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). 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 sodium borate, and water for injection. The product does not contain a preservative or antibiotics.

PHARMACOLOGY

Mechanism of Action

GARDASIL contains HPV 6,11,16,18 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.

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 4 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 5,746 (FUTURE I) and 12,157 (FUTURE II) subjects. Together, these studies evaluated 20,845 women 16 to 26 years of age at enrolment, the majority of whom had been sexually active. 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 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 subjects were naïve to all 4 vaccine HPV types at enrollment. These subjects were at risk for infection and disease caused by all 4 vaccine HPV types.

Prophylactic Efficacy

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 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).

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 (<0.0, 100.0)
FUTURE I	2,200	0	2,222	19	100.0 (78.5, 100.0)
FUTURE II	5,301	0	5,258	21	100.0** (80.9, 100.0)
Combined Protocols	8,487	0	8,460	53	100.0** (92.9, 100.0)
HPV 6-, 11-,16-, 18-related CIN (CIN 1, CIN 2/3) or AIS					
Protocol 007	235	0	233	3	100.0 (<0.0, 100.0)
FUTURE I	2240	0	2,258	37	100.0** (89.5, 100.0)
FUTURE II	5,383	4	5,370	43	90.7 (74.4, 97.6)
Combined Protocols	7,858	4	7,861	83	95.2 (87.2, 98.7)
HPV 6-, 11-, 16-, or 18-related Genital Lesions (Genital Warts, VIN, VaIN)					
Protocol 007	235	0	233	3	100.0 (<0.0, 100.0)
FUTURE I	2,261	0	2,279	40	100.0** (90.3, 100.0)
FUTURE II	5,401	1	5,387	70	98.6 (91.8, 100.0)
Combined Protocols	7,897	1	7,899	113	99.1 (95.0, 100.0)

*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); 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).
n= Number of subjects with at least one follow-up visit after Month 7
Note: Point estimates and confidence intervals are adjusted for person-time of follow-up.

GARDASIL was equally efficacious against HPV disease caused by each of the four vaccine HPV types. Evidence of efficacy was observed during the vaccination period. Among women who were naïve to the relevant HPV types prior to vaccination, GARDASIL was 91% efficacious in preventing cases of CIN (any grade) caused by HPV 6, HPV 11, HPV 16, HPV 18, and 95% efficacious in preventing cases of CIN 2 or worse caused by HPV 16 or HPV 18, resulting from infections acquired during the vaccination period.
In a supplemental analysis, the efficacy of GARDASIL against HPV 16/18-related disease was 100% (95% CI: 87.9%, 100.0%) for FIGO Stage 0 cervical cancer (CIN 3 or AIS) and 100% (95% CI: 55.5%, 100.0%) for VIN 2/3 or VaIN 2/3.

Efficacy in Subjects with Current or Prior Infection of HPV

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 enrollment and who received GARDASIL did not show a statistically significant reduction of CIN or AIS compared to placebo. Estimated vaccine efficacy was 27% (95% CI: <0.0%, 47.0%). Early infection was defined as infection with a vaccine HPV type at enrollment, but no evidence of immune response to it.

Population Impact

GARDASIL does not prevent disease caused by HPV types not targeted by the vaccine.

An interim analysis was conducted to evaluate the impact of GARDASIL with respect to CIN 2/3 or AIS caused by infection with vaccine or non-vaccine HPV types acquired after enrollment. The Phase II and Phase III efficacy studies did not include a screening phase, so the study populations included subjects who were already infected with vaccine and non-vaccine HPV types at enrollment.

To focus on the impact of GARDASIL on CIN 2/3 or AIS cases caused by infections acquired after enrollment, the analysis was conducted in subjects who, at Day 1, were naïve to all 4 vaccine HPV types and had a negative Pap test. Case counting started 30 Days Postdose 1. These analysis conditions eliminated most, but not all, of the CIN 2/3 and AIS cases caused by infection that was already present at baseline. The results from the analysis of this partially HPV-naïve population are presented in Table 2. Administration of GARDASIL reduced the overall incidence of CIN 2/3 caused by new infections. The magnitude of impact observed with GARDASIL compared with placebo increased over the observation period. Cases of disease due to non-vaccine types were observed among recipients of both GARDASIL and placebo.

