cervical definitive therapy procedures (including loop electrosurgical excision procedure [LEEP] or conization). See Table 2.

Table 2: 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	38	97.4 (85.0, 99.9)
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3 or AIS#	5949	1	5943	35	97.1 (83.5, 99.9)
CIN2	5949	1	5943	32	96.9 (81.5, 99.8)
CIN3	5949	0	5943	7	100 (39.4, 100)
HPV 31-, 33-, 45-, 52-, 58-related CIN 1	5949	1	5943	87	98.9 (94.1, 99.9)
HPV 31-, 33-, 45-, 52-, 58-related Vulvar or Vaginal Disease♭	6009	1	6012	18	94.4 (67.7, 99.7)
VIN2/3# and VaIN2/3	6009	0	6012	3	100.0 (-71.5, 100.0)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥6 Months♯	5941	41	5955	946	96.0 (94.6, 97.1)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥12 Months♮	5941	23	5955	657	96.7 (95.1, 97.9)
HPV 31-, 33-, 45-, 52-, 58-related ASC-US HR-HPV Positive or Worse Pap♭ Abnormality	5883	37	5882	506	92.9 (90.2, 95.1)
HPV 31-, 33-, 45-, 52-, 58-related Cervical Biopsy	6013	6	6014	253	97.7 (95.1, 99.0)
HPV 31-, 33-, 45-, 52-, 58-related Cervical Definitive Therapy Procedure♂	6013	4	6014	41	90.2 (75.0, 96.8)

*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 who remained PCR negative to the relevant HPV type(s) through 1 month postdose 3 (Month 7). The data are from Protocol 001.

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

‡n=Number of individuals contributing to the analysis

§Number of cases= number of individuals with at least one follow-up visit after Month 7

¶Subjects were followed for up to 67 months postdose 3 (median 43 months postdose 3)

#No cases of cervical cancer, VIN2/3, vulvar and vaginal cancer were diagnosed in the PPE population.

Þincludes VIN1/2/3, VaIN1/2/3, condyloma

ðloop electrosurgical excision procedure (LEEP) or conization

ßPersistent infection detected in samples from two or more consecutive visits 6 months (±1 month visit windows) apart

àPersistent infection detected in samples from three or more consecutive visits 6 months (±1 month visit windows) apart

èPapanicolaou test

CI=Confidence Interval

ASC-US=Atypical squamous cells of undetermined significance

HR=High Risk

Studies Supporting the Efficacy of GARDASIL 9 in Prevention of HPV-Related Oropharyngeal and Other Head and Neck Cancers

The efficacy of GARDASIL 9 against oropharyngeal and other head and neck cancers is inferred based on the efficacy of GARDASIL and GARDASIL 9 to prevent persistent infection and anogenital disease caused by HPV types covered by the vaccine.

Long-term Effectiveness Studies

A subset of subjects who received 3 doses is being followed up for 10 to 14 years after GARDASIL 9 vaccination for safety, immunogenicity, and effectiveness against clinical diseases related to the HPV types 6/11/16/18/31/33/45/52/58.

Clinical protection has been observed in all subjects in the long-term extension of Protocol 001 registry study in the PPE population. No cases of high-grade CIN were observed through 13.6 years postdose 3 (median duration of follow-up of 10.4 years) in girls and women who were 16 through 26 years of age at time of vaccination.

In the long-term extension of Protocol 002, in the PPE population, no cases of high-grade intraepithelial neoplasia or genital warts were observed through 11 years postdose 3 (median duration of follow-up of 10.0 years) in girls and through 10.6 years postdose 3 (median duration of follow-up of 9.9 years) in boys who were 9 through 15 years of age at time of vaccination with GARDASIL 9. In girls and boys, incidence rates of 6-month persistent infections related to vaccine HPV types observed during the study were 52.4 and 54.6 per 10,000 person-years, respectively, and within ranges of incidence rates expected in vaccinated cohorts of similar age (based on results from previous efficacy studies of GARDASIL 9 and GARDASIL vaccine).

Immunogenicity of GARDASIL 9

Immune Response to GARDASIL 9 at Month 7 in Clinical Studies

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. In clinical studies 99.2% 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 women 16 through 26 year of age, and higher in boys than in girls and women. As expected for women 27 through 45 years of age (Protocol 004), the observed GMTs were lower than those seen in girls and women 16 through 26 years of age.

