

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 the prevention of high-grade cervical dysplasia (CIN 2/3), cervical carcinoma, high-grade vulvar dysplastic lesions (VIN 2/3), and external genital warts (condyloma acuminata) causally related to Human Papillomavirus (HPV) types 6, 11, 16 and 18.

The indication is based on the demonstration of efficacy of Gardasil in adult females 16 to 26 years of age and on the demonstration of immunogenicity of Gardasil in 9- to 15-year old children and adolescents. Protective efficacy has not been evaluated in males (see section 5.1).

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

4.2 Posology and method of administration

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

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

The need for a booster dose has not been established.

Paediatric population: Gardasil is not recommended for use in children below 9 years of age due to insufficient data on immunogenicity, safety and efficacy (see section 5.1).

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

Gardasil must not be injected intravascularly. Subcutaneous and intradermal administration have not been studied, and therefore 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 subjects 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

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.

As with any vaccine, vaccination with Gardasil may not result in protection in all vaccine recipients. Also, Gardasil will only protect against diseases that are caused by HPV types 6, 11, 16 and 18. Therefore, appropriate precautions against sexually transmitted diseases should continue to be used.

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.

Vaccination is not a substitute for routine cervical screening. Since no vaccine is 100% effective and Gardasil will not provide protection against non-vaccine HPV types, or against existing HPV infections, routine cervical screening remains critically important and should follow local recommendations.

There are no data on the use of Gardasil in subjects with impaired immune responsiveness. Individuals with impaired immune responsiveness, whether due to the use of potent immunosuppressive therapy, a genetic defect, Human Immunodeficiency Virus (HIV) infection, or other causes, may not respond to the vaccine.

This vaccine should be given with caution to individuals with 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).

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 subjects 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.

The concomitant administration of Gardasil with vaccines other than hepatitis B (recombinant) vaccine has not been studied.

Use with hormonal contraceptives

In clinical studies, 57.5% of women (age 16 to 26 years) who received Gardasil used hormonal contraceptives. Use of hormonal contraceptives did not appear to affect the immune response to Gardasil.

4.6 Pregnancy and lactation

Specific studies of the vaccine in pregnant women were not conducted. However, during the prelicensure clinical development program, 2,266 women (vaccine = 1,115 vs. placebo = 1,151) reported at least one pregnancy. Overall, the proportions of pregnancies with an adverse outcome were comparable in subjects who received Gardasil and subjects who received placebo. For pregnancies with estimated onset within 30 days of vaccination, 5 cases of congenital anomaly were observed in the group that received Gardasil compared to 0 cases of congenital anomaly in the group that received placebo. Conversely, in pregnancies with onset more than 30 days following vaccination, 10 cases of congenital anomaly were observed in the group that received Gardasil compared with 16 cases of congenital anomaly in the group that received placebo. The types of anomalies observed were consistent with those generally observed in pregnancies in women aged 16 to 26 years.

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

The data on Gardasil administered during pregnancy did not indicate any safety signal. However, these data are insufficient to recommend use of Gardasil during pregnancy. Vaccination should, therefore, be postponed until after completion of pregnancy.

A total of 995 breastfeeding mothers were 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.

Gardasil can be given to breastfeeding women.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

In 5 clinical trials (4 placebo-controlled), subjects were administered Gardasil or placebo on the day of enrolment and approximately 2 and 6 months thereafter. Few subjects (0.2%) discontinued due to adverse reactions. Safety was evaluated in either the entire study population (4 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 subjects who were monitored using VRC-aided surveillance included 6,160 subjects (5,088 females 9 to 26 years of age and 1,072 males 9 to 15 years of age at enrolment) who received Gardasil and 4,064 subjects who received placebo.

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

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

General disorders and administration site conditions:

Very common: pyrexia.

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

Common: At the injection site: bleeding, pruritus.

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

Respiratory, thoracic and mediastinal disorders:

Very rare: bronchospasm.

Skin and subcutaneous tissue disorder:

Rare: urticaria.

Seven cases (0.06%) of urticaria were reported in the Gardasil group and 17 cases (0.18%) were seen in the adjuvant-containing placebo group.

In the clinical studies, subjects in the Safety Population reported any new medical conditions during the follow-up of up to 4 years. Among 11,813 subjects who received Gardasil and 9,701 subjects who received placebo, there were 8 cases of non-specific arthritis reported, 6 in the Gardasil group and 2 in the placebo group.

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 a non-infectious recombinant quadrivalent vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid L1 protein of HPV types 6, 11, 16 and 18. The 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 an humoral immune response.

