

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
- 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

Posology

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.

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

Paediatric population: The safety and efficacy of Gardasil in children below 9 years of age have not been established. No data are available (see section 5.1).

Method of administration

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).

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 should take into account the risk for previous HPV exposure and 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), sometimes associated with falling, can occur following, or even before, any vaccination, especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia, and tonic-clonic limb movements during recovery. Therefore, vaccinees should be observed for approximately 15 minutes after vaccine administration. It is important that procedures are in place to avoid injury from faints.

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 individuals 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.

Safety and immunogenicity of the vaccine have been assessed in individuals aged from 7 to 12 years who are known to be infected with human immunodeficiency virus (HIV) (see section 5.1). Individuals with impaired immune responsiveness, due to either the use of potent immunosuppressive therapy, a genetic defect, or other causes, may not respond to the vaccine.

This vaccine should be given with caution to individuals with thrombocytopaenia 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 Fertility, pregnancy and lactation

Pregnancy

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. These data on pregnant women (more than 1000 exposed outcomes) indicate no malformative nor feto/ neonatal toxicity.

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 be postponed until completion of pregnancy.

Breastfeeding

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 used during breast-feeding.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). No effects on male fertility were observed in rats (see section 5.3).

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

A. Summary of the safety profile

In 7 clinical trials (6 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 (6 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 10,088 individuals (6,995 females 9 to 45 years of age and 3,093 males 9 to 26 years of age at enrollment) who received Gardasil and 7,995 individuals (5,692 females and 2,303 males) who received placebo.

The most common adverse reactions observed were injection-site adverse reactions (77.1% of vaccinees within 5 days following any vaccination visit) and headache (16.6% of the vaccinees). These adverse reactions usually were mild or moderate in intensity.

B. Tabulated summary of adverse reactions

Clinical Trials

Table 1 presents vaccine-related adverse reactions which 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 ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Very Rare ($< 1/10,000$)]

Post-Marketing Experience

Table 1 also includes additional adverse events which have been spontaneously reported during the post-marketing use of Gardasil worldwide. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Consequently, the frequency of these adverse events is qualified as "not known".

Table 1: Adverse Events Following Administration of Gardasil from Clinical Trials and Post-Marketing Surveillance

System Organ Class	Frequency	Adverse Events
Infections and infestations	Not known	Injection-site cellulitis *
Blood and lymphatic system disorders	Not known	Idiopathic thrombocytopenic purpura*, lymphadenopathy*
Immune system disorders	Not known	Hypersensitivity reactions including anaphylactic/anaphylactoid reactions*
Nervous system disorders	Very common	Headache
	Not known	Dizziness ¹ *, Guillain-Barré syndrome*, syncope sometimes accompanied by tonic-clonic movements*
Gastrointestinal disorders	Common	Nausea
	Not known	Vomiting*
Musculoskeletal and Connective Tissue Disorders	Common	Pain in extremity
	Not known	Arthralgia*, Myalgia*
General disorders and administration site conditions	Very common	At the injection site: erythema, pain, swelling
	Common	Pyrexia At the injection site: hematoma, pruritus
	Not known	Asthenia*, chills*, fatigue*, malaise*

* Post Marketing adverse events (frequency cannot be estimated from the available data).

¹ During clinical trials, dizziness was observed as a common adverse reaction in females. In males, dizziness was not observed at a greater frequency in vaccine recipients than in placebo recipients.

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 disorders:

Rare: urticaria.

Nine cases (0.06%) of urticaria were reported in the Gardasil group and 20 cases (0.15%) 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. Among 15,706 individuals who received Gardasil and 13,617 individuals who received placebo, there were 39 cases of non-specific arthritis/arthropathy reported, 24 in the Gardasil group and 15 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.

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 in males 16 to 26 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 2.

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

Table 2: 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 3.

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

*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 4. 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 4: 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.

Efficacy in men 16 through 26 years

Efficacy was evaluated against HPV 6-, 11-, 16-, 18-related external genital warts, penile/perineal/perianal intraepithelial neoplasia (PIN) grades 1/2/3, and persistent infection.

The efficacy of Gardasil in 16- through 26-year-old men was assessed in 1 placebo-controlled, double-blind, randomized Phase III clinical study (Protocol 020) including a total of 4,055 men who were enrolled and vaccinated without pre-screening for the presence of HPV infection. The median duration of follow-up was 2.9 years.

In a subset of 598 men (GARDASIL = 299; placebo = 299) in Protocol 020 who self-identified as having sex with men (MSM) efficacy against anal intraepithelial neoplasia (AIN grades 1/2/3) and anal cancer, and intra-anal persistent infection was evaluated.

MSM are at higher risk of anal HPV infection compared to the general population; the absolute benefit of vaccination in terms of prevention of anal cancer in the general population is expected to be very low.

HIV infection was an exclusion criterion (see also section 4.4).

Efficacy in Men naïve to the relevant vaccine HPV types

The primary analyses of efficacy, with respect to vaccine HPV types (HPV 6, 11, 16, 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, 83% of men (87% of heterosexual subjects and 61% of MSM subjects) were naïve (PCR negative and seronegative) to all 4 HPV types at enrollment.

Anal Intraepithelial Neoplasia (AIN) Grade 2/3 (moderate to high-grade dysplasia) was used in the clinical trials as a surrogate marker for anal cancer.

The efficacy results for relevant endpoints analysed at end of study (median duration of follow-up 2.4 years) in the per-protocol population are presented in the Table 5. Efficacy against PIN grades 1/2/3 was not demonstrated.

