

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gardasil, suspension for injection.

Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml) contains approximately:

Human Papillomavirus ¹ Type 6 L1 protein ^{2,3}	20 micrograms
Human Papillomavirus ¹ Type 11 L1 protein ^{2,3}	40 micrograms
Human Papillomavirus ¹ Type 16 L1 protein ^{2,3}	40 micrograms
Human Papillomavirus ¹ Type 18 L1 protein ^{2,3}	20 micrograms.

¹Human Papillomavirus = HPV.

²L1 protein in the form of virus-like particles produced in yeast cells (*Saccharomyces cerevisiae* CANADE 3C-5 (Strain 1895)) by recombinant DNA technology.

³adsorbed on amorphous aluminium hydroxyphosphate sulphate adjuvant (225 micrograms Al).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

Prior to agitation, Gardasil may appear as a clear liquid with a white precipitate. After thorough agitation, it is a white, cloudy liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gardasil is a vaccine for use from the age of 9 years for the prevention of:

- premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types
- external genital warts (condyloma acuminata) causally related to specific HPV types.

See sections 4.4 and 5.1 for important information on the data that support this indication.

The use of Gardasil should be in accordance with official recommendations.

4.2 Posology and method of administration

The primary vaccination series consists of 3 separate 0.5 ml doses administered according to the following schedule: 0, 2, 6 months.

If an alternate vaccination schedule is necessary, the second dose should be administered at least one month after the first dose and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period.

The need for a booster dose has not been established.

Paediatric population: There is no experience with the use of Gardasil in children below 9 years of age (see section 5.1).

The vaccine should be administered by intramuscular injection. The preferred site is the deltoid area of the upper arm or in the higher anterolateral area of the thigh.

Gardasil must not be injected intravascularly. Neither subcutaneous nor intradermal administration has been studied. These methods of administration are not recommended (see section 6.6).

It is recommended that individuals who receive a first dose of Gardasil complete the 3-dose vaccination course with Gardasil (see section 4.4).

4.3 Contraindications

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

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

Administration of Gardasil should be postponed in individuals suffering from an acute severe febrile illness. However, the presence of a minor infection, such as a mild upper respiratory tract infection or low-grade fever, is not a contraindication for immunisation.

4.4 Special warnings and precautions for use

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

As with all injectable vaccines, appropriate medical treatment should always be readily available in case of rare anaphylactic reactions following the administration of the vaccine.

Syncope (fainting) may follow any vaccination, especially in adolescents and young adults. Syncope, sometimes associated with falling, has occurred after vaccination with Gardasil (See section 4.8). Therefore, vaccinees should be carefully observed for approximately 15 minutes after administration of Gardasil.

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

Gardasil will only protect against diseases that are caused by HPV types 6, 11, 16 and 18 and to a limited extent against diseases caused by certain related HPV types (See section 5.1). Therefore, appropriate precautions against sexually transmitted diseases should continue to be used.

Gardasil is for prophylactic use only and has no effect on active HPV infections or established clinical disease. Gardasil has not been shown to have a therapeutic effect. The vaccine is therefore not indicated for treatment of cervical cancer, high-grade cervical, vulvar and vaginal dysplastic lesions or genital warts. It is also not intended to prevent progression of other established HPV-related lesions.

Gardasil does not prevent lesions due to a vaccine HPV type in women infected with that HPV type at the time of vaccination (see section 5.1).

The use of Gardasil in adult women should take into consideration the variability of HPV type prevalence in different geographical areas.

Vaccination is not a substitute for routine cervical screening. Since no vaccine is 100% effective and Gardasil will not provide protection against every HPV type, or against existing HPV infections, routine cervical screening remains critically important and should follow local recommendations. There are no data on the use of Gardasil in individuals with impaired immune responsiveness.

Individuals with impaired immune responsiveness, whether due to the use of potent immunosuppressive therapy, a genetic defect, Human Immunodeficiency Virus (HIV) infection, or other causes, may not respond to the vaccine.

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.

The duration of protection is currently unknown. Sustained protective efficacy has been observed for 4.5 years after completion of the 3-dose series. Longer term follow-up studies are ongoing (see section 5.1).

