PRODUCT INFORMATION

GARDASIL®

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

DESCRIPTION

GARDASIL® is a recombinant, quadrivalent vaccine.

The quadrivalent Human Papillomavirus Virus-Like Particle vaccine (HPV VLP vaccine) is a sterile liquid suspension prepared from the highly purified virus-like particles (VLPs) of the recombinant major capsid (L1) protein of HPV Types 6, 11, 16, and 18. The L1 proteins are produced by separate fermentations in recombinant *Saccharomyces cerevisiae* CANADE 3C-5 (Strain 1895) and self-assembled into VLPs. The VLPs for each type are purified and adsorbed on aluminum-containing adjuvant (amorphous aluminum hydroxyphosphate sulfate, or AAHS). The quadrivalent HPV VLP vaccine is prepared by combining the adsorbed VLPs of each HPV type, the aluminum-containing adjuvant formulation, and a 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 borax, and water for injection. The product does not contain a preservative or antibiotics.

PHARMACOLOGY

Mechanism of Action

GARDASIL contains HPV 6,11,16 and 18 L1 VLPs. Each VLP is composed of a unique recombinant L1 major capsid protein for the respective HPV type. Because the virus-like particles contain no viral DNA, they cannot infect cells or reproduce.

Pre-clinical data suggests that the efficacy of L1 VLP vaccines is mediated by the development of humoral immune responses. Induction of anti-papillomavirus antibodies with L1 VLP vaccines resulted in protection against infection. Administration of serum from vaccinated to unvaccinated animals resulted in the transfer of protection against HPV to the unvaccinated animals.

The induction of a strong anamnestic (immune memory) response has been further demonstrated in clinical trials (See Clinical Studies, *Immune Memory (Anamnestic) Responses).*

CLINICAL STUDIES

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

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

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

The efficacy of GARDASIL or the HPV component of GARDASIL was assessed in 5 placebo-controlled, double-blind, randomized Phase II and III clinical studies. One Phase II study evaluated all four components (i.e., HPV 6, 11, 16, and 18) of GARDASIL (Protocol 007, N = 551). An additional phase II study evaluated the HPV 16 component of GARDASIL (Protocol 005, N=2,391). The Phase III studies, termed FUTURE (Females United To Unilaterally Reduce Endo/Ectocervical Disease), evaluated GARDASIL in 5,442 (FUTURE I), 12,157 (FUTURE II), and 3,817 (FUTURE III) subjects. Together, these studies evaluated 24,358 women 16 through 45 years of age at enrolment, the majority of whom had been sexually active.

The median duration of follow-up was 4.0, 3.0, 3.0, 3.0 and 2.2 years for Protocol 005, Protocol 007, FUTURE I, FUTURE II and FUTURE III, respectively, with a maximum follow-up of 5 years. Subjects received vaccine or placebo on the day of enrolment and 2 and 6 months thereafter. Efficacy was analyzed for each study individually and for all studies combined.

In the clinical studies, HPV status was not assessed before subjects were enrolled. Thus, individuals who had been exposed to a vaccine HPV type prior to enrolment were included in the studies for evaluation. Overall, 73% of 16 through 26 year old subjects and 67% of 24 through 45 year old subjects were naïve to all 4 vaccine HPV types at enrolment. The naïve subjects continued to be at risk for infection and disease caused by all 4 vaccine HPV types. Amoung the 24 through 45 year old subjects only 0.4% had been exposed to all 4 vaccine HPV types.

Clinical Studies in 16 Through 26 Year Old Females

Prophylactic Efficacy against HPV Types 6, 11, 16 and 18

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

Table 1
Analysis of Efficacy of GARDASIL in the PPE Population of 16 Through 26 Year Old Women

Population	GARDASIL		Placebo		
	n	Number of cases	n	Number of cases	% Efficacy (95% CI)
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 (<0.0, 100.0)
FUTURE I	2,201	0	2,222	36	100.0 (89.2, 100.0)
FUTURE II	5,306	2**	5,262	63	96.9 (88.2, 99.6)
Combined Protocols***	8,493	2**	8,464	112	98.2 (93.5, 99.8)
HPV 16- or 18-related VIN 2/3					
Protocol 007	231	0	230	0	Not calculated
FUTURE I	2,219	0	2,239	6	100.0 (14.4, 100.0)
FUTURE II	5,322	0	5,275	4	100.0 (<0.0, 100.0)
Combined Protocols***	7,772	0	7,744	10	100.0 (55.5, 100.0)
HPV 16- or 18-related VaIN 2/3					
Protocol 007	231	0	230	0	Not calculated
FUTURE I	2,219	0	2,239	5	100.0 (<0.0, 100.0)
FUTURE II	5,322	0	5,275	4	100.0 (<0.0, 100.0)
Combined Protocols***	7,772	0	7,744	9	100.0 (49.5, 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 (<0.0, 100.0)
FUTURE I	2241	0	2,258	77	100.0 (95.1, 100.0)
FUTURE II	5,388	9†	5,374	145	93.8 (88.0, 97.2)
Combined Protocols***	7,864	9†	7,865	225	96.0 (92.3, 98.2)
HPV 6-, 11-, 16-, or 18-related Genital Lesions (Genital Warts, VIN, VaIN, Vulvar Cancer, and Vaginal Cancer)					
Protocol 007	235	0	233	3	100.0 (<0.0, 100.0)
FUTURE I	2,261	0	2,279	74	100.0 (94.9, 100.0)
FUTURE II	5,404	2	5,390	150	98.7 (95.2, 99.8)

GARDASIL was equally efficacious against HPV 16/18-related CIN 3, AIS, VIN 2/3, and VaIN 2/3 in the PPE population (Table 3).

