

GARDASIL[®] **[Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant]**

DESCRIPTION

GARDASIL^{*} is a non-infectious recombinant, quadrivalent vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18. The L1 proteins are produced by separate fermentations in recombinant *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 preformed aluminum-containing adjuvant (amorphous aluminum hydroxyphosphate sulfate). The quadrivalent 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 and the final purification buffer.

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

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

After thorough agitation, GARDASIL is a white, cloudy liquid.

CLINICAL PHARMACOLOGY

Disease Burden

Human Papillomavirus (HPV) causes squamous cell cervical cancer (and its histologic precursor lesions Cervical Intraepithelial Neoplasia [CIN] 1 or low grade dysplasia and CIN 2/3 or moderate to high grade dysplasia) and cervical adenocarcinoma (and its precursor lesion adenocarcinoma *in situ* [AIS]). HPV also causes approximately 35-50% of vulvar and vaginal cancers. Vulvar Intraepithelial Neoplasia (VIN) Grade 2/3 and Vaginal Intraepithelial Neoplasia (VaIN) Grade 2/3 are immediate precursors to these cancers.

Cervical cancer prevention focuses on routine screening and early intervention. This strategy has reduced cervical cancer rates by approximately 75% in compliant individuals by monitoring and removing premalignant dysplastic lesions.

HPV also causes genital warts (condyloma acuminata) which are growths of the cervicovaginal, vulvar, and the external genitalia that rarely progress to cancer. HPV 6, 11, 16, and 18 are common HPV types.

HPV 16 and 18 cause approximately:

- 70% of cervical cancer, AIS, CIN 3, VIN 2/3, and VaIN 2/3 cases; and
- 50% of CIN 2 cases.

HPV 6, 11, 16, and 18 cause approximately:

- 35 to 50% of all CIN 1, VIN 1, and VaIN 1 cases; and
- 90% of genital wart cases.

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Mechanism of Action

HPV only infects humans, but animal studies with analogous (animal, not human) papillomaviruses suggest that the efficacy of L1 VLP vaccines is mediated by the development of humoral immune responses.

CLINICAL STUDIES

CIN 2/3 and AIS are the immediate and necessary precursors of squamous cell carcinoma and adenocarcinoma of the cervix, respectively. Their detection and removal has been shown to prevent cancer; thus, they serve as surrogate markers for prevention of cervical cancer.

Efficacy was assessed in 4 placebo-controlled, double-blind, randomized Phase II and III clinical studies. The first Phase II study evaluated the HPV 16 component of GARDASIL (Protocol 005, N = 2391) and the second evaluated all components of GARDASIL (Protocol 007, N = 551). The Phase III studies, termed FUTURE (Females United To Unilaterally Reduce Endo/Ectocervical Disease), evaluated GARDASIL in 5442 (FUTURE I or Protocol 013) and 12,157 (FUTURE II or Protocol 015) subjects. Together, these four studies evaluated 20,541 women 16 to 26 years of age at enrollment. The median duration of follow-up was 4.0, 3.0, 2.4, and 2.0 years for Protocol 005, Protocol 007, FUTURE I, and FUTURE II, respectively. Subjects received vaccine or placebo on the day of enrollment, and 2 and 6 months thereafter. Efficacy was analyzed for each study individually and for all studies combined according to a prospective clinical plan.

Prophylactic Efficacy

GARDASIL is designed to prevent HPV 6-, 11-, 16-, and/or 18-related cervical cancer, cervical dysplasias, vulvar or vaginal dysplasias, or genital warts. GARDASIL was administered without prescreening for presence of HPV infection and the efficacy trials allowed enrollment of subjects regardless of baseline HPV status (i.e., Polymerase Chain Reaction [PCR] status or serostatus). Subjects who were infected with a particular vaccine HPV type (and who may already have had disease due to that infection) were not eligible for prophylactic efficacy evaluations for that type.

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

Overall, 73% of subjects were naïve (i.e., PCR negative and seronegative for all 4 vaccine HPV types) to all 4 vaccine HPV types at enrollment.

A total of 27% of subjects had evidence of prior exposure to or ongoing infection with at least 1 of the 4 vaccine HPV types. Among these subjects, 74% had evidence of prior exposure to or ongoing infection with only 1 of the 4 vaccine HPV types and were naïve (PCR negative and seronegative) to the remaining 3 types.

In subjects who were naïve (PCR negative and seronegative) to all 4 vaccine HPV types, CIN, genital warts, VIN, and VaIN caused by any of the 4 vaccine HPV types were counted as endpoints.

Among subjects who were positive (PCR positive and/or seropositive) for a vaccine HPV type at Day 1, endpoints related to that type were not included in the analyses of prophylactic efficacy. Endpoints related to the remaining types for which the subject was naïve (PCR negative and seronegative) were counted.

For example, in subjects who were HPV 18 positive (PCR positive and/or seropositive) at Day 1, lesions caused by HPV 18 were not counted in the prophylactic efficacy evaluations. Lesions caused by HPV 6, 11, and 16 were included in the prophylactic efficacy evaluations. The same approach was used for the other types.

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 in those who were PCR negative and seronegative at baseline (Table 1).

