ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gardasil 9 suspension for injection
Gardasil 9 suspension for injection in multidose container
Gardasil 9 suspension for injection in pre-filled syringe

Human Papillomavirus 9-valent Vaccine (recombinant, adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 mL) contains approximately:

Human Papillomavirus[1] Type 6 L1 protein[2,3]	30 micrograms
Human Papillomavirus[1] Type 11 L1 protein[2,3]	40 micrograms
Human Papillomavirus[1] Type 16 L1 protein[2,3]	60 micrograms
Human Papillomavirus[1] Type 18 L1 protein[2,3]	40 micrograms
Human Papillomavirus[1] Type 31 L1 protein[2,3]	20 micrograms
Human Papillomavirus[1] Type 33 L1 protein[2,3]	20 micrograms
Human Papillomavirus[1] Type 45 L1 protein[2,3]	20 micrograms
Human Papillomavirus[1] Type 52 L1 protein[2,3]	20 micrograms
Human Papillomavirus[1] Type 58 L1 protein[2,3]	20 micrograms

[1]Human Papillomavirus=HPV.
[2]L1 protein in the form of virus-like particles produced in yeast cells (*Saccharomyces cerevisiae* CANADE 3C-5 (Strain 1895)) by recombinant DNA technology.
[3]adsorbed on amorphous aluminium hydroxyphosphate sulfate adjuvant (0.5 milligrams Al).

Excipient with known effect

This medicinal product contains 0.05 mg of polysorbate 80 in each 0.5 mL dose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection (Injection).

Clear liquid with white precipitate.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gardasil 9 is indicated for active immunisation of individuals from the age of 9 years against the following HPV diseases:

- Premalignant lesions and cancers affecting the cervix, vulva, vagina and anus caused by vaccine HPV types.
- Genital warts (*Condyloma acuminata*) caused by specific HPV types.

See sections 4.4 and 5.1 for important information on the data that support these indications.

The use of Gardasil 9 should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Individuals 9 to and including 14 years of age at time of first injection
Gardasil 9 can be administered according to a 2-dose (0, 6 – 12 months) schedule (see section 5.1). The second dose should be administered between 5 and 13 months after the first dose. If the second vaccine dose is administered earlier than 5 months after the first dose, a third dose should always be administered.

Gardasil 9 can be administered according to a 3-dose (0, 2, 6 months) schedule. 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.

Individuals 15 years of age and older at time of first injection
Gardasil 9 should be administered according to a 3-dose (0, 2, 6 months) schedule.

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 use of Gardasil 9 should be in accordance with official recommendations.

It is recommended that individuals who receive a first dose of Gardasil 9 complete the vaccination course with Gardasil 9 (see section 4.4).

The need for a booster dose has not been established.

Studies using a mixed regimen (interchangeability) of HPV vaccines were not performed for Gardasil 9.

Subjects previously vaccinated with a 3-dose regimen of quadrivalent HPV types 6, 11, 16, and 18 vaccine (Gardasil), hereafter referred to as qHPV vaccine, may receive 3 doses of Gardasil 9 (see section 5.1). qHPV vaccine was also known as Silgard in some countries.

Paediatric population (children < 9 years of age)
The safety and efficacy of Gardasil 9 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 9 must not be injected intravascularly, subcutaneously or intradermally. The vaccine should not be mixed in the same syringe with any other vaccines and solution.

For instructions on the handling of the vaccine before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Individuals with hypersensitivity after previous administration of Gardasil 9 or Gardasil/Silgard should not receive Gardasil 9.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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 and supervision 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 vaccination. It is important that procedures are in place to avoid injury from fainting.

Vaccination 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.

As with any vaccine, vaccination with Gardasil 9 may not result in protection in all vaccine recipients.

The vaccine will only protect against diseases that are caused by HPV types targeted by the vaccine (see section 5.1). Therefore, appropriate precautions against sexually transmitted diseases should continue to be used.

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

Gardasil 9 does not prevent lesions due to a vaccine HPV type in individuals infected with that HPV type at the time of vaccination.

Vaccination is not a substitute for routine cervical screening. Since no vaccine is 100 % effective and Gardasil 9 will not provide protection against every HPV type, or against HPV infections present at the time of vaccination, routine cervical screening remains critically important and should follow local recommendations.

There are no data on the use of Gardasil 9 in individuals with impaired immune responsiveness. Safety and immunogenicity of a qHPV vaccine have been assessed in individuals aged 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, 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.

Long-term follow-up studies are currently ongoing to determine the duration of protection (see section 5.1).

There are no safety, immunogenicity or efficacy data to support interchangeability of Gardasil 9 with bivalent or quadrivalent HPV vaccines.

Excipients with known effect

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Polysorbate 80
This medicinal product contains 0.05 mg of polysorbate 80 in each 0.5 mL dose of suspension for injection. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Safety and immunogenicity in individuals who have received immunoglobulin or blood-derived products during the 3 months prior to vaccination have not been studied in clinical studies.

Use with other vaccines

Gardasil 9 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. This is based on the results from a clinical study in which a combined dTap-IPV vaccine was administered concomitantly with the first dose of Gardasil 9 (see section 4.8).

Use with hormonal contraceptives

In clinical studies, 60.2 % of women aged 16 to 26 years who received Gardasil 9 used hormonal contraceptives during the vaccination period of the clinical studies. Use of hormonal contraceptives did not appear to affect the type-specific immune responses to Gardasil 9.

4.6 Fertility, pregnancy and lactation

Pregnancy

Post-marketing data on pregnant women indicates no malformative nor foeto/neonatal toxicity of Gardasil 9 when administered during pregnancy.

Animal studies do not indicate reproductive toxicity (see section 5.3).

A six-year pregnancy registry for Gardasil 9 prospectively followed 180 women of which there were 69 pregnancies with known outcomes. Frequencies of miscarriage and major birth defects were 4.3 % of pregnancies (3/69) and 4.5 % of live born infants (3/67), respectively. These frequencies were consistent with estimated background frequencies. These data support similar findings from a five-year pregnancy registry for qHPV vaccine in which 1 640 pregnancies with known outcomes were included.

However, these data are considered insufficient to recommend use of Gardasil 9 during pregnancy. Vaccination should be postponed until completion of pregnancy (see section 5.1).

Breast-feeding

Gardasil 9 can be used during breast-feeding.

A total of 92 women were breast-feeding during the vaccination period of the clinical studies of Gardasil 9 in women aged 16 to 26 years. In the studies, vaccine immunogenicity was comparable between breast-feeding women and women who did not breast-feed. In addition, the safety profile for breast-feeding women was comparable to that of the women in the overall safety population. There were no vaccine-related serious adverse events reported in infants who were breast-feeding during the vaccination period.

Fertility

No human data on the effect of Gardasil 9 on fertility are available. Animal studies do not indicate harmful effects on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Gardasil 9 has no or negligible influence on the ability to drive or use machines. However, some of the effects mentioned under section 4.8 "Undesirable effects" may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

In 7 clinical studies, individuals were administered Gardasil 9 on the day of enrolment and approximately 2 and 6 months thereafter. Safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of Gardasil 9. A total of 15 776 individuals (10 495 subjects aged 16 to 26 years and 5 281 adolescents aged 9 to 15 years at enrolment) received Gardasil 9. Few individuals (0.1 %) discontinued due to adverse experiences.

In one of these clinical studies which enrolled 1 053 healthy adolescents aged 11 to 15 years, administration of the first dose of Gardasil 9 concomitantly with a combined diphtheria, tetanus, pertussis [acellular, component] and poliomyelitis [inactivated] booster vaccine showed that more injection-site reactions (swelling, erythema), headache and pyrexia were reported. The differences observed were < 10 % and in the majority of subjects, the adverse events were reported as mild to moderate in intensity (see section 4.5).

In a clinical study that included 640 individuals aged 27 to 45 years and 570 individuals aged 16 to 26 years who received Gardasil 9, the safety profile of Gardasil 9 was comparable between the two age groups.

The most common adverse reactions observed with Gardasil 9 were injection-site adverse reactions (84.8 % of vaccinees within 5 days following any vaccination visit) and headache (13.2 % of the vaccinees within 15 days following any vaccination visit). These adverse reactions usually were mild or moderate in intensity.

Tabulated list of adverse reactions

The adverse reactions are categorised by frequency using the following convention:

- Very common (≥ 1/10)
- Common (≥ 1/100 to < 1/10)
- Uncommon (≥ 1/1 000 to < 1/100)
- Rare (≥ 1/10 000 to < 1/1 000)
- Not known (cannot be estimated from the available data)

Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Clinical studies

Table 1 presents adverse reactions considered as being at least possibly related to vaccination and observed in recipients of Gardasil 9 at a frequency of at least 1.0 % from 7 clinical studies (PN 001, 002, 003, 005, 006, 007 and 009, N=15 776 individuals) (see section 5.1 for description of the clinical studies).

Post-marketing experience

Table 1 also includes adverse events which have been spontaneously reported during the post-marketing use of Gardasil 9 worldwide. Their frequencies were estimated based on relevant clinical studies.