Table 2
Impact of GARDASIL on the Incidence of CIN 2/3 or AIS Caused by New Infections with Vaccine or non-vaccine HPV Types in the Partially HPV-Naive Population

	GARDASIL (N=9,075)		Placebo (N=9075)			
Endpoint	n	Number of Cases	n	Number of Cases	% Impact	95% CI
CIN 2/3 or AIS	5,638	59	5,701	96	37.9	(13.2, 55.9)
CIN 2	5,638	42	5,701	74	42.6	(15.1, 61.7)
CIN 3 or AIS	5,638	28	5,701	52	45.5	(12.2, 66.9)

Subjects are counted once in each applicable endpoint category. A subject may appear in more than one category.
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects evaluable, i.e., number of subjects in the given population who also have at least one follow-up visit.
CI = Confidence interval; CIN = Cervical intraepithelial neoplasia

Overall Impact on Pap Test Abnormalities and Procedures to Treat HPV-related Disease

In a population that approximates young adult women (including HPV-infected and HPV-naïve women), administration of GARDASIL was associated with a 10% reduction in the incidence of Pap test diagnosis of CIN 1 or worse through 2 years of follow up.
GARDASIL reduced the incidence of definitive therapy procedures associated with a diagnosis of CIN 2/3 or chronic CIN 1 (e.g., loop electrosurgical excision procedure) by 16.5%.
GARDASIL reduced the incidence of definitive therapy procedures to treat genital warts by 26.5%.

Because GARDASIL has not been shown to protect against the consequences of all HPV types and will not protect against established disease caused by the HPV types contained in the vaccine the overall efficacy of GARDASIL will depend on the baseline prevalence of HPV infection and disease in the population vaccinated.

Immunogenicity

The immunogenicity of GARDASIL was assessed in 12,315 subjects (GARDASIL N = 7,208; placebo N = 5,107). 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.

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 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.

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. Overall, 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 enrollment.

In a study that measured immune responses to a 3-dose regimen of GARDASIL during the course of the vaccination regimen, Postdose 2 anti-HPV levels were higher than those observed during long term follow up of the Phase III studies. Overall, 97.6 to 100% became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive by 1 month Postdose 2. These results support the observation that the protective efficacy of GARDASIL begins during the course of the 3-dose vaccination regimen.

Immunogenicity in Young Adolescents

A clinical study compared anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses in 10 to 15 year old boys and girls with responses in 16 to 23 year old adolescent and young adult women. Among subjects who received GARDASIL, 99.5 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 to 15 year old girls and 10 to 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 to 15 year old girls with 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 comparable to the efficacy of GARDASIL observed in the Phase III studies in 16 to 26 year old adolescent and young adult women.

Evidence for Anamnestic (Immune Memory) Responses

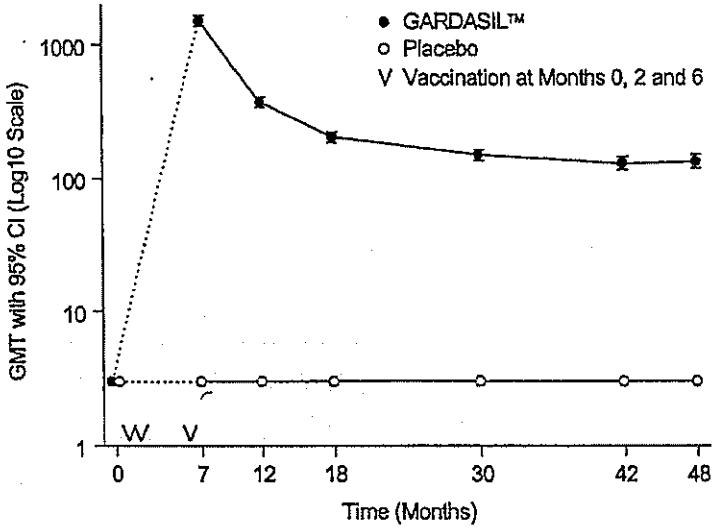
GARDASIL boosts immunologically primed individuals (i.e., individuals with evidence of a previous natural infection). For each HPV type, anti-HPV GMTs measured 1 month Postdose 3 were ≥2-fold higher in individuals with detectable antibodies for that type at Day 1 compared with subjects who were seronegative for that type at Day 1.

There was no interference in the immune responses 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.