Table 5: Efficacy of Gardasil against external genital lesions in the PPE population of 16-26 year old men*

Endpoint	Gardasil		Placebo		% Efficacy (95%CI)
	N	Number of cases	N	Number of cases	
HPV 6/11/16/18-related external genital lesions					
External genital lesions	1394	3	1404	32	90.6 (70.1, 98.2)
Genital warts	1394	3	1404	28	89.3 (65.3, 97.9)
PIN1/2/3	1394	0	1404	4	100.0 (-52.1, 100.0)

*The individuals in the PPE population received all 3 vaccinations within 1 year of enrollment, had no major protocol deviations, and were naïve to the relevant HPV type(s) prior to dose 1 and through 1 month Postdose 3 (Month 7).

At end of study analysis for anal lesions in the MSM population (median duration of follow-up was 2.15 years), the preventive effect against HPV 6-, 11-, 16-, 18-related AIN 2/3 was 74.9% (95 % CI: 8.8, 95.4;

3/194 versus 13/208) and against HPV 16- or 18-related AIN 2/3 86.6% (95 % CI: 0.0, 99.7; 1/194 versus 8/208).

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

The Full Analysis Set population included men 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 men with respect to prevalence of HPV infection or disease at enrollment.

The efficacy of GARDASIL against HPV 6-, 11-, 16-, 18-related external genital warts was 68.1% (95% CI: 48.8, 79.3).

The efficacy of GARDASIL against HPV 6-, 11-, 16-, 18-related AIN 2/3 and HPV 16- or 18-related AIN 2/3, in the MSM substudy, was 54.2% (95% CI: 18.0, 75.3; 18/275 versus 39/276) and 57.5% (95% CI: -1.8, 83.9; 8/275 versus 19/276 cases), respectively.

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

The impact of Gardasil against the overall risk for external genital lesions was evaluated after the first dose in 2,545 individuals enrolled in the Phase III efficacy trial (Protocol 020). Among men who were naïve to 14 common HPV types, administration of Gardasil reduced the incidence of external genital lesions caused by vaccine- or non-vaccine HPV types by 81.5% (95% CI: 58.0, 93.0). In the Full Analysis Set (FAS) population, the benefit of the vaccine with respect to the overall incidence of EGL was lower, with a reduction of 59.3% (95% CI: 40.0, 72.9), as Gardasil does not impact the course of infections or disease that are present at vaccination onset.

Impact on Biopsy and Definitive Therapy Procedures

The impact of Gardasil on rates of biopsy and treatment of EGL regardless of causal HPV types was evaluated in 2,545 individuals enrolled in Protocol 020. In the HPV naïve population (naïve to 14 common HPV types), Gardasil reduced the proportion of men who had a biopsy by 54.2% (95% CI: 28.3, 71.4) and who were treated by 47.7% (95% CI: 18.4, 67.1) at end of study. In the FAS population, the corresponding reduction was 45.7% (95% CI: 29.0, 58.7) and 38.1% (95% CI: 19.4, 52.6).

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, 5,417 (Gardasil n = 3,109; placebo n = 2,308) boys and men 9 to 26 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. In the clinical study in men 16 to 26 years, 98.9%, 99.2%, 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 Women to Girls

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

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

Table 6: Immunogenicity bridging between 9- to 15-year-old girls and 16- to 26-year-old women (per-protocol population) based on titres as measured by cLIA

	9- to 15-Year-Old Girls (Protocols 016 and 018)		16- to 26-Year-Old Women (Protocols 013 and 015)	
	n	GMT (95% CI)	n	GMT (95% CI)
HPV 6	915	929 (874, 987)	2631	543 (526, 560)
HPV 11	915	1303 (1223, 1388)	2655	762 (735, 789)
HPV 16	913	4909 (4548, 5300)	2570	2294 (2185, 2408)
HPV 18	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 were non-inferior to anti-HPV responses in 16- to 26-year-old 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.

Bridging the Efficacy of Gardasil from Men to Boys

Three clinical studies (Protocols 016, 018 and 020) were used to compare the immunogenicity of Gardasil in 9- to 15-year-old boys to 16- to 26-year-old men. In the vaccine group, 97.4 to 99.9% became seropositive to all vaccine serotypes by 1 month Postdose 3.

Table 7 compares the 1 month Postdose 3 anti-HPV 6, 11, 16, and 18 GMTs in 9- to 15-year-old boys with those in 16- to 26-year-old men.

Table 7: Immunogenicity bridging between 9- to 15-year-old boys and 16- to 26-year-old men (per-protocol population) based on titres as measured by cLIA

	9- to 15-Year-Old Boys		16- to 26-Year-Old Men	
	n	GMT (95% CI)	n	GMT (95% CI)
HPV 6	884	1038 (964, 1117)	1093	448 (419, 479)
HPV 11	885	1387 (1299, 1481)	1093	624 (588, 662)
HPV 16	882	6057 (5601, 6549)	1136	2403 (2243, 2575)
HPV 18	887	1357 (1249, 1475)	1175	403 (375, 433)

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

Anti-HPV responses at Month 7 among 9- to 15-year-old boys were non-inferior to anti-HPV responses in 16- to 26-year-old men 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.

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

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 Phase III study in men 16 through 26 years, after a median follow-up of 2.9 years, 88.9 %, 94.0 %, 97.9 % and 57.1% 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 and men 16 to 26 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.

HIV infected subjects

An academic study documenting safety and immunogenicity of Gardasil has been performed in 126 HIV infected subjects aged from 7-12 years (of which 96 received Gardasil). Seroconversion to all four antigens occurred in more than ninety-six percent of the subjects. The GMTs were somewhat lower than reported in non-HIV infected subjects of the same age in other studies. The clinical relevance of the lower response is unknown. The safety profile was similar to non-HIV infected subjects in other studies. The CD4% or plasma HIV RNA was not affected by vaccination.

5.2 Pharmacokinetic properties

Not applicable.

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.