There are no safety, immunogenicity or efficacy data to support interchangeability of Gardasil with other HPV vaccines.

4.5 Interaction with other medicinal products and other forms of interaction

In all clinical trials, individuals who had received immunoglobulin or blood-derived products during the 6 months prior to the first vaccine dose were excluded.

Use with other vaccines

Administration of Gardasil at the same time (but, for injected vaccines, at a different injection site) as hepatitis B (recombinant) vaccine did not interfere with the immune response to the HPV types. The seroprotection rates (proportion of individuals reaching seroprotective level anti-HBs ≥ 10 mIU/ml) were unaffected (96.5% for concomitant vaccination and 97.5% for hepatitis B vaccine only). Anti-HBs geometric mean antibody titres were lower on co-administration, but the clinical significance of this observation is not known.

Gardasil may be administered concomitantly with a combined booster vaccine containing diphtheria (d) and tetanus (T) with either pertussis [acellular, component] (ap) and/or poliomyelitis [inactivated] (IPV) (dTap, dT-IPV, dTap-IPV vaccines) with no significant interference with antibody response to any of the components of either vaccine. However, a trend of lower anti-HPV GMTs was observed in the concomitant group. The clinical significance of this observation is not known. This is based on the results from a clinical trial in which a combined dTap-IPV vaccine was administered concomitantly with the first dose of Gardasil. (see section 4.8).

The concomitant administration of Gardasil with vaccines other than the ones above has not been studied.

Use with hormonal contraceptives

In clinical studies, 57.5% of women aged 16 to 26 years and 31.2% of women aged 24 to 45 years who received Gardasil used hormonal contraceptives during the vaccination period. Use of hormonal contraceptives did not appear to affect the immune response to Gardasil.

4.6 Pregnancy and lactation

Specific studies of the vaccine in pregnant women were not conducted. During the clinical development program, 3,819 women (vaccine = 1,894 vs. placebo = 1,925) reported at least one pregnancy. There were no significant differences in types of anomalies or proportion of pregnancies with an adverse outcome in Gardasil and placebo treated individuals.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

The data on Gardasil administered during pregnancy did not indicate any safety signal. However, these

data are insufficient to recommend use of Gardasil during pregnancy. Vaccination should, therefore, be postponed until completion of pregnancy.

In breastfeeding mothers given Gardasil or placebo during the vaccination period of the clinical trials the rates of adverse reactions in the mother and the breastfed infant were comparable between the vaccination and the placebo groups. In addition, vaccine immunogenicity was comparable among breastfeeding mothers and women who did not breastfeed during the vaccine administration.

Therefore Gardasil can be given to breastfeeding women.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

In 6 clinical trials (5 placebo-controlled), individuals were administered Gardasil or placebo on the day of enrollment and approximately 2 and 6 months thereafter. Few individuals (0.2%) discontinued due to adverse reactions. Safety was evaluated in either the entire study population (5 studies) or in a predefined subset (one study) of the study population using vaccination report card (VRC)-aided surveillance for 14 days after each injection of Gardasil or placebo. The individuals who were monitored using VRC-aided surveillance included 8,068 individuals (6,996 females 9 to 45 years of age and 1,072 males 9 to 15 years of age at enrollment) who received Gardasil and 5,966 individuals who received placebo.

The following vaccine-related adverse reactions were observed among recipients of Gardasil at a frequency of at least 1.0% and also at a greater frequency than observed among placebo recipients. They are ranked under headings of frequency using the following convention:

[Very Common ($\geq 1/10$); Common ($\geq 1/100$, $< 1/10$); Uncommon ($\geq 1/1,000$, $< 1/100$); Rare ($\geq 1/10,000$, $< 1/1,000$); Very Rare ($< 1/10,000$), including isolated reports]

Musculoskeletal and Connective Tissue Disorders:

Common: pain in extremity.

General disorders and administration site conditions:

Very common: pyrexia.

Very common: at the injection site: erythema, pain, swelling.

Common: at the injection site: bruising, pruritus.

In addition, in clinical trials adverse reactions that were judged to be vaccine- or placebo-related by the study investigator were observed at frequencies lower than 1%:

Respiratory, thoracic and mediastinal disorders:

Very rare: bronchospasm.