Table 1: Adverse reactions following administration of Gardasil 9 from clinical studies and adverse events from post-marketing data

System organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Uncommon	Lymphadenopathy*
Immune system disorders	Rare	Hypersensitivity*
	Not known	Anaphylactic reactions*
Nervous system disorders	Very common	Headache
	Common	Dizziness
	Uncommon	Syncope sometimes accompanied by tonic-clonic movements*
Gastrointestinal disorders	Common	Nausea
	Uncommon	Vomiting*
Skin and subcutaneous tissue disorders	Uncommon	Urticaria*
Musculoskeletal and connective tissue disorders	Uncommon	Arthralgia*, myalgia*
General disorders and administration site conditions	Very common	At the injection site: pain, swelling, erythema
	Common	Pyrexia, fatigue, at the injection site: pruritus, bruising
	Uncommon	Asthenia*, chills*, malaise*, injection site nodule*

*Adverse events reported during post-marketing use of Gardasil 9. The frequency was estimated based on relevant clinical studies. For events not observed in clinical studies the frequency is indicated as 'Not known'.

qHPV vaccine

Table 2 includes adverse experiences that have been spontaneously reported during post-approval use of qHPV vaccine. The post-marketing safety experience with qHPV vaccine is relevant to Gardasil 9 since the vaccines contain L1 HPV proteins of 4 of the same HPV types.

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

Table 2: Adverse reactions reported from post-marketing experience with qHPV vaccine

System organ class	Frequency	Adverse reactions
Infections and infestations	Not known	Injection-site cellulitis
Blood and lymphatic system disorders	Not known	Idiopathic thrombocytopaenic purpura
Immune system disorders	Not known	Anaphylactoid reactions, bronchospasm
Nervous system disorders	Not known	Acute disseminated encephalomyelitis, Guillain-Barré syndrome

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No cases of overdose have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, Papillomavirus vaccines, ATC code: J07BM03

Mechanism of action

Gardasil 9 is an adjuvanted non-infectious recombinant 9-valent vaccine. It is prepared from the highly purified virus-like particles (VLPs) of the major capsid L1 protein from the same four HPV types (6, 11, 16, 18) in qHPV vaccine and from 5 additional HPV types (31, 33, 45, 52, 58). It uses the same amorphous aluminium hydroxyphosphate sulfate adjuvant as qHPV vaccine. The VLPs cannot infect cells, reproduce or cause disease. The efficacy of L1 VLP vaccines is thought to be mediated by the development of a humoral immune response. The genotypes for the vaccine comprised of HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58 will be referred to as vaccine HPV types.

Based on epidemiology studies, Gardasil 9 is anticipated to protect against the HPV types that cause approximately: 90 % of cervical cancers, more than 95 % of adenocarcinoma *in situ* (AIS), 75-85 % of high-grade cervical intraepithelial neoplasia (CIN 2/3), 85-90 % of HPV related vulvar cancers, 90-95 % of HPV related high-grade vulvar intraepithelial neoplasia (VIN 2/3), 80-85 % of HPV related vaginal cancers, 75-85 % of HPV related high-grade vaginal intraepithelial neoplasia (VaIN 2/3), 90-95 % of HPV related anal cancer, 85-90 % of HPV related high-grade anal intraepithelial neoplasia (AIN 2/3), and 90 % of genital warts.

The indication of Gardasil 9 is based on:

- demonstration of efficacy of qHPV vaccine to prevent persistent infection and disease related to HPV types 6, 11, 16 and 18 in females aged 16 to 45 years and males aged 16 to 26 years.
- demonstration of non-inferior immunogenicity between Gardasil 9 and the qHPV vaccine for HPV types 6, 11, 16 and 18 in girls aged 9 to 15 years, women and men aged 16 to 26 years;

efficacy for Gardasil 9 against persistent infection and disease related to HPV types 6, 11, 16, or 18 can be inferred to be comparable to that of the qHPV vaccine.

- demonstration of efficacy against persistent infection and disease related to HPV types 31, 33, 45, 52 and 58 in girls and women aged 16 to 26 years, and
- demonstration of non-inferior immunogenicity against the Gardasil 9 HPV types in boys and girls aged 9 to 15 years, men aged 16 to 26 years and women aged 27 to 45 years, compared to girls and women aged 16 to 26 years.

Clinical studies for Gardasil 9

Efficacy and/or immunogenicity of Gardasil 9 were assessed in ten clinical studies. Clinical studies evaluating the efficacy of Gardasil 9 against placebo were not acceptable because HPV vaccination is recommended and implemented in many countries for protection against HPV infection and disease.

Therefore, the pivotal clinical study (Protocol 001) evaluated the efficacy of Gardasil 9 using qHPV vaccine as a comparator.

Efficacy against HPV types 6, 11, 16, and 18 was primarily assessed using a bridging strategy that demonstrated comparable immunogenicity (as measured by Geometric Mean Titres [GMT]) of Gardasil 9 compared with qHPV vaccine (Protocol 001, GDS01C/Protocol 009 and GDS07C/Protocol 020).

In the pivotal study Protocol 001, the efficacy of Gardasil 9 against HPV types 31, 33, 45, 52, and 58 was evaluated compared to qHPV vaccine in women aged 16 to 26 years (N=14 204: 7 099 receiving Gardasil 9; 7 105 receiving qHPV vaccine).

Protocol 002 evaluated immunogenicity of Gardasil 9 in girls and boys aged 9 to 15 years and women aged 16 to 26 years (N=3 066: 1 932 girls; 666 boys; and 468 women receiving Gardasil 9).

Protocol 003 evaluated immunogenicity of Gardasil 9 in men aged 16 to 26 years and women aged 16 to 26 years (N=2 515:1 103 Heterosexual Men [HM]; 313 Men Who Have Sex with Men [MSM]; and 1 099 women receiving Gardasil 9).

Protocol 004 evaluated immunogenicity of Gardasil 9 in women aged 16 to 45 years (N=1 210: 640 women aged 27 to 45 years and 570 women aged 16 to 26 years).

Protocols 005 and 007 evaluated Gardasil 9 concomitantly administered with vaccines recommended routinely in girls and boys aged 11 to 15 years (N=2 295).

Protocol 006 evaluated administration of Gardasil 9 to girls and women aged 12 to 26 years previously vaccinated with qHPV vaccine (N=921; 615 receiving Gardasil 9 and 306 receiving placebo).

GDS01C/Protocol 009 evaluated immunogenicity of Gardasil 9 in girls aged 9 to 15 years (N=600; 300 receiving Gardasil 9 and 300 receiving qHPV vaccine).

GDS07C/Protocol 020 evaluated immunogenicity of Gardasil 9 in men aged 16 to 26 years (N=500; 249 receiving Gardasil 9 and 251 receiving qHPV vaccine).

Protocol 010 evaluated the immunogenicity of 2 doses of Gardasil 9 in girls and boys aged 9 to 14 years and 3 doses of Gardasil 9 in girls aged 9 to 14 years and women aged 16 to 26 years (N=1 518; 753 girls; 451 boys and 314 women).

Studies supporting the efficacy of Gardasil 9 against HPV types 6, 11, 16, 18

Efficacy of qHPV vaccine against HPV types 6, 11, 16, 18
The efficacy and long-term effectiveness of qHPV vaccine against HPV 6-, 11-, 16-, and 18-related disease endpoints have been demonstrated in clinical studies in the PPE (Per Protocol Efficacy)

population. The PPE population consisted of individuals who received all 3 vaccinations with qHPV vaccine in the base study within 1 year of enrolment without major deviations from the study protocol, were seronegative to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1, and among subjects 16 years and older at enrolment in the base study, PCR negative to the relevant HPV type(s) prior to dose 1 through one month postdose 3 (month 7).

In 16 to 26 year-old women (N=20 541) efficacy against HPV 16- and 18-related CIN2/3, AIS or cervical cancer was 98.2 % (95 % CI: 93.5, 99.8) based on follow-up to 4 years (median 3.6 years); efficacy against HPV 6, 11, 16 or 18-related diseases was 96.0 % (95 % CI: 92.3, 98.2) for CIN or AIS, 100 % (95 % CI: 67.2, 100) for VIN2/3, 100 % (95 % CI: 55.4, 100) for VaIN2/3, and 99.0 % (95 % CI: 96.2, 99.9) for genital warts.

In 24 to 45 year-old women (N=3 817) efficacy against HPV 6, 11, 16 and 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).

In 16 to 26 year-old men (N=4 055) efficacy against HPV 6, 11, 16 or 18-related diseases was 74.9 % (95 % CI: 8.8, 95.4) for AIN 2/3 (median duration of follow-up of 2.15 years), 100.0 % (95 % CI: -52.1, 100) for penile/perineal/perianal intraepithelial neoplasia (PIN) 1/2/3, and 89.3 % (95 % CI: 65.3, 97.9) for genital warts (median duration of follow-up of 4 years).

In the long-term extension registry study for 16 to 23 year old women (n=2 121), no cases of high-grade CIN were observed up to approximately 14 years. In this study, a durable protection was statistically demonstrated to approximately 12 years.

In long-term extensions of clinical studies, no cases of high-grade intraepithelial neoplasia and no cases of genital warts were observed:

- through 10.7 years in girls (n=369) and 10.6 years in boys (n=326), 9-15 years of age at time of vaccination (median follow-up of 10.0 years and 9.9 years, respectively);
- through 11.5 years in men (n=917), 16-26 years of age at time of vaccination (median follow-up of 9.5 years); and through 10.1 years in women (n=685), 24-45 years of age at time of vaccination (median follow-up of 8.7 years).