Table 3
Supplemental Analyses of Cancer-Related Endpoints: Efficacy Against HPV 16/18-Related Invasive Cancer Precursors for the Combined Protocols in the PPE* Population of 16 through 26 Year Old Women

Population	GARDASIL		Placebo		% Efficacy (95% CI)
	n	Number of cases	n	Number of cases	
HPV 16- or 18-related CIN 3					
Per-protocol	8,493	2**	8,464	64	96.9 (88.4, 99.6)
HPV 16- or 18-related AIS					
Per-protocol	8,493	0	8,464	7	100.0 (30.6, 100.0)

*The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrolment, 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).

** There were two cases of CIN 3 that occurred in the group that received GARDASIL (FUTURE II). In the first case HPV 16 and HPV 52 were detected. This individual was chronically infected with HPV 52 (infection at Day 1, and Months 32.5 and 33.6) in 8 of 11 specimens, including tissue that was excised during LEEP (Loop Electro-Excision Procedure). HPV 16 was found in 1 of 11 specimens at Month 32.5. HPV 16 was not detected in tissue that was excised during LEEP. In the second case HPV 16, HPV 51, and HPV 56 were detected. This individual was infected with HPV 51 (infection detected by PCR at Day 1) in 2 of 9 specimens. HPV 56 was detected (in tissue excised during LEEP) in 3 of 9 specimens at Month 52. HPV 16 was detected in 1 of 9 specimens at a month 51 biopsy. Given that these cases occurred in the context of mixed infection, with the dominant type being the non-vaccine HPV type, it is likely that the relevant vaccine HPV type was not the causal HPV type. Based on this assessment, it can be inferred that vaccine efficacy against HPV 16/18-related CIN 2/3 or AIS was 100%.

n = Number of subjects with at least one follow-up visit after Day 1.

CI = Confidence Interval

Note: Point estimates and confidence intervals are adjusted for person-time of follow-up

Efficacy against HPV 16/18-related disease was 96.7% (95% CI: 90.2%, 99.3%) and 100.0% (95% CI: 60.0%, 100.0%) for CIN 3 and AIS, respectively, in the MITT-2 population.

The supplemental analysis also evaluated efficacy against immediate precursors to vulvar and vaginal cancer (VIN 2/3 or VaIN 2/3). In this analysis the efficacy of GARDASIL against VIN 2/3 or VaIN 2/3 due to HPV 16 and 18 was 100% (95% CI: 78.6%, 100.0%) in the per-protocol population, and 97.0% (95% CI: 82.4%, 99.9%) in the MITT-2 population.

Long-term Prophylactic Efficacy

The efficacy of GARDASIL against HPV 6-, 11-, 16-, or 18-related persistent infection or disease through 60 months was 95.8% (95% CI: 83.8%, 99.5%), with efficacy against disease due to these HPV types being 100% (95% CI: 12.4, 100), a function of sustained immunity.

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

Cross Protection Efficacy against HPV Types 31, 33, 45, 52, 56, 58 and 59

The World Health Organization recommends that the evaluation of cross protection focus on the efficacy of the vaccine against CIN (any grade), CIN 2/3, or AIS, demonstrated by the reduction in the incidence of lesions, caused by oncogenic non-vaccine types. Viral persistence (at least 12 months) can also be used to demonstrate cross protection.

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

Further post-hoc analyses considered efficacy in a generally HPV-naïve population (negative to 14 common HPV types and had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1), approximating a population of sexually-naïve adolescents and young adult women plus young adult women prior to or shortly after sexual debut. When GARDASIL was administered to the generally HPV naïve subjects, there were statistically significant reductions in the incidences of CIN (grades 1,2,3) or AIS caused by HPV 31, 33, 52 , and 58 (Table 4). Although there was a trend of reduction in the incidence of CIN (grades 1, 2, 3) or AIS caused by HPV 56 or 59, statistically significant reduction has not been demonstrated.