Skin and subcutaneous tissue disorder:

Rare: urticaria.

Nine cases (0.07%) of urticaria were reported in the Gardasil group and 16 cases (0.14%) were seen in the adjuvant-containing placebo group.

In the clinical studies, individuals in the Safety Population reported any new medical conditions during the follow-up of up to 4 years. Among 13,686 individuals who received Gardasil and 11,588 individuals who received placebo, there were 38 cases of non-specific arthritis/arthropathy reported, 24 in the Gardasil group and 14 in the placebo group.

In a clinical trial of 843 healthy adolescent males and females 11-17 years of age, administration of the first dose of Gardasil concomitantly with a combined diphtheria, tetanus, pertussis [acellular, component] and poliomyelitis [inactivated] booster vaccine showed that there was more injection-site swelling and headache reported following concomitant administration. The differences observed were < 10% and in the majority of subjects, the adverse events were reported as mild to moderate in intensity.

Post Marketing Experience

Post Marketing adverse events have been spontaneously reported for Gardasil and are not listed above.

Because these events were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish, for all events, a causal relationship to vaccine exposure.

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

Immune system disorders: hypersensitivity reactions including anaphylactic/anaphylactoid reactions.

Nervous system disorders: Guillain-Barré syndrome, dizziness, 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.

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Viral Vaccine, ATC code: J07BM01

Mechanism of Action

Gardasil is an adjuvanted 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 VLPs contain no viral DNA, they cannot infect cells, reproduce or cause disease. HPV only infects humans, but animal studies with analogous papillomaviruses suggest that the efficacy of LI VLP vaccines is mediated by the development of a humoral immune response.

HPV 16 and HPV 18 are estimated to be responsible for approximately 70% of cervical cancers; 80% of adenocarcinoma in situ (AIS); 45-70% of high-grade cervical intraepithelial neoplasia (CIN 2/3); 25% of low grade cervical intraepithelial neoplasia (CIN 1); approximately 70% of HPV related high-grade vulvar (VIN 2/3) and vaginal (VaIN 2/3) intraepithelial neoplasia. HPV 6 and 11 are responsible

for approximately 90% of genital warts and 10% of low grade cervical intraepithelial neoplasia (CIN 1). CIN 3 and AIS have been accepted as immediate precursors of invasive cervical cancer.

The term "pre-malignant genital lesions" in section 4.1 corresponds to high-grade cervical intraepithelial neoplasia (CIN 2/3), high-grade vulvar intraepithelial neoplasia (VIN 2/3) and high-grade vaginal intraepithelial neoplasia (VaIN 2/3).

The indication is based on the demonstration of efficacy of Gardasil in females 16 to 45 years of age and on the demonstration of immunogenicity of Gardasil in 9- to 15-year old children and adolescents.

Clinical Studies

Efficacy in women 16 through 26 years

The efficacy of Gardasil in 16- through 26- year-old women was assessed in 4 placebo-controlled, double-blind, randomized Phase II and III clinical studies including a total of 20,541 women, who were enrolled and vaccinated without pre-screening for the presence of HPV infection.

The primary efficacy endpoints included HPV 6-, 11-, 16-, or 18-related vulvar and vaginal lesions (genital warts, VIN, VaIN) and CIN of any grade and cervical cancers (Protocol 013, FUTURE I), HPV 16- or 18-related CIN 2/3 and AIS and cervical cancers (Protocol 015, FUTURE II), HPV 6-, 11-, 16-, or 18-related persistent infection and disease (Protocol 007), and HPV 16-related persistent infection (Protocol 005).

Efficacy results are presented for the combined analysis of study protocols. The efficacy for HPV 16/18 related CIN 2/3 or AIS is based on data from protocols 005 (16-related endpoints only), 007, 013, and 015. The efficacy for all other endpoints is based on protocols 007, 013, and 015. The median duration of follow-up for these studies was 4.0, 3.0, 3.0, and 3.0 years for Protocol 005, Protocol 007, Protocol 013, and Protocol 015, respectively. The median duration of follow-up for the combined protocols (005, 007, 013, and 015) was 3.6 years. Results of individual studies support the results from the combined analysis. Gardasil was efficacious against HPV disease caused by each of the four vaccine HPV types. At end of study, individuals enrolled in the two Phase-III studies (Protocol-013 and Protocol-015), were followed for up to 4 years (median 3.7 years).