Immunogenicity bridging from qHPV vaccine to Gardasil 9 for HPV types 6, 11, 16, 18
Comparison of Gardasil 9 with qHPV vaccine with respect to HPV types 6, 11, 16, and 18 were conducted in a population of women aged 16 to 26 years from Protocol 001, girls aged 9 to 15 years from GDS01C/Protocol 009 and men aged 16 to 26 years from GDS07C/Protocol 020.

A statistical analysis of non-inferiority was performed at month 7 comparing cLIA anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs between individuals administered Gardasil 9 and individuals administered Gardasil. Immune responses, measured by GMT, for Gardasil 9 were non-inferior to immune responses for Gardasil (Table 3). In clinical studies 98.2 % to 100 % who received Gardasil 9 became seropositive for antibodies against all 9 vaccine types by month 7 across all groups tested. In Protocol 001, GMTs for HPV-6, -11, -16 and -18 were comparable in subjects who received qHPV vaccine or Gardasil 9 for at least 3.5 years.

Table 3: Comparison of immune responses (based on cLIA) between Gardasil 9 and qHPV vaccine for HPV types 6, 11, 16, and 18 in the PPI (Per Protocol Immunogenicity)* population of 9 to 15 year-old girls and 16 to 26 year old women and men

Population	Gardasil 9		qHPV vaccine		Gardasil 9/ qHPV vaccine	
	N (n)	GMT (95 % CI) mMU[§]/mL	N (n)	GMT (95 % CI) mMU[§]/mL	GMT Ratio	(95 % CI) [#]
Anti-HPV 6						
9 to 15 year old girls	300 (273)	1 679.4 (1 518.9, 1 856.9)	300 (261)	1 565.9 (1 412.2, 1 736.3)	1.07	(0.93, 1.23)
16 to 26 year old women	6 792 (3 993)	893.1 (871.7, 915.1)	6 795 (3 975)	875.2 (854.2, 896.8)	1.02	(0.99, 1.06)[¶]
16 to 26 year old men	249 (228)	758.3 (665.9, 863.4)	251 (226)	618.4 (554.0, 690.3)	1.23	(1.04, 1.45)[¶]
Anti-HPV 11						
9 to 15 year old girls	300 (273)	1 315.6 (1 183.8, 1 462.0)	300 (261)	1 417.3 (1 274.2, 1 576.5)	0.93	(0.80, 1.08)
16 to 26 year old women	6 792 (3 995)	666.3 (649.6, 683.4)	6 795 (3 982)	830.0 (809.2, 851.4)	0.80	(0.77, 0.83)[¶]
16 to 26 year old men	249 (228)	681.7 (608.9, 763.4)	251 (226)	769.1 (683.5, 865.3)	0.89	(0.76, 1.04)[¶]
Anti-HPV 16						
9 to 15 year old girls	300 (276)	6 739.5 (6 134.5, 7 404.1)	300 (270)	6 887.4 (6 220.8, 7 625.5)	0.97	(0.85, 1.11)[¶]
16 to 26 year old women	6 792 (4 032)	3 131.1 (3 057.1, 3 206.9)	6 795 (4 062)	3 156.6 (3 082.3, 3 232.7)	0.99	(0.96, 1.03)[¶]
16 to 26 year old men	249 (234)	3 924.1 (3 513.8, 4 382.3)	251 (237)	3 787.9 (3 378.4, 4 247.0)	1.04	(0.89, 1.21)[¶]
Anti-HPV 18						
9 to 15 year old girls	300 (276)	1 956.6 (1 737.3, 2 203.7)	300 (269)	1 795.6 (1 567.2, 2 057.3)	1.08	(0.91, 1.29)[¶]
16 to 26 year old women	6 792 (4 539)	804.6 (782.7, 827.1)	6 795 (4 541)	678.7 (660.2, 697.7)	1.19	(1.14, 1.23)[¶]
16 to 26 year old men	249 (234)	884.3 (766.4, 1 020.4)	251 (236)	790.9 (683.0, 915.7)	1.12	(0.91, 1.37)[¶]

*The PPI population consisted of individuals who received all three vaccinations within predefined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the month 6 and month 7 visit, seronegative to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1, and among 16 to 26 year old women, were PCR negative to the relevant HPV type(s) prior to dose 1 through one month postdose 3 (month 7).

[§]mMU=milli-Merck units.

[¶]p-value < 0.001.

[#]Demonstration of non-inferiority required that the lower bound of the 95 % CI of the GMT ratio be greater than 0.67.

CI=Confidence Interval.

GMT=Geometric Mean Titres.

cLIA=Competitive Luminex Immunoassay.

N=Number of individuals randomised to the respective vaccination group who received at least one injection.

n=Number of individuals contributing to the analysis.

Studies supporting the efficacy of Gardasil 9 against HPV types 31, 33, 45, 52, and 58

The efficacy of Gardasil 9 in women aged 16 to 26 years was assessed in an active comparator-controlled, double-blind, randomised clinical study (Protocol 001) that included a total of 14 204 women (Gardasil 9=7 099; qHPV vaccine=7 105). Subjects were followed up to 67 months postdose 3 with a median duration of 43 months postdose 3.

Gardasil 9 was efficacious in preventing HPV 31-, 33-, 45-, 52-, and 58-related persistent infection and disease (Table 4). Gardasil 9 also reduced the incidence of HPV 31-, 33-, 45-, 52-, and 58-related Pap test abnormalities, cervical and external genital procedures (i.e. biopsies), and cervical definitive therapy procedures (Table 4).

Table 4: Analysis of efficacy of Gardasil 9 against HPV types 31, 33, 45, 52, and 58 in the PPE[‡] population of 16 to 26 year old women

Disease endpoint	**Gardasil 9 N=7 099**		**qHPV vaccine N=7 105**		**% efficacy** (95 % CI)**
	n	Number of cases*	n	Number of cases*	
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3, AIS, cervical cancer, VIN 2/3, VaIN 2/3, vulvar cancer, and vaginal cancer[α]	6 016	1	6 017	38	97.4 (85.0, 99.9)
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3 or AIS[α]	5 949	1	5 943	35	97.1 (83.5, 99.9)
HPV 31-, 33-, 45-, 52-, 58-related CIN2	5 949	1	5 943	32	96.9 (81.5, 99.8)
HPV 31-, 33-, 45-, 52-, 58-related CIN3	5 949	0	5 943	7	100 (39.4, 100)
HPV 31-, 33-, 45-, 52-, 58-related VIN 2/3, VaIN 2/3	6 009	0	6 012	3	100.0 (-71.5, 100.0)
HPV 31-, 33-, 45-, 52-, 58-related persistent infection ≥ 6 months[§]	5 941	41	5 955	946	96.0 (94.6, 97.1)
HPV 31-, 33-, 45-, 52-, 58-related persistent infection ≥ 12 months[¶]	5 941	23	5 955	657	96.7 (95.1, 97.9)
HPV 31-, 33-, 45-, 52-, 58-related ASC-US HR-HPV positive or worse Pap[#] abnormality	5 883	37	5 882	506	92.9 (90.2, 95.1)
HPV 31-, 33-, 45-, 52-, 58-related cervical definitive therapy procedures[†]	6 013	4	6 014	41	90.2 (75.0, 96.8)

[‡]The PPE population consisted of individuals who received all 3 vaccinations within one year of enrolment, did not have major deviations from the study protocol, were naïve (PCR negative and seronegative) to the relevant HPV type(s) (types 31, 33, 45, 52, and 58) prior to dose 1, and who remained PCR negative to the relevant HPV type(s) through one month postdose 3 (month 7).
N=Number of individuals randomised to the respective vaccination group who received at least one injection.
n=Number of individuals contributing to the analysis.
[§]Persistent infection detected in samples from two or more consecutive visits 6 months (±1 month visit windows) apart.
[¶]Persistent infection detected in samples from three or more consecutive visits 6 months (±1 month visit windows) apart.
[#]Papanicolaou test.
CI=Confidence Interval.
ASC-US=Atypical squamous cells of undetermined significance.
HR=High Risk.
*Number of individuals with at least one follow-up visit after month 7.
**Subjects were followed for up to 67 months postdose 3 (median 43 months postdose 3).
[α]No cases of cervical cancer, VIN2/3, vulvar and vaginal cancer were diagnosed in the PPE population.
[†]Loop electrosurgical excision procedure (LEEP) or conisation.

Additional efficacy evaluation of Gardasil 9 against vaccine HPV types

Since the efficacy of Gardasil 9 could not be evaluated against placebo, the following exploratory analyses were conducted.

Efficacy evaluation of Gardasil 9 against cervical high grade diseases caused by vaccine HPV types in the PPE
The efficacy of Gardasil 9 against CIN 2 and worse related to vaccine HPV types compared to qHPV vaccine was 94.4 % (95 % CI 78.8, 99.0) with 2/5 952 versus 36/5 947 cases. The efficacy of

Gardasil 9 against CIN 3 related to vaccine HPV types compared to qHPV vaccine was 100 % (95 % CI 46.3, 100.0) with 0/5 952 versus 8/5 947 cases.