Table 4
Impact of GARDASIL on the Rates of CIN (any Grade) or AIS for the Combined FUTURE I and FUTURE II Disease Cross Protection Data Set in 16 Through 26 Year old Women

HPV Types	Population	% Reduction	95% CI
HPV 31/45-related**	Generally HPV-naïve* (n = 9,296)	43.6	12.9, 64.1
HPV 31/33/45/52/58-related***	Generally HPV-naïve	29.2	8.3, 45.5
HPV 31/33/52/58-related	Generally HPV-naïve	33.8	13.4, 49.6
HPV 56-related	Generally HPV-naïve	27.6	<0.0, 49.3
HPV 59-related	Generally HPV-naïve	22.3	<0.0, 58.9

*Generally HPV-naïve population included subjects who, at Day 1, had a negative for SIL Pap test and were negative to all of the following HPV types: HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59; and had follow-up after Day 30 of the study. Case counting started at Day 30.

**Primary pre-specified endpoint of the analysis.

***Secondary pre-specified endpoint of the analysis.

CI = Confidence Interval

Population Impact

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

Individuals, who had early HPV infection at the time of enrolment and who received GARDASIL did not show a statistically significant reduction of CIN or AIS compared to placebo. Estimated vaccine efficacy was 21.6% (95% CI: <0.0%, 42.1%). Early infection was defined as infection with a vaccine HPV type at enrolment, but no evidence of immune response to it.

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

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

The benefit of the vaccine with respect to the overall incidence of CIN 2/3 or AIS (caused by any HPV type) became more apparent over time (Figure 1). GARDASIL does not impact the course of infections or disease present at vaccination onset. Over a longer duration of follow-up, the proportion of disease in unvaccinated women due to new infection will increase, and the estimated efficacy against disease due to any HPV-type will become more apparent.

Figure 1
Cumulative Incidence of CIN 2/3 or AIS Lesions (Caused by Any HPV Type) Among a Generally HPV-naïve Population of Women in the Phase III Clinical Trials (FUTURE I and FUTURE II) in 16 Through 26 Year Old Women

FUTURE II	5,322	0	5,275	4	100.0 (<0.0, 100.0)
Combined Protocols***	7,772	0	7,744	10	100.0 (55.5, 100.0)
HPV 16- or 18-related VaIN 2/3					
Protocol 007	231	0	230	0	Not calculated
FUTURE I	2,219	0	2,239	5	100.0 (<0.0, 100.0)
FUTURE II	5,322	0	5,275	4	100.0 (<0.0, 100.0)
Combined Protocols***	7,772	0	7,744	9	100.0 (49.5, 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 (<0.0, 100.0)
FUTURE I	2241	0	2,258	77	100.0 (95.1, 100.0)
FUTURE II	5,388	9†	5,374	145	93.8 (88.0, 97.2)
Combined Protocols***	7,864	9†	7,865	225	96.0 (92.3, 98.2)
HPV 6-, 11-, 16-, or 18-related Genital Lesions (Genital Warts, VIN, VaIN, Vulvar Cancer, and Vaginal Cancer)					
Protocol 007	235	0	233	3	100.0 (<0.0, 100.0)
FUTURE I	2,261	0	2,279	74	100.0 (94.9, 100.0)
FUTURE II	5,404	2	5,390	150	98.7 (95.2, 99.8)
Combined Protocols***	7,900	2	7,902	227	99.1 (96.8, 99.9)

*Evaluated only the HPV 16 L1 VLP vaccine component of GARDASIL

**There were two cases of CIN 3 that occurred in the group that received GARDASIL. In the first case HPV 16 and HPV 52 were detected. This individual was chronically infected with HPV 52 (infection at Day 1, and Months 32.5 and 33.6) in 8 of 11 specimens, including tissue that was excised during LEEP (Loop Electro-Excision Procedure). HPV 16 was found in 1 of 11 specimens at Month 32.5. HPV 16 was not detected in tissue that was excised during LEEP. In the second case HPV 16, HPV 51, and HPV 56 were detected. This individual was infected with HPV 51 (infection detected by PCR at Day 1) in 2 of 9 specimens. HPV 56 was detected (in tissue excised during LEEP) in 3 of 9 specimens at Month 52. HPV 16 was detected in 1 of 9 specimens at a Month 51 biopsy. Given that these cases occurred in the context of mixed infection, with the dominant type being the non-vaccine HPV type, it is likely that the relevant vaccine HPV type was not the causal HPV type. Based on this assessment, it can be inferred that vaccine efficacy against HPV 16/18-related CIN 2/3 or AIS was 100%.

***Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria.

†Amoung 9 cases of HPV 6, 11,16 or 18 related CIN (any grade) or AIS detected in the PPE population, 6 cases are likely to be due to non vaccine HPV types and not to a vaccine HPV type.

n= Number of subjects with at least one follow-up visit after Month 7

CI = Confidence Interval

Note 1: Point estimates and confidence intervals are adjusted for person-time of follow-up.

Note 2: 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); efficacy against HPV 6/11/16/18-related CIN is >20% (FUTURE I); and efficacy against HPV 6/11/16/18-related external genital lesions (EGL) is >20% (FUTURE I).