Table 1
Analysis of Efficacy of GARDASIL in the PPE* Population**

Population	GARDASIL		Placebo		% Efficacy (95% CI)
	n	Number of cases	n	Number of cases	
HPV 16- or 18-related CIN 2/3 or AIS					
Protocol 005***	755	0	750	12	100.0 (65.1, 100.0)
Protocol 007	231	0	230	1	100.0 (-3734.9, 100.0)
FUTURE I	2200	0	2222	19	100.0 (78.5, 100.0)
FUTURE II	5301	0	5258	21	100.0† (80.9, 100.0)
Combined Protocols‡	8487	0	8460	53	100.0† (92.9, 100.0)
HPV 6-, 11-, 16-, 18-related CIN (CIN 1, CIN 2/3) or AIS					
Protocol 007	235	0	233	3	100.0 (-137.8, 100.0)
FUTURE I	2240	0	2258	37	100.0† (89.5, 100.0)
FUTURE II	5383	4	5370	43	90.7 (74.4, 97.6)
Combined Protocols	7858	4	7861	83	95.2 (87.2, 98.7)
HPV 6-, 11-, 16-, or 18-related Genital Warts					
Protocol 007	235	0	233	3	100.0 (-139.5, 100.0)
FUTURE I	2261	0	2279	29	100.0 (86.4, 100.0)
FUTURE II	5401	1	5387	59	98.3 (90.2, 100.0)
Combined Protocols	7897	1	7899	91	98.9 (93.7, 100.0)

*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 6, 11, 16, and 18) prior to dose 1 and through 1 month Postdose 3 (Month 7).
**See Table 2 for analysis of vaccine impact in the general population.
***Evaluated only the HPV 16 L1 VLP vaccine component of GARDASIL.
†P-values were computed for pre-specified primary hypothesis tests. All p-values were <0.001, supporting the following conclusions: efficacy against HPV 16/18-related CIN 2/3 is >0% (FUTURE II); efficacy against HPV 16/18-related CIN 2/3 is >25% (Combined Protocols); and efficacy against HPV 6/11/16/18-related CIN is >20% (FUTURE I).
‡Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria.
n = Number of subjects with at least 1 follow-up visit after Month 7.
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: FUTURE I refers to Protocol 013; FUTURE II refers to Protocol 015.

GARDASIL was efficacious against HPV disease caused by each of the 4 vaccine HPV types.

In a pre-defined analysis, the efficacy of GARDASIL against HPV 16/18-related disease was 100% (95% CI: 87.9%, 100.0%) for CIN 3 or AIS and 100% (95% CI: 55.5%, 100.0%) for VIN 2/3 or VaIN 2/3. The efficacy of GARDASIL against HPV 6-, 11-, 16-, and 18-related VIN 1 or VaIN 1 was 100% (95% CI: 75.8%, 100.0%). These analyses were conducted in the PPE population that consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month Postdose 3 (Month 7).

Efficacy in Subjects with Current or Prior Infection

GARDASIL is a prophylactic vaccine.

There was no clear evidence of protection from disease caused by HPV types for which subjects were PCR positive and/or seropositive at baseline.

Individuals who were already infected with 1 or more vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the remaining vaccine HPV types.

General Population Impact

The general population of young American women includes women who are HPV-naïve (PCR negative and seronegative) and women who are HPV-non-naïve (PCR positive and/or seropositive), some of whom have HPV-related disease. The clinical trials population approximated the general population of American women with respect to prevalence of HPV infection and disease at enrollment. Analyses were conducted to evaluate the overall impact of GARDASIL with respect to HPV 6-, 11-, 16-, and 18-related cervical and genital disease in the general population. Here, analyses included events arising from HPV infections that were present at the start of vaccination as well as events that arose from infections that were acquired after the start of vaccination.

The impact of GARDASIL in the general population is shown in Table 2. Impact was measured starting 1 month Postdose 1. Prophylactic efficacy denotes the vaccine's efficacy in women who are naïve (PCR negative and seronegative) to the relevant HPV types at vaccination onset. General population impact denotes vaccine impact among women regardless of baseline PCR status and serostatus. The majority of CIN and genital warts, VIN, and VaIN detected in the group that received GARDASIL occurred as a consequence of HPV infection with the relevant HPV type that was already present at Day 1.

Table 2
General Population Impact for Vaccine HPV Types

Endpoints	Analysis	GARDASIL or HPV 16 L1 VLP Vaccine		Placebo		% Reduction (95% CI)
		N	Cases	N	Cases	
HPV 16- or 18-related CIN 2/3 or AIS	Prophylactic Efficacy*	9342	1	9400	81	98.8 (92.9, 100.0)
	HPV 16 and/or HPV 18 Positive at Day 1	--	121	--	120	--
	General Population Impact**	9831	122	9896	201	39.0 (23.3, 51.7)
HPV 16- or 18-related VIN 2/3 and VaIN 2/3	Prophylactic Efficacy*	8641	0	8667	24	100.0 (83.3, 100.0)
	HPV 16 and/or HPV 18 Positive at Day 1	--	8	--	2	--
	General Population Impact**	8954	8	8962	26	69.1 (29.8, 87.9)
HPV 6-, 11-, 16-, 18-related CIN (CIN 1, CIN 2/3) or AIS	Prophylactic Efficacy*	8625	9	8673	143	93.7 (87.7, 97.2)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1	--	161***	--	174***	--
	General Population Impact**	8814	170	8846	317	46.4 (35.2, 55.7)
HPV 6-, 11-, 16-, or 18-related Genital Warts	Prophylactic Efficacy*	8760	9	8786	136	93.4 (87.0, 97.0)
	HPV 6, HPV 11, HPV 16, and/or HPV 18 Positive at Day 1	--	49	--	48 [†]	--
	General Population Impact**	8954	58	8962	184	68.5 (57.5, 77.0)

*Includes all subjects who received at least 1 vaccination and who were naïve (PCR negative and seronegative) to HPV 6, 11, 16, and/or 18 at Day 1. Case counting started at 1 Month Postdose 1.