Cervical Intraepithelial Neoplasia (CIN) Grade 2/3 (moderate to high-grade dysplasia) and adenocarcinoma in situ (AIS) were used in the clinical trials as a surrogate marker for cervical cancer.

Efficacy in women naïve to the relevant vaccine HPV type(s)

The primary analyses of efficacy, with respect to vaccine HPV types (HPV 6, 11, 16, and 18), were conducted in the per-protocol efficacy (PPE) population (i.e. all 3 vaccinations within 1 year of enrollment, no major protocol deviations and naïve to the relevant HPV type(s) prior to dose 1 and through 1 month Postdose 3 (Month 7)). Efficacy was measured starting after the Month 7 visit. Overall, 73% of women were naïve (PCR negative and seronegative) to all 4 HPV types at enrollment.

The efficacy results for relevant endpoints analysed at 2 years post-enrollment and at end of study (median duration of follow-up = 3.6 years) in the per-protocol population are presented in the Table 1.

In a supplemental analysis, the efficacy of Gardasil was evaluated against HPV 16/18-related CIN 3 and AIS.

Table 1: Analysis of efficacy of Gardasil against high grade cervical lesions in the PPE population

	Gardasil	Placebo	% Efficacy at 2 years (95% CI)	Gardasil	Placebo	% Efficacy*** at end of study (95% CI)
	Number of cases	Number of cases		Number of cases	Number of cases	
	Number of individuals*	Number of individuals*		Number of individuals*	Number of individuals*	
HPV 16/18- related CIN 2/3 or AIS	0 8487	53 8460	100.0 (92.9, 100.0)	2** 8493	112 8464	98.2 (93.5, 99.8)
HPV 16/18- related CIN 3	0 8487	29 8460	100 (86.5, 100.0)	2** 8493	64 8464	96.9 (88.4, 99.6)
HPV 16/18- related AIS	0 8487	6 8460	100 (14.8, 100.0)	0 8493	7 8464	100 (30.6, 100.0)

*Number of individuals with at least one follow-up visit after Month 7

**Based on virologic evidence, the first CIN 3 case in a patient chronically infected with HPV 52 is likely to be causally related to HPV 52. In only 1 of 11 specimens HPV 16 was found (at Month 32.5) and was not detected in tissue excised during LEEP (Loop Electro-Excision Procedure). In the second CIN 3 case observed in a patient infected with HPV 51 at Day 1 (in 2 of 9 specimens); HPV 16 was detected at a Month 51 biopsy (in 1 of 9 specimens) and HPV 56 was detected in 3 of 9 specimens at Month 52 in tissue excised during LEEP.

***Patients were followed for up to 4 years (median 3.6 years)

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

At end of study and in the combined protocols,

the efficacy of Gardasil against HPV 6-, 11-, 16-, 18-related CIN 1 was 95.9 % (95% CI: 91.4, 98.4)

the efficacy of Gardasil against HPV 6-, 11-, 16-, 18-related CIN (1, 2, 3) or AIS was 96.0% (95% CI: 92.3, 98.2)

the efficacy of Gardasil against HPV 6-, 11-, 16-, 18-related VIN2/3 and VaIN 2/3 was 100% (95% CI: 67.2, 100) and 100% (95% CI: 55.4, 100) respectively

the efficacy of Gardasil against HPV 6-, 11-, 16-, 18-related genital warts was 99.0% (95% CI: 96.2, 99.9).

In Protocol 012 the efficacy of Gardasil against the 6 month definition of persistent infection [samples positive on two or more consecutive visits 6 months apart (± 1 month) or longer] related to HPV 16 was 98.7 % (95% CI: 95.1, 99.8) and 100.0% (95% CI: 93.2, 100.0) for HPV 18 respectively, after a follow-up of up to 4 years (mean of 3.6 years). For the 12 month definition of persistent infection, efficacy against HPV 16 was 100.0 % (95% CI: 93.9, 100.0) and 100.0 % (95% CI: 79.9, 100.0) for HPV 18 respectively.