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

Table 2
Analysis of Efficacy of GARDASIL in the PPE Population By HPV Type in the Combined Protocol

Population	GARDASIL		Placebo		% Efficacy (95% CI)
	n	Number of cases	n	Number of cases	
HPV 16- or 18-related CIN 2/3 or AIS*	8,493	2**	8,464	112	98.2 (93.5, 99.8)
HPV 16-related	7402	2**	7205	93	97.9 (92.3, 99.8)
HPV 18-related	7382	0	7316	29	100.0 (86.6, 100.0)
HPV 6-, 11-,16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS***	7,864	9†	7,865	225	96.0 (92.3, 98.2)
HPV 6-related	6902	0	6828	47	100.0 (92.0, 100.0)
HPV 11-related	6902	0	6828	12	100.0 (64.5, 100.0)
HPV 16-related	6647	8†	6455	137	94.3 (88.5, 97.6)
HPV 18-related	7382	1†	7316	61	98.4 (90.6, 100.0)
HPV 6- or 11- related Genital Warts***	6,932	2	6,856	189	99.0 (96.2, 99.9)
HPV 6-related	6,932	2	6,856	166	98.8 (95.7, 99.9)
HPV 11-related	6,932	0	6,856	32	100.0 (88.0, 100.0)

*Protocols 005, 007, 013 (FUTURE I), and 015 (FUTURE II) combined. Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria. Subjects in Protocol 005 do not contribute to the endpoints related to Type 18.

**There were two cases of CIN 3 that occurred in the group that received GARDASIL (FUTURE II).In the first case HPV 16 and HPV 52 were detected. This individual was chronically infected with HPV 52 (infection at Day 1, and Months 32.5 and 33.6) in 8 of 11 specimens, including tissue that was excised during LEEP (Loop Electro-Excision Procedure). HPV 16 was found in 1 of 11 specimens at Month 32.5. HPV 16 was not detected in tissue that was excised during LEEP. In the second case HPV 16, HPV 51, and HPV 56 were detected. This individual was infected with HPV 51 (infection detected by PCR at Day 1) in 2 of 9 specimens. HPV 56 was detected (in tissue excised during LEEP) in 3 of 9 specimens at Month 52. HPV 16 was detected in 1 of 9 specimens at a month 51 biopsy. Given that these cases occurred in the context of mixed infection, with the dominant type being the non-vaccine HPV type, it is likely that the relevant vaccine HPV type was not the causal HPV type. Based on this assessment, it can be inferred that vaccine efficacy against HPV 16/18-related CIN 2/3 or AIS was 100%.

***Protocols 007, 013 (FUTURE I), and 015 (FUTURE II) combined. Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria.

†Among 9 cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade) or AIS detected in the PPE population, 6 cases are likely to be due to a non-vaccine HPV type and not to a vaccine HPV type.

n= Number of subjects with at least one follow-up visit after Month 7

CI = Confidence Interval

Note: Point estimates and confidence intervals are adjusted for person-time of follow-up.

Evidence of efficacy was observed during the vaccination period. Among women who were naïve to the relevant HPV types prior to vaccination, GARDASIL was 95% efficacious in preventing cases of CIN (any grade) caused by HPV 6, HPV 11, HPV 16, HPV 18, and 97% efficacious in preventing cases of CIN 2 or worse caused by HPV 16 or HPV 18, resulting from infections acquired during the vaccination period (MITT 2 Population).

Prophylactic Efficacy against Cancer Endpoints

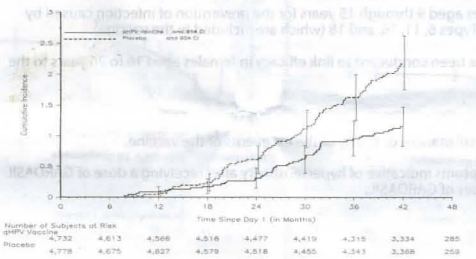
In a supplemental analysis, the efficacy of GARDASIL was evaluated against HPV 16/18-related FIGO Stage 0 cervical cancer (CIN 3 and AIS) in the per-protocol efficacy (PPE) population and the modified intention to treat-2 (MITT-2) population. The "MITT-2 population" consisted of individuals who were naïve to the relevant HPV types(s) (types 6, 11, 16, and 18) prior to dose 1, received at least one dose of vaccine or placebo, and had at least one follow-up visit post-Day 30. The MITT-2 population differs from the PPE population in that it includes individuals with major protocol violations and also individuals who became infected with a vaccine HPV type during the vaccination period. Cases were counted starting after Day 30.

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

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

The benefit of the vaccine with respect to the overall incidence of CIN 2/3 or AIS (caused by any HPV type) became more apparent over time (Figure 1). GARDASIL does not impact the course of infections or disease present at vaccination onset. Over a longer duration of follow-up, the proportion of disease in unvaccinated women due to new infection will increase, and the estimated efficacy against disease due to any HPV-type will become more apparent.