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

Women 27 Years of Age and Older

Effectiveness of GARDASIL 9 against persistent infection and disease related to vaccine HPV types in 27- through 45-year-old women was inferred based on non-inferiority of GMTs following vaccination with GARDASIL 9 in 27- through 45-year-old women compared to 16- through 26-year-old girls and women and demonstration of efficacy of GARDASIL in girls and women 16 through 45 years of age. In Protocol 004, GARDASIL 9 elicited seroconversion rates for all nine vaccine HPV types greater than 99% in girls and women 16 through 45 years of age. Anti-HPV antibody GMTs at Month 7 among women 27 through 45 years of age were non-inferior to anti-HPV antibody GMTs among girls and women 16 through 26 years of age for HPV 16, 18, 31, 33, 45, 52, and 58, with GMT ratios between 0.66 and 0.73. In a post hoc analysis for HPV 6 and 11, non-inferiority criteria were also met, with GMT ratios of 0.81 and 0.76, respectively. These results support the efficacy of GARDASIL 9 in women 27 through 45 years of age.

Table 3: Comparison of Immune Responses (Based on cLIA) Between the PPI* Populations of 27-through 45-Year-Old Women and 16- through 26-Year-Old Girls and Women for GARDASIL 9 Vaccine HPV Types

Population	N†	n‡	GMT mMU§/mL	GMT ratio relative to 16-through 26-year-old girls and women (95% CI)#
Anti-HPV 6				

27- through 45-year-old women	640	448	638.4	0.81 (0.73, 0.90)
16- through 26-year-old girls and women	570	421	787.8	1
Anti-HPV 11				
27- through 45-year-old women	640	448	453.5	0.76 (0.69, 0.83)
16- through 26-year-old girls and women	570	421	598.7	1
Anti-HPV 16				
27- through 45-year-old women	640	448	2147.5	0.70 (0.63, 0.77)¶
16- through 26-year-old girls and women	570	436	3075.8	1
Anti-HPV 18				
27- through 45-year-old women	640	471	532.1	0.71 (0.64, 0.80)¶
16- through 26-year-old girls and women	570	421	744.5	1
Anti-HPV 31				
27- through 45-year-old women	640	488	395.7	0.66 (0.60, 0.74)¶
16- through 26-year-old girls and women	570	447	596.1	1
Anti-HPV 33				
27- through 45-year-old women	640	493	259.0	0.73 (0.67, 0.80)¶
16- through 26-year-old girls and women	570	457	354.5	1
Anti-HPV 45				
27- through 45-year-old women	640	515	145.6	0.68 (0.60, 0.76)¶
16- through 26-year-old girls and women	570	470	214.9	1
Anti-HPV 52				
27- through 45-year-old women	640	496	244.7	0.71 (0.64, 0.78)¶
16- through 26-year-old girls and women	570	456	346.5	1
Anti-HPV 58				
27- through 45-year-old women	640	478	296.4	0.69 (0.63, 0.76)¶
16- through 26-year-old girls and women	570	451	428.0	1

*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

seronegative to the relevant HPV type(s) (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) prior to dose 1. The data are from Protocol 004.

†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

#Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.50

cLIA=Competitive Luminex Immunoassay

CI=Confidence Interval

GMT=Geometric Mean Titers

Men 27 Years of Age and Older

GARDASIL 9 has not been studied in men 27 years of age and older. In men 27 years of age and older, efficacy of GARDASIL 9 is inferred based on (1) high efficacy of GARDASIL in girls and women 16 through 45 years of age and (2) comparable efficacy and immunogenicity of GARDASIL and GARDASIL 9 in individuals less than 27 years of age and (3) robust immunogenicity of GARDASIL in boys and men 16 through 45 years of age.

Persistence of Immune Response to GARDASIL 9

The persistence of antibody response following a complete schedule of vaccination with GARDASIL 9 is being studied in a subset of individuals who will be followed up for at least 10 years after vaccination for safety, immunogenicity and effectiveness.

In 9- through 15-year-old boys and girls (Protocol 002), persistence of antibody response has been demonstrated for at least 10 years; depending on HPV type, 81 to 98 % of subjects were seropositive.

In 16- through 26-year-old girls and women (Protocol 001), persistence of antibody response has been demonstrated for at least 5 years; depending on HPV type, 78 to 100% of subjects were seropositive. Efficacy was maintained in all subjects regardless of seropositivity status for any vaccine HPV type through the end of the study (up to 67 months postdose 3; median follow-up duration of 43 months).

GMTs for HPV-6, -11, -16 and -18 were numerically comparable in subjects who received GARDASIL or GARDASIL 9 for at least 3.5 years.

Evidence of Anamnestic (Immune Memory) Response

Evidence of an anamnestic response was seen in vaccinated women who were seropositive to relevant HPV type(s) prior to vaccination. In addition, women (n = 150) who received 3 doses of GARDASIL 9 in Protocol 001 and a challenge dose 5 years later, exhibited a rapid and strong anamnestic response that exceeded the anti-HPV GMTs observed 1 month postdose 3.

