

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

¹Human Papillomavirus = HPV.

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

³Adsorbed on amorphous aluminium hydroxyphosphate sulphate adjuvant (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 girls and women 9 to 26 years of age 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.

Gardasil 9 is indicated for active immunisation of boys and men 9 to 26 years of age against the following HPV diseases:

- Premalignant lesions and cancers affecting the 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

Girls and Boys 9 to and including 14 years of age at time of first injection

Gardasil 9 can be administered according to a 2-dose 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.

Women and Men 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 (girls and boys <9 years of age)

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

Woman population ≥ 27 years of age

The safety and efficacy of Gardasil 9 in women 27 years of age and older have not been studied (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 cancers, 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 (see section 5.1).

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 from 7 to 12 years who are known to be infected with human immunodeficiency virus (HIV) (see section 5.1).

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

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

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 through 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

A large amount of data on pregnant women (more than 1000 pregnancy outcomes) indicates no malformative nor foeto/neonatal toxicity of Gardasil 9 (see section 5.1).

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

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 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 16 through 26 years of age and 5,281 girls and boys 9 through 15 years of age 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 girls and boys 11-15 years of age, 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).

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 categorized by frequency using the following convention:

- Very common ($\geq 1/10$)
- Common ($\geq 1/100$ to $< 1/10$)
- Uncommon ($\geq 1/1,000$ to $< 1/100$)
- Rare ($\geq 1/10,000$ to $< 1/1,000$)
- 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

The following adverse experiences have been spontaneously reported during post-approval use of qHPV vaccine and may also be seen in post-marketing experience with Gardasil 9. 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.

Infections and infestations: Injection-site cellulitis.

Blood and lymphatic system disorders: Idiopathic thrombocytopenic purpura.

Immune system disorders: Anaphylactoid reactions, bronchospasm.

Nervous system disorders: 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 Gardasil and from 5 additional HPV types (31, 33, 45, 52, 58). It uses the same amorphous aluminium hydroxyphosphate sulphate 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.

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 (AIN2/3), and 90% of genital warts.

The indication of Gardasil 9 is based on:

- non-inferior immunogenicity between Gardasil 9 and the qHPV vaccine for HPV Types 6, 11, 16 and 18 in girls and women 9 to 26 years of age; consequently, 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 16 to 26 years of age, and
- demonstration of non-inferior immunogenicity against the Gardasil 9 HPV Types in boys and girls 9 to 15 years of age and men 16 to 26 years of age, compared to girls and women 16 to 26 years of age.

Clinical studies for qHPV vaccine

Efficacy in 16-26 year-old women and men

Efficacy was assessed in 6 placebo-controlled, double-blind, randomized Phase II and III clinical studies evaluating 28,413 individuals (20,541 girls and women 16 through 26 years of age, 4,055 boys and men 16 through 26 years of age, 3,817 women 24 through 45 years of age). The qHPV vaccine was efficacious in reducing the incidence of CIN (any grade including CIN 2/3); AIS; genital warts; VIN 2/3; and VaIN 2/3 related to vaccine HPV types 6, 11, 16, or 18 in those girls and women who were PCR negative and seronegative at baseline (Table 2). The qHPV vaccine was efficacious in reducing the incidence of genital warts related to vaccine HPV types 6 and 11 in boys and men who

were PCR negative and seronegative at baseline. Efficacy against penile/perineal/perianal intraepithