

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

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.

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 = 651). 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 reassessed 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 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/or 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 (-374.9, 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-, or 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 seropositive) 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		% Reduction (95% CI)
		N	Cases	
HPV 16- or 18-related CIN 2/3 or AIS	Prophylactic Efficacy*	9342	1	9400 (81, 9400)
	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 on 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 (PI) 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 PI* Population				
Study Time	GARDASIL N** = 276		Aluminum-Containing Placebo N = 275	
	n***	Geometric Mean Titer (95% CI) mIU/mL	n	Geometric Mean Titer (95% CI) mIU/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 PI population consisted of individuals who received all 3 vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met prespecified 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.

† mIU = milli-Units/mL.

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	552.0 (532.3, 573.1)	1785	780.7 (709.3, 771.5)	1737†	2400.0 (2263.3, 2544.3)	1894†	472.9 (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)

* 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 mIU/mL; mIU = milli-Merk units.

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 3								
Early**	495	493.1 (460.8, 527.8)	501	658.6 (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, 781.9)	2015	2415.0 (2286.3, 2560.9)	2214	486.0 (464.7, 508.2)
Late**	335	580.0 (537.0, 645.9)	339	865.3 (782.6, 946.7)	328	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 mIU/mL; mIU = milli-Merk 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, 980.8)	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, 5269.5)	2570	2293.9	(2185.0, 2408.2)
Anti-HPV 18	920	1039.8	(964.9, 1110.4)	2796	461.6	(444.0, 480.0)

Note: GMT = Geometric mean titer in mIU/mL; mIU = 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

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.

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.

HOW SUPPLIED

Vials

GARDASIL is supplied as a carton of one 0.5-mL single-dose vial.

GARDASIL is supplied as a carton of ten 0.5-mL single-dose vials.

Syringes

GARDASIL is supplied as a carton of one 0.5-mL single-dose prefilled Luer Lock syringes with tip caps.

Not all pack may be marketed

Storage

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

(THIS IS A MEDICAMENT)

— Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

— Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament.

— The doctor and the pharmacist are experts in medicine, its benefits and risks.

— Do not by yourself interrupt the period of treatment prescribed for you.

— Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

Issued December 2007

Patient Information about

GARDASIL™

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

Read this information with care before you or your child gets GARDASIL™. You or your child will need 3 doses of the vaccine. It is important to read this leaflet when you receive each dose. This leaflet does not take the place of talking with your health care professional about GARDASIL.

What is GARDASIL and what is it used for?

GARDASIL is a vaccine (injection/shot) that helps protect against the following diseases caused by Human Papillomavirus (HPV) Types in the vaccine (6, 11, 16, and 18):

- Cervical cancer (cancer of the lower end of the uterus or womb).
- Abnormal and precancerous cervical lesions.
- Abnormal and precancerous vaginal lesions.
- Abnormal and precancerous vulvar lesions.
- Genital warts.

GARDASIL helps prevent these diseases – but it will not treat them.

You or your child cannot get these diseases from GARDASIL.

What other key information about GARDASIL should I know?

Vaccination does not substitute for routine cervical cancer screening. Females who receive GARDASIL should continue cervical cancer screening.

As with all vaccines, GARDASIL may not fully protect everyone who gets the vaccine.

Gardasil will not protect against diseases due to non-vaccine HPV types. There are more than 100 HPV types; GARDASIL helps protect against 4 types (6, 11, 16, and 18). These 4 types have been selected for GARDASIL because they cause approximately 70% of cervical cancers and 90% of genital warts.

This vaccine will not protect you against HPV types to which you may have already been exposed.

GARDASIL also will not protect against other diseases that are not caused by HPV.

GARDASIL works best when given before you or your child has any contact with certain types of HPV (i.e., HPV types 6, 11, 16, and 18).

Who can receive GARDASIL?

GARDASIL is for girls and women 9 through 26 years of age.

See "Who should not receive GARDASIL?" below.

Who should not receive GARDASIL?

Anyone who:

- is allergic to any of the ingredients in the vaccine. A list of ingredients can be found at the end of this leaflet.
- has an allergic reaction after getting a dose of the vaccine.