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.

Immune Responses to GARDASIL 9 using a 2-dose schedule in individuals 9 through 14 years of age

Protocol 010 measured HPV antibody responses to the 9 HPV types after GARDASIL 9 vaccination in the following cohorts: girls and boys 9 through 14 years of age receiving 2 doses at 6-month or 12-month interval (+/- 1 month); girls 9 through 14 years of age receiving 3 doses (at 0, 2, 6 months); and women 16 through 26 years of age receiving 3 doses (at 0, 2, 6 months).

GMTs were non-inferior in girls and boys who received 2 doses of GARDASIL 9 (at either 0, 6 months or 0, 12 months) to GMTs in 16- through 26-year-old girls and women who received 3 doses of GARDASIL 9 (at 0, 2, 6 months) for each of the 9 vaccine HPV types. On the basis of this immunogenicity bridging, the efficacy of a 2-dose regimen of GARDASIL 9 in 9- through 14-year-old girls and boys is inferred. One month following the last dose of the assigned regimen, between 97.9% and 100% of subjects across all groups became seropositive for antibodies against the 9 vaccine HPV types.

In the same study, in girls and boys 9 through 14 years of age, GMTs at one month after the last vaccine dose were numerically lower for some vaccine types after a 2-dose schedule than in girls 9 through 14 years of age after a 3-dose schedule (i.e. HPV types 18, 31, 45 and 52 after 0, 6 months and HPV type 45 after 0, 12 months). The clinical relevance of these findings is unknown.

Persistence of antibody response to GARDASIL 9 was observed for 3 years in girls and boys who were 9 through 14 years of age at time of vaccination receiving 2 doses at 6-month or 12-month interval. At Month 36, non-inferiority criteria were also met for GMTs in girls and boys 9 through 14 years of age receiving 2 doses at a 6-month interval (+/-1 month) compared to GMTs in women 16 through 26 years of age receiving 3 doses of GARDASIL 9.

Duration of protection of a 2-dose schedule of GARDASIL 9 has not been established.

PHARMACOKINETIC PROPERTIES

Evaluation of pharmacokinetic properties is not required for vaccines.

V. INDICATIONS

GARDASIL 9 is a vaccine indicated in girls and women from 9 years of age onward for the prevention of cervical, vulvar, vaginal, and anal, oropharyngeal and other head and neck cancers; precancerous or dysplastic lesions; genital warts; and persistent infections caused by Human Papillomavirus (HPV).

GARDASIL 9 is indicated to prevent the following diseases:

- Cervical, vulvar, vaginal, anal, oropharyngeal and other head and neck cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And persistent infections and the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- 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
- VIN grade 1 and VaIN grade 1
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

GARDASIL 9 is indicated in boys and men from 9 years of age onward for the prevention of anal, oropharyngeal and other head and neck cancers, anal precancerous or dysplastic lesions; external genital lesions (including genital warts); and persistent infections caused by HPV.

GARDASIL 9 is indicated to prevent the following diseases:

- Anal, oropharyngeal and other head and neck cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And persistent infections and the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

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

VI. DOSAGE AND ADMINISTRATION

6.1 General

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. 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 14 years of age, GARDASIL 9 can be administered according to a 2-dose schedule; the second dose should be administered between 5 and 13 months after the first dose. If the second vaccine dose is administered earlier than 5 months after the first dose, a third dose should always be administered.

The use of GARDASIL 9 should be in accordance with official recommendations.

Method of Administration

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.

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

It is recommended that individuals who receive a first dose of GARDASIL 9 complete the vaccination course with GARDASIL 9.

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

If the decision is made to administer GARDASIL 9 after receiving 3 doses of GARDASIL, there should be an interval of at least 12 months between completion of vaccination with GARDASIL and the start of vaccination with GARDASIL 9.

Instruction for Use

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 9 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

For single-use vials a separate sterile syringe and needle must be used for each individual. 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

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

VII. CONTRAINDICATIONS

GARDASIL 9 is contraindicated in patients with hypersensitivity to either GARDASIL 9 or GARDASIL or any of the inactive ingredients in either vaccine.

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

VIII. PRECAUTIONS

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, anal, oropharyngeal and other head and neck cancers; CIN, VIN, VaIN, or AIN.

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 HPV vaccination. Therefore, vaccinees should be carefully observed for approximately 15 minutes after administration of GARDASIL 9.