Impact of Gardasil 9 against cervical biopsy and definite therapy related to vaccine HPV types in the PPE
The efficacy of Gardasil 9 against cervical biopsy related to vaccine HPV types compared to qHPV vaccine was 95.9 % (95 % CI 92.7, 97.9) with 11/6 016 versus 262/6 018 cases. The efficacy of Gardasil 9 against cervical definitive therapy (including loop electrosurgical excision procedure [LEEP] or conisation) related to vaccine HPV types compared to qHPV vaccine was 90.7 % (95 % CI 76.3, 97.0) with 4/6 016 versus 43/6 018 cases.

Long-term effectiveness studies
A subset of subjects is being followed up for 10 to 14 years after Gardasil 9 vaccination for safety, immunogenicity, and effectiveness against clinical diseases related to the HPV types in the vaccine.

In the long-term extensions of clinical studies Protocols 001 and 002, effectiveness was observed in the PPE population. The PPE population consisted of individuals:
- who received all 3 vaccinations within 1 year of enrolment, without major deviations from the study protocol,
- who were seronegative to the relevant vaccine HPV type(s) prior to dose 1 and among women aged 16 to 26 years, PCR negative to the relevant vaccine HPV type(s) prior to dose 1 through one month postdose 3 (month 7).

In Protocol 001 registry study, no cases of vaccine HPV types related high-grade CIN were observed through 13.6 years postdose 3 (median follow-up of 10.4 years) in women (n=1 628) who were aged 16 to 26 years at time of vaccination with Gardasil 9.

In Protocol 002 extension study, no cases of high-grade intraepithelial neoplasia or genital warts were observed through 11.0 years postdose 3 (median follow-up of 10.0 years) in girls (n=872) and through 10.6 years postdose 3 (median follow-up of 9.9 years) in boys (n=262) who were aged 9 to 15 years at time of vaccination with Gardasil 9. Incidence rates of vaccine HPV types related 6-month persistent infections in girls and boys observed during the study were 52.4 and 54.6 per 10 000 person-years, respectively, and within ranges of incidence rates expected in vaccinated cohorts of similar age (based on results from previous efficacy studies of Gardasil 9 and qHPV vaccine).

Immunogenicity

The minimum anti-HPV titre that confers protective efficacy has not been determined.

Type-specific immunoassays with type-specific standards were used to assess immunogenicity to each vaccine HPV type. These assays measured antibodies against neutralising epitopes for each HPV type. The scales for these assays are unique to each HPV type; thus, comparisons across types and to other assays are not appropriate.

Immune response to Gardasil 9 at month 7

Immunogenicity was measured by (1) the percentage of individuals who were seropositive for antibodies against the relevant vaccine HPV type, and (2) the Geometric Mean Titre (GMT).

Gardasil 9 induced robust anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 responses measured at month 7, in Protocols 001, 002, 004, 005, 007, and GDS01C/Protocol 009. In clinical studies 99.2 % to 100 % who received Gardasil 9 became seropositive for antibodies against all 9 vaccine types by month 7 across all groups tested. GMTs were higher in girls and boys than in women aged 16 to 26 years, and higher in boys than in girls and women. As expected for women 27 to 45 years of age (Protocol 004), the observed GMTs were lower than those seen in women aged 16 to 26 years.

Anti-HPV responses at month 7 among girls/boys aged 9 to 15 years were comparable to anti-HPV responses in women aged 16 to 26 years in the combined database of immunogenicity studies for Gardasil 9.

On the basis of this immunogenicity bridging, the efficacy of Gardasil 9 in girls and boys aged 9 to 15 years is inferred.

In Protocol 003, anti-HPV antibody GMTs at month 7 among boys and men (HM) aged 16 to 26 years were comparable to anti-HPV antibody GMTs among girls and women aged 16 to 26 years for vaccine HPV types. High immunogenicity in MSM aged 16 to 26 years was also observed, although lower than in HM, similarly to qHPV vaccine. In Protocol 020/GDS07C, anti-HPV antibody GMTs at month 7 among boys and men (HM) aged 16 to 26 years were comparable to anti-HPV antibody GMTs among boys and men (HM) aged 16 to 26 years administered with the qHPV vaccine for HPV 6, 11, 16 and 18. These results support the efficacy of Gardasil 9 in the male population.

In Protocol 004, anti-HPV antibody GMTs at month 7 among women aged 27 to 45 years were non-inferior to anti-HPV antibody GMTs among girls and women aged 16 to 26 years for HPV 16, 18, 31, 33, 45, 52, and 58 with GMT ratios between 0.66 and 0.73. In a post hoc analysis for HPV 6 and 11, the GMT ratios were 0.81 and 0.76 respectively. These results support the efficacy of Gardasil 9 in women aged 27 to 45 years.

Persistence of immune response to Gardasil 9

In long-term follow-up extension of clinical studies Protocols 001 and 002, persistence of antibody responses was observed:

- for at least 5 years in women who were aged 16 to 26 years at time of vaccination with Gardasil 9, depending on HPV type, 78 to100 % of subjects were seropositive; however, efficacy was maintained in all subjects regardless of seropositivity status for any vaccine HPV type through the end of the study (up to 67 months postdose 3, median follow-up duration of 43 months postdose 3),
- for at least 10 years in girls and boys who were aged 9 to 15 years at time of vaccination with Gardasil 9; depending on HPV type, 81 to 98 % of subjects were seropositive.

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, women (n=150) who received 3 doses of Gardasil 9 in Protocol 001 and a challenge dose 5 years later, exhibited a rapid and strong anamnestic response that exceeded the anti-HPV GMTs observed 1 month postdose 3.

Administration of Gardasil 9 to individuals previously vaccinated with qHPV vaccine

Protocol 006 evaluated the immunogenicity of Gardasil 9 in 921 girls and women (aged 12 to 26 years) who had previously been vaccinated with qHPV vaccine. For subjects receiving Gardasil 9 after receiving 3 doses of qHPV vaccine, there was an interval of at least 12 months between completion of vaccination with qHPV vaccine and the start of vaccination with Gardasil 9 with a 3-dose regimen (the time interval ranged from approximately 12 to 36 months).

Seropositivity to vaccine HPV types in the per protocol population ranged from 98.3 to 100 % by month 7 in individuals who received Gardasil 9. The GMTs to HPV types 6, 11, 16, 18 were higher than in the population who had not previously received qHPV vaccine in other studies whereas the GMTs to HPV types 31, 33, 45, 52 and 58 were lower. The clinical significance of this observation is not known.

Immunogenicity in HIV infected subjects

No clinical study of Gardasil 9 was conducted in HIV-infected individuals.

A study documenting safety and immunogenicity of qHPV vaccine has been performed in 126 HIV infected subjects aged 7 to12 years with baseline CD4 % ≥ 15 and at least 3 months of highly active antiretroviral therapy (HAART) for subjects with a CD4 % < 25 (of which 96 received qHPV vaccine). Seroconversion to all four antigens occurred in more than 96 % 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.

Immune responses to Gardasil 9 using a 2-dose schedule in individuals 9 through 14 years of age

Protocol 010 measured HPV antibody responses to the 9 HPV types after Gardasil 9 vaccination in the following cohorts: girls and boys aged 9 to 14 years receiving 2 doses at a 6-month or 12-month interval (+/- 1-month); girls aged 9 to 14 years receiving 3 doses (at 0, 2, 6 months); and women aged 16 to 26 years receiving 3 doses (at 0, 2, 6 months).

One month following the last dose of the assigned regimen, between 97.9 % and 100 % of subjects across all groups became seropositive for antibodies against the 9 vaccine HPV types. GMTs were higher in girls and boys who received 2 doses of Gardasil 9 (at either 0, 6 months or 0, 12 months) than in girls and women 16 to 26 years of age who received 3 doses of Gardasil 9 (at 0, 2, 6 months) for each of the 9 vaccine HPV types. On the basis of this immunogenicity bridging, the efficacy of a 2-dose regimen of Gardasil 9 in girls and boys aged 9 to 14 years is inferred.

In the same study, in girls and boys aged 9 to14 years, GMTs at one month after the last vaccine dose were numerically lower for some vaccine types after a 2-dose schedule than after a 3-dose schedule (i.e. HPV types 18, 31, 45, and 52 after 0, 6 months and HPV type 45 after 0, 12 months). The clinical relevance of these findings is unknown.

In girls and boys receiving 2 doses at 6- or 12-month interval (+/- 1-month), persistence of antibody response was demonstrated through month 36; depending on HPV type, 81 % to 99 % of girls and boys receiving 2 doses at 6-month interval and 88 % to 100 % of girls and boys receiving 2 doses at 12-month interval were seropositive. At month 36, the GMTs in girls and boys aged 9 to 14 years receiving 2 doses at a 6-month interval (+/- 1-month) remained non-inferior to GMTs in women aged 16 to 26 years receiving 3 doses of Gardasil 9.

In a clinical study, persistence of antibody response has been demonstrated for at least 10 years in girls aged 9 to13 years who received 2 doses of qHPV vaccine.

Duration of protection of a 2-dose schedule of Gardasil 9 has not been established.

Pregnancy

Specific studies of Gardasil 9 in pregnant women were not conducted. The qHPV vaccine was used as an active control during the clinical development program for Gardasil 9.