Of the HPV types in the vaccine:

- HPV 16 and 18 are responsible for approximately 70% of high grade cervical dysplasia (CIN 2/3) and adenocarcinoma in situ (AIS) cases, and approximately 70% of high grade vulvar dysplasia (VIN 2/3) cases in young premenopausal females. HPV 16 and 18 are also responsible for a majority of high grade squamous vaginal lesions (VaIN 2/3). Other HPV types not contained in the vaccine are responsible for 20 - 30% of remaining cases of CIN 2/3, VIN 2/3 and VaIN 2/3. CIN 3 is an accepted immediate precursor of invasive cervical cancer. VIN 3 is an important risk factor for the development of vulvar cancer in young premenopausal females infected with carcinogenic HPV types.
- HPV 6 and 11 are responsible for approximately 90% of genital warts cases.
- HPV 6, 11, 16 and 18 are responsible for 35 to 50% of CIN 1 or low grade cervical dysplasia.

Clinical Studies

The efficacy of Gardasil was assessed in 4 placebo-controlled, double-blind, randomized Phase II and III clinical studies including a total of 20,541 16- to 26-year old 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 (Protocol 013, Future I), HPV 16- or 18-related CIN 2/3 and AIS (Protocol 015, FUTURE II), HPV 6-, 11-, 16-, or 18-related persistent infection (Protocol 007), and HPV 16-related persistent infection (Protocol 005).

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

Prophylactic Efficacy

The primary analyses of efficacy were conducted in the per-protocol efficacy (PPE) population (n= all 3 vaccinations within 1 year of enrolment, 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 subjects were naïve (PCR negative and seronegative) to all 4 HPV types at enrolment.

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

The efficacy results for relevant endpoints in the per-protocol population are presented in the Table 1.

Table 1: Analysis of efficacy of Gardasil against CIN 2/3 and genital warts in the PPE population

	Gardasil		Placebo		% Efficacy (95% CI)
	n	Number of cases	n	Number of cases	
HPV 16- or HPV 18-related CIN 2/3 or AIS					
Protocol 005*	755	0	750	12	100.0 (65.1, 100.0)
Protocol 007	231	0	230	1	100.0 (<0.0, 100.0)
Protocol 013	2200	0	2222	19	100.0 (78.5, 100.0)
Protocol 015	5301	0	5258	21	100.0 (80.9, 100.0)
<i>Combined protocols</i>	8487	0	8460	53	100.0 (92.9, 100.0)
HPV 6/11/16/18-related genital warts					

Protocol 007	235	0	233	3	100.0 (<0, 100.0)
Protocol 013	2261	0	2279	29	100.0 (86.4, 100.0)
Protocol 015	5401	1	5387	59	98.3 (90.2, 100.0)
<i>Combined protocols</i>	7897	1	7899	91	98.9 (93.7, 100.0)

* Evaluated only the HPV 16 L1 VLP component of Gardasil.

The efficacy of Gardasil against HPV 6-, 11-, 16-, 18-related CIN (1, 2, 3) or AIS was 100% (97.5% CI: 87.4, 100.0) in Protocol 013 where it was the primary end-point and 95.2% (95% CI: 87.2, 98.7) in the combined protocols.

The efficacy of Gardasil against HPV 6-, 11-, 16-, 18-related CIN 1 was 100% (95% CI: 84.1, 100.0) in Protocol 013 and in the combined analysis it was 93.1% (95% CI: 81.4, 98.2).

In the integrated analysis (Protocols 007, 013, 015) the efficacy of Gardasil against high-grade HPV 6-, 11-, 16-, or 18-related vulvar lesions (VIN 2/3) was 100% (95% CI: 41.4, 100.0). Vaccine efficacy against high-grade vaginal lesions (VaIN 2/3) did not reach statistical significance. Altogether there were 8 cases of VIN 2/3 and 5 cases of VaIN 2/3, all occurred in the placebo group.

On the basis of a 12 month definition of persistent infection (i.e. at least 2 positive specimens over a minimum interval of 12 months) the efficacy against persistent HPV 16 infection was 93.3% (95% CI: 79.1, 98.7) in Protocol 005. In Protocol 007, the efficacy of Gardasil against persistent HPV 16 or HPV 18 infection was 100% (95% CI: 43.3, 100.0). There were six cases of persistent HPV 16 infection, and two cases of persistent HPV 18 infection, all in the placebo group.

Efficacy in subjects with current or prior infection

There was no evidence of protection from disease caused by HPV types for which subjects were PCR positive and/or seropositive at baseline. However, individuals who were already infected with one or more vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the remaining vaccine HPV types.

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

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

Endpoints	Gardasil or HPV 16 L1 VLP vaccine		Placebo		% Reduction (95% CI)
	n	Cases	n	Cases	
HPV 16/18-related CIN 2/3 or AIS #	9831	122	9896	201	39.0 (23.3, 51.7)
HPV 16/18-related VIN 2/3 *	8954	7	8962	18	61.0 (2.1, 86.2)
HPV 6/11/16/18-related genital warts *	8954	58	8962	184	68.5 (57.5, 77.0)

Protocols 005, 007, 013 and 015 combined.