**Includes all subjects who received at least 1 vaccination (regardless of baseline HPV status at Day 1). Case counting started at 1 Month Postdose 1.

***Includes 2 subjects (1 in each vaccination group) who underwent colposcopy for reasons other than an abnormal Pap and 1 placebo subject with missing serology/PCR data at day 1.

[†]Includes 1 subject with missing serology/PCR data at day 1.

Note 1: The 16- and 18-related CIN 2/3 or AIS composite endpoint included data from studies 005, 007, 013, and 015. All other endpoints only included data from studies 007, 013, and 015.

Note 2: Positive status at Day 1 denotes PCR positive and/or seropositive for the respective type at Day 1.

Note 3: Percent reduction includes the prophylactic efficacy of GARDASIL as well as the impact of GARDASIL on the course of infections present at the start of the vaccination.

Note 4: Table 2 does not include disease due to non-vaccine HPV types.

GARDASIL does not prevent infection with the HPV types not contained in the vaccine. Cases of disease due to non-vaccine types were observed among recipients of GARDASIL and placebo in Phase II and Phase III efficacy studies.

Among cases of CIN 2/3 or AIS caused by vaccine or non-vaccine HPV types in subjects in the general population who received GARDASIL, 79% occurred in subjects who had an abnormal Pap test at Day 1 and/or who were positive (PCR positive and/or seropositive) to HPV 6, 11, 16, and/or 18 at Day 1.

An interim analysis of the general population impact for GARDASIL was performed from studies 007, 013, and 015 that had a median duration of follow-up of 1.9 years. GARDASIL reduced the overall rate of CIN 2/3 or AIS caused by vaccine or non-vaccine HPV types by 12.2% (95% CI: -3.2%, 25.3%), compared with placebo.

An analysis of overall population impact for the HPV 16 L1 VLP vaccine was conducted from study 005 that had a median duration of follow-up of 3.9 years. The HPV 16 L1 VLP vaccine reduced the overall incidence of CIN 2/3 caused by vaccine or non-vaccine HPV types by 32.7% (95% CI: -34.7%, 67.3%) through a median duration of follow-up of 1.9 years (fixed case analysis) and by 45.3% (95% CI: 10.9%, 67.1%), through a median duration of follow-up of 3.9 years (end of study).

GARDASIL reduced the incidence of definitive therapy (e.g., loop electrosurgical excision procedure, laser conization, cold knife conization) by 16.5% (95% CI: 2.9%, 28.2%), and surgery to excise external

genital lesions by 26.5% (95% CI: 3.6%, 44.2%), compared with placebo for all HPV-related diseases. These analyses were performed in the general population of women which includes women regardless of baseline HPV PCR status or serostatus. GARDASIL has not been shown to protect against the diseases caused by all HPV types and will not treat existing disease caused by the HPV types contained in the vaccine. The overall efficacy of GARDASIL, described above, will depend on the baseline prevalence of HPV infection related to vaccine types in the population vaccinated and the incidence of HPV infection due to types not included in the vaccine.

Immunogenicity

Assays to Measure Immune Response

Because there were few disease cases in subjects naïve (PCR negative and seronegative) to vaccine HPV types at baseline in the group that received GARDASIL, it has not been possible to establish minimum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 antibody levels that protect against clinical disease caused by HPV 6, 11, 16, and/or 18.

The immunogenicity of GARDASIL was assessed in 8915 women (GARDASIL N = 4666; placebo N = 4249) 18 to 26 years of age and female adolescents 9 to 17 years of age (GARDASIL N = 1471; placebo N = 583).

Type-specific competitive 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

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

Overall, 99.8%, 99.8%, 99.8%, and 99.5% of girls and women who received GARDASIL became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive, respectively, by 1 month Postdose 3 across all age groups tested. Anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs peaked at Month 7. GMTs declined through Month 24 and then stabilized through Month 36 at levels above baseline (Table 3). The duration of immunity following a complete schedule of immunization with GARDASIL has not been established.