Efficacy in women with evidence of HPV 6, 11, 16, or 18 infection or disease at day 1

There was no evidence of protection from disease caused by vaccine HPV types for which women were PCR positive at day 1. Women 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.

Efficacy in women with and without prior infection or disease due to HPV 6, 11, 16, or 18

The modified intention to treat (ITT) population included women regardless of baseline HPV status at Day 1, who received at least one vaccination and in whom case counting started at 1 month Postdose 1. This population approximates to the general population of women with respect to prevalence of HPV infection or disease at enrollment. The results are summarised in Table 2.

Table 2: Efficacy of Gardasil in high grade cervical lesions in the modified ITT-population including women regardless of baseline HPV status

	Gardasil	Placebo	% Efficacy** at 2 years (95% CI)	Gardasil	Placebo	% Efficacy** at end of study (95% CI)
	Number of cases	Number of cases		Number of cases	Number of cases	
	Number of individuals*	Number of individuals*		Number of individuals*	Number of individuals*	
HPV 16- or HPV 18-related CIN 2/3 or AIS	122 9831	201 9896	39.0 (23.3, 51.7)	146 9836	303 9904	51.8 (41.1, 60.7)
HPV 16/18-related CIN 3	83 9831	127 9896	34.3 (12.7, 50.8)	103 9836	191 9904	46.0 (31.0, 57.9)
HPV 16/18-related AIS	5 9831	11 9896	54.3 (<0, 87.6)	6 9836	15 9904	60.0 (<0, 87.3)

*Number of individuals with at least one follow-up visit after 30 days after Day 1

**Percent efficacy is calculated from the combined protocols. The efficacy for HPV 16/18 related CIN 2/3 or AIS is based on data from protocols 005 (16-related endpoints only), 007, 013, and 015. Patients were followed for up to 4 years (median 3.6 years).

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

Efficacy against HPV 6-, 11-, 16-, 18-related VIN 2/3 was 73.3% (95% CI: 40.3, 89.4), against HPV 6-, 11-, 16-, 18-related VaIN 2/3 was 85.7% (95% CI: 37.6, 98.4), and against HPV 6-, 11-, 16-, 18-related genital warts was 80.3% (95% CI: 73.9, 85.3) in the combined protocols at end of study.

Overall 12% of the combined study population had an abnormal Pap test suggestive of CIN at Day 1. Among women with an abnormal Pap test at Day 1 who were naïve to the relevant vaccine HPV types at Day 1, efficacy of the vaccine remained high. Among women with an abnormal Pap test at Day 1 who were already infected with the relevant vaccine HPV types at Day 1, no vaccine efficacy was observed.

Protection Against the Overall Burden of Cervical HPV disease in 16- Through 26-Year-Old Women

The impact of Gardasil against the overall risk for cervical, HPV disease (i.e., disease caused by any HPV type) was evaluated starting 30 days after the first dose in 17,599 individuals enrolled in the two phase III efficacy trials (Protocols 013 and 015). Among women who were naïve to 14 common HPV types and had a negative Pap test at Day 1, administration of Gardasil reduced the incidence of CIN 2/3 or AIS caused by vaccine- or non-vaccine HPV types by 42.7% (95% CI: 23.7, 57.3) and of genital warts by 82.8% (95% CI: 74.3, 88.8) at end of study.

In the modified ITT population, the benefit of the vaccine with respect to the overall incidence of CIN 2/3 or AIS (caused by any HPV type) and of genital warts was much lower, with a reduction of 18.4% (95% CI: 7.0, 28.4) and 62.5% (95% CI: 54.0, 69.5), respectively, as Gardasil does not impact the course of infections or disease that are present at vaccination onset.

Impact on Definitive Cervical Therapy Procedures

The impact of Gardasil on rates of Definitive Cervical Therapy Procedures regardless of causal HPV types was evaluated in 18,150 individuals enrolled in Protocol 007, Protocols 013 and 015. In the HPV naïve population (naïve to 14 common HPV types and had a negative Pap test at Day 1), Gardasil reduced the proportion of women who experienced a definitive cervical therapy procedure (Loop Electro-Excision Procedure or Cold-Knife Conization) by 41.9% (95% CI: 27.7, 53.5) at end of study. In the ITT population the corresponding reduction was 23.9% (95% CI: 15.2, 31.7).