*Protocols 007, 013, and 015 combined.

The efficacy of Gardasil against HPV 6-, 11-, 16-, 18-related CIN (1, 2, 3) or AIS was 46.4% (95% CI: 35.2, 55.7) in this same population.

Overall 12% of the combined study population had an abnormal Pap test suggestive of CIN at Day 1. Among subjects 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 subjects 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.

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 8,915 (Gardasil n = 4,666; placebo n = 4,249) women 18 to 26 years of age and 3,400 female (Gardasil n = 1,471; placebo n = 583) and male (Gardasil n = 1,071; placebo n = 275) adolescents 9 to 17 years of age.

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 neutralizing epitopes for each HPV type.

Immune Responses to Gardasil

Overall, 99.9%, 99.8%, 99.8%, and 99.6% of individuals who received Gardasil became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV-18 seropositive, respectively, by 1 month Postdose 3 across all age groups tested. Gardasil induced high anti-HPV Geometric Mean Titres (GMTs) 1 month Postdose 3 in all age groups tested.

Anti-HPV levels in placebo subjects who had cleared an HPV infection (seropositive and PCR negative) were substantially lower than those induced by the vaccine. Furthermore, anti-HPV levels in vaccinated subjects remained higher during the long-term follow-up of the phase III studies.

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

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

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

Table 3: Immunogenicity bridging between 9- to 15-year-old male and female subjects and 16- to 26-year-old adult women (per-protocol population) based on antibody titres measured with cLIA

	9- to 15-Year-Old Males (Protocols 016 and 018)		9- to 15-Year-Old Females (Protocols 016 and 018)		16- to 26-Year-Old Females (Protocols 013 and 015)	
	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)
HPV 6	901	1038 (975, 1105)	927	931 (877, 989)	2827	542 (527, 559)
HPV 11	901	1392 (1304, 1485)	927	1306 (1226, 1390)	2827	766 (741, 793)
HPV 16	900	6091 (5640, 6579)	929	4945 (4584, 5335)	2707	2314 (2206, 2427)
HPV 18	905	1359 (1256, 1470)	932	1046 (971, 1127)	3040	461 (444, 478)

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

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

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

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

Persistence

In Protocol 007 peak anti-HPV 6, 11, 16, 18 GMTs were observed at month 7. The GMTs declined through Month 24 and then stabilized until at least Month 60. The observation period is currently limited to 2 years in the Phase III trials of young women and 18 months in trials of adolescents. The exact duration of immunity following a 3-dose series has not been established.

Evidence of Anamnestic (Immune Memory) Response

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

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic studies is not required for vaccines.

5.3 Preclinical safety data

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
L-histidine
Polysorbate 80
Sodium borate
Water for Injections.

For adjuvant, see section 2.

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

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

6.5 Nature and contents of container

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

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 product if particulates are present or if it appears discoloured.

Single-dose Vial Use

Withdraw the 0.5 ml dose of vaccine from the single-dose vial using a sterile needle and syringe free of preservatives, antiseptics, and detergents. Once the single-dose vial has been penetrated, the withdrawn vaccine should be used promptly, and the vial must be discarded.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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 the prevention of high-grade cervical dysplasia (CIN 2/3), cervical carcinoma, high-grade vulvar dysplastic lesions (VIN 2/3), and external genital warts (condyloma acuminata) causally related to Human Papillomavirus (HPV) types 6, 11, 16 and 18.

The indication is based on the demonstration of efficacy of Gardasil in adult females 16 to 26 years of age and on the demonstration of immunogenicity of Gardasil in 9- to 15-year old children and adolescents. Protective efficacy has not been evaluated in males (see section 5.1).

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

4.2 Posology and method of administration

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

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

The need for a booster dose has not been established.

Paediatric population: Gardasil is not recommended for use in children below 9 years of age due to insufficient data on immunogenicity, safety and efficacy (see section 5.1).

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

Gardasil must not be injected intravascularly. Subcutaneous and intradermal administration have not been studied, and therefore 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 subjects 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

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.

As with any vaccine, vaccination with Gardasil may not result in protection in all vaccine recipients. Also, Gardasil will only protect against diseases that are caused by HPV types 6, 11, 16 and 18. Therefore, appropriate precautions against sexually transmitted diseases should continue to be used.

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.

Vaccination is not a substitute for routine cervical screening. Since no vaccine is 100% effective and Gardasil will not provide protection against non-vaccine HPV types, or against existing HPV infections, routine cervical screening remains critically important and should follow local recommendations.

There are no data on the use of Gardasil in subjects with impaired immune responsiveness. Individuals with impaired immune responsiveness, whether due to the use of potent immunosuppressive therapy, a genetic defect, Human Immunodeficiency Virus (HIV) infection, or other causes, may not respond to the vaccine.