During the clinical development of Gardasil 9; 2 586 women (1 347 in the Gardasil 9 group vs. 1 239 in the qHPV vaccine group) reported at least one pregnancy. The types of anomalies or proportion of pregnancies with an adverse outcome in individuals who received Gardasil 9 or qHPV vaccine were comparable and consistent with the general population (see section 4.6).

Prevention of juvenile-onset recurrent respiratory papillomatosis (JoRRP) by vaccination of girls and women of childbearing potential

JoRRP is caused by upper airway infection primarily with HPV types 6 and 11, acquired vertically (mother-to-child) during childbirth. Observational studies in the US and Australia have shown that the introduction of qHPV vaccine since 2006 has led to declines in the incidence of JoRRP at population level.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

A repeat dose toxicity study in rats, which included an evaluation of single-dose toxicity and local tolerance, revealed no special hazards to humans.

Gardasil 9 administered to female rats had no effects on mating performance, fertility, or embryonic/foetal development.

Gardasil 9 administered to female rats had no effects on development, behaviour, reproductive performance or fertility of the offspring. Antibodies against all 9 HPV types were transferred to the offspring during gestation and lactation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Histidine
Polysorbate 80 (E 433)
Borax (E 285)
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

Gardasil 9 suspension for injection
Gardasil 9 suspension for injection in multidose container
Gardasil 9 suspension for injection in pre-filled syringe

3 years

Gardasil 9 suspension for injection in multidose container

After first opening

After first opening, immediate use is recommended. If not used immediately, the vaccine should be stored in a refrigerator (2 °C – 8 °C). If not used within 6 hours, it should be discarded.

6.4 Special precautions for storage

Gardasil 9 suspension for injection
Gardasil 9 suspension for injection in multidose container
Gardasil 9 suspension for injection in pre-filled syringe

Store in a refrigerator (2 °C – 8 °C).

Do not freeze. Keep the vial, the multidose container or the pre-filled syringe in the outer carton in order to protect from light.

Gardasil 9 should be administered as soon as possible after being removed from the refrigerator.

Stability data indicate that the vaccine components are stable for 96 hours when stored at temperatures from 8 °C to 40 °C or for 72 hours when stored at temperatures from 0 °C to 2 °C. At the end of this period Gardasil 9 should be used or discarded. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

Gardasil 9 suspension for injection in multidose container

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Gardasil 9 suspension for injection:

0.5 mL suspension in a single-dose vial (glass) (0.5 mL/dose) with stopper (halobutyl) and a flip-off plastic cap (aluminium crimp band) in a pack size of 1.

Gardasil 9 suspension for injection in multidose container

1 mL suspension in a multidose container (glass) for two doses (0.5 mL/dose) with stopper (halobutyl) and a flip-off plastic cap (aluminium crimp band) in a pack size of 10.

Gardasil 9 suspension for injection in pre-filled syringe

0.5 mL suspension in a pre-filled syringe (glass) (0.5 mL/dose) with plunger stopper (siliconised FluroTec-laminated bromobutyl elastomer) and a tip cap (synthetic isoprene-bromobutyl blend) in pack sizes of 1 or 10 with needles or in a pack size of 10 without needles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Gardasil 9 suspension for injection:

- Gardasil 9 may appear as a clear liquid with a white precipitate prior to agitation.
- Shake well before use, to make a suspension. After thorough agitation, it is a white, cloudy liquid.
- Inspect the suspension visually for particulate matter and discolouration prior to administration. Discard the vaccine if particulates are present and/or if it appears discoloured.
- When using a single-dose vial, withdraw the 0.5 mL dose of vaccine from the single-dose vial using a sterile needle and syringe.

- When using a multidose container, withdraw the 0.5 mL dose of vaccine from the multidose container using a sterile needle and syringe. Each 0.5 mL dose should be withdrawn using a sterile needle and syringe; precautions should be taken to avoid contamination of the contents.

- Inject immediately using the intramuscular (IM) route, preferably in the deltoid area of the upper arm or in the higher anterolateral area of the thigh.

- The vaccine should be used as supplied. The full recommended dose of the vaccine should be used.

Gardasil 9 suspension for injection in pre-filled syringe

- Gardasil 9 may appear as a clear liquid with a white precipitate prior to agitation.

- Shake well before use, to make a suspension. After thorough agitation, it is a white, cloudy liquid.

- Inspect the suspension visually for particulate matter and discolouration prior to administration. Discard the vaccine if particulates are present and/or if it appears discoloured.

- Choose an appropriate needle to ensure an intramuscular (IM) administration depending on your patient's size and weight.

- In packs with needles, two needles of different lengths are provided per syringe.

- 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.

- Inject immediately using the intramuscular (IM) route, preferably in the deltoid area of the upper arm or in the higher anterolateral area of the thigh.

- The vaccine should be used as supplied. The full recommended dose of the vaccine should be used.

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

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

Gardasil 9 suspension for injection

EU/1/15/1007/001

Gardasil 9 suspension for injection in multidose container

EU/1/15/1007/005

Gardasil 9 suspension for injection in pre-filled syringe

EU/1/15/1007/002
EU/1/15/1007/003
EU/1/15/1007/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 June 2015
Date of latest renewal: 16 January 2020

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substances

Merck Sharp & Dohme LLC
2778 South East Side Highway
Elkton, Virginia 22827
USA

Merck Sharp & Dohme LLC
770 Sumneytown Pike
West Point, Pennsylvania 19486
USA

Boehringer Ingelheim RCV GmbH & Co KG
Dr. Boehringer-Gasse 5-11
Meidling, Vienna, 1121
Austria

Name and address of the manufacturer responsible for batch release

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT
Single-dose vial, pack of 1

1. NAME OF THE MEDICINAL PRODUCT

Gardasil 9 suspension for injection
Human Papillomavirus 9-valent Vaccine (recombinant, adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 mL):

HPV Type 6 L1 protein	30 µg
HPV Type 11 and 18 L1 protein	40 µg
HPV Type 16 L1 protein	60 µg
HPV Type 31, 33, 45, 52 and 58 L1 protein	20 µg

adsorbed on amorphous aluminium hydroxyphosphate sulfate (0.5 mg Al).

3. LIST OF EXCIPIENTS

Excipients: Sodium chloride, histidine, polysorbate 80, borax, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
1 vial (0.5 mL/dose)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Shake well before use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1007/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL TEXT
Single-dose vial

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

Gardasil 9 injection
HPV vaccine
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 mL)

6. OTHER

MSD

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT
Multidose container, pack of 10

1. NAME OF THE MEDICINAL PRODUCT

Gardasil 9 suspension for injection in multidose container
Human Papillomavirus 9-valent Vaccine (recombinant, adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 mL):

HPV Type 6 L1 protein	30 µg
HPV Type 11 and 18 L1 protein	40 µg
HPV Type 16 L1 protein	60 µg
HPV Type 31, 33, 45, 52 and 58 L1 protein	20 µg

adsorbed on amorphous aluminium hydroxyphosphate sulfate (0.5 mg Al).

3. LIST OF EXCIPIENTS

Excipients: Sodium chloride, histidine, polysorbate 80, borax, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
10 multidose containers
10 x 2 doses (0.5 mL/dose)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Shake well before use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

After first opening, use immediately or within 6 hours if stored in a refrigerator.

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

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1007/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL TEXT
Multidose container, pack of 10

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

Gardasil 9 injection
HPV vaccine
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 doses (0.5 mL/dose)

6. OTHER

MSD

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT
Pre-filled syringe with 2 needles, pack of 1, 10

1. NAME OF THE MEDICINAL PRODUCT

Gardasil 9 suspension for injection in pre-filled syringe
Human Papillomavirus 9-valent Vaccine (recombinant, adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 mL):

HPV Type 6 L1 protein	30 µg
HPV Type 11 and 18 L1 protein	40 µg
HPV Type 16 L1 protein	60 µg
HPV Type 31, 33, 45, 52 and 58 L1 protein	20 µg

adsorbed on amorphous aluminium hydroxyphosphate sulfate (0.5 mg Al).

3. LIST OF EXCIPIENTS

Excipients: Sodium chloride, histidine, polysorbate 80, borax, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
1 pre-filled syringe (0.5 mL) with 2 needles
10 pre-filled syringes (0.5 mL) with 2 needles each

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Shake well before use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1007/002
EU/1/15/1007/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT
Pre-filled syringe, pack of 10 (without needles)

1. NAME OF THE MEDICINAL PRODUCT

Gardasil 9 suspension for injection in pre-filled syringe
Human Papillomavirus 9-valent Vaccine (recombinant, adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 mL):

HPV Type 6 L1 protein	30 µg
HPV Type 11 and 18 L1 protein	40 µg
HPV Type 16 L1 protein	60 µg
HPV Type 31, 33, 45, 52 and 58 L1 protein	20 µg

adsorbed on amorphous aluminium hydroxyphosphate sulfate (0.5 mg Al).

