GARDASIL™9
[Human Papillomavirus 9-valent Vaccine, Recombinant]

Fulfills Part A of the WHO Guidelines for Recombinant Human Papillomavirus Virus-like Particle Vaccines

1. NAME OF THE MEDICINAL PRODUCT

Gardasil™9 suspension for injection
Human Papillomavirus 9-valent Vaccine (Recombinant)

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).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for 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.

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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).

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 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.

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

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 trials.

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 trial 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 adverse experience profile for breast-feeding women was comparable to that of the women in the overall safety population. There were no vaccine-related serious adverse experiences 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

A. Summary of the safety profile

In 7 clinical trials, 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 trials 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 trial 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.

B. Tabulated summary 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)

Clinical trials
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 trials (PN 001, 002, 003, 005, 006, 007 and 009, N=15,776 individuals) (see section 5.1 for description of the clinical trials).

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 trials.

Table 1: Adverse reactions following administration of Gardasil 9 from clinical trials 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*

*Adverse events reported during post-marketing use of Gardasil 9. The frequency was estimated based on relevant clinical trials. For events not observed in clinical trials 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.

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- through 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- through 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- through 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 16-23 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)	1679.4 (1518.9, 1856.9)	300 (261)	1565.9 (1412.2, 1736.3)	1.07	(0.93, 1.23)
16 to 26 year old women	6792 (3993)	893.1 (871.7, 915.1)	6795 (3975)	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)	1315.6 (1183.8, 1462.0)	300 (261)	1417.3 (1274.2, 1576.5)	0.93	(0.80, 1.08)
16 to 26 year old women	6792 (3995)	666.3 (649.6, 683.4)	6795 (3982)	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)	6739.5 (6134.5, 7404.1)	300 (270)	6887.4 (6220.8, 7625.5)	0.97	(0.85, 1.11)[¶]
16 to 26 year old women	6792 (4032)	3131.1 (3057.1, 3206.9)	6795 (4062)	3156.6 (3082.3, 3232.7)	0.99	(0.96, 1.03)[¶]
16 to 26 year old men	249 (234)	3924.1 (3513.8, 4382.3)	251 (237)	3787.9 (3378.4, 4247.0)	1.04	(0.89, 1.21)[¶]
Anti-HPV 18						
9 to 15 year old girls	300 (276)	1956.6 (1737.3, 2203.7)	300 (269)	1795.6 (1567.2, 2057.3)	1.08	(0.91, 1.29)[¶]
16 to 26 year old women	6792 (4539)	804.6 (782.7, 827.1)	6795 (4541)	678.7 (660.2, 697.7)	1.19	(1.14, 1.23)[¶]
16 to 26 year old men	249 (234)	884.3 (766.4, 1020.4)	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=7099**		**qHPV Vaccine N=7105**		**%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]	6016	1	6017	38	97.4 (85.0, 99.9)
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3 or AIS[α]	5949	1	5943	35	97.1 (83.5, 99.9)
HPV 31-, 33-, 45-, 52-, 58-related CIN2	5949	1	5943	32	96.9 (81.5, 99.8)
HPV 31-, 33-, 45-, 52-, 58-related CIN3	5949	0	5943	7	100 (39.4, 100)
HPV 31-, 33-, 45-, 52-, 58-related VIN 2/3, VaIN 2/3	6009	0	6012	3	100.0 (-71.5, 100.0)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥6 Months[§]	5941	41	5955	946	96.0 (94.6, 97.1)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥12 Months[¶]	5941	23	5955	657	96.7 (95.1, 97.9)
HPV 31-, 33-, 45-, 52-, 58-related ASC-US HR-HPV Positive or Worse Pap[#] Abnormality	5883	37	5882	506	92.9 (90.2, 95.1)
HPV 31-, 33-, 45-, 52-, 58-related cervical definitive therapy procedures[†]	6013	4	6014	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 HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58

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 HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in the PPE

The efficacy of Gardasil 9 against CIN 2 and worse related to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 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 HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 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 HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in the PPE

The efficacy of Gardasil 9 against cervical biopsy related to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 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 HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 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 9.5 years postdose 3 (median follow-up of 6.3 years) in women (n = 1,448) 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.

<u>Evidence of anamnestic (Immune Memory) response</u>

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, and 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 to 14 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 trial, 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.

<u>Pregnancy</u>

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
L-histidine
Polysorbate 80
Sodium borate
Water for injections

For adjuvant, see section 2.

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

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

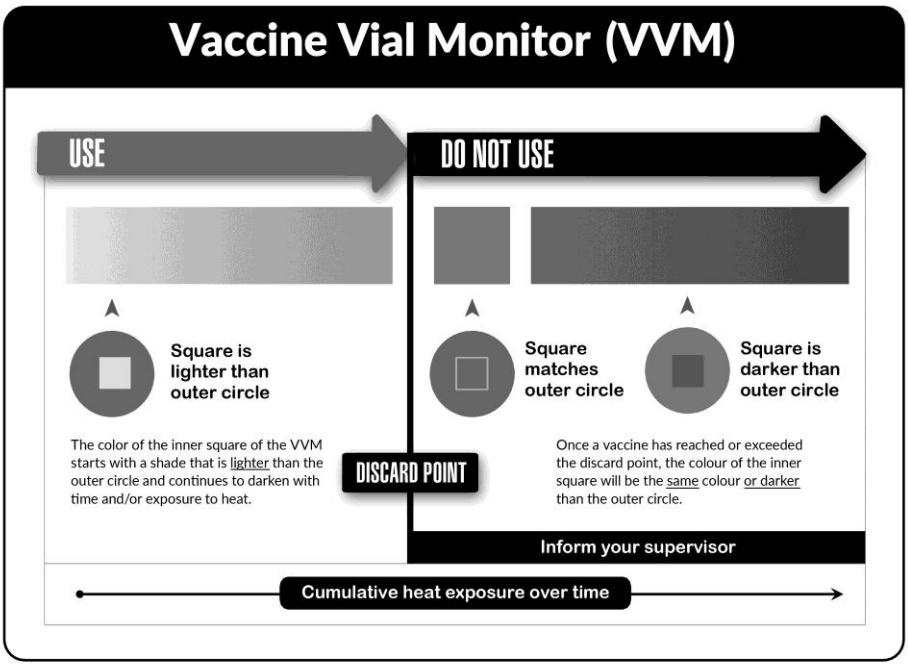
Gardasil 9 should be administered as soon as possible after being removed from the refrigerator.

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.

6.5 Presentation

Vials
Gardasil 9 is supplied as a carton of ten 0.5-mL single-dose vials.

Figure 1: The Vaccine Vial Monitor



The Vaccine Vial Monitors (VVMs) are incorporated into the vial label of Gardasil 9 manufactured by Merck Sharp & Dohme LLC. The color dot which appears on the label of the vial is a VVM. This is a time-temperature sensitive dot that provides an indication of the cumulative heat to which the vial has been exposed. It warns the end user when exposure to heat is likely to have degraded the vaccine beyond an acceptable level.

The interpretation of the VVM is simple. Focus on the central square. Its color will change progressively. As long as the color of this square is lighter than the color of the ring, then the vaccine can be used. As soon as the color of the central square is the same color as the ring or of a darker color than the ring, then the vial should be discarded.

6.6 Special precautions for disposal and other handling

Single-dose vial.

- 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.
- Withdraw the 0.5 ml dose of vaccine from the single-dose vial using a sterile needle and syringe.
- 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.