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

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

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 subjects 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.

The concomitant administration of Gardasil with vaccines other than hepatitis B (recombinant) vaccine has not been studied.

Use with hormonal contraceptives

In clinical studies, 57.5% of women (age 16 to 26 years) who received Gardasil used hormonal contraceptives. Use of hormonal contraceptives did not appear to affect the immune response to Gardasil.

4.6 Pregnancy and lactation

Specific studies of the vaccine in pregnant women were not conducted. However, during the prelicensure clinical development program, 2,266 women (vaccine = 1,115 vs. placebo = 1,151) reported at least one pregnancy. Overall, the proportions of pregnancies with an adverse outcome were comparable in subjects who received Gardasil and subjects who received placebo. For pregnancies with estimated onset within 30 days of vaccination, 5 cases of congenital anomaly were observed in the group that received Gardasil compared to 0 cases of congenital anomaly in the group that received placebo. Conversely, in pregnancies with onset more than 30 days following vaccination, 10 cases of congenital anomaly were observed in the group that received Gardasil compared with 16 cases of congenital anomaly in the group that received placebo. The types of anomalies observed were consistent with those generally observed in pregnancies in women aged 16 to 26 years.

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

The data on Gardasil administered during pregnancy did not indicate any safety signal. However, these data are insufficient to recommend use of Gardasil during pregnancy. Vaccination should, therefore, be postponed until after completion of pregnancy.

A total of 995 breastfeeding mothers were 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.

Gardasil can be given to breastfeeding women.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

In 5 clinical trials (4 placebo-controlled), subjects were administered Gardasil or placebo on the day of enrolment and approximately 2 and 6 months thereafter. Few subjects (0.2%) discontinued due to adverse reactions. Safety was evaluated in either the entire study population (4 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 subjects who were monitored using VRC-aided surveillance included 6,160 subjects (5,088 females 9 to 26 years of age and 1,072 males 9 to 15 years of age at enrolment) who received Gardasil and 4,064 subjects who received placebo.

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

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

General disorders and administration site conditions:

Very common: pyrexia.

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

Common: At the injection site: bleeding, pruritus.

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

Respiratory, thoracic and mediastinal disorders:

Very rare: bronchospasm.

Skin and subcutaneous tissue disorder:

Rare: urticaria.

Seven cases (0.06%) of urticaria were reported in the Gardasil group and 17 cases (0.18%) were seen in the adjuvant-containing placebo group.

In the clinical studies, subjects in the Safety Population reported any new medical conditions during the follow-up of up to 4 years. Among 11,813 subjects who received Gardasil and 9,701 subjects who received placebo, there were 8 cases of non-specific arthritis reported, 6 in the Gardasil group and 2 in the placebo group.

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 a non-infectious recombinant quadrivalent vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid L1 protein of HPV types 6, 11, 16 and 18. The 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 an humoral immune response.

Of the HPV types in the vaccine:

- HPV 16 and 18 are responsible for approximately 70% of high grade cervical dysplasia (CIN 2/3) and adenocarcinoma in situ (AIS) cases, and approximately 70% of high grade vulvar dysplasia (VIN 2/3) cases in young premenopausal females. HPV 16 and 18 are also responsible for a majority of high grade squamous vaginal lesions (VaIN 2/3). Other HPV types not contained in the vaccine are responsible for 20 - 30% of remaining cases of CIN 2/3, VIN 2/3 and VaIN 2/3. CIN 3 is an accepted immediate precursor of invasive cervical cancer. VIN 3 is an important risk factor for the development of vulvar cancer in young premenopausal females infected with carcinogenic HPV types.
- HPV 6 and 11 are responsible for approximately 90% of genital warts cases.
- HPV 6, 11, 16 and 18 are responsible for 35 to 50% of CIN 1 or low grade cervical dysplasia.

Clinical Studies

The efficacy of Gardasil was assessed in 4 placebo-controlled, double-blind, randomized Phase II and III clinical studies including a total of 20,541 16- to 26-year old 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 (Protocol 013, Future I), HPV 16- or 18-related CIN 2/3 and AIS (Protocol 015, FUTURE II), HPV 6-, 11-, 16-, or 18-related persistent infection (Protocol 007), and HPV 16-related persistent infection (Protocol 005).

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

Prophylactic Efficacy

The primary analyses of efficacy were conducted in the per-protocol efficacy (PPE) population (n= all 3 vaccinations within 1 year of enrolment, 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 subjects were naïve (PCR negative and seronegative) to all 4 HPV types at enrolment.

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

The efficacy results for relevant endpoints in the per-protocol population are presented in the Table 1.