3. LIST OF EXCIPIENTS

Excipients: Sodium chloride, histidine, polysorbate 80, borax, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
10 pre-filled syringes (0.5 mL)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use.
Shake well before use.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1007/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL TEXT
Pre-filled syringe

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

Gardasil 9 injection
HPV vaccine
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 mL)

6. OTHER

MSD

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Gardasil 9 suspension for injection
Gardasil 9 suspension for injection in multidose container
Human Papillomavirus 9-valent Vaccine (recombinant, adsorbed)

Read all of this leaflet carefully before you or your child are vaccinated because it contains important information for you or your child.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor, pharmacist or nurse.
- If you or your child get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Gardasil 9 is and what it is used for
2. What you need to know before you or your child receive Gardasil 9
3. How Gardasil 9 is given
4. Possible side effects
5. How to store Gardasil 9
6. Contents of the pack and other information

1. What Gardasil 9 is and what it is used for

Gardasil 9 is a vaccine for children and adolescents from 9 years of age and adults. It is given to protect against diseases caused by Human Papillomavirus (HPV) types 6, 11, 16, 18, 31, 33, 45, 52 and 58.

These diseases include pre-cancerous lesions and cancers of the female genitals (cervix, vulva, and vagina), pre-cancerous lesions and cancers of the anus and genital warts in males and females.

Gardasil 9 has been studied in males 9 to 26 years of age and females 9 to 45 years of age.

Gardasil 9 protects against the HPV types that cause most cases of these diseases.

Gardasil 9 is intended to prevent these diseases. The vaccine is not used to treat HPV related diseases. Gardasil 9 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 9 can still protect against diseases associated with the other HPV types in the vaccine.

Gardasil 9 cannot cause HPV-related diseases.

When an individual is vaccinated with Gardasil 9, the immune system (the body's natural defence system) stimulates production of antibodies against the nine vaccine HPV types, to help protect against the diseases caused by these viruses.

If you or your child receive a first dose of Gardasil 9, you have to complete the full vaccination course with Gardasil 9.

If you or your child already received an HPV vaccine, ask your doctor if Gardasil 9 is right for you.

Gardasil 9 should be used in accordance with official guidelines.

2. What you need to know before you or your child receive Gardasil 9

Do not receive Gardasil 9 if you or your child
- is allergic to any of the active substances or any of the other ingredients of this vaccine (listed under "other ingredients", in section 6).
- developed an allergic reaction after receiving a dose of Gardasil or Silgard (HPV types 6, 11, 16, and 18) or Gardasil 9.

Warnings and precautions
Talk to your doctor, pharmacist or nurse 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;
- suffer from an illness with high fever. However, a mild fever or upper respiratory infection (for example having a cold) itself is not a reason to delay vaccination.

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

As with any vaccine, Gardasil 9 may not fully protect all of those who get the vaccine.

Gardasil 9 will not protect against every type of Human Papillomavirus. Therefore appropriate precautions against sexually transmitted disease should continue to be used.

Vaccination is not a substitute for routine cervical screening. If you are a woman, **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 9
The duration of protection is not yet known. Longer term follow-up studies are ongoing to determine whether a booster dose is needed.

Other medicines and Gardasil 9
Tell your doctor or pharmacist if you or your child are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Gardasil 9 can be given 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, for example the other arm or leg) during the same visit.

Gardasil 9 may not have an optimal effect if used with medicines that suppress the immune system.

Hormonal contraceptives (for example the pill) did not reduce the protection obtained by Gardasil 9.

Pregnancy and breast-feeding
If you are pregnant, think that you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you receive this vaccine. Information from pregnant women vaccinated with Gardasil 9 does not show a higher risk for miscarriages or babies with birth defects.

However, if you are pregnant or if you become pregnant during the course of vaccination, it is recommended to postpone or interrupt vaccination until you are no longer pregnant.

Gardasil 9 may be given to women who are breast-feeding or intend to breast-feed.

Driving and using machines
Gardasil 9 may slightly and temporarily affect the ability to drive or use machines (see section 4 "Possible side effects").

Gardasil 9 contains sodium chloride and polysorbate 80
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.
This medicine contains 0.05 mg of polysorbate 80 in each 0.5 mL dose of suspension for injection. Polysorbates may cause allergic reactions. Tell your doctor if you or your child have any known allergies.

3. How Gardasil 9 is given

Gardasil 9 is given as an injection by your doctor, pharmacist or nurse. Gardasil 9 is intended for adolescents and adults from 9 years of age onwards.

If you are from 9 to and including 14 years of age at time of first injection
Gardasil 9 can be administered according to a 2-dose schedule:
- First injection: at chosen date
- Second injection: given between 5 and 13 months after first injection

If the second vaccine dose is administered earlier than 5 months after the first dose, a third dose should always be administered.

Gardasil 9 can be administered according to a 3-dose schedule:
- First injection: at chosen date
- Second injection: 2 months after first injection (not earlier than one month after the first dose)
- Third injection: 6 months after first injection (not earlier than 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.

If you are from 15 years of age at time of first injection
Gardasil 9 should be administered according to a 3-dose schedule:
- First injection: at chosen date
- Second injection: 2 months after first injection (not earlier than one month after the first dose)
- Third injection: 6 months after first injection (not earlier than 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.

It is recommended that individuals who receive a first dose of Gardasil 9 complete the vaccination course with Gardasil 9.

Gardasil 9 will be given as an injection through the skin into the muscle (preferably the muscle of the upper arm or thigh).

If you forget one dose of Gardasil 9
If a scheduled injection is missed, your doctor will decide when to give the missed dose.
It is important that you follow your doctor or nurse's instructions 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 9 is given as your first dose, the completion of the vaccination course should be done with Gardasil 9, and not another HPV vaccine.

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

4. Possible side effects

Like all vaccines, this vaccine can cause side effects, although not everybody gets them.

The following side effects can be seen after the use of Gardasil 9:

Very common (may affect more than 1 in 10 people): side effects found at the injection site (pain, swelling, and redness) and headache.

Common (may affect up to 1 in 10 people): side effects found at the injection site (bruising, and itching), fever, tiredness, dizziness and nausea.

Uncommon (may affect up to 1 in 100 people): swollen glands (neck, armpit, or groin), hives (urticaria), fainting sometimes accompanied by shaking or stiffening, vomiting; joint pain, aching muscles, unusual tiredness or weakness, chills, generally feeling unwell, lump (nodule) at the injection site.

Rare (may affect up to 1 in 1 000 people): allergic reactions.

Unknown (frequency cannot be estimated from the available data): serious allergic reactions (anaphylactic reaction).

When Gardasil 9 was given with a combined diphtheria, tetanus, pertussis [acellular, component] and poliomyelitis [inactivated] booster vaccine during the same visit, there was more injection-site swelling.

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.

The following side effects have been reported with GARDASIL or SILGARD and may also be seen after getting GARDASIL 9:
Allergic reactions have been reported. Some of these reactions have been severe. Symptoms may include difficulty breathing and wheezing.

As with other vaccines, side effects that have been reported during general use include: muscle weakness, abnormal sensations, tingling in the arms, legs and upper body, or confusion (Guillain-Barré syndrome, acute disseminated encephalomyelitis); bleeding or bruising more easily than normal and skin infection at the injection site.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Gardasil 9

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

Do not use this vaccine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

Gardasil 9 suspension for injection
Store in a refrigerator (2 ºC - 8 ºC). Do not freeze. Keep the vial or the multidose container in the outer carton in order to protect from light.

Gardasil 9 suspension for injection in multidose container
After first opening, immediate use is recommended. If not used immediately, the vaccine should be stored in a refrigerator (2 °C - 8 °C). If not used within 6 hours, it should be discarded.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Gardasil 9 contains
The active substances are: highly purified non-infectious protein for each of the Human Papillomavirus types (6, 11, 16, 18, 31, 33, 45, 52, and 58).

1 dose (0.5 mL) contains approximately:

Human Papillomavirus[1] Type 6 L1 protein[2,3]	30 micrograms
Human Papillomavirus[1] Type 11 L1 protein[2,3]	40 micrograms
Human Papillomavirus[1] Type 16 L1 protein[2,3]	60 micrograms
Human Papillomavirus[1] Type 18 L1 protein[2,3]	40 micrograms
Human Papillomavirus[1] Type 31 L1 protein[2,3]	20 micrograms
Human Papillomavirus[1] Type 33 L1 protein[2,3]	20 micrograms
Human Papillomavirus[1] Type 45 L1 protein[2,3]	20 micrograms
Human Papillomavirus[1] Type 52 L1 protein[2,3]	20 micrograms
Human Papillomavirus[1] Type 58 L1 protein[2,3]	20 micrograms

[1]Human Papillomavirus=HPV
[2]L1 protein in the form of virus like particles produced in yeast cells (*Saccharomyces cerevisiae* CANADE 3C-5 (Strain 1895)) by recombinant DNA technology.
[3]adsorbed on amorphous aluminium hydroxyphosphate sulfate adjuvant (0.5 milligrams Al).

Amorphous aluminium hydroxyphosphate sulfate is included in the vaccine as an adjuvant. Adjuvants are included to improve the immune response of vaccines.

The other ingredients in the vaccine suspension are: sodium chloride, histidine, polysorbate 80 (E 433), borax (E 285) and water for injections.

What Gardasil 9 looks like and contents of the pack
1 dose of Gardasil 9 suspension for injection contains 0.5 mL.

Prior to agitation, Gardasil 9 may appear as a clear liquid with a white precipitate. After thorough agitation, it is a white, cloudy liquid.