Cross-protective efficacy

The efficacy of Gardasil against CIN (any grade) and CIN 2/3 or AIS caused by 10 non-vaccine HPV types (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) structurally related to HPV 16 or HPV 18 was evaluated in the combined Phase III efficacy database (N = 17,599) after a median follow-up of 3.7 years (at end of study). Efficacy against disease endpoints caused by pre-specified combinations of non-vaccine HPV types was measured. The studies were not powered to assess efficacy against disease caused by individual HPV types.

The primary analysis was done in type-specific populations that required women to be negative for the type being analyzed, but who could be positive for other HPV types (96% of the overall population). The primary time point analysis after 3 years did not reach statistical significance for all pre-specified endpoints. The final end-of-study results for the combined incidence of CIN 2/3 or AIS in this population after a median follow-up of 3.7 years are shown in Table 3. For composite endpoints, statistically significant efficacy against disease was demonstrated against HPV types phylogenetically related to HPV 16 (primarily HPV 31) whereas no statistically significant efficacy was observed for HPV types phylogenetically related to HPV 18 (including HPV 45). For the 10 individual HPV types, statistical significance was only reached for HPV 31.

Table 3: Results for CIN 2/3 or AIS in Type-Specific HPV-Naïve Individuals[†] (end of study results)

Naïve to ≥ 1 HPV Type				
Composite Endpoint	Gardasil	Placebo	% Efficacy	95% CI
	cases	cases		
(HPV 31/45) [‡]	34	60	43.2%	12.1, 63.9
(HPV 31/33/45/52/58) [§]	111	150	25.8%	4.6, 42.5
10 non-vaccine HPV Types	162	211	23.0%	5.1, 37.7
HPV-16 related types (A9 species)	111	157	29.1%	9.1, 44.9
HPV 31	23	52	55.6%	26.2, 74.1 [†]
HPV 33	29	36	19.1%	<0, 52.1 [†]
HPV 35	13	15	13.0%	<0, 61.9 [†]
HPV 52	44	52	14.7%	<0, 44.2 [†]
HPV 58	24	35	31.5%	<0, 61.0 [†]
HPV-18 related types (A7 species)	34	46	25.9%	<0, 53.9
HPV 39	15	24	37.5%	<0, 69.5 [†]
HPV 45	11	11	0.0%	<0, 60.7 [†]
HPV 59	9	15	39.9%	<0, 76.8 [†]
A5 species (HPV 51)	34	41	16.3%	<0, 48.5 [†]
A6 species (HPV 56)	34	30	-13.7%	<0, 32.5 [†]

[†] The studies were not powered to assess efficacy against disease caused by individual HPV types.

[‡] Efficacy was based on reductions in HPV 31-related CIN 2/3 or AIS

[§] Efficacy was based on reductions in HPV 31-, 33-, 52-, and 58-related CIN 2/3 or AIS

^{||} Includes assay-identified non-vaccine HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.

Efficacy in women 24 through 45 years

The efficacy of Gardasil in 24- through 45-year-old women was assessed in 1 placebo-controlled, double-blind, randomized Phase III clinical study (Protocol 019, FUTURE III) including a total of 3,817 women, who were enrolled and vaccinated without pre-screening for the presence of HPV infection.

The primary efficacy endpoints included the combined incidence of HPV 6-, 11-, 16- or 18-related and the combined incidence of HPV 16- or HPV 18-related persistent infection (6 month definition),

genital warts, vulvar and vaginal lesions, CIN of any grade, AIS, and cervical cancers. The median duration of follow-up for this study was 4.0 years.

Efficacy in women naïve to the relevant vaccine HPV type(s)

The primary analyses of efficacy were conducted in the per-protocol efficacy (PPE) population (i.e. all 3 vaccinations within 1 year of enrollment, no major protocol deviations and naïve to the relevant HPV type(s) prior to dose 1 and through 1 month Postdose 3 (Month 7)). Efficacy was measured starting after the Month 7 visit. Overall, 67% of individuals were naïve (PCR negative and seronegative) to all 4 HPV types at enrollment.