GARDASIL administered to male rats at the full human dose (120 mcg total protein) had no effects on reproductive performance including fertility, sperm count, and sperm motility, and there were no vaccine-related gross or histomorphologic changes on the testes and no effects on testes weights.

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 (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 discolouration prior to administration. Discard the vaccine 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

EU/1/06/357/002

EU/1/06/357/018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2006

Date of latest renewal: 22 September 2011

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>

1. NAME OF THE MEDICINAL PRODUCT

Gardasil, suspension for injection in a pre-filled syringe.

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 in a pre-filled syringe.

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
- 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

Posology

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.

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

Paediatric population: The safety and efficacy of Gardasil in children below 9 years of age have not been established. No data are available (see section 5.1).

Method of administration

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).

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 should take into account the risk for previous HPV exposure and 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), sometimes associated with falling, can occur following, or even before, any vaccination, especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia, and tonic-clonic limb movements during recovery. Therefore, vaccinees should be observed for approximately 15 minutes after vaccine administration. It is important that procedures are in place to avoid injury from faints.

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 individuals 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.

Safety and immunogenicity of the vaccine have been assessed in individuals aged from 7 to 12 years who are known to be infected with human immunodeficiency virus (HIV) (see section 5.1). Individuals with impaired immune responsiveness, due to either the use of potent immunosuppressive therapy, a genetic defect, or other causes, may not respond to the vaccine.

This vaccine should be given with caution to individuals with thrombocytopaenia 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 Fertility, pregnancy and lactation

Pregnancy

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. These data on pregnant women (more than 1000 exposed outcomes) indicate no malformative nor feto/ neonatal toxicity.

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 be postponed until completion of pregnancy.

Breastfeeding

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 used during breast-feeding.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). No effects on male fertility were observed in rats (see section 5.3).

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

A. Summary of the safety profile

In 7 clinical trials (6 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 (6 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 10,088 individuals (6,995 females 9 to 45 years of age and 3,093 males 9 to 26 years of age at enrollment) who received Gardasil and 7,995 individuals (5,692 females and 2,303 males) who received placebo.

The most common adverse reactions observed were injection-site adverse reactions (77.1% of vaccinees within 5 days following any vaccination visit) and headache (16.6% of the vaccinees). These adverse reactions usually were mild or moderate in intensity.

B. Tabulated summary of adverse reactions

Clinical Trials

Table 1 presents vaccine-related adverse reactions which 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 ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Very Rare ($< 1/10,000$)]

Post-Marketing Experience

Table 1 also includes additional adverse events which have been spontaneously reported during the post-marketing use of Gardasil worldwide. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Consequently, the frequency of these adverse events is qualified as "not known".

Table 1: Adverse Events Following Administration of Gardasil from Clinical Trials and Post-Marketing Surveillance

System Organ Class	Frequency	Adverse Events
Infections and infestations	Not known	Injection-site cellulitis*
Blood and lymphatic system disorders	Not known	Idiopathic thrombocytopenic purpura*, lymphadenopathy*
Immune system disorders	Not known	Hypersensitivity reactions including anaphylactic/anaphylactoid reactions*
Nervous system disorders	Very common	Headache
	Not known	Dizziness ¹ *, Guillain-Barré syndrome*, syncope sometimes accompanied by tonic-clonic movements*
Gastrointestinal disorders	Common	Nausea
	Not known	Vomiting*
Musculoskeletal and Connective Tissue Disorders	Common	Pain in extremity
	Not known	Arthralgia*, Myalgia*
General disorders and administration site conditions	Very common	At the injection site: erythema, pain, swelling
	Common	Pyrexia At the injection site: hematoma, pruritus
	Not known	Asthenia*, chills*, fatigue*, malaise*

* Post Marketing adverse events (frequency cannot be estimated from the available data).

¹ During clinical trials, dizziness was observed as a common adverse reaction in females. In males, dizziness was not observed at a greater frequency in vaccine recipients than in placebo recipients.

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 disorders:

Rare: urticaria.

Nine cases (0.06%) of urticaria were reported in the Gardasil group and 20 cases (0.15%) 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. Among 15,706 individuals who received Gardasil and 13,617 individuals who received placebo, there were 39 cases of non-specific arthritis/arthropathy reported, 24 in the Gardasil group and 15 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.

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 in males 16 to 26 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 2.

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

Table 2: 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 3.

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

*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 4. 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 4: 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.

Efficacy in men 16 through 26 years

Efficacy was evaluated against HPV 6-, 11-, 16-, 18-related external genital warts, penile/perineal/perianal intraepithelial neoplasia (PIN) grades 1/2/3, and persistent infection.

The efficacy of Gardasil in 16- through 26-year-old men was assessed in 1 placebo-controlled, double-blind, randomized Phase III clinical study (Protocol 020) including a total of 4,055 men who were enrolled and vaccinated without pre-screening for the presence of HPV infection. The median duration of follow-up was 2.9 years.

In a subset of 598 men (GARDASIL = 299; placebo = 299) in Protocol 020 who self-identified as having sex with men (MSM) efficacy against anal intraepithelial neoplasia (AIN grades 1/2/3) and anal cancer, and intra-anal persistent infection was evaluated.

MSM are at higher risk of anal HPV infection compared to the general population; the absolute benefit of vaccination in terms of prevention of anal cancer in the general population is expected to be very low.

HIV infection was an exclusion criterion (see also section 4.4).

Efficacy in Men naïve to the relevant vaccine HPV types

The primary analyses of efficacy, with respect to vaccine HPV types (HPV 6, 11, 16, 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, 83% of men (87% of heterosexual subjects and 61% of MSM subjects) were naïve (PCR negative and seronegative) to all 4 HPV types at enrollment.

Anal Intraepithelial Neoplasia (AIN) Grade 2/3 (moderate to high-grade dysplasia) was used in the clinical trials as a surrogate marker for anal cancer.