Table 3
Summary of Anti-HPV cLIA Geometric Mean Titers in the PPI* Population

Study Time	GARDASIL N** = 276		Aluminum-Containing Placebo N = 275	
	n***	Geometric Mean Titer (95% CI) mMU/mL [†]	n	Geometric Mean Titer (95% CI) mMU/mL
Anti-HPV 6				
Month 07	208	582.2 (527.2, 642.8)	198	4.6 (4.3, 4.8)
Month 24	192	93.7 (82.2, 106.9)	188	4.6 (4.3, 5.0)
Month 36	183	93.8 (81.0, 108.6)	184	5.1 (4.7, 5.6)
Anti-HPV 11				
Month 07	208	696.5 (617.8, 785.2)	198	4.1 (4.0, 4.2)
Month 24	190	97.1 (84.2, 112.0)	188	4.2 (4.0, 4.3)
Month 36	174	91.7 (78.3, 107.3)	180	4.4 (4.1, 4.7)
Anti-HPV 16				
Month 07	193	3889.0 (3318.7, 4557.4)	185	6.5 (6.2, 6.9)
Month 24	174	393.0 (335.7, 460.1)	175	6.8 (6.3, 7.4)
Month 36	176	507.3 (434.6, 592.0)	170	7.7 (6.8, 8.8)
Anti-HPV 18				
Month 07	219	801.2 (693.8, 925.4)	209	4.6 (4.3, 5.0)
Month 24	204	59.9 (49.7, 72.2)	199	4.6 (4.3, 5.0)
Month 36	196	59.7 (48.5, 73.5)	193	4.8 (4.4, 5.2)

*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 subjects randomized to the respective vaccination group who received at least 1 injection.
***Number of subjects in the per-protocol analysis with data at the specified study time point.
[†]mMU = milli-Merck units.
Note: These data are from Protocol 007.

Table 4 compares anti-HPV GMTs 1 month Postdose 3 among subjects who received Dose 2 between Month 1 and Month 3 and subjects who received Dose 3 between Month 4 and Month 8 (Table 4).

Table 4
Summary of GMTs for Variation of Dosing Regimen

Variation of Dosing Regimen	Anti-HPV 6		Anti-HPV 11		Anti-HPV 16		Anti-HPV 18	
	N	GMT (95% CI)	N	GMT (95% CI)	N	GMT (95% CI)	N	GMT (95% CI)
Dose 2								
Early*	883	570.9 (542.2, 601.2)	888	824.6 (776.7, 875.5)	854	2625.3 (2415.1, 2853.9)	926	517.7 (482.9, 555.0)
On Time*	1767	552.3 (532.3, 573.1)	1785	739.7 (709.3, 771.5)	1737	2400.0 (2263.9, 2544.3)	1894	473.9 (451.8, 497.1)
Late*	313	447.4 (405.3, 493.8)	312	613.9 (550.8, 684.2)	285	1889.7 (1624.4, 2198.5)	334	388.5 (348.3, 433.3)
Dose 3								
Early**	495	493.1 (460.8, 527.8)	501	658.9 (609.5, 712.2)	487	2176.6 (1953.4, 2425.3)	521	423.4 (388.8, 461.2)
On Time**	2081	549.6 (531.1, 568.8)	2093	752.8 (723.8, 782.9)	2015	2415.0 (2286.3, 2550.9)	2214	486.0 (464.7, 508.2)
Late**	335	589.0 (537.0, 645.9)	339	865.3 (782.6, 956.7)	326	2765.9 (2408.7, 3176.2)	361	498.5 (446.2, 557.0)

*Early = 36 to 50 days Postdose 1; On Time = 51 to 70 days Postdose 1; Late = 71 to 84 days Postdose 1.
**Early = 80 to 105 days Postdose 2; On Time = 106 to 137 days Postdose 2; Late = 138 to 160 days Postdose 2.
Note: GMT = Geometric mean titer in mMU/mL (mMU = milli-Merck units.)

Bridging the Efficacy of GARDASIL from Young Adult Women to Adolescent Girls

A clinical study compared anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs in 10- to 15-year-old girls with responses in 16- to 23-year-old adolescent and young adult women. Among subjects who received GARDASIL, 99.1 to 100% became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive by 1 month Postdose 3.

Table 5 compares the 1 month Postdose 3 anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs in 9- to 15-year-old girls with those in 16- to 26-year-old adolescent and young adult women.

Table 5
Immunogenicity Bridging Between 9- to 15-year-old Female Adolescents and 16- to 26-year-old Adult Women

Assay (cLIA)	9- to 15-year-old Female Adolescents (Protocols 016 and 018) N = 1121			16- to 26-year-old Adult Women (Protocols 013 and 015) N = 4229		
	n	GMT	(95% CI)	n	GMT	(95% CI)
Anti-HPV 6	915	928.7	(874.0, 986.8)	2631	542.6	(526.2, 559.6)
Anti-HPV 11	915	1303.0	(1223.1, 1388.0)	2655	761.5	(735.3, 788.6)
Anti-HPV 16	913	4909.2	(4547.6, 5299.5)	2570	2293.9	(2185.0, 2408.2)
Anti-HPV 18	920	1039.8	(964.9, 1120.4)	2796	461.6	(444.0, 480.0)

Note: GMT = Geometric mean titer in mMU/mL (mMU = milli-Merck units).

Anti-HPV responses 1 month Postdose 3 among 9- to 15-year-old girls were non-inferior to anti-HPV responses in 16- to 26-year-old adolescent and young adult women in the combined database of immunogenicity studies for GARDASIL.