The efficacy of Gardasil against the combined incidence of HPV 6-, 11-, 16-, or 18-related persistent infection, genital warts, vulvar and vaginal lesions, CIN of any grade, AIS, and cervical cancers was 88.7% (95% CI: 78.1, 94.8).

The efficacy of Gardasil against the combined incidence of HPV 16- or 18-related persistent infection, genital warts, vulvar and vaginal lesions, CIN of any grade, AIS, and cervical cancers was 84.7% (95% CI: 67.5, 93.7).

Efficacy in women with and without prior infection or disease due to HPV 6, 11, 16, or 18

The Full Analysis Set population (also known as the ITT population) included women regardless of baseline HPV status at Day 1, who received at least one vaccination and in whom case counting started at Day 1. This population approximates to the general population of women with respect to prevalence of HPV infection or disease at enrollment.

The efficacy of Gardasil against the combined incidence of HPV 6-, 11-, 16-, or 18-related persistent infection, genital warts, vulvar and vaginal lesions, CIN of any grade, AIS, and cervical cancers was 47.2% (95% CI: 33.5, 58.2).

The efficacy of Gardasil against the combined incidence of HPV 16- or 18-related persistent infection, genital warts, vulvar and vaginal lesions, CIN of any grade, AIS, and cervical cancers was 41.6% (95% CI: 24.3, 55.2).

Efficacy in women (16 to 45 years) with evidence of a prior infection with a vaccine HPV type (seropositive) that was no longer detectable at vaccination onset (PCR negative)

In post hoc analyses of individuals (who received at least one vaccination) with evidence of a prior infection with a vaccine HPV type (seropositive) no longer detectable (PCR negative) at vaccination onset, the efficacy of Gardasil to prevent conditions due to the recurrence of the same HPV type was 100% (95% CI: 62.8, 100.0; 0 vs. 12 cases [n = 2572 from pooled studies in young women]) against HPV 6-, 11-, 16-, and 18-related CIN 2/3, VIN 2/3, VaIN 2/3, and genital warts in women 16 to 26 years. Efficacy was 68.2% (95% CI: 17.9, 89.5; 6 vs. 20 cases [n= 832 from studies in young and adult women combined]) against HPV 16- and 18-related persistent infection in women 16 to 45 years.

Immunogenicity

Assays to Measure Immune Response

No minimum antibody level associated with protection has been identified for HPV vaccines.

The immunogenicity of Gardasil was assessed in 20,132 (Gardasil n = 10,723; placebo n = 9,409) girls and women 9 to 26 years of age, 1,346 (Gardasil n = 1,071; placebo n = 275) boys 9 to 15 years of age and 3,819 women 24 to 45 years of age (Gardasil n = 1,911, placebo n = 1,908).

Type-specific immunoassays, competitive Luminex-based immunoassay (cLIA), with type-specific

standards were used to assess immunogenicity to each vaccine type. This assay measures antibodies against a single neutralizing epitope for each individual HPV type.

Immune Responses to Gardasil at 1 month post dose 3

In the clinical studies in women 16 to 26 years of age, 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. In the clinical study in women 24 to 45 years, 98.4%, 98.1%, 98.8%, and 97.4% 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. Gardasil induced high anti-HPV Geometric Mean Titres (GMTs) 1 month Postdose 3 in all age groups tested.

As expected for women 24 to 45 years of age (Protocol 019), the observed antibody titres were lower than that seen in women 16 to 26 years.

Anti-HPV levels in placebo individuals who had cleared an HPV infection (seropositive and PCR negative) were substantially lower than those induced by the vaccine. Furthermore, anti-HPV levels (GMTs) in vaccinated individuals remained at or above serostatus cut-off during the long-term follow-up of the phase III studies (see below under *Persistence of Immune Response of Gardasil in Clinical Studies*).

Bridging the Efficacy of Gardasil from Young Adult Women to Young Adolescents

A clinical study (Protocol 016) compared the immunogenicity of Gardasil in 10- to 15-year-old boys and girls to those in 16- to 23-year old adolescent and young women. In the vaccine group, 99.1 to 100% became seropositive to all vaccine serotypes by 1 month Postdose 3.