The efficacy results for relevant endpoints analysed at end of study (median duration of follow-up 2.4 years) in the per-protocol population are presented in the Table 5. Efficacy against PIN grades 1/2/3 was not demonstrated.

Table 5: Efficacy of Gardasil against external genital lesions in the PPE population of 16-26 year old men*

Endpoint	Gardasil		Placebo		% Efficacy (95%CI)
	N	Number of cases	N	Number of cases	
HPV 6/11/16/18-related external genital lesions					
External genital lesions	1394	3	1404	32	90.6 (70.1, 98.2)
Genital warts	1394	3	1404	28	89.3 (65.3, 97.9)
PIN1/2/3	1394	0	1404	4	100.0 (-52.1, 100.0)

*The individuals in the PPE population received all 3 vaccinations within 1 year of enrollment, had no major protocol deviations, and were naïve to the relevant HPV type(s) prior to dose 1 and through 1 month Postdose 3 (Month 7).

At end of study analysis for anal lesions in the MSM population (median duration of follow-up was 2.15 years), the preventive effect against HPV 6-, 11-, 16-, 18-related AIN 2/3 was 74.9% (95 % CI: 8.8, 95.4;

3/194 versus 13/208) and against HPV 16- or 18-related AIN 2/3 86.6% (95 % CI: 0.0, 99.7; 1/194 versus 8/208).

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

The Full Analysis Set population included men 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 men with respect to prevalence of HPV infection or disease at enrollment.

The efficacy of GARDASIL against HPV 6-, 11-, 16-, 18-related external genital warts was 68.1% (95% CI: 48.8, 79.3).

The efficacy of GARDASIL against HPV 6-, 11-, 16-, 18-related AIN 2/3 and HPV 16- or 18-related AIN 2/3, in the MSM substudy, was 54.2% (95% CI: 18.0, 75.3; 18/275 versus 39/276) and 57.5% (95% CI: -1.8, 83.9; 8/275 versus 19/276 cases), respectively.

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

The impact of Gardasil against the overall risk for external genital lesions was evaluated after the first dose in 2,545 individuals enrolled in the Phase III efficacy trial (Protocol 020). Among men who were naïve to 14 common HPV types, administration of Gardasil reduced the incidence of external genital lesions caused by vaccine- or non-vaccine HPV types by 81.5% (95% CI: 58.0, 93.0). In the Full Analysis Set (FAS) population, the benefit of the vaccine with respect to the overall incidence of EGL was lower, with a reduction of 59.3% (95% CI: 40.0, 72.9), as Gardasil does not impact the course of infections or disease that are present at vaccination onset.

Impact on Biopsy and Definitive Therapy Procedures

The impact of Gardasil on rates of biopsy and treatment of EGL regardless of causal HPV types was evaluated in 2,545 individuals enrolled in Protocol 020. In the HPV naïve population (naïve to 14 common HPV types), Gardasil reduced the proportion of men who had a biopsy by 54.2% (95% CI: 28.3, 71.4) and who were treated by 47.7% (95% CI: 18.4, 67.1) at end of study. In the FAS population, the corresponding reduction was 45.7% (95% CI: 29.0, 58.7) and 38.1% (95% CI: 19.4, 52.6).

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, 5,417 (Gardasil n = 3,109; placebo n = 2,308) boys and men 9 to 26 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. In the clinical study in men 16 to 26 years, 98.9%, 99.2%, 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 Women to Girls

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

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

Table 6: Immunogenicity bridging between 9- to 15-year-old girls and 16- to 26-year-old women (per-protocol population) based on titres as measured by cLIA

	9- to 15-Year-Old Girls (Protocols 016 and 018)		16- to 26-Year-Old Women (Protocols 013 and 015)	
	n	GMT (95% CI)	n	GMT (95% CI)
HPV 6	915	929 (874, 987)	2631	543 (526, 560)
HPV 11	915	1303 (1223, 1388)	2655	762 (735, 789)
HPV 16	913	4909 (4548, 5300)	2570	2294 (2185, 2408)
HPV 18	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 were non-inferior to anti-HPV responses in 16- to 26-year-old 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.

Bridging the Efficacy of Gardasil from Men to Boys

Three clinical studies (Protocols 016, 018 and 020) were used to compare the immunogenicity of Gardasil in 9- to 15-year-old boys to 16- to 26-year-old men. In the vaccine group, 97.4 to 99.9% became seropositive to all vaccine serotypes by 1 month Postdose 3.

Table 7 compares the 1 month Postdose 3 anti-HPV 6, 11, 16, and 18 GMTs in 9- to 15-year-old boys with those in 16- to 26-year-old men.

Table 7: Immunogenicity bridging between 9- to 15-year-old boys and 16- to 26-year-old men (per-protocol population) based on titres as measured by cLIA

	9- to 15-Year-Old Boys		16- to 26-Year-Old Men	
	N	GMT (95% CI)	n	GMT (95% CI)
HPV 6	884	1038 (964, 1117)	1093	448 (419, 479)
HPV 11	885	1387 (1299, 1481)	1093	624 (588, 662)
HPV 16	882	6057 (5601, 6549)	1136	2403 (2243, 2575)
HPV 18	887	1357 (1249, 1475)	1175	403 (375, 433)

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

Anti-HPV responses at Month 7 among 9- to 15-year-old boys were non-inferior to anti-HPV responses in 16- to 26-year-old men 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.

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

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 Phase III study in men 16 through 26 years, after a median follow-up of 2.9 years, 88.9 %, 94.0 %, 97.9 % and 57.1% 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 and men 16 to 26 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.