Figure 1
Cumulative Incidence of CIN 2/3 or AIS Lesions (Caused by Any HPV Type) Among a Generally HPV-naïve Population of Women in the Phase III Clinical Trials (FUTURE I and FUTURE II) in 16 Through 26 Year Old Women



Clinical Studies in 24 Through 45 Year Old Females

Prophylactic Efficacy Analysis in the Per-Protocol Population

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

GARDASIL was highly efficacious in reducing the incidence of persistent infection; CIN (any grade); and external genital lesions (EGL) caused by HPV types 6, 11, 16, and 18. GARDASIL was also highly efficacious in reducing the incidence of a HPV 16/18-related Pap Test diagnosis of ASC-US (Atypical Squamous Cells of Undetermined Significance) positive for high-risk HPV. The primary analyses of efficacy, with respect to HPV types 6, 11, 16, and 18, were conducted in the per-protocol efficacy (PPE) population. Efficacy was measured starting after the Month 7 visit (Table 5).

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

Table 5
Analysis of Efficacy of GARDASIL in the PPE Population of 24- Through 45-Year-Old Women

Endpoint	GARDASIL		Placebo		% Efficacy (95% CI)
	n	Number of cases	n	Number of cases	
HPV 6-, 11-, 16-, or 18-related CIN (any grade), Persistent Infection, or EGL	1,615	4*	1,607	41	90.5 (73.7, 97.5)
HPV 16- or 18-related CIN (any grade), Persistent Infection, or EGL	1,601	4*	1,579	23	83.1 (50.6, 95.8)
HPV 6- or 11-related CIN (any grade), Persistent Infection, or EGL	1,329	0	1,323	19	100.0 (79.0, 100.0)
HPV 16/18-related Pap Diagnosis of ASC-US Positive for High-risk HPV	1,579	1	1,565	17	94.2 (63.2, 99.9)

*There were 3 cases of HPV 16 infection and 1 case of CIN 2 (HPV 16 and HPV 51 identified) in the PPE group. All 4 cases occurred early in the follow-up period. Two of the 3 cases of persistent infection had antibody levels to HPV 16 at Month 7 that were very high and suggestive of an anamnestic response to a previous infection. The third persistent infection case had anti-HPV 16 levels that were higher than the anti - HPV 16 GMT amoung subjects who received HPV vaccine within the Per-Protocol Immunogenicity population of Protocol 019. HPV 16 infection was detected in Month 18 and Month 24 swabs. The CIN 2 case was positive for HPV types 16 and 51 at a Month 18 biopsy.

CI = Confidence interval

ASC-US = Atypical Squamous Cells of Undetermined Significance

Immunogenicity

The immunogenicity of GARDASIL was assessed in 23,951 9- through 45- year old girls and women (GARDASIL N = 12,634; placebo N = 11,317) and 1,346 male (GARDASIL N=1,071; placebo N=275) adolescents 9 through 15 years of age. Because of the very high efficacy of GARDASIL in clinical trials, it has not been possible to establish minimum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 antibody levels that protect against clinical HPV disease.

Type-specific assays 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, rather than the total antibodies directed at the VLPs in the vaccine. The scales for these assays are unique to each HPV type; thus, comparisons across types and to other assays are not meaningful. The assays used to measure the immune responses to GARDASIL were demonstrated to correlate with the capacity to neutralize live HPV virions.

There was no interference in the immune response to vaccine HPV types induced by GARDASIL. Seropositivity at Day 1 for one vaccine HPV type did not have a negative impact on Postdose 3 anti-HPV responses to other vaccine HPV types.

The primary immunogenicity analyses were conducted in a per-protocol immunogenicity (PPI) population. This population consisted of individuals who were seronegative and Polymerase Chain Reaction (PCR) negative to the relevant HPV type(s) at enrolment, 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.

In all age groups tested GARDASIL induced anti-HPV Geometric Mean Titers (GMTs) 1 month Postdose 3 which were substantially higher than those measured in women with evidence of a previous infection. In the clinical studies, 99.8%, 99.8%, 99.8%, and 99.5% of individuals 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 levels induced by the vaccine were substantially higher than those measured in women with evidence of having had an infection who then mounted an immune response that led to clearance of infection prior to enrolment.

Immune Response to GARDASIL at Month 7 (Time Point Approximating Peak Immunogenicity)
In the per-protocol immunogenicity population of 9- through 45-year-old women, seropositivity at Month 7 ranged from 96.4% to 99.9% across all 4 vaccine types and across populations defined by age range. Anti-HPV GMTs for all types decreased with age. The largest decrease was observed between the 9- through 17-year-olds and the 18- through 26-year olds. This finding is expected, as the immune responses to vaccines generally decrease with age at vaccination. The efficacy of GARDASIL remained high despite the observed age-related decrease in anti-HPV GMTs.