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

Studies with Other Vaccines

The safety and immunogenicity of co-administration of GARDASIL with hepatitis B vaccine (recombinant) (same visit, injections at separate sites) were evaluated in a randomized study of 1871 women aged 16 to 24 years at enrollment. Immune response to both hepatitis B vaccine (recombinant) and GARDASIL was non-inferior whether they were administered at the same visit or at a different visit.

INDICATIONS AND USAGE

GARDASIL is a vaccine indicated in girls and women 9-26 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types 6, 11, 16, and 18:

- Cervical cancer
 - Genital warts (condyloma acuminata)
- and the following precancerous or dysplastic lesions:
- Cervical adenocarcinoma *in situ* (AIS)
 - Cervical intraepithelial neoplasia (CIN) grade 2 and grade 3
 - Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
 - Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
 - Cervical intraepithelial neoplasia (CIN) grade 1

CONTRAINDICATIONS

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

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

PRECAUTIONS*General*

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

This vaccine is not intended to be used for treatment of active genital warts; cervical cancer; CIN, VIN, or VaIN.

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

GARDASIL has not been shown to protect against diseases due to non-vaccine HPV types.

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 PRECAUTIONS, *Drug Interactions*).

As with other intramuscular injections, GARDASIL should not be given to individuals with bleeding disorders such as hemophilia or thrombocytopenia, or to persons on anticoagulant therapy unless the potential benefits clearly outweigh the risk of administration. If the decision is made to administer GARDASIL to such persons, it should be given with steps to avoid the risk of hematoma following the injection.

Information for the Patient, Parent, or Guardian

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

The health care provider should provide the vaccine information required to be given with each vaccination to the patient, parent, or guardian.

The health care provider should inform the patient, parent, or guardian of the benefits and risks associated with vaccination. For risks associated with vaccination, see PRECAUTIONS and ADVERSE REACTIONS.

GARDASIL is not recommended for use in pregnant women.

The health care provider should inform the patient, parent, or guardian of the importance of completing the immunization series unless contraindicated.

Patients, parents, or guardians should be instructed to report any adverse reactions to their health care provider.

Drug Interactions

Use with Other Vaccines

Results from clinical studies indicate that GARDASIL may be administered concomitantly (at a separate injection site) with hepatitis B vaccine (recombinant) (see CLINICAL PHARMACOLOGY, *Studies with Other Vaccines*). Co-administration of GARDASIL with other vaccines has not been studied.

Use with Hormonal Contraceptives

In clinical studies, 13,293 subjects (vaccine = 6644; placebo = 6649) who had post-Month 7 follow-up used hormonal contraceptives for a total of 17,597 person-years (65.1% of the total follow-up time in the studies). Use of hormonal contraceptives or lack of use of hormonal contraceptives among study participants did not alter vaccine efficacy in the PPE population.

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, *General*).

Carcinogenesis, Mutagenesis, Impairment of Fertility

GARDASIL has not been evaluated for the potential to cause carcinogenicity or genotoxicity.

GARDASIL administered to female rats at a dose of 120 mcg total protein, which corresponds to approximately 300-fold excess relative to the projected human dose, had no effects on mating performance, fertility, or embryonic/fetal survival.

Pregnancy

Pregnancy Category B:

Reproduction studies have been performed in female rats at doses up to 300 times the human dose (on a mg/kg basis) and have revealed no evidence of impaired female fertility or harm to the fetus due to GARDASIL. However, it is not known whether GARDASIL can cause fetal harm when administered to a pregnant woman or if it can affect reproductive capacity. GARDASIL should be given to a pregnant woman only if clearly needed. An evaluation of the effect of GARDASIL on embryo-fetal, pre- and postweaning development was conducted using rats. One group of rats was administered GARDASIL twice prior to gestation, during the period of organogenesis (gestation day 6) and on lactation day 7. A second group of pregnant rats was administered GARDASIL during the period of organogenesis (gestation day 6) and on lactation day 7 only. GARDASIL was administered at 0.5 mL/rat/occasion (approximately 300-fold excess relative to the projected human dose on a mg/kg basis) by intramuscular injection. 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 this study. In addition, there were no treatment-related effects on developmental signs, behavior, reproductive performance, or fertility of the offspring. The effect of GARDASIL on male fertility has not been studied.

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

During clinical trials, 2266 women (vaccine = 1115 vs. placebo = 1151) reported at least 1 pregnancy each. Overall, the proportions of pregnancies with an adverse outcome were comparable in subjects who received GARDASIL and subjects who received placebo. Overall, 40 and 41 subjects in the group that received GARDASIL or placebo, respectively (3.6% and 3.6% of all subjects who reported a pregnancy in the respective vaccination groups), experienced a serious adverse experience during pregnancy. The most common events reported were conditions that can result in Caesarean section (e.g., failure of labor, malpresentation, cephalopelvic disproportion), premature onset of labor (e.g., threatened abortions, premature rupture of membranes), and pregnancy-related medical problems (e.g., pre-eclampsia, hyperemesis). The proportions of pregnant subjects who experienced such events were comparable between the vaccination groups.

There were 15 cases of congenital anomaly in pregnancies that occurred in subjects who received GARDASIL and 16 cases of congenital anomaly in pregnancies that occurred in subjects who received placebo.