Table 1: Analysis of efficacy of Gardasil against CIN 2/3 and genital warts in the PPE population

	Gardasil		Placebo		% Efficacy (95% CI)
	n	Number of cases	n	Number of cases	
HPV 16- or HPV 18-related CIN 2/3 or AIS					
Protocol 005*	755	0	750	12	100.0 (65.1, 100.0)
Protocol 007	231	0	230	1	100.0 (<0.0, 100.0)
Protocol 013	2200	0	2222	19	100.0 (78.5, 100.0)
Protocol 015	5301	0	5258	21	100.0 (80.9, 100.0)
<i>Combined protocols</i>	8487	0	8460	53	100.0 (92.9, 100.0)

HPV 6/11/16/18-related genital warts					
Protocol 007	235	0	233	3	100.0 (<0, 100.0)
Protocol 013	2261	0	2279	29	100.0 (86.4, 100.0)
Protocol 015	5401	1	5387	59	98.3 (90.2, 100.0)
<i>Combined protocols</i>	7897	1	7899	91	98.9 (93.7, 100.0)

* Evaluated only the HPV 16 L1 VLP component of Gardasil.

The efficacy of Gardasil against HPV 6-, 11-, 16-, 18-related CIN (1, 2, 3) or AIS was 100% (97.5% CI: 87.4, 100.0) in Protocol 013 where it was the primary end-point and 95.2% (95% CI: 87.2, 98.7) in the combined protocols.

The efficacy of Gardasil against HPV 6-, 11-, 16-, 18-related CIN 1 was 100% (95% CI: 84.1, 100.0) in Protocol 013 and in the combined analysis it was 93.1% (95% CI: 81.4, 98.2).

In the integrated analysis (Protocols 007, 013, 015) the efficacy of Gardasil against high-grade HPV 6-, 11-, 16-, or 18-related vulvar lesions (VIN 2/3) was 100% (95% CI: 41.4, 100.0). Vaccine efficacy against high-grade vaginal lesions (VaIN 2/3) did not reach statistical significance. Altogether there were 8 cases of VIN 2/3 and 5 cases of VaIN 2/3, all occurred in the placebo group.

On the basis of a 12 month definition of persistent infection (i.e. at least 2 positive specimens over a minimum interval of 12 months) the efficacy against persistent HPV 16 infection was 93.3% (95% CI: 79.1, 98.7) in Protocol 005. In Protocol 007, the efficacy of Gardasil against persistent HPV 16 or HPV 18 infection was 100% (95% CI: 43.3, 100.0). There were six cases of persistent HPV 16 infection, and two cases of persistent HPV 18 infection, all in the placebo group.

Efficacy in subjects with current or prior infection

There was no evidence of protection from disease caused by HPV types for which subjects were PCR positive and/or seropositive at baseline. However, individuals who were already infected with one or more vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the remaining vaccine HPV types.

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

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

Endpoints	Gardasil or HPV 16 L1 VLP vaccine		Placebo		% Reduction (95% CI)
	n	Cases	n	Cases	
HPV 16/18-related CIN 2/3 or AIS #	9831	122	9896	201	39.0 (23.3, 51.7)
HPV 16/18-related VIN 2/3 *	8954	7	8962	18	61.0 (2.1, 86.2)
HPV 6/11/16/18-related genital warts *	8954	58	8962	184	68.5 (57.5, 77.0)

Protocols 005, 007, 013 and 015 combined.

*Protocols 007, 013, and 015 combined.

The efficacy of Gardasil against HPV 6-, 11-, 16-, 18-related CIN (1, 2, 3) or AIS was 46.4 (95% CI: 35.2, 55.7) in this same population.

Overall 12% of the combined study population had an abnormal Pap test suggestive of CIN at Day 1. Among subjects 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 subjects 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.

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 8,915 (Gardasil n = 4,666; placebo n = 4,249) women 18 to 26 years of age and 3,400 female (Gardasil n = 1,471; placebo n = 583) and male (Gardasil n = 1,071; placebo n = 275) adolescents 9 to 17 years of age.

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 neutralizing epitopes for each HPV type.

Immune Responses to Gardasil

Overall, 99.9%, 99.8%, 99.8%, and 99.6% of individuals who received Gardasil became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV-18 seropositive, respectively, by 1 month Postdose 3 across all age groups tested. Gardasil induced high anti-HPV Geometric Mean Titres (GMTs) 1 month Postdose 3 in all age groups tested.

Anti-HPV levels in placebo subjects who had cleared an HPV infection (seropositive and PCR negative) were substantially lower than those induced by the vaccine. Furthermore, anti-HPV levels in vaccinated subjects remained higher during the long-term follow-up of the phase III studies.