Immunogenicity in Young Adolescents

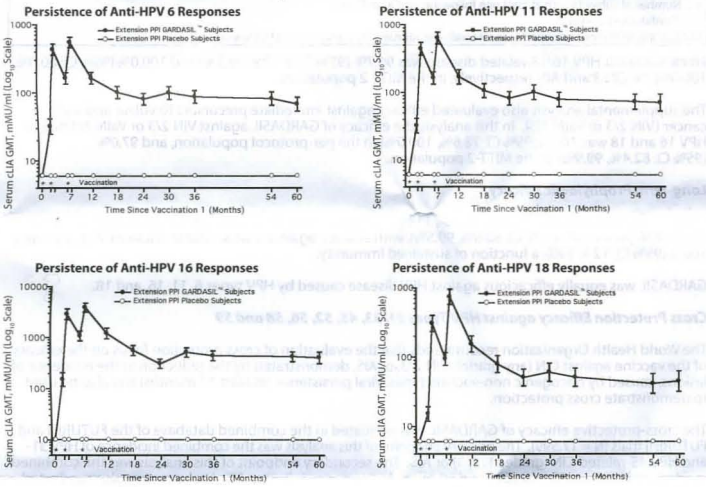
A clinical study compared anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses in 10 through 15 year old boys and girls with responses in 16 through 23 year old adolescents and young adult women. Among subjects who received GARDASIL, 99.1 to 100% became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive by 1 month Postdose 3. Anti-HPV responses in both 10 through 15 year old girls and 10 through 15 year old boys were significantly superior to those observed in 16 to 23 year olds.

Similar outcomes were observed in a comparison of the anti-HPV responses 1 month Postdose 3 among 9 through 15 year old girls with anti-HPV responses in 16 through 26 year old adolescents 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 through 15 year old girls is comparable to the efficacy of GARDASIL observed in the Phase III studies in 16 through 26 year old adolescents and young adult women.

Persistence of Immune Response of GARDASIL
In Protocol 007, peak anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs were observed at Month 7. The GMTs decreased through Month 24 and then stabilized until at least Month 60 (see Figure 2).

Figure 2
Persistence of Anti-HPV Responses Following a 3-dose Regimen of GARDASIL



Immune Memory (Anamnestic) Responses
GARDASIL boosts immunologically primed individuals (i.e., individuals with evidence of a previous natural infection). For each HPV type, anti-HPV GMTs measured 1 month Postdose 3 were approximately 1.4- to 2.4-fold higher in individuals with detectable antibodies for that type at Day 1 compared with subjects who were seronegative for that type at Day 1.

To simulate the potential impact of natural exposure, a study to evaluate immune memory was conducted. Individuals who received a 3-dose primary series of vaccine were given a challenge dose of GARDASIL 5 years after the onset of vaccination.

These individuals exhibited a rapid and strong anamnestic response that exceeded the anti-HPV GMTs observed 1 month Postdose 3 (Month 7) (Table 6).

Table 6
Comparison of HPV Antibody Responses At Month 7, Month 60, 1 Week Post-Challenge Dose, and 1 Month Post-Challenge Dose for GARDASIL in The Extension Per-Protocol Population*

Time Postdose	n	GMT (mMU/mL)	95% Confidence Interval	Fold Change from Month 7	Fold Change Pre-challenge vs. Post-challenge
HPV 6					
Month 7	80	549.2	(460.6, 654.7)	-	
Month 60 (Pre-challenge)	79	67.7	(53.5, 85.7)	-	
Month 60 + 1 Week Post-challenge	79	503.3	(344.2, 736.1)	0.9	
Month 61 (Post-challenge)	80	693.2	(451.9, 1063.3)	1.3	10.2
HPV 11					
Month 7	80	635.5	(521.3, 774.9)	-	
Month 60 (Pre-challenge)	79	70.1	(52.5, 93.7)	-	
Month 60 + 1 Week Post-challenge	79	1417.5	(1009.0, 1991.4)	2.2	
Month 61 (Post-challenge)	80	2652.4	(1956.7, 3595.3)	4.2	37.8
HPV 16					
Month 7	82	3870.0	(3157.0, 4744.0)	-	
Month 60 (Pre-challenge)	82	404.2	(312.9, 522.1)	-	
Month 60 + 1 Week Post-challenge	81	4466.4	(3095.2, 6445.0)	1.2	
Month 61 (Post-challenge)	81	5714.0	(3829.7, 8525.4)	1.5	14.1
HPV 18					
Month 7	86	741.2	(576.8, 952.4)	-	
Month 60 (Pre-challenge)	85	44.7	(31.8, 62.8)	-	
Month 60 + 1 Week Post-challenge	84	1033.2	(753.9, 1415.8)	1.4	
Month 61 (Post-challenge)	86	1230.0	(904.5, 1672.5)	1.7	27.5

*The extension per-protocol population includes all extension subjects who received 3 primary injections of GARDASIL and antigen challenge of GARDASIL at month 60, were seronegative and Polymerase Chain Reaction (PCR) negative at Day 1 to the respective vaccine HPV types, PCR negative through Month 60 to the respective vaccine HPV types, and had valid serology data 4 weeks post-challenge.
Note: GMT = Geometric mean titer in mMU/mL (mMU = milli-Merck units).