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 or placebo. For pregnancies with estimated onset within 30 days of vaccination, 5 cases of congenital anomaly were observed in the group that received GARDASIL compared to 0 cases of congenital anomaly in the group that received placebo. The congenital anomalies seen in pregnancies with estimated onset within 30 days of vaccination included pyloric stenosis, congenital megacolon, congenital hydronephrosis, hip dysplasia and club foot. Conversely, in pregnancies with onset more than 30 days following vaccination, 10 cases of congenital anomaly were observed in the group that received GARDASIL compared with 16 cases of congenital anomaly in the group that received placebo. The types of anomalies observed were consistent (regardless of when pregnancy occurred in relation to vaccination) with those generally observed in pregnancies in women aged 16 to 26 years.

Pregnancy Registry for GARDASIL

Merck & Co., Inc. maintains a Pregnancy Registry to monitor fetal outcomes of pregnant women exposed to GARDASIL. Patients and health care providers are encouraged to report any exposure to GARDASIL during pregnancy by calling (800) 986-8999.

Lactation

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

Because many drugs are excreted in human milk, caution should be exercised when GARDASIL is administered to a nursing woman.

A total of 995 nursing mothers (vaccine = 500, placebo = 495) were given GARDASIL or placebo during the vaccination period of the clinical trials. GMTs in nursing and non-nursing mothers were as follows:

The GMTs in nursing mothers were 595.9 (95% CI: 522.5, 679.5) for anti-HPV 6, 864.3 (95% CI: 754.0, 990.8) for anti-HPV 11, 3056.9 (95% CI: 2594.4, 3601.8) for anti-HPV 16, and 527.2 (95% CI: 450.9, 616.5) for anti-HPV 18. The GMTs for women who did not nurse during vaccine administration were 540.1 (95% CI: 523.5, 557.2) for anti-HPV 6, 746.3 (95% CI: 720.4, 773.3) for anti-HPV 11, 2290.8 (95% CI: 2180.7, 2406.3) for anti-HPV 16, and 456.0 (95% CI: 438.4, 474.3) for anti-HPV 18.

Overall, 17 and 9 infants of subjects who received GARDASIL or placebo, respectively (representing 3.4% and 1.8% of the total number of subjects who were breast-feeding during the period in which they received GARDASIL or placebo, respectively), experienced a serious adverse experience. None was judged by the investigator to be vaccine related.

In clinical studies, a higher number of breast-feeding infants (n = 6) whose mothers received GARDASIL had acute respiratory illnesses within 30 days post-vaccination of the mother as compared to infants (n = 2) whose mothers received placebo. In these studies, the rates of other adverse experiences in the mother and the nursing infant were comparable between vaccination groups.

Pediatric Use

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

Geriatric Use

The safety and efficacy of GARDASIL have not been evaluated in adults above the age of 26 years.

ADVERSE REACTIONS

In 5 clinical trials (4 placebo-controlled), subjects were administered GARDASIL or placebo on the day of enrollment, and approximately 2 and 6 months thereafter. Few subjects (0.1%) discontinued due to adverse experiences. In all except 1 of the clinical trials, safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of GARDASIL or placebo. The subjects who were monitored using VRC-aided surveillance included 5088 girls and women 9 through 26 years of age at enrollment who received GARDASIL and 3790 girls and women who received placebo.

Common Adverse Experiences

Vaccine-related Common Adverse Experiences

The vaccine-related adverse experiences that were observed among female recipients of GARDASIL at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients are shown in Table 6.

Table 6
Vaccine-related Injection-site and Systemic Adverse Experiences*

Adverse Experience (1 to 5 Days Postvaccination)	GARDASIL (N = 5088) %	Aluminum-Containing Placebo (N = 3470) %	Saline Placebo (N = 320) %
<i>Injection Site</i>			
Pain	83.9	75.4	48.6
Swelling	25.4	15.8	7.3
Erythema	24.6	18.4	12.1
Pruritus	3.1	2.8	0.6
<i>Systemic</i>			
Fever	10.3	8.6	
Nausea	4.2	4.1	
Dizziness	2.8	2.6	

*The vaccine-related adverse experiences that were observed among recipients of GARDASIL were at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients.

All-cause Common Systemic Adverse Experiences

All-cause systemic adverse experiences for female subjects that were observed at a frequency of greater than or equal to 1% where the incidence in the vaccine group was greater than or equal to the incidence in the placebo group are shown in Table 7.

Table 7
All-cause Common Systemic Adverse Experiences

Adverse Experience (1 to 15 Days Postvaccination)	GARDASIL (N = 5088) %	Placebo (N = 3790) %
Pyrexia	13.0	11.2
Nausea	6.7	6.6
Nasopharyngitis	6.4	6.4
Dizziness	4.0	3.7
Diarrhea	3.6	3.5
Vomiting	2.4	1.9
Myalgia	2.0	2.0
Cough	2.0	1.5
Toothache	1.5	1.4
Upper respiratory tract infection	1.5	1.5
Malaise	1.4	1.2
Arthralgia	1.2	0.9
Insomnia	1.2	0.9
Nasal congestion	1.1	0.9

Evaluation of Injection-site Adverse Experiences by Dose

An analysis of injection-site adverse experiences in female subjects by dose is shown in Table 8. Overall, 94.3% of subjects who received GARDASIL judged their injection-site adverse experience to be mild or moderate in intensity.