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

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

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

Table 3: Immunogenicity bridging between 9- to 15-year-old male and female subjects and 16- to 26-year-old adult women (per-protocol population) based on antibody titres measured with cLIA

	9- to 15-Year-Old Males (Protocols 016 and 018)		9- to 15-Year-Old Females (Protocols 016 and 018)		16- to 26-Year-Old Females (Protocols 013 and 015)	
	n	GMT (95% CI)	n	GMT (95% CI)	n	GMT (95% CI)
HPV 6	901	1038 (975, 1105)	927	931 (877, 989)	2827	542 (527, 559)
HPV 11	901	1392 (1304, 1485)	927	1306 (1226, 1390)	2827	766 (741, 793)
HPV 16	900	6091 (5640, 6579)	929	4945 (4584, 5335)	2707	2314 (2206, 2427)
HPV 18	905	1359 (1256, 1470)	932	1046 (971, 1127)	3040	461 (444, 478)

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

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

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

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

Persistence

In Protocol 007 peak anti-HPV 6, 11, 16, 18 GMTs were observed at month 7. The GMTs declined through Month 24 and then stabilized until at least Month 60. The observation period is currently limited to 2 years in the Phase III trials of young women and 18 months in trials of adolescents. The exact duration of immunity following a 3-dose series has not been established.

Evidence of Anamnestic (Immune Memory) Response

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

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic studies is not required for vaccines.

5.3 Preclinical safety data

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
L-histidine
Polysorbate 80
Sodium borate
Water for Injections.

For adjuvant, see section 2.

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze. Keep the 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 (Type 1 glass) with plunger stopper (siliconized FluroTec-coated bromobutyl elastomer or non-coated chlorobutyl elastomer) and tip cap (bromobutyl) with needle guard (safety) device, without needle or with one or two needle(s) - pack size of 1,10 or 20.

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

Not all pack sizes are marketed.

6.6 Special precautions for disposal and other handling

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

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

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the product if particulates are present or if it appears discoloured.

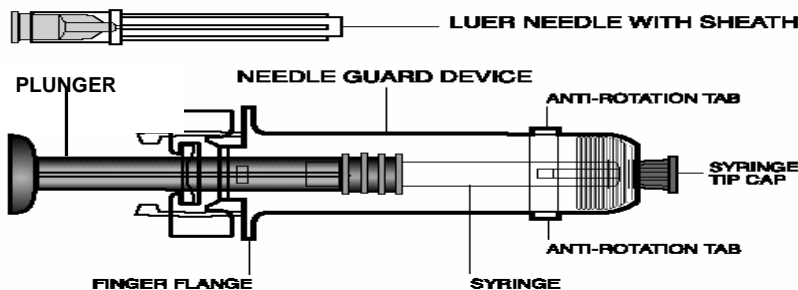
Pre-filled syringe use

NOTE: Please use one of the enclosed needles for administration. Two detachable labels containing details of the batch number, expiry date and product name are provided.

Disposal

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

Instructions for using the pre-filled single dose syringes pre-assembled with needle guard (safety) deviceThe needle guard (safety) device is designed to cover the needle after release of the plunger.



Attach the needle

Remove syringe tip cap. Attach Luer Needle. Depress both Anti-Rotation Tabs to secure syringe and attach Luer Needle by twisting in clockwise direction, until the needle fits securely on the syringe. Remove Needle Sheath.

If a different needle is chosen to those enclosed, it should fit securely on the syringe and be no longer than 25mm to ensure proper functioning of the needle guard (safety) device.

Administer the vaccine

Administer injection per standard protocol as stated above and in section 4.2 (Posology and method of administration). Depress the Plunger while grasping the Finger Flange until the entire dose has been given.

The needle guard (safety) device will NOT activate unless the ENTIRE dose has been given.

Remove needle from the vaccine recipient. Release the plunger to allow the syringe to move up until the entire needle is guarded. The labels can only be removed after the needle is guarded.

Instructions for using the pre-filled single dose syringes pre-assembled without needle guard (safety) device

Hold the syringe barrel and attach the needle by twisting in clockwise direction, until the needle fits securely on the syringe.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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 & Co., INC
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 is in place and functioning before the product is placed on the market and for as long as the marketed product remains in use.

Risk Management plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan.

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**

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.

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/0/00/000/000 – pack of 1
EU/0/00/000/000 – pack of 10

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

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.

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/0/00/000/000 – pack of 1

EU/0/00/000/000 – pack of 10

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

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.

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/0/00/000/000 – pack of 1

EU/0/00/000/000 – pack of 10

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

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.