Schedule flexibility

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

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 1,871 women 16 through 24 years of age at enrolment. Immune response and safety profile to both hepatitis B vaccine (recombinant) and GARDASIL were similar whether they were administered at the same visit or at a different visit.

INDICATIONS

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

GARDASIL is indicated in males aged 9 through 15 years for the prevention of infection caused by Human Papillomavirus (HPV) Types 6, 11, 16, and 18 (which are included in the vaccine).

Paediatric Use

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

Use in the Elderly

The safety and efficacy of GARDASIL have not been evaluated in the elderly population.

Use in other special populations

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

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). GARDASIL has not been studied in clinical trials with other vaccines.

Use with Common Medications

In clinical studies, 11.9%, 9.5%, 6.9%, and 4.3% of individuals used analgesics, anti-inflammatory drugs, antibiotics, and vitamin preparations respectively. The efficacy, immunogenicity, and safety of the vaccine were not impacted by the use of these medications.

Use with Hormonal Contraceptives

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

Use with Steroids

In clinical studies, 1.7% (n = 158), 0.6% (n = 56), and 1.0% (n = 89) of individuals used inhaled, topical, and parenteral immunosuppressants, respectively, administered close to the time of administration of a dose of GARDASIL. These medicines did not appear to affect the immune responses to GARDASIL. Very few subjects in the clinical studies were taking steroids and the amount of immunosuppression is presumed to have been low.

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

ADVERSE REACTIONS

In 6 clinical trials (5 placebo-controlled), subjects were administered GARDASIL or placebo on the day of enrolment, and approximately 2 and 6 months thereafter. GARDASIL demonstrated a favorable safety profile when compared with placebo (aluminum or non-aluminum containing). Few subjects (≤0.3%) discontinued due to adverse experiences. In all except one of the clinical trials, safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of GARDASIL or placebo. The subjects who were monitored using VRC-aided surveillance included 6,160 subjects (6,996 females 9 through 26 years of age, 1,072 males 9 through 16 years of age at enrolment) who received GARDASIL and 5,966 subjects who received placebo.

The following vaccine-related adverse experiences were observed among recipients of GARDASIL at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients are shown in Table 7.

Table 7
Vaccine-related Injection-site and Systemic Adverse Experiences*

Adverse Experience (1 to 5 Days Postvaccination)	GARDASIL (N = 8,068) %	AAHS** Adjuvant – containing Placebo (N = 5,372) %	Saline Placebo (N = 594) %
Injection Site			
Pain	79.9	70.7	45.4
Swelling	22.9	14.2	7.7
Erythema	21.4	15.6	13.2
Pruritus	2.5	2.3	0.9

Adverse Experience (1 to 15 Days Postvaccination)	GARDASIL (N = 8,068) %	Placebo (N = 5,966) %
Systemic		
Fever	9.9	8.6
Pain in extremity	1.3	1.0

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

All-cause Common Systemic Adverse Experiences
All-cause systemic adverse experiences for 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 8.

Table 8
All-cause Common Systemic Adverse Experiences

Adverse Experience (1 to15 Days Postvaccination)	GARDASIL (n = 8068) %	Placebo* (n = 5966 %
Pyrexia	12.6	11.4
Nausea	5.5	5.4
Diarrhea	3.5	3.4
Abdominal Pain, upper	2.6	2.6
Pain in extremity	2.6	2.3
Vomiting	2.1	1.8
Myalgia	1.8	1.6
Cough	1.7	1.5
Upper respiratory tract infection	1.6	1.4
Toothache	1.4	1.3
Arthralgia	1.1	1.0

*Aluminum and/or non-aluminum containing placebo

Overall, 94.3% of subjects who received GARDASIL judged their injection-site adverse experience to be mild or moderate in intensity.

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

The safety of GARDASIL when administered concomitantly with hepatitis B vaccine (recombinant) was evaluated in a placebo-controlled study. The frequency of adverse experiences observed with concomitant administration was similar to the frequency when GARDASIL was administered 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 sometimes accompanied by tonic-clonic movements.

Gastrointestinal disorders: nausea, vomiting.

Musculoskeletal and connective tissue disorders: arthralgia, myalgia

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

Schedule flexibility

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

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 1,871 women 16 through 24 years of age at enrolment. Immune response and safety profile to both hepatitis B vaccine (recombinant) and GARDASIL were similar whether they were administered at the same visit or at a different visit.

INDICATIONS

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

GARDASIL is indicated in males aged 9 through 15 years for the prevention of infection caused by Human Papillomavirus (HPV) Types 6, 11, 16, and 18 (which are included in the vaccine).

*Immunogenicity studies have been conducted to link efficacy in females aged 16 to 26 years to the younger populations.

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, vulvar, or vaginal cancers; CIN, VIN, or VaIN related to HPV vaccine types or non-vaccine serotypes.

This vaccine will not protect against diseases that are not caused by HPV. Oncogenic HPV types other than HPV 16 and 18 may cause cervical cancer. Vaccination may therefore not prevent HPV infection and disease due to these other oncogenic types (see Clinical Studies). Routine cervical screening and detection and removal of cervical lesions should be continued in individuals who receive the vaccine.