Table 4 compares the 1 month Postdose 3 anti-HPV 6, 11, 16, and 18 GMTs in 9- to 15-year-old boys and girls with those in 16- to 26-year old young women.

Table 4: Immunogenicity bridging between 9- to 15-year-old male and female individuals and 16- to 26-year-old adult women (per-protocol population) based on titres as measured by cLIA

	9- to 15-Year-Old Males (Protocols 016 and 018)		9- to 15-Year-Old Females (Protocols 016 and 018)		16- to 26-Year-Old Females (Protocols 013 and 015)	
	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)
HPV 6	883	1038 (975, 1106)	915	929 (874, 987)	2631	543 (526, 560)
HPV 11	884	1387 (1299, 1481)	915	1303 (1223, 1388)	2655	762 (735, 789)
HPV 16	881	6053 (5599, 6543)	913	4909 (4548, 5300)	2570	2294 (2185, 2408)
HPV 18	886	1356 (1253, 1469)	920	1040 (965, 1120)	2796	462 (444, 480)

GMT- Geometric mean titre in mMU/ml (mMU = milli-Merck units)

Anti-HPV responses at Month 7 among 9- to 15-year-old girls and boys were non-inferior to anti-HPV responses in 16- to 26-year-old young women for whom efficacy was established in the phase III studies. Immunogenicity was related to age and Month 7 anti-HPV levels were significantly higher in younger individuals below 12 years of age than in those above that age.

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

Immunogenicity and safety of Gardasil have been demonstrated in 9- to 15-year-old boys. Protective efficacy has not been evaluated in males.

Persistence of Immune Response of Gardasil in Clinical Studies

In women 16-26 years of age, the longest follow-up of immunogenicity was in Protocol 007 where

peak anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs were observed at Month 7. The GMTs declined through Month 24 and then stabilized until at least Month 60. The exact duration of immunity following a 3-dose series has not been established.

In phase III studies in women 16 through 26 years, at end of study, 90%, 95%, 98% and 60% of individuals who received Gardasil in the per-protocol immunogenicity population were anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti HPV 18 seropositive in the cLIA, respectively.

In the Phase III study in women 24 through 45 years, after a median follow-up of 4.0 years, 91.5 %, 92.0 %, 97.4 % and 47.9 % of individuals who received Gardasil in the per-protocol immunogenicity population were anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 seropositive in the cLIA, respectively.

In the longer term follow-up in women 16 to 45 years, individuals who were seronegative for anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 in the cLIA, at end of study, were still protected against clinical disease.

Evidence of Anamnestic (Immune Memory) Response

Evidence of an anamnestic response was seen in vaccinated women who were seropositive to relevant HPV type(s) prior to vaccination. In addition, a subset of vaccinated women who received a challenge dose of Gardasil 5 years after the onset of vaccination, exhibited a rapid and strong anamnestic response that exceeded the anti-HPV GMTs observed 1 month Postdose 3.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic studies is not required for vaccines.

5.3 Preclinical safety data

Single-dose and repeated-dose toxicity and local tolerance studies revealed no special hazards to humans.

Gardasil induced specific antibody responses against HPV types 6, 11, 16, and 18 in pregnant rats, following one or multiple intramuscular injections. Antibodies against all four HPV types were transferred to the offspring during gestation and possibly during lactation. There were no treatment-related effects on developmental signs, behaviour, reproductive performance, or fertility of the offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
L-histidine
Polysorbate 80
Sodium borate
Water for injections

For adjuvant, see section 2.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze. Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

0.5 ml suspension in a vial (Type 1 glass) with stopper (FluroTec-coated or Teflon-coated chlorobutyl elastomer) and flip-off plastic cap (aluminium crimp band) in a pack size of 1, 10 or 20.

Not all pack sizes are marketed.

6.6 Special precautions for disposal and other handling

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.

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.

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.

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi Pasteur MSD SNC, 8 rue Jonas Salk, F-69007 Lyon, France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/357/001

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20th September 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency
<http://www.ema.europa.eu>