HIV-infected subjects

An academic study documenting safety and immunogenicity of Gardasil has been performed in 126 HIV infected subjects aged from 7 to 12 years (of which 96 received Gardasil). Seroconversion to all four antigens occurred in more than ninety-six percent of the subjects. The GMTs were somewhat lower than those reported in non-HIV infected subjects of the same age in other studies. The clinical relevance of the lower response is unknown. The safety profile was similar to non-HIV infected subjects in other studies. The CD4% or plasma HIV RNA was not affected by vaccination.

5.2 Pharmacokinetic properties

Not applicable.

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.

GARDASIL administered to male rats at the full human dose (120 mcg total protein) had no effects on reproductive performance including fertility, sperm count, and sperm motility, and there were no vaccine-related gross or histomorphologic changes on the testes and no effects on testes weights.

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 pre-filled syringe in the outer carton in order to protect from light.

6.5 Nature and contents of container

0.5 ml suspension in a pre-filled syringe (glass) with plunger stopper (siliconized FluroTec-coated bromobutyl elastomer or non-coated chlorobutyl elastomer) and tip cap (bromobutyl) without needle or with one or two needle(s) - pack size of 1, 10 or 20.

Not all pack sizes are marketed.

6.6 Special precautions for disposal and other handling

- Gardasil is available in a pre-filled syringe ready to use for intramuscular injection (IM), preferably in the deltoid area of the upper arm.
- If 2 needles of different lengths are provided in the pack, choose the appropriate needle to ensure an IM administration depending on your patient's size and weight.
- Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. Discard the vaccine if particulates are present or if it appears discoloured. Any unused product or waste material should be disposed of in accordance with local requirements.

Using the pre-filled syringe

Shake well before use. Attach the needle by twisting in a clockwise direction until the needle fits securely on the syringe. Administer the entire dose as per standard protocol.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/357/003
EU/1/06/357/004
EU/1/06/357/005
EU/1/06/357/006
EU/1/06/357/007
EU/1/06/357/008
EU/1/06/357/019
EU/1/06/357/020
EU/1/06/357/021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2006

Date of latest renewal: 22 September 2011

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>

ANNEX II

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE
SUBSTANCE(S) AND MANUFACTURING AUTHORISATION
HOLDER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Merck Sharp & Dohme Corp.
Sumneytown Pike
P.O.Box 4
West Point
PA 19486
USA

Name and address of the manufacturer(s) responsible for batch release

Merck Sharp & Dohme B.V.
Waarderweg 39
Postbus 581
NL-2031 Haarlem
The Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to medical prescription.

• CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

• OTHER CONDITIONS

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance as presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 7 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR). In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

PSURs

The MAH will submit PSURs on a yearly basis.

Official batch release: in accordance with Article 114 Directive 2001/83/EC as amended, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON TEXT
Gardasil, suspension for injection – single dose vial, pack of 1, 10, 20

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml) contains:
HPV Type 6 L1 protein 20 µg
HPV Type 11 L1 protein 40 µg
HPV Type 16 L1 protein 40 µg
HPV Type 18 L1 protein 20 µg

Adsorbed on amorphous aluminium hydroxyphosphate sulphate (225 µg Al).

3. LIST OF EXCIPIENTS

Sodium chloride, L-histidine, polysorbate 80, sodium borate, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
1 dose vial, 0.5 ml.
10 single dose vials, 0.5 ml each.
20 single dose vials, 0.5 ml each.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular (IM) use.
Shake well before use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/357/001 – pack of 1
EU/1/06/357/002– pack of 10
EU/1/06/357/018– pack of 20

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS VIAL LABEL TEXT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

Gardasil, suspension for injection.
IM use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP MM/YYYY

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

1 dose, 0.5 ml.

6. OTHER

Sanofi Pasteur MSD SNC

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON TEXT

Gardasil, suspension for injection – pre-filled syringe without needle, pack of 1, 10, 20

1. NAME OF THE MEDICINAL PRODUCT

Gardasil, suspension for injection in a pre-filled syringe.
Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed).

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml) dose contains:

HPV Type 6 L1 protein	20 µg
HPV Type 11 L1 protein	40 µg
HPV Type 16 L1 protein	40 µg
HPV Type 18 L1 protein	20 µg

Adsorbed on amorphous aluminium hydroxyphosphate sulphate (225 µg Al).

3. LIST OF EXCIPIENTS

Sodium chloride, L-histidine, polysorbate 80, sodium borate, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a pre-filled syringe.
1 dose, 0.5 ml pre-filled syringe without needle.
10 single doses, 0.5 ml pre-filled syringes without needles.
20 single doses, 0.5 ml pre-filled syringes without needles.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular (IM) use.
Shake well before use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/357/003 – pack of 1
EU/1/06/357/004 – pack of 10
EU/1/06/357/019 – pack of 20

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON TEXT

Gardasil, suspension for injection – pre-filled syringe with 1 needle, pack of 1, 10, 20

1. NAME OF THE MEDICINAL PRODUCT

Gardasil, suspension for injection in a pre-filled syringe.
Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed).

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml) dose contains:

HPV Type 6 L1 protein	20 µg
HPV Type 11 L1 protein	40 µg
HPV Type 16 L1 protein	40 µg
HPV Type 18 L1 protein	20 µg

Adsorbed on amorphous aluminium hydroxyphosphate sulphate (225 µg Al).

3. LIST OF EXCIPIENTS

Sodium chloride, L-histidine, polysorbate 80, sodium borate, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a pre-filled syringe.

1 dose, 0.5 ml pre-filled syringe with 1 needle.

10 single doses, 0.5 ml pre-filled syringes with 1 needle each.

20 single doses, 0.5 ml pre-filled syringes with 1 needle each.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular (IM) use.

Shake well before use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/357/005 – pack of 1
EU/1/06/357/006 – pack of 10
EU/1/06/357/020 – pack of 20

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON TEXT

Gardasil, suspension for injection – pre-filled syringe with 2 needles, pack of 1, 10, 20

1. NAME OF THE MEDICINAL PRODUCT

Gardasil, suspension for injection in a pre-filled syringe.
Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed).