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

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 DRUG INTERACTIONS).

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

Carcinogenicity

GARDASIL has not been evaluated for carcinogenic potential.

Genotoxicity

GARDASIL has not been evaluated for genotoxic potential

Effects on Fertility

Female rats were given the clinical dose of GARDASIL (500mcL) intramuscularly twice (during early gestation and one week postnatal) or four times (five and two weeks prior to mating, during early gestation, and one week postnatal). Mating performance and fertility of the dams or their offspring were not affected. The effect of GARDASIL administration on male fertility has not been studied.

Use in Pregnancy (Category B2)

Female rats were given the clinical dose of GARDASIL (500mcL) intramuscularly twice (during early gestation and one week postnatal) or four times (five and two weeks prior to mating, during early gestation, and one week postnatal). Maternal toxicity or adverse effects on offspring were not observed. High titers of HPV-type specific antibodies were detected in maternal blood during gestation, in near-term fetal blood, and in blood of offspring at weaning and at 11 weeks postnatal, indicative of transplacental and lactational transfer of antibodies (see Use in Lactation). The effect of GARDASIL administration of vaccine-treated males on offspring 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. Such non-standard regimens resulted in Postdose 3 anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses that were comparable to those observed in women who received a standard 0, 2, and 6 month vaccination regimen (see DOSAGE AND ADMINISTRATION).

During clinical trials, 3,620 women (vaccine N = 1,796 vs. placebo N = 1,824) reported at least one pregnancy. The overall proportions of pregnancies that resulted in an adverse outcome defined as the combined numbers of spontaneous abortion, late fetal death, congenital anomaly cases out of the total number of pregnancy outcomes for which an outcome was known (and excluding elective terminations), were 23.3% (423/1, 812) in subjects who received GARDASIL and 24.1% (438/1, 820) in subjects who received placebo.

Further sub-analyses were done to evaluate pregnancies with estimated onset within 30 days or more than 30 days from administration of a dose of GARDASIL or placebo. For pregnancies with estimated onset within 30 days of vaccination, 5 cases of congenital anomaly were observed in the group that received GARDASIL compared to 1 case of congenital anomaly in the group that received placebo. Conversely, in pregnancies with onset more than 30 days following vaccination, 35 cases of congenital anomaly were observed in the group that received GARDASIL compared with 29 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 16 through 45 years of age.

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

Use in Lactation

Female rats were given the clinical dose of GARDASIL (500mcL) intramuscularly twice (during early gestation and one week postnatal) or four times (five and two weeks prior to mating, during early gestation, and one week postnatal). Maternal toxicity or adverse effects on offspring were not observed. Offspring of dams receiving the two doses had higher serum titres of HPV-type specific antibodies at weaning than near term fetuses, suggesting transfer of antibodies in milk as well as via the placenta (see Use in Pregnancy). Antibodies were still present in offspring at postnatal week 11 when they were last measured.

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

GARDASIL may be administered to lactating women.

GARDASIL or placebo were given to a total of 1,132 women who were breast feeding at any time during the relevant Phase III clinical studies. In these studies, the rates of adverse experiences in the mother and the nursing infant were comparable between vaccination groups. In addition, vaccine immunogenicity was comparable among nursing mothers and women who did not nurse during the vaccine administration.

Overall, 94.3% of subjects who received GARDASIL judged their injection-site adverse experience to be mild or moderate in intensity.

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

The safety of GARDASIL when administered concomitantly with hepatitis B vaccine (recombinant) was evaluated in a placebo-controlled study. The frequency of adverse experiences observed with concomitant administration was similar to the frequency when GARDASIL was administered 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 sometimes accompanied by tonic-clonic movements.

Gastrointestinal disorders: nausea, vomiting.

Musculoskeletal and connective tissue disorders: arthralgia, myalgia

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

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

DOSAGE AND ADMINISTRATION

GARDASIL is recommended for females and males aged 9 through 15 years and females aged 16 through 45 years (see INDICATIONS).

Dosage

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

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

Individuals are encouraged to adhere to the 0, 2, and 6 months vaccination schedule. However, in clinical studies, efficacy has been demonstrated in individuals who have received all 3 doses within a 1-year period. If an alternate vaccination schedule is necessary, the second dose should be administered at least 1 month after the first dose and the third dose should be administered at least 3 months after the second dose. (see CLINICAL STUDIES, Schedule Flexibility).

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.

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.

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

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

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

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

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

Prefilled Syringe Use
Inject the entire contents of the syringe.

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.

NOTE: When choosing a needle, it should fit securely on the syringe.

PRESENTATION & STORAGE CONDITIONS

Presentation

GARDASIL is a sterile cloudy white liquid.

Storage

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

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

OVERDOSAGE

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

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POISONS SCHEDULE

Schedule 4 – Prescription Medicine

This product information was approved by the Therapeutic Goods Administration on 29 April 2009