Gardasil 9 is available in a pack of 1 single-dose vial (glass) (0.5 mL/dose) and in a pack of 10 multidose containers (glass) for two doses (0.5 mL/dose).

Marketing Authorisation Holder and Manufacturer
Merck Sharp & 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
MSD Belgium
Tél/Tel: +32(0)27766211
dpoc_belux@msd.com

Lietuva
UAB Merck Sharp & Dohme
Tel: +370 5 2780 247
dpoc_lithuania@msd.com

България
Мерк Шарп и Доум България ЕООД
тел.: +359 2 819 3737
info-msdbg@msd.com

Česká republika
Merck Sharp & Dohme s.r.o.
Tel: +420 277 050 000
dpoc_czechslovak@msd.com

Danmark
MSD Danmark ApS
Tlf.: +45 4482 4000
dkmail@msd.com

Deutschland
MSD Sharp & Dohme GmbH
Tel: +49 (0) 89 20 300 4500
medinfo@msd.de

Eesti
Merck Sharp & Dohme OÜ
Tel: +372 614 4200
dpoc.estonia@msd.com

Ελλάδα
MSD Α.Φ.Ε.Ε.
Τηλ: +30 210 98 97 300
dpoc.greece@msd.com

España
Merck Sharp & Dohme de España, S.A.
Tel: +34 91 321 06 00
msd_info@msd.com

France
MSD France
Tél: +33 (0)1 80 46 40 40

Hrvatska
Merck Sharp & Dohme d.o.o.
Tel: +385 1 6611 333
dpoc.croatia@msd.com

Ireland
Merck Sharp & Dohme Ireland (Human Health) Limited
Tel: +353 (0)1 2998700
medinfo_ireland@msd.com

Ísland
Vistor ehf.
Sími: +354 535 7000

Luxembourg/Luxemburg
MSD Belgium
Tél/Tel: +32(0)27766211
dpoc_belux@msd.com

Magyarország
MSD Pharma Hungary Kft.
Tel.: +36 1 888 5300
hungary_msd@msd.com

Malta
Merck Sharp & Dohme Cyprus Limited
Tel: 8007 4433 (+356 99917558)
dpoccyprus@msd.com

Nederland
Merck Sharp & Dohme B.V.
Tel: 0800 9999000
(+31 23 5153153)
medicalinfo.nl@msd.com

Norge
MSD (Norge) AS
Tlf: +47 32 20 73 00
medinfo.norway@msd.com

Österreich
Merck Sharp & Dohme Ges.m.b.H.
Tel: +43 (0) 1 26 044
dpoc_austria@msd.com

Polska
MSD Polska Sp. z o.o.
Tel.: +48 22 549 51 00
msdpolska@msd.com

Portugal
Merck Sharp & Dohme, Lda
Tel: +351 21 4465700
inform_pt@msd.com

România
Merck Sharp & Dohme Romania S.R.L.
Tel: +40 21 529 29 00
msdromania@msd.com

Slovenija
Merck Sharp & Dohme, inovativna zdravila d.o.o.
Tel: +386 1 520 4201
msd.slovenia@msd.com

Slovenská republika
Merck Sharp & Dohme, s. r. o.
Tel: +421 2 58282010
dpoc_czechslovak@msd.com

Italia
MSD Italia S.r.l.
Tel: 800 23 99 89 (+39 06 361911)
dpoc.italy@msd.com

Κύπρος
Merck Sharp & Dohme Cyprus Limited
Τηλ: 800 00 673 (+357 22866700)
dpoccyprus@msd.com

Latvija
SIA Merck Sharp & Dohme Latvija
Tel: +371 67025300
dpoc.latvia@msd.com

Suomi/Finland
MSD Finland Oy
Puh/Tel: +358 (0)9 804 650
info@msd.fi

Sverige
Merck Sharp & Dohme (Sweden) AB
Tel: +46 77 5700488
medicinskinfo@msd.com

This leaflet was last revised in

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

The following information is intended for healthcare professionals only:

Gardasil 9 suspension for injection

- Gardasil 9 may appear as a clear liquid with a white precipitate prior to agitation.
- Shake well before use, to make a suspension. After thorough agitation, it is a white, cloudy liquid.
- Inspect the suspension visually for particulate matter and discolouration prior to administration. Discard the vaccine if particulates are present and/or if it appears discoloured.
- When using a single-dose vial, withdraw the 0.5 mL dose of vaccine from the vial using a sterile needle and syringe.
- When using a multidose container, withdraw the 0.5 mL dose of vaccine from the multidose container using a sterile needle and syringe. Each 0.5 mL dose should be withdrawn using a sterile needle and syringe; precautions should be taken to avoid contamination of the contents.
- Inject immediately using the intramuscular (IM) route, preferably in the deltoid area of the upper arm or in the higher anterolateral area of the thigh.
- The vaccine should be used as supplied. The full recommended dose of the vaccine should be used.

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

Package leaflet: Information for the user

Gardasil 9 suspension for injection in pre-filled syringe
Human Papillomavirus 9-valent Vaccine (recombinant, adsorbed)

Read all of this leaflet carefully before you or your child are vaccinated because it contains important information for you or your child.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor, pharmacist or nurse.
- If you or your child get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Gardasil 9 is and what it is used for
2. What you need to know before you or your child receive Gardasil 9
3. How Gardasil 9 is given
4. Possible side effects
5. How to store Gardasil 9
6. Contents of the pack and other information

1. What Gardasil 9 is and what it is used for

Gardasil 9 is a vaccine for children and adolescents from 9 years of age and adults. It is given to protect against diseases caused by Human Papillomavirus (HPV) types 6, 11, 16, 18, 31, 33, 45, 52 and 58.

These diseases include pre-cancerous lesions and cancers of the female genitals (cervix, vulva, and vagina), pre-cancerous lesions and cancers of the anus and genital warts in males and females.

Gardasil 9 has been studied in males 9 to 26 years of age and females 9 to 45 years of age.

Gardasil 9 protects against the HPV types that cause most cases of these diseases.

Gardasil 9 is intended to prevent these diseases. The vaccine is not used to treat HPV related diseases. Gardasil 9 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 9 can still protect against diseases associated with the other HPV types in the vaccine.

Gardasil 9 cannot cause HPV-related diseases.

When an individual is vaccinated with Gardasil 9, the immune system (the body's natural defence system) stimulates production of antibodies against the nine vaccine HPV types, to help protect against the diseases caused by these viruses.

If you or your child receive a first dose of Gardasil 9, you have to complete the full vaccination course with Gardasil 9.

If you or your child already received an HPV vaccine, ask your doctor if Gardasil 9 is right for you.

Gardasil 9 should be used in accordance with official guidelines.

2. What you need to know before you or your child receive Gardasil 9

Do not receive Gardasil 9 if you or your child
- is allergic to any of the active substances or any of the other ingredients of this vaccine (listed under "other ingredients", in section 6).
- developed an allergic reaction after receiving a dose of Gardasil or Silgard (HPV types 6, 11, 16, and 18) or Gardasil 9.

Warnings and precautions
Talk to your doctor, pharmacist or nurse 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;
- suffer from an illness with high fever. However, a mild fever or upper respiratory infection (for example having a cold) itself is not a reason to delay vaccination.

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

As with any vaccine, Gardasil 9 may not fully protect all of those who get the vaccine.

Gardasil 9 will not protect against every type of Human Papillomavirus. Therefore appropriate precautions against sexually transmitted disease should continue to be used.

Vaccination is not a substitute for routine cervical screening. If you are a woman, **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 9
The duration of protection is not yet known. Longer term follow-up studies are ongoing to determine whether a booster dose is needed.

Other medicines and Gardasil 9
Tell your doctor or pharmacist if you or your child are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Gardasil 9 can be given 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, for example the other arm or leg) during the same visit.

Gardasil 9 may not have an optimal effect if used with medicines that suppress the immune system.

Hormonal contraceptives (for example the pill) did not reduce the protection obtained by Gardasil 9.

Pregnancy and breast-feeding
If you are pregnant, think that you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you receive this vaccine. Information from pregnant women vaccinated with Gardasil 9 does not show a higher risk for miscarriages or babies with birth defects.

However, if you are pregnant or if you become pregnant during the course of vaccination, it is recommended to postpone or interrupt vaccination until you are no longer pregnant.

Gardasil 9 may be given to women who are breast-feeding or intend to breast-feed.

Driving and using machines
Gardasil 9 may slightly and temporarily affect the ability to drive or use machines (see section 4 "Possible side effects").

Gardasil 9 contains sodium chloride and polysorbate 80
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.
This medicine contains 0.05 mg of polysorbate 80 in each 0.5 mL dose of suspension for injection. Polysorbates may cause allergic reactions. Tell your doctor if you or your child have any known allergies.

3. How Gardasil 9 is given

Gardasil 9 is given as an injection by your doctor, pharmacist or nurse. Gardasil 9 is intended for adolescents and adults from 9 years of age onwards.

If you are from 9 to and including 14 years of age at time of first injection
Gardasil 9 can be administered according to a 2-dose schedule:
- First injection: at chosen date
- Second injection: given between 5 and 13 months after first injection

If the second vaccine dose is administered earlier than 5 months after the first dose, a third dose should always be administered.