Table 8
Postdose Evaluation of Injection-site Adverse Experiences

Adverse Experience	Vaccine (% occurrence)				Aluminum-Containing Placebo (% occurrence)				Saline Placebo (% occurrence)			
	Post-dose 1	Post-dose 2	Post-dose 3	Post Any Dose	Post-dose 1	Post-dose 2	Post-dose 3	Post Any Dose	Post-dose 1	Post-dose 2	Post-dose 3	Post Any Dose
Pain	63.4	60.7	62.7	83.9	57.0	47.8	49.5	75.4	33.7	20.3	27.3	48.6
Mild/Moderate	62.5	59.7	61.2	81.1	56.6	47.3	48.9	74.1	33.3	20.3	27.0	48.0
Severe	0.9	1.0	1.5	2.8	0.4	0.5	0.6	1.3	0.3	0.0	0.3	0.6
Swelling*	10.2	12.8	15.1	25.4	8.2	7.5	7.6	15.8	4.4	3.0	3.3	7.3
Mild/Moderate	9.6	11.9	14.3	23.3	8.0	7.2	7.3	15.2	4.4	3.0	3.3	7.3
Severe	0.6	0.8	0.8	2.0	0.2	0.3	0.2	0.6	0.0	0.0	0.0	0.0
Erythema*	9.2	12.1	14.7	24.7	9.8	8.4	8.9	18.4	7.3	5.3	5.7	12.1
Mild/Moderate	9.0	11.7	14.3	23.7	9.5	8.3	8.8	18.0	7.3	5.3	5.7	12.1
Severe	0.2	0.3	0.4	0.9	0.3	0.1	0.1	0.4	0.0	0.0	0.0	0.0

*Intensity of swelling and erythema was measured by size (inches): Mild = 0 to ≤1; Moderate = >1 to ≤2; Severe = >2.

Evaluation of Fever by Dose

An analysis of fever in girls and women by dose is shown in Table 9.

Table 9
Postdose Evaluation of Fever

Temperature (°F)	Vaccine (% occurrence)			Placebo (% occurrence)		
	Postdose 1	Postdose 2	Postdose 3	Postdose 1	Postdose 2	Postdose 3
≥100 to <102	3.7	4.1	4.4	3.1	3.8	3.6
≥102	0.3	0.5	0.5	0.3	0.4	0.6

Serious Adverse Experiences

A total of 102 subjects out of 21,464 total subjects (9- to 26-year-old girls and women and 9- to 15-year-old boys) who received both GARDASIL and placebo reported a serious adverse experience on Day 1-15 following any vaccination visit during the clinical trials for GARDASIL. The most frequently reported serious adverse experiences for GARDASIL compared to placebo and regardless of causality were:

headache (0.03% GARDASIL vs. 0.02% Placebo),
gastroenteritis (0.03% GARDASIL vs. 0.01% Placebo),
appendicitis (0.02% GARDASIL vs. 0.01% Placebo),
pelvic inflammatory disease (0.02% GARDASIL vs. 0.01% Placebo).

One case of bronchospasm and 2 cases of asthma were reported as serious adverse experiences that occurred during Day 1-15 of any vaccination visit.

Deaths

Across the clinical studies, 17 deaths were reported in 21,464 male and female subjects. The events reported were consistent with events expected in healthy adolescent and adult populations. The most common cause of death was motor vehicle accident (4 subjects who received GARDASIL and 3 placebo subjects), followed by overdose/suicide (1 subject who received GARDASIL and 2 subjects who received placebo), and pulmonary embolus/deep vein thrombosis (1 subject who received GARDASIL and 1 placebo subject). In addition, there were 2 cases of sepsis, 1 case of pancreatic cancer, and 1 case of arrhythmia in the group that received GARDASIL, and 1 case of asphyxia in the placebo group.

Systemic Autoimmune Disorders

In the clinical studies, subjects were evaluated for new medical conditions that occurred over the course of up to 4 years of follow up. The number of subjects who received both GARDASIL and placebo and developed a new medical condition potentially indicative of a systemic immune disorder is shown in Table 10.

Table 10
Summary of Subjects Who Reported an Incident Condition Potentially Indicative of Systemic Autoimmune Disorder After Enrollment in Clinical Trials of GARDASIL

Potential Autoimmune Disorder	GARDASIL (N = 11,813)	Placebo (N = 9701)
Specific Terms	3 (0.025%)	1 (0.010%)
Juvenile arthritis	1	0
Rheumatoid arthritis	2	0
Systemic lupus erythematosus	0	1
Other Terms	6 (0.051%)	2 (0.021%)
Arthritis	5	2
Reactive Arthritis	1	0

N = Number of subjects enrolled

Safety in Concomitant Use with Other Vaccines

The safety of GARDASIL when administered concomitantly with hepatitis B vaccine (recombinant) was evaluated in a placebo-controlled study. There were no statistically significant higher rates in systemic or injection-site adverse experiences among subjects who received concomitant vaccination compared with those who received GARDASIL or hepatitis B vaccine alone.

Post-Marketing Reports

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

Blood and lymphatic system disorders: Lymphadenopathy.

Nervous system disorders: Dizziness, Guillain-Barré syndrome, headache, syncope.