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml) dose contains:

HPV Type 6 L1 protein	20 µg
HPV Type 11 L1 protein	40 µg
HPV Type 16 L1 protein	40 µg
HPV Type 18 L1 protein	20 µg

adsorbed on amorphous aluminium hydroxyphosphate sulphate (225 µg Al).

3. LIST OF EXCIPIENTS

Sodium chloride, L-histidine, polysorbate 80, sodium borate, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a pre-filled syringe.

1 dose, 0.5 ml pre-filled syringe with 2 needles.

10 single doses, 0.5 ml pre-filled syringes with 2 needles each.

20 single doses, 0.5 ml pre-filled syringes with 2 needles each.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular (IM) use.

Shake well before use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/357/007 – pack of 1
EU/1/06/357/008 – pack of 10
EU/1/06/357/021 – pack of 20

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS Pre-filled syringe label text

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

Gardasil, suspension for injection in a pre-filled syringe.

IM use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP MM/YYYY

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

1 dose, 0.5 ml.

6. OTHER

Sanofi Pasteur MSD SNC

**B. PACKAGE LEAFLET
(VIAL)**

PACKAGE LEAFLET: INFORMATION FOR THE USER

Gardasil, suspension for injection

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

Read all of this leaflet carefully before you or your child are vaccinated.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Gardasil is and what it is used for
2. Before you receive Gardasil
3. How Gardasil is given
4. Possible side effects
5. How to store Gardasil
6. Further information

1. WHAT GARDASIL IS AND WHAT IT IS USED FOR

Gardasil is a vaccine. Vaccination with Gardasil is intended to protect against diseases caused by Human Papillomavirus (HPV) types 6, 11, 16, and 18.

These diseases include cervical cancer; pre-cancerous lesions of the female genitals (cervix, vulva, and vagina); and genital warts in males and females. HPV types 16 and 18 are responsible for approximately 70% of cervical cancer cases and 70% of HPV-related pre-cancerous lesions of the vulva and vagina. HPV types 6 and 11 are responsible for approximately 90% of genital wart cases.

Gardasil is intended to prevent these diseases. The vaccine is not used to treat HPV related diseases. Gardasil does not have any effect in individuals who already have a persistent infection or disease associated with any of the HPV types in the vaccine. However, in individuals who are already infected with one or more of the vaccine HPV types, Gardasil can still protect against diseases associated with the other HPV types in the vaccine.

Gardasil cannot cause the diseases it protects against.

Gardasil produces type-specific antibodies and has been shown in clinical trials to prevent HPV 6-, 11-, 16-, and 18-related diseases in women 16-45 years of age and in men 16-26 years of age. The vaccine also produces type-specific antibodies in 9- to 15-year-old children and adolescents.

Gardasil should be used in accordance with official guidelines.

2. BEFORE YOU RECEIVE GARDASIL

Do not receive Gardasil if:

- you or your child is allergic (hypersensitive) to any of the active substances or any of the other

- ingredients of Gardasil (listed under “other ingredients”– see section 6).
- you or your child developed an allergic reaction after receiving a dose of Gardasil.
- you or your child suffer from an illness with high fever. However, a mild fever or upper respiratory infection (for example cold) itself is not a reason to delay vaccination.

Take special care with Gardasil:

You should tell your doctor if you or your child:

- has a bleeding disorder (a disease that makes you bleed more than normal), for example haemophilia
- has a weakened immune system, for example due to a genetic defect, HIV infection or medicines that affect the immune system.

Fainting, sometimes accompanied by falling, can occur (mostly in adolescents) following any needle injection. Therefore tell the doctor or nurse if you fainted with a previous injection.

As with any vaccine, Gardasil may not fully protect 100% of those who get the vaccine.

Gardasil will not protect against every type of Human Papillomavirus. Therefore appropriate precautions against sexually transmitted disease should continue to be used.

Gardasil will not protect against other diseases that are not caused by Human Papillomavirus.

Vaccination is not a substitute for routine cervical screening. You should continue to follow your doctor’s advice on cervical smear/Pap tests and preventative and protective measures.

What other important information should you or your child know about Gardasil

The duration of protection is currently unknown. Longer term follow-up studies are ongoing to determine whether a booster dose is needed.

Taking other medicines:

Gardasil can be given with a Hepatitis B vaccine or 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) at a separate injection site (another part of your body, e.g. the other arm or leg) during the same visit.

Gardasil may not have an optimal effect if:

- used with medicines that suppress the immune system.

In clinical trials, oral or other contraceptives (e.g. the pill) did not reduce the protection obtained by Gardasil.

Please tell your doctor or pharmacist if you or your child are taking or have taken recently any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding:

Consult your doctor if the person to be vaccinated is pregnant, trying to become pregnant or becomes pregnant during the course of vaccination.

Gardasil may be given to women who are breast-feeding or intend to breast-feed.

Driving and using machines:

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

3. HOW GARDASIL IS GIVEN

Gardasil is given as an injection by your doctor. Gardasil is intended for adolescents and adults from 9 years of age onwards. The person to be vaccinated will receive three doses of the vaccine.

First injection: at chosen date

Second injection: ideally 2 months after first injection

Third injection: ideally 6 months after first injection

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. Please speak to your doctor for more information.

The person to be vaccinated should complete the three-dose vaccination course; otherwise the person to be vaccinated may not be fully protected.

Gardasil will be given as an injection through the skin into the muscle (preferably the muscle of the upper arm or thigh).

The vaccine should not be mixed in the same syringe with any other vaccines and solutions.

If you forget to take Gardasil:

If you miss a scheduled injection, your doctor will decide when to give the missed dose.