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/0/00/000/000– pack of 1

EU/0/00/000/000 – pack of 10

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 a needle guard and no 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) 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 a needle guard and no needles.
10 single doses, 0.5 ml pre-filled syringes with needle guards and no needles.
20 single doses, 0.5 ml pre-filled syringes with needle guards and no 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/0/00/000/000– pack of 1
EU/0/00/000/000 – pack of 10
EU/0/00/000/000 – 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 a needle guard and 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) 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 a needle guard and 1 needle.
10 single doses, 0.5 ml pre-filled syringes with needle guards and 1 needle each.
20 single doses, 0.5 ml pre-filled syringes with needle guards and 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/0/00/000/000– pack of 1
EU/0/00/000/000 – pack of 10
EU/0/00/000/000 – 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 a needle guard and 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) 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 a needle guard and 2 needles.
10 single doses, 0.5 ml pre-filled syringes with needle guards and 2 needles each.
20 single doses, 0.5 ml pre-filled syringes with needle guards and 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/0/00/000/000– pack of 1

EU/0/00/000/000 – pack of 10

EU/0/00/000/000 – 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

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.
- This vaccine has been prescribed for you or your child. Do not pass it on to others.
- 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 use Gardasil
3. How to use Gardasil
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 (including cervix, and vulva), and genital warts. HPV types 16 and 18 are responsible for ~70% of cervical cancer cases and HPV types 6, 11, for approximately 90% of genital wart cases.

Gardasil cannot cause the diseases it protects against.

Gardasil produces type-specific antibodies and have in clinical trials been shown to prevent these HPV 6, 11-, 16-, and 18-related diseases in adult women 16-26 years of age. The vaccine also produces antibodies in 9- to 15- year old children and adolescents. Whether these type-specific antibodies prevent disease in adult males has not been evaluated.

Gardasil should be used in accordance with official guidelines.

The most benefit from Gardasil is expected before infection with any of the Human Papillomavirus types covered by the vaccine. However, in individuals who are already infected by one or more of the vaccine HPV types, the vaccine will protect against the remaining vaccine related HPV types.

2. BEFORE YOU USE GARDASIL

Do not use Gardasil if:

the person to be vaccinated

- is allergic (hypersensitive) to any of the active substances or any of the other ingredients of Gardasil (listed under “other ingredients”– see section 6).
- has developed an allergic reaction after receiving a dose of Gardasil.

- suffers 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 the person to be vaccinated:

- 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 or HIV infection

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

Gardasil will not protect against all types 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 I 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 Hepatitis B vaccine at a separate injection site (another part of your body, e.g. the other arm or leg) at 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 the person for whom the vaccine is intended is taking or has recently taken 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:

There is no information to suggest that Gardasil affects your ability to drive or use machinery.

3. HOW TO USE GARDASIL

Gardasil is given as an injection by your doctor. 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

The dosing schedule can be more flexible, 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.

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 are 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. Fever was also seen.

Commonly (more than 1 in 100 patients), side effects found at the injection site include: bleeding, itching.

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

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

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 or 10 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	Italia Sanofi Pasteur MSD Spa, Tel: +39.06.664.092.11
Česká republika, Eesti, France, Κύπρος, Latvija, Lietuva, Magyarország, Malta, Polska, Slovenija, Slovenská republika Sanofi Pasteur MSD SNC, Tél: +33.4.37.28.40.00	Luxembourg/Luxemburg Sanofi Pasteur MSD, Tél: +32.2.726.95.84
Danmark Sanofi Pasteur MSD Tlf: +45.45.26.77.00	Nederland Sanofi Pasteur MSD, Tel: +31.20.647.37.19
Deutschland Sanofi Pasteur MSD GmbH, Tel: +49.6224.5940	Norge Sanofi Pasteur MSD, Tlf: +47.23.12.05.00
España Sanofi Pasteur MSD S.A., Tel: +34.91.371.78.00	Österreich Sanofi Pasteur MSD GmbH, Tel: +43.1.86.67.02.22.02
Ελλάδα BIANEE A.E., Τηλ: +30.210.8009111	Portugal Sanofi Pasteur MSD, SA, Tel: +351 21 470 45 50
Ireland Sanofi Pasteur MSD Ltd, Tel: +3531.404.1688	Suomi/Finland Sanofi Pasteur MSD, Puh/Tel: +358.9.2510.700
Ísland Sanofi Pasteur MSD, Sími: +32.2.726.95.84	Sverige Sanofi Pasteur MSD, Tel: +46.8.564.888.60
	United Kingdom Sanofi Pasteur MSD Ltd, Tel: +44.1.628.785.291

This leaflet was last approved in:

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

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.
- This vaccine has been prescribed for you or your child. Do not pass it on to others.
- 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 use Gardasil
3. How to use Gardasil
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 (including cervix, and vulva), and genital warts. HPV types 16 and 18 are responsible for ~70% of cervical cancer cases and HPV types 6, 11, for approximately 90% of genital wart cases.

Gardasil cannot cause the diseases it protects against.

Gardasil produces type-specific antibodies and have in clinical trials been shown to prevent these HPV 6-, 11-, 16-, and 18-related diseases in adult women 16-26 years of age. The vaccine also produces antibodies in 9- to 15- year old children and adolescents. Whether these type-specific antibodies prevent disease in adult males has not been evaluated.

Gardasil should be used in accordance with official guidelines.