What should I tell my health care professional before I am vaccinated or my child is vaccinated with GARDASIL?

It is very important to tell your health care professional if you or your child:

- has had an allergic reaction to the vaccine.
- has a bleeding disorder and cannot receive injections in the arm.
- has a weakened immune system, for example, due to a genetic defect or HIV infection.
- is pregnant or is planning to get pregnant. GARDASIL is not recommended for use in pregnant women.
- has any illness with a fever more than 100°F (37.8°C).
- takes or plans to take any medicines, even those you can buy over the counter.

Your health care professional will decide if you or your child should receive the vaccine.

How is GARDASIL given?

GARDASIL is given as an injection.

You or your child will receive 3 doses of the vaccine. Ideally the doses are given as:

- First dose: at a date you and your health care professional choose.
- Second dose: 2 months after the first dose.
- Third dose: 6 months after the first dose.

Make sure that you or your child gets all 3 doses. This allows you or your child to get the full benefits of GARDASIL. If you or your child misses a dose, your health care professional will decide when to give the missed dose.

What are the possible side effects of GARDASIL?

As with all vaccines, there may be some side effects with GARDASIL. GARDASIL has been shown to be generally well tolerated in women and girls as young as 9 years of age.

The most common side effects reported included:

- pain, swelling, itching, and redness at the injection site.
- fever.
- nausea.
- dizziness.
- vomiting.
- fainting.

Fainting can occur after vaccination, most commonly among adolescents and young adults. Although fainting episodes are uncommon, patients should be observed for 15 minutes after they receive HPV vaccine.

Allergic reactions that may include difficulty breathing, wheezing (bronchospasm), hives, and rash have been reported. Some of these reactions have been severe.

Additional side effects reported include swollen glands (neck, armpit, or groin), Guillain-Barré syndrome, headache, joint pain, aching muscles, unusual tiredness or weakness, and generally feeling unwell.

If you or your child has any unusual or severe symptoms after receiving GARDASIL, contact your health care professional right away.

For a more complete list of side effects, ask your health care professional.

What are the ingredients in GARDASIL?

The main ingredients are purified inactive proteins that come from HPV Types 6, 11, 16, and 18.

It also contains amorphous aluminum hydroxyphosphate sulfate, sodium chloride, L-histidine, polysorbate 80, sodium borate, and water for injection.

What are cervical cancer, precancerous lesions, and genital warts?

Cancer of the cervix is a serious disease that can be life-threatening. This disease is caused by certain HPV types that can cause the cells in the lining of the cervix to change from normal to precancerous lesions. If these are not treated, they can turn cancerous.

Genital warts are caused by certain types of HPV. They often appear as skin-colored growths. They are found on the inside or outside of the genitals. They can hurt, itch, bleed, and cause discomfort. These lesions are usually not precancerous. Sometimes, it takes multiple treatments to eliminate these lesions.

What is Human Papillomavirus (HPV)?

HPV is a common virus. There are many different types of HPV; some cause no harm. Others can cause diseases of the genital area. For most people the virus goes away on its own. When the virus does not go away it can develop into cervical cancer, precancerous lesions, or genital warts, depending on the HPV type. See "What other key information about GARDASIL should I know?"

Who is at risk for Human Papillomavirus?

In 2005, the Centers for Disease Control and Prevention (CDC) estimated that at least 50% of sexually active people catch HPV during their lifetime. A male or female of any age who takes part in any kind of sexual activity that involves genital contact is at risk.

Many people who have HPV may not show any signs or symptoms. This means that they can pass on the virus to others and not know it.

Will GARDASIL help me if I already have Human Papillomavirus?

You may benefit from GARDASIL if you already have HPV. This is because most people are not infected with all four types of HPV contained in the vaccine. In clinical trials, individuals with current or past infection with one or more vaccine-related HPV types prior to vaccination were protected from disease caused by the remaining vaccine HPV types. GARDASIL is not intended to be used for treatment for the above mentioned diseases. Talk to your health care professional for more information.

This leaflet is a summary of information about GARDASIL. If you would like more information, please talk to your health care professional.

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