It is important that you follow the instructions of your doctor or nurse regarding return visits for the follow-up doses. If you forget or are not able to go back to your doctor at the scheduled time, ask your doctor for advice. When Gardasil is given as your first dose, the following two doses to complete the 3-dose vaccination course should also be Gardasil, and not another HPV vaccine.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all vaccines and medicines, Gardasil can cause side effects, although not everybody gets them.

The following side effects can be seen after the use of Gardasil:

Very commonly (more than 1 in 10 patients), side effects found at the injection site include: pain, swelling and redness. Headache was also seen.

Commonly (more than 1 in 100 patients), side effects found at the injection site include: bruising, itching, pain in extremity. Fever and nausea have also been reported.

Rarely (less than 1 in 1000 patients): hives (urticaria).

Very rarely (less than 1 in 10,000 patients), difficulty breathing (bronchospasm) has been reported.

When Gardasil was given with a combined diphtheria, tetanus, pertussis [acellular, component] and poliomyelitis [inactivated] booster vaccine during the same visit, there was more headache and injection-site swelling.

Side effects that have been reported during marketed use include:

Fainting, sometimes accompanied by shaking or stiffening, has been reported. Although fainting episodes are uncommon, patients should be observed for 15 minutes after they receive HPV vaccine.

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

As with other vaccines, side effects that have been reported during general use include: swollen glands (neck, armpit, or groin), Guillain-Barré Syndrome (muscle weakness, abnormal sensations, tingling in the arms, legs and upper body), dizziness, vomiting, joint pain, aching muscles, unusual tiredness or weakness, chills, generally feeling unwell, bleeding or bruising more easily than normal, and skin infection at the injection site.

If any of the side effects gets serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE GARDASIL

Keep this vaccine out of the reach and sight of children.

The vaccine should not be used after the expiry date which is stated on the vial label and the outer carton (after EXP). The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C). Do not freeze. Keep the vial in the outer carton in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. These measures will help to protect the environment.

6. FURTHER INFORMATION

If you have any further questions on Gardasil after reading this leaflet, please ask your doctor or pharmacist.

What Gardasil contains

The active substances are: highly purified non-infectious protein for each of the Human Papillomavirus types (6, 11, 16, and 18).

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).

The other ingredients in the vaccine suspension are:

Sodium chloride, L-histidine, polysorbate 80, sodium borate and water for injections.

What Gardasil looks like and contents of the pack

1 dose of Gardasil suspension for injection contains 0.5 ml.

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

Gardasil is available in packs of 1, 10 or 20 vials.

Not all pack sizes are marketed.

Marketing Authorisation Holder: Sanofi Pasteur MSD SNC, 8 rue Jonas Salk, F-69007 Lyon, France

Manufacturer: Merck Sharp and Dohme, B.V., Waarderweg, 39, 2031 BN Haarlem, The Netherlands

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien Sanofi Pasteur MSD Tél/Tel: +32.2.726.95.84	Luxembourg/Luxemburg Sanofi Pasteur MSD, Tél: +32.2.726.95.84
България, Česká republika, Eesti, France, Hrvatska, Κύπρος, Latvija, Lietuva, Magyarország, Malta, Polska, România, Slovenija, Slovenská republika Sanofi Pasteur MSD SNC, Tél: +33.4.37.28.40.00	Nederland Sanofi Pasteur MSD, Tel: +31.23.567.96.00
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This leaflet was last approved in:

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

The following information is intended for medical or healthcare professionals only:

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 discolouration prior to administration. Discard the product if particulates are present or if it appears discoloured.

**B PACKAGE LEAFLET
(REFILLED SYRINGE)**

PACKAGE LEAFLET: INFORMATION FOR THE USER

Gardasil, suspension for injection in a pre-filled syringe

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

Read all of this leaflet carefully before you or your child are vaccinated.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Gardasil is and what it is used for
2. Before you receive Gardasil
3. How Gardasil is given
4. Possible side effects
5. How to store Gardasil
6. Further information

1. WHAT GARDASIL IS AND WHAT IT IS USED FOR

Gardasil is a vaccine. Vaccination with Gardasil is intended to protect against diseases caused by Human Papillomavirus (HPV) types 6, 11, 16, and 18.

These diseases include cervical cancer; pre-cancerous lesions of the female genitals (cervix, vulva, and vagina); and genital warts in males and females. HPV types 16 and 18 are responsible for approximately 70% of cervical cancer cases and 70% of HPV-related pre-cancerous lesions of the vulva and vagina. HPV types 6 and 11 are responsible for approximately 90% of genital wart cases.

Gardasil is intended to prevent these diseases. The vaccine is not used to treat HPV related diseases. Gardasil does not have any effect in individuals who already have a persistent infection or disease associated with any of the HPV types in the vaccine. However, in individuals who are already infected with one or more of the vaccine HPV types, Gardasil can still protect against diseases associated with the other HPV types in the vaccine.

Gardasil cannot cause the diseases it protects against.

Gardasil produces type-specific antibodies and has been shown in clinical trials to prevent HPV 6-, 11-, 16-, and 18-related diseases in women 16-45 years of age and in men 16-26 years of age. The vaccine also produces type-specific antibodies in 9- to 15-year-old children and adolescents.

Gardasil should be used in accordance with official guidelines.

2. BEFORE YOU RECEIVE GARDASIL

Do not receive Gardasil if:

- you or your child is allergic (hypersensitive) to any of the active substances or any of the other

- ingredients of Gardasil (listed under “other ingredients”– see section 6).
- you or your child developed an allergic reaction after receiving a dose of Gardasil.
 - you or your child suffer from an illness with high fever. However, a mild fever or upper respiratory infection (for example cold) itself is not a reason to delay vaccination.