Gardasil 9 can be administered according to a 3-dose schedule:
- First injection: at chosen date
- Second injection: 2 months after first injection (not earlier than one month after the first dose)
- Third injection: 6 months after first injection (not earlier than 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.

If you are from 15 years of age at time of first injection
Gardasil 9 should be administered according to a 3-dose schedule:
- First injection: at chosen date
- Second injection: 2 months after first injection (not earlier than one month after the first dose)
- Third injection: 6 months after first injection (not earlier than 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.

It is recommended that individuals who receive a first dose of Gardasil 9 complete the vaccination course with Gardasil 9.

Gardasil 9 will be given as an injection through the skin into the muscle (preferably the muscle of the upper arm or thigh).

If you forget one dose of Gardasil 9
If a scheduled injection is missed, your doctor will decide when to give the missed dose.
It is important that you follow your doctor or nurse's instructions 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 9 is given as your first dose, the completion of the vaccination course should be done with Gardasil 9, and not another HPV vaccine.

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

4. Possible side effects

Like all vaccines, this vaccine can cause side effects, although not everybody gets them.

The following side effects can be seen after the use of Gardasil 9:

Very common (may affect more than 1 in 10 people): side effects found at the injection site (pain, swelling, and redness) and headache.

Common (may affect up to 1 in 10 people): side effects found at the injection site (bruising, and itching), fever, tiredness, dizziness and nausea.

Uncommon (may affect up to 1 in 100 people): swollen glands (neck, armpit, or groin), hives (urticaria), fainting sometimes accompanied by shaking or stiffening, vomiting; joint pain, aching muscles, unusual tiredness or weakness, chills, generally feeling unwell, lump (nodule) at the injection site.

Rare (may affect up to 1 in 1 000 people): allergic reactions.

Unknown (frequency cannot be estimated from the available data): serious allergic reactions (anaphylactic reaction).

When Gardasil 9 was given with a combined diphtheria, tetanus, pertussis [acellular, component] and poliomyelitis [inactivated] booster vaccine during the same visit, there was more injection-site swelling.

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.

The following side effects have been reported with GARDASIL or SILGARD and may also be seen after getting GARDASIL 9:
Allergic reactions have been reported. Some of these reactions have been severe. Symptoms may include difficulty breathing and wheezing.

As with other vaccines, side effects that have been reported during general use include: muscle weakness, abnormal sensations, tingling in the arms, legs and upper body, or confusion (Guillain-Barré syndrome, acute disseminated encephalomyelitis); bleeding or bruising more easily than normal and skin infection at the injection site.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Gardasil 9

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

Do not use this vaccine after the expiry date which is stated on the carton and syringe label after EXP. The expiry date refers to the last day of that month.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Gardasil 9 contains
The active substances are: highly purified non-infectious protein for each of the Human Papillomavirus types (6, 11, 16, 18, 31, 33, 45, 52, and 58).

1 dose (0.5 mL) contains approximately:

Human Papillomavirus[1] Type 6 L1 protein[2,3]	30 micrograms
Human Papillomavirus[1] Type 11 L1 protein[2,3]	40 micrograms
Human Papillomavirus[1] Type 16 L1 protein[2,3]	60 micrograms
Human Papillomavirus[1] Type 18 L1 protein[2,3]	40 micrograms
Human Papillomavirus[1] Type 31 L1 protein[2,3]	20 micrograms
Human Papillomavirus[1] Type 33 L1 protein[2,3]	20 micrograms
Human Papillomavirus[1] Type 45 L1 protein[2,3]	20 micrograms
Human Papillomavirus[1] Type 52 L1 protein[2,3]	20 micrograms
Human Papillomavirus[1] Type 58 L1 protein[2,3]	20 micrograms

[1]Human Papillomavirus=HPV
[2]L1 protein in the form of virus like particles produced in yeast cells (*Saccharomyces cerevisiae* CANADE 3C-5 (Strain 1895)) by recombinant DNA technology.
[3]adsorbed on amorphous aluminium hydroxyphosphate sulfate adjuvant (0.5 milligrams Al).

Amorphous aluminium hydroxyphosphate sulfate is included in the vaccine as an adjuvant. Adjuvants are included to improve the immune response of vaccines.

The other ingredients in the vaccine suspension are: sodium chloride, histidine, polysorbate 80 (E 433), borax (E 285) and water for injections.

What Gardasil 9 looks like and contents of the pack
1 dose of Gardasil 9 suspension for injection contains 0.5 mL.

Prior to agitation, Gardasil 9 may appear as a clear liquid with a white precipitate. After thorough agitation, it is a white, cloudy liquid.

Gardasil 9 is available in packs of 1 or 10 pre-filled syringes (glass) (0.5 mL/dose) with needles or in packs of 10 pre-filled syringes (glass) (0.5 mL/dose) without needles.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Merck Sharp & 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
MSD Belgium
Tél/Tel: +32(0)27766211
dpoc_belux@msd.com

Lietuva
UAB Merck Sharp & Dohme
Tel. +370 5 2780 247
dpoc_lithuania@msd.com

България
Мерк Шарп и Доум България ЕООД
тел.: +359 2 819 3737
info-msdbg@msd.com

Česká republika
Merck Sharp & Dohme s.r.o.
Tel.: +420 277 050 000
dpoc_czechslovak@msd.com

Danmark
MSD Danmark ApS
Tlf.: +45 4482 4000
dkmail@msd.com

Deutschland
MSD Sharp & Dohme GmbH
Tel.: +49 (0) 89 20 300 4500
medinfo@msd.de

Eesti
Merck Sharp & Dohme OÜ
Tel: +372 614 4200
dpoc.estonia@msd.com

Ελλάδα
MSD Α.Φ.Ε.Ε.
Τηλ: +30 210 98 97 300
dpoc.greece@msd.com

España
Merck Sharp & Dohme de España, S.A.
Tel: +34 91 321 06 00
msd_info@msd.com

France
MSD France
Tél: +33 (0)1 80 46 40 40

Hrvatska
Merck Sharp & Dohme d.o.o.
Tel: +385 1 6611 333
dpoc.croatia@msd.com

Ireland
Merck Sharp & Dohme Ireland (Human Health) Limited
Tel: +353 (0)1 2998700
medinfo_ireland@msd.com

Ísland
Vistor ehf.
Sími: +354 535 7000

Luxembourg/Luxemburg
MSD Belgium
Tél/Tel: +32(0)27766211
dpoc_belux@msd.com

Magyarország
MSD Pharma Hungary Kft.
Tel.: +36 1 888 5300
hungary_msd@msd.com

Malta
Merck Sharp & Dohme Cyprus Limited
Tel: 8007 4433 (+356 99917558)
dpoccyprus@msd.com

Nederland
Merck Sharp & Dohme B.V.
Tel: 0800 9999000
(+31 23 5153153)
medicalinfo.nl@msd.com

Norge
MSD (Norge) AS
Tlf: +47 32 20 73 00
medinfo.norway@msd.com

Österreich
Merck Sharp & Dohme Ges.m.b.H.
Tel: +43 (0) 1 26 044
dpoc_austria@msd.com

Polska
MSD Polska Sp. z o.o.
Tel.: +48 22 549 51 00
msdpolska@msd.com

Portugal
Merck Sharp & Dohme, Lda
Tel.: +351 21 4465700
inform_pt@msd.com

România
Merck Sharp & Dohme Romania S.R.L.
Tel.: +40 21 529 29 00
msdromania@msd.com

Slovenija
Merck Sharp & Dohme, inovativna zdravila d.o.o.
Tel: +386 1 520 4201
msd.slovenia@msd.com

Slovenská republika
Merck Sharp & Dohme, s. r. o.
Tel.: +421 2 58282010
dpoc_czechslovak@msd.com

Italia
MSD Italia S.r.l.
Tel: 800 23 99 89 (+39 06 361911)
dpoc.italy@msd.com

Κύπρος
Merck Sharp & Dohme Cyprus Limited
Τηλ.: 800 00 673 (+357 22866700)
dpoccyprus@msd.com

Latvija
SIA Merck Sharp & Dohme Latvija
Tel.: +371 67025300
dpoc.latvia@msd.com

Suomi/Finland
MSD Finland Oy
Puh/Tel: +358 (0)9 804 650
info@msd.fi

Sverige
Merck Sharp & Dohme (Sweden) AB
Tel: +46 77 5700488
medicinskinfo@msd.com

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

The following information is intended for healthcare professionals only:

Gardasil 9 suspension for injection in pre-filled syringe

- Gardasil 9 may appear as a clear liquid with a white precipitate prior to agitation.
- Shake well before use, to make a suspension. After thorough agitation, it is a white, cloudy liquid.
- Inspect the suspension visually for particulate matter and discolouration prior to administration. Discard the vaccine if particulates are present and/or if it appears discoloured.
- Choose an appropriate needle to ensure an intramuscular (IM) administration depending on your patient's size and weight.
- In packs with needles, two needles of different lengths are provided per syringe.
- 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.
- Inject immediately using the intramuscular (IM) route, preferably in the deltoid area of the upper arm or in the higher anterolateral area of the thigh.
- The vaccine should be used as supplied. The full recommended dose of the vaccine should be used.

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