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 9 DRUG INTERACTIONS, 9.3 Use with Steroids and 14 IMMUNOCOMPROMISED INDIVIDUALS.]*

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. DRUG INTERACTIONS

9.1 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).

9.2 Use with Hormonal Contraceptives

In 7,269 women (16 through 26 years of age, from Protocols 001 and 002), 60.2% used hormonal contraceptives during the vaccination period of the clinical studies. Use of hormonal contraceptives did not appear to affect the type specific immune responses to GARDASIL 9.

9.3 Use with Steroids

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 14 IMMUNOCOMPROMISED INDIVIDUALS.]*

X. PREGNANCY

Pregnancy

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 fetus due to GARDASIL 9.

An evaluation of the effect of GARDASIL 9 on embryo-fetal, pre- and postweaning development was conducted in studies using rats. No adverse effects on mating, fertility, pregnancy, parturition, lactation, embryo-fetal or pre- and postweaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis noted. In addition, there were no treatment-related effects on developmental signs, behavior, 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 the period of gestation and lactation.

Clinical Studies in Humans

There are no adequate and well-controlled studies in pregnant women. Data from more than 1,000 pregnancy exposures to GARDASIL 9 in clinical studies and post-marketing experience do not demonstrate vaccine-associated increase in risk of major birth defects and miscarriages when GARDASIL 9 is administered during pregnancy. These pregnancies occurred in women who were pregnant at time of vaccination or became pregnant during the follow-up period in clinical studies. As a precautionary measure, the administration of GARDASIL 9 during pregnancy should be avoided. Women who become or plan to become pregnant during the vaccination series should be advised to interrupt or postpone the vaccination regimen until completion of pregnancy.

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 fetal death and congenital anomaly cases out of the total number of pregnancy outcomes for which an outcome was known (and excluding elective terminations), was 12.9% (174/1,353) in women who received GARDASIL 9 and 14.4% (187/1,303) 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, 30 and 24 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.

Post-marketing Experience

A six-year pregnancy registry for GARDASIL 9 enrolled 185 women who were inadvertently exposed to GARDASIL 9 within one month prior to the last menstrual period (LMP) or at any time during pregnancy, 180 of whom were prospectively followed. After excluding elective terminations (n=1), ectopic pregnancies (n=0) and those lost to follow-up (n=110), there were 69 pregnancies with known outcomes. Frequencies of miscarriage and major birth defects were 4.3% of pregnancies (3/69) and 4.5% of live born infants (3/67), respectively. These frequencies of the assessed outcomes in the prospective population were consistent with estimated background frequencies.

Data for adverse pregnancy outcomes for GARDASIL are included below as they are relevant to GARDASIL 9 since the vaccines are similar in composition and contain HPV L1 proteins of 4 of the same HPV types.

A five-year pregnancy registry for GARDASIL enrolled 2,942 women who were inadvertently exposed to GARDASIL within one month prior to the LMP or at any time during pregnancy, 2,566 of whom were prospectively followed. After excluding elective terminations (n=107), ectopic pregnancies (n=5) and those lost to follow-up (n=814), there were 1,640 pregnancies with known outcomes. Frequencies of miscarriage and major birth defects were 6.8% of pregnancies (111/1,640) and 2.4% of live born infants (37/1,527), respectively. These frequencies of the assessed outcomes in the prospective population were consistent with estimated background frequencies.

In two post-marketing studies of GARDASIL (one conducted in the U.S., and the other in Nordic countries), pregnancy outcomes among subjects who received GARDASIL within one month prior to the LMP or at any time during pregnancy were evaluated retrospectively. In the U.S. study database, 2,678 pregnancies were assessed for adverse pregnancy outcomes. Among GARDASIL exposed pregnancies with known outcomes (n=1,740), the estimated frequency of confirmed miscarriages was no greater than 8%. The frequency of major birth defects was 3.6% of live born infants (24/665). In the Nordic registry study, 499 live born infants were assessed for major birth defects. The frequency of major birth defects was 5.4% (27/499). In both studies, frequencies of the assessed outcomes did not suggest an increased risk with the administration of GARDASIL within one month prior to the LMP or at any time during pregnancy.

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

XI. NURSING MOTHERS

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 92 women were breast feeding during the vaccination period of the clinical studies for GARDASIL 9 in women aged 16 to 26 years. In these studies, vaccine immunogenicity was comparable between nursing women and women who did not nurse. In addition, the adverse experience profile for nursing women was comparable to that of the women in the overall safety population. There were no vaccine-related serious adverse experiences reported in infants who were nursing during the vaccination period.