Take special care with Gardasil:

You should tell your doctor if you or your child:

- has a bleeding disorder (a disease that makes you bleed more than normal), for example haemophilia
- has a weakened immune system, for example due to a genetic defect, HIV infection or medicines that affect the immune system.

Fainting, sometimes accompanied by falling, can occur (mostly in adolescents) following any needle injection. Therefore tell the doctor or nurse if you fainted with a previous injection.

As with any vaccine, Gardasil may not fully protect 100% of those who get the vaccine.

Gardasil will not protect against every type of Human Papillomavirus. Therefore appropriate precautions against sexually transmitted disease should continue to be used.

Gardasil will not protect against other diseases that are not caused by Human Papillomavirus.

Vaccination is not a substitute for routine cervical screening. You should continue to follow your doctor’s advice on cervical smear/Pap tests and preventative and protective measures.

What other important information should you or your child know about Gardasil

The duration of protection is currently unknown. Longer term follow-up studies are ongoing to determine whether a booster dose is needed.

Taking other medicines:

Gardasil can be given with a Hepatitis B vaccine or 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) at a separate injection site (another part of your body, e.g. the other arm or leg) during the same visit.

Gardasil may not have an optimal effect if:

- used with medicines that suppress the immune system.

In clinical trials, oral or other contraceptives (e.g. the pill) did not reduce the protection obtained by Gardasil.

Please tell your doctor or pharmacist if you or your child are taking or have taken recently any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding:

Consult your doctor if the person to be vaccinated is pregnant, trying to become pregnant or becomes pregnant during the course of vaccination.

Gardasil may be given to women who are breast-feeding or intend to breast-feed.

Driving and using machines:

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

3. HOW GARDASIL IS GIVEN

Gardasil is given as an injection by your doctor. Gardasil is intended for adolescents and adults from 9 years of age onwards. The person to be vaccinated will receive three doses of the vaccine.

First injection: at chosen date

Second injection: ideally 2 months after first injection

Third injection: ideally 6 months after first injection

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. Please speak to your doctor for more information.

The person to be vaccinated should complete the three-dose vaccination course; otherwise the person to be vaccinated may not be fully protected.

Gardasil will be given as an injection through the skin into the muscle (preferably the muscle of the upper arm or thigh).

The vaccine should not be mixed in the same syringe with any other vaccines and solutions.

If you forget to take Gardasil:

If you miss a scheduled injection, your doctor will decide when to give the missed dose.

It is important that you follow the instructions of your doctor or nurse regarding return visits for the follow-up doses. If you forget or are not able to go back to your doctor at the scheduled time, ask your doctor for advice. When Gardasil is given as your first dose, the following two doses to complete the 3-dose vaccination course should also be Gardasil, and not another HPV vaccine.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all vaccines and medicines, Gardasil can cause side effects, although not everybody gets them.

The following side effects can be seen after the use of Gardasil:

Very commonly (more than 1 in 10 patients), side effects found at the injection site include: pain, swelling and redness. Headache was also seen.

Commonly (more than 1 in 100 patients), side effects found at the injection site include: bruising, itching, pain in extremity. Fever and nausea have also been reported.

Rarely (less than 1 in 1000 patients): hives (urticaria).

Very rarely (less than 1 in 10,000 patients), difficulty breathing (bronchospasm) has been reported.

When Gardasil was given with a combined diphtheria, tetanus, pertussis [acellular, component] and poliomyelitis [inactivated] booster vaccine during the same visit, there was more headache and injection-site swelling.

Side effects that have been reported during marketed use include:

Fainting, sometimes accompanied by shaking or stiffening, has been reported. Although fainting episodes are uncommon, patients should be observed for 15 minutes after they receive HPV vaccine.

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

As with other vaccines, side effects that have been reported during general use include: swollen glands (neck, armpit, or groin), Guillain-Barré Syndrome (muscle weakness, abnormal sensations, tingling in the arms, legs and upper body), dizziness, vomiting, joint pain, aching muscles, unusual tiredness or weakness, chills, generally feeling unwell, bleeding or bruising more easily than normal, and skin infection at the injection site.

If any of the side effects gets serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE GARDASIL

Keep this vaccine out of the reach and sight of children.

The vaccine should not be used after the expiry date which is stated on the syringe label and the outer carton (after EXP). The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C). Do not freeze. Keep the syringe in the outer carton in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. These measures will help to protect the environment.

6. FURTHER INFORMATION

If you have any further questions on Gardasil after reading this leaflet, please ask your doctor or pharmacist.

What Gardasil contains

The active substances are: highly purified non-infectious protein for each of the Human Papillomavirus types (6, 11, 16, and 18).

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).

The other ingredients in the vaccine suspension are:

Sodium chloride, L-histidine, polysorbate 80, sodium borate and water for injections.

What Gardasil looks like and contents of the pack

1 dose of Gardasil suspension for injection contains 0.5 ml.

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

Gardasil is available in packs of 1, 10 or 20 pre-filled syringes.

Not all pack sizes are marketed.

Marketing Authorisation Holder: Sanofi Pasteur MSD SNC, 8 rue Jonas Salk, F-69007 Lyon, France

Manufacturer: Merck Sharp and Dohme, B.V., Waarderweg, 39, 2031 BN Haarlem, The Netherlands

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

The following information is intended for medical or healthcare professionals only:

- Gardasil is available in a pre-filled syringe ready to use for intramuscular injection (IM), preferably in the deltoid area of the upper arm.
- If 2 needles of different lengths are provided in the pack, choose the appropriate needle to ensure an IM administration depending on your patient's size and weight.
- Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. Discard the product if particulates are present or if it appears discoloured. Any unused product or waste material should be disposed of in accordance with local requirements.

Shake well before use. Attach the needle by twisting in a clockwise direction until the needle fits securely on the syringe. Administer the entire dose as per standard protocol.