Persistence

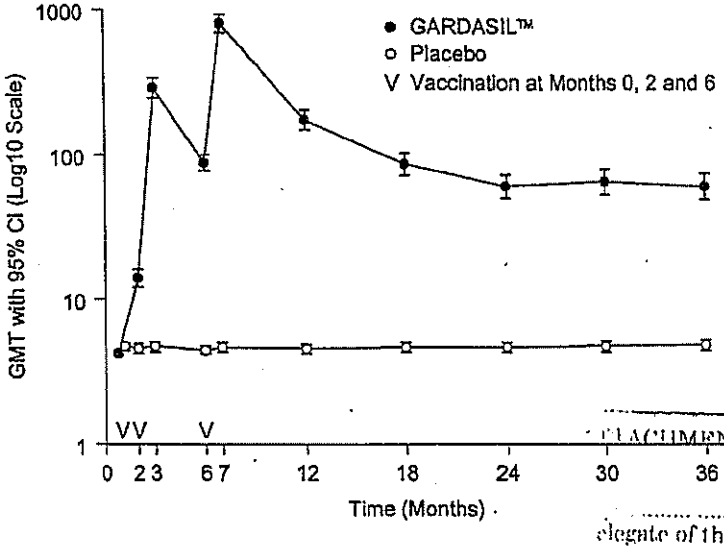
In a study that evaluated the HPV 16 component of GARDASIL in 16 to 23 year old women, anti-HPV 16 GMTs were robust at Month 7. GMTs declined through Month 24 and then stabilized but remained above GMTs reported for natural infections (see Figure 1).

Figure 1
Anti-HPV 16 Responses Through Long Term Follow Up



In a study that evaluated GARDASIL in 16 to 23 year old women, anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs were robust at Month 7. GMTs declined through Month 24 and then stabilized but remained above GMTs reported for natural infections (e.g., anti-HPV 18 response – see Figure 2).

Figure 2
Anti-HPV 18 Responses Through Long Term Follow Up



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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 1,869 women 16 to 24 years of age at enrollment. 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 to 26 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 to 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. This vaccine has not been definitively shown to protect against disease caused by HPV types that are not included in the vaccine. Routine cervical screening and detection and removal of cervical lesions should be continued in individuals who receive the vaccine.

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, 2,266 women (vaccine = 1,115 vs. placebo = 1,151) reported at least one pregnancy. Overall, the proportions of pregnancies with an adverse outcome were comparable in subjects who received GARDASIL and 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 0 cases of congenital anomaly in the group that received placebo. Conversely, in pregnancies with onset more than 30 days following vaccination, 10 cases of congenital anomaly were observed in the group that received GARDASIL compared with 16 cases of congenital anomaly in the group that received placebo. The types of anomalies observed were

consistent (regardless of when pregnancy occurred in relation to vaccination) with those generally observed in pregnancies in women 16 to 26 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.

A total of 995 nursing mothers were given GARDASIL or placebo during the vaccination period of the clinical trials. 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.

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).

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

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In clinical studies 57.5% of women (16 to 26 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 5 clinical trials (4 placebo-controlled), subjects were administered GARDASIL or placebo on the day of enrollment, and approximately 2 and 6 months thereafter. GARDASIL demonstrated a favorable safety profile when compared with placebo (aluminum or non-aluminum containing). Few subjects (0.2%) 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 (5,088 females 9 to 26 years of age, 1,072 males 9 to 16 years of age at enrolment) who received GARDASIL and 4,064 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 2.

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Table 3
Vaccine-Related Injection-Site and Systemic Adverse Experiences*

Adverse Experience (1 to 5 Days Postvaccination)	GARDASIL (N = 6,160) %	Aluminum-Containing Placebo (N = 3,470) %	Saline Placebo (N = 594) %
Injection Site			
Pain	81.3	75.4	45.4
Swelling	24.2	15.8	7.7
Erythema	23.6	18.4	13.2
Hemorrhage	3.2	3.9	2.6
Pruritus	2.7	2.8	0.9

Adverse Experience (1 to 15 Days Postvaccination)	GARDASIL (N = 6,160) %	Placebo (N = 4,064) %
Systemic		
Fever	10.1	8.4

*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.

Overall, 94.4% 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.

DOSAGE AND ADMINISTRATION

GARDASIL is recommended for females and males aged 9 to 15 years and females aged 16 to 26 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)

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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.

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 discolored.

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. When out of refrigeration at room temperature, or below 25°C, administration may be delayed for up to 3 days.

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

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Delegate of the Secretary
2005-2965-2
APPLN No. Date 16/1/06

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