The most benefit from Gardasil is expected before infection with any of the Human Papillomavirus types covered by the vaccine. However, in individuals who are already infected by one or more of the vaccine HPV types, the vaccine will protect against the remaining vaccine related HPV types.

2. BEFORE YOU USE GARDASIL

Do not use Gardasil if:

the person to be vaccinated

- is allergic (hypersensitive) to any of the active substances or any of the other ingredients of Gardasil (listed under “other ingredients”– see section 6).
- has developed an allergic reaction after receiving a dose of Gardasil.

- suffers 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 the person to be vaccinated:

- 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 or HIV infection

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

Gardasil will not protect against all types 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 I 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 Hepatitis B vaccine at a separate injection site (another part of your body, e.g. the other arm or leg) at 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 the person for whom the vaccine is intended is taking or has recently taken 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:

There is no information to suggest that Gardasil affects your ability to drive or use machinery.

3. HOW TO USE GARDASIL

Gardasil is given as an injection by your doctor. 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

The dosing schedule can be more flexible, 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.

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 are 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. Fever was also seen.

Commonly (more than 1 in 100 patients), side effects found at the injection site include: bleeding, itching.

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

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

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 with or without a needle guard (safety) device.

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	Italia Sanofi Pasteur MSD Spa, Tel: +39.06.664.092.11
Česká republika, Eesti, France, Κύπρος, Latvija, Lietuva, Magyarország, Malta, Polska, Slovenija, Slovenská republika Sanofi Pasteur MSD SNC, Tél: +33.4.37.28.40.00	Luxembourg/Luxemburg Sanofi Pasteur MSD, Tél: +32.2.726.95.84
Danmark Sanofi Pasteur MSD Tlf: +45.45.26.77.00	Nederland Sanofi Pasteur MSD, Tel: +31.20.647.37.19
Deutschland Sanofi Pasteur MSD GmbH, Tel: +49.6224.5940	Norge Sanofi Pasteur MSD, Tlf: +47.23.12.05.00
España Sanofi Pasteur MSD S.A., Tel: +34.91.371.78.00	Österreich Sanofi Pasteur MSD GmbH, Tel: +43.1.86.67.02.22.02
Ελλάδα BIANEE A.E., Τηλ: +30.210.8009111	Portugal Sanofi Pasteur MSD, SA, Tel: +351 21 470 45 50
Ireland Sanofi Pasteur MSD Ltd, Tel: +3531.404.1688	Suomi/Finland Sanofi Pasteur MSD, Puh/Tel: +358.9.2510.700
Ísland Sanofi Pasteur MSD, Sími: +32.2.726.95.84	Sverige Sanofi Pasteur MSD, Tel: +46.8.564.888.60
	United Kingdom Sanofi Pasteur MSD Ltd, Tel: +44.1.628.785.291

This leaflet was last approved in:

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

Pre-filled syringe use

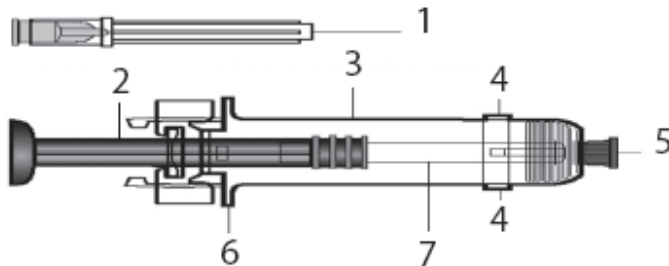
NOTE: Please use one of the enclosed needles for administration. Two detachable labels containing details of the batch number, expiry date and product name are provided.

Disposal

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

Instructions for using the pre-filled single dose syringes pre-assembled with needle guard (safety) device

The needle guard (safety) device is designed to cover the needle after release of the plunger.



1. Luer needle with sheath; 2. Plunger; 3. Needle guard device; 4. Anti-rotation tab; 5. Syringe tip cap; 6. Finger flange; 7. Syringe.

Attach the needle

Remove syringe tip cap. Attach Luer needle. Depress both Anti-Rotation Tabs to secure syringe and attach Luer needle by twisting in clockwise direction, until the needle fits securely on the syringe. Remove needle sheath.

If a different needle is chosen to those enclosed, it should fit securely on the syringe and be no longer than 25mm to ensure proper functioning of the needle guard (safety) device.

Administer the vaccine

Administer injection per standard protocol as stated above and in section 3 (How to use Gardasil). Depress the plunger while grasping the finger flange until the entire dose has been given. The needle guard (safety) device will NOT activate unless the ENTIRE dose has been given. Remove needle from the vaccine recipient. Release the plunger to allow the syringe to move up until the entire needle is guarded. The labels can only be removed after the needle is guarded.

Instructions for using the pre-filled single dose syringes pre-assembled without needle guard (safety device)

Hold the syringe barrel and attach the needle by twisting in clockwise direction, until the needle fits securely on the syringe.