XII. PEDIATRIC USE

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

XIII. GERIATRIC USE

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

XIV. IMMUNOCOMPROMISED INDIVIDUALS

The immunologic response to GARDASIL 9 may be diminished in immunocompromised individuals *[see 9 DRUG INTERACTIONS, 9.3 Use with Steroids]*.

XV. ADVERSE REACTIONS

15.1 Clinical Trials Experience

Clinical Trials Experience with GARDASIL 9 and GARDASIL

The safety of GARDASIL 9 was evaluated in 7 clinical studies (Protocols 001, 002, 003, 005, 006, 007, 009) that included 15,776 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 9,102 girls and women 16 through 26 years of age, 1,394 boys and men 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 girls and women 16 through 26 years of age and 300 girls 9 through 15 years of age at enrollment who received GARDASIL.

Safety was also evaluated in a clinical trial that included 640 women 27 through 45 years of age and 570 girls and women 16 through 26 years of age who received GARDASIL 9. The safety profile of GARDASIL 9 was comparable between the two age groups.

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 4 and 5. 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, men, girls and boys.

Table 4: 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	Subjects 9 Through 26 Years of Age
	GARDASIL 9 (N=15,776) %
Injection-Site Adverse Reactions (1 to 5 Days Postvaccination)	
Pain†	83.2
Swelling†	36.1
Erythema†	30.8
Pruritus	4.0
Bruising	1.6
Systemic Adverse Reactions (1 to 15 Days Postvaccination)	
Headache	13.2
Pyrexia	6.1
Nausea	3.2
Dizziness	2.3
Fatigue	1.9

*Data from Protocols 001,002, 003, 005, 006, 007, 009

†Designates a solicited adverse reaction

N=number of subjects vaccinated with safety follow-up

Table 5: 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 6.

Table 6: 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=15,614 %	Dose 2 N=15,243 %	Dose 3 N=15,062 %	Any Dose N=15,676 %
Temperature	< 37.8 °C (100.0 °F)	97.1	97.4	96.9	92.5
	≥ 37.8 °C (100.0 °F) < 38.9 °C (102.0 °F)	2.5	2.3	2.5	6.3
	≥ 38.9 °C (102.0 °F) < 39.9 °C (103.8 °F)	0.3	0.3	0.5	1.1
	≥ 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=15,773**	**Dose 2 N=15,549**	**Dose 3 N=15,378**	**Any Dose N=15,776**
Pain	Mild	52.3	46.7	44.4	51.1
	Moderate	10.8	15.1	16.7	28.5
	Severe	0.6	1.4	2.1	3.5
Swelling†	Mild	9.6	14.7	17.9	24.8
	Moderate	1.7	3.7	4.6	7.3
	Severe	0.8	1.6	2.5	4.0
Erythema†	Mild	8.7	13.6	16.1	24.7
	Moderate	0.9	2.0	2.5	4.4
	Severe	0.2	0.5	1.1	1.7

*Data from Protocols 001, 002, 003, 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 safety follow-up

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 7. 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 7: 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 Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content) (dTap-IPV) or Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap) and 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.

15.2 Post-marketing Experience

The post-marketing adverse experiences were reported voluntarily from a population of uncertain size, therefore, it is not possible to reliably estimate their frequency or to establish a causal relationship to vaccine exposure.

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

GARDASIL 9

In addition to the adverse reactions reported in the clinical studies, the following adverse experiences have been spontaneously reported during post-approval use of GARDASIL 9:

Nervous system disorders: syncope sometimes accompanied by tonic-clonic movements.

Gastrointestinal disorders: vomiting.

General disorder and administration site conditions: injection-site nodule.

GARDASIL

Additionally, the following post-marketing adverse experiences have been spontaneously reported for GARDASIL:

Infections and infestations: cellulitis.

Blood and lymphatic system disorders: idiopathic thrombocytopenic purpura, lymphadenopathy.

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

Nervous system disorders: acute disseminated encephalomyelitis, Guillain-Barré syndrome.

Musculoskeletal and connective tissue disorders: arthralgia, myalgia.

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

XVI. OVERDOSAGE

There have been no reports of administration of higher than recommended doses of GARDASIL 9.

XVII. STORAGE

Precautions for 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 multiple excursion) time out of refrigeration (at temperatures between 8°C and 25°C) does not exceed 72 hours. Cumulative multiple excursions between 0°C and 2°C are also permitted as long as the total time between 0°C and 2°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.

XVIII. AVAILABILITY

GARDASIL 9 is available in a single-dose 0.5 mL vial.

GARDASIL 9 is available in a single-dose 0.5 mL prefilled syringe with needle size 1 inch.

Imported by **MSD (THAILAND) LTD.**
Bangkok, Thailand

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