Gastrointestinal disorders: Nausea, vomiting.

Musculoskeletal and connective tissue disorders: Arthralgia, myalgia.

General disorders and administration site conditions: Asthenia, fatigue, malaise.

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

Reporting of Adverse Events

The US Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986. For information or a copy of the vaccine reporting form, call the VAERS toll-free number at 1-800-822-7967 or report on line to www.vaers.hhs.gov.

DOSAGE AND ADMINISTRATION

Dosage

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

First dose: at elected date

Second dose: 2 months after the first dose

Third dose: 6 months after the first dose

Method of Administration

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

GARDASIL must not be injected intravascularly. Subcutaneous and intradermal administration have not been studied, and therefore are not recommended.

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

The prefilled syringe is for single use only and should not be used for more than 1 individual. For single-use vials a separate sterile syringe and needle must be used for each individual.

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

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

After thorough agitation, GARDASIL is a white, cloudy liquid. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use the product if particulates are present or if it appears discolored.

Single-Dose Vial Use

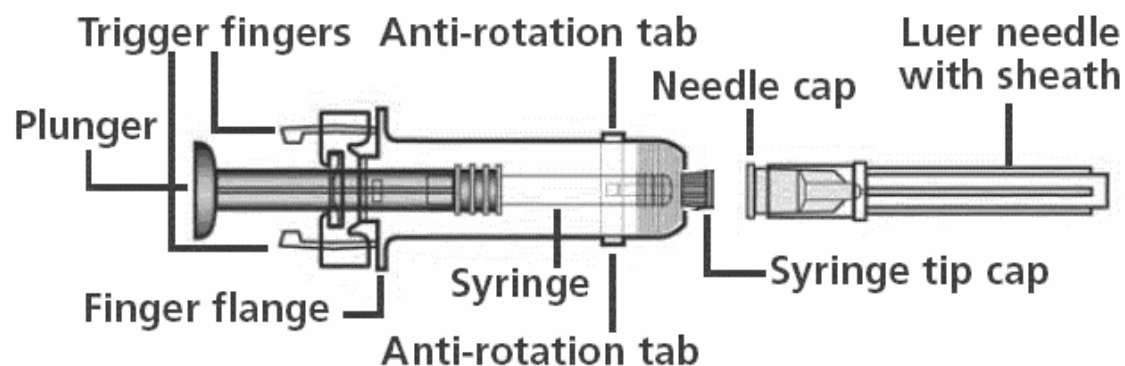
Withdraw the 0.5-mL dose of vaccine from the single-dose vial using a sterile needle and syringe free of preservatives, antiseptics, and detergents. Once the single-dose vial has been penetrated, the withdrawn vaccine should be used promptly, and the vial must be discarded.

Prefilled Syringe Use With and Without Needle Guard (Safety) Device

Prefilled Syringe With Needle Guard (Safety) Device

Inject the entire contents of the syringe.

Instructions for using the prefilled single-dose syringes preassembled with needle guard (safety) device



NOTE: Please use the enclosed needle for administration. If a different needle is chosen, it should fit securely on the syringe and be no longer than 1 inch to ensure proper functioning of the needle guard device. Two detachable labels are provided which can be removed after the needle is guarded.

At any of the following steps, avoid contact with the Trigger Fingers to keep from activating the safety device prematurely.

Remove Syringe Tip Cap and Needle Cap. Attach Luer Needle by pressing both Anti-Rotation Tabs to secure syringe and by twisting the Luer Needle in a clockwise direction until secured to the syringe. **Remove Needle Sheath. Administer injection** per standard protocol as stated above under DOSAGE AND ADMINISTRATION. Depress the Plunger while grasping the Finger Flange **until the entire dose has been given**. The Needle Guard Device will **NOT** activate to cover and protect the needle unless the **ENTIRE** dose has been given. While the Plunger is still depressed, remove needle from the vaccine recipient. Slowly release the Plunger and allow syringe to move up until the entire needle is guarded. For documentation of vaccination, remove detachable labels by pulling slowly on them. **Dispose in approved sharps container.**

Prefilled Syringe Without Needle Guard (Safety) Device

This package does not contain a needle guard (safety device) or a needle. Shake well before use. Attach the needle by twisting in a clockwise direction until the needle fits securely on the syringe. Administer the entire dose as per standard protocol.

GARDASIL[®]

[Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant]

9682307

HOW SUPPLIED

Vials

No. 4045 — GARDASIL is supplied as a carton of one 0.5-mL single-dose vial, **NDC 0006-4045-00**.

No. 4045 — GARDASIL is supplied as a carton of ten 0.5-mL single-dose vials, **NDC 0006-4045-41**.

Syringes

No. 4109 — GARDASIL is supplied as a carton of six 0.5-mL single-dose prefilled Luer Lock syringes, preassembled with UltraSafe Passive^{®†} delivery system. One-inch, 25-gauge needles are provided separately in the package. **NDC 0006-4109-06**.

No. 4109 — GARDASIL is supplied as a carton of six 0.5-mL single-dose prefilled Luer Lock syringes with tip caps. **NDC 0006-4109-09**.

Storage

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

Manuf. and Dist. by:
 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

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[†]UltraSafe Passive[®] delivery system is a Trademark of Safety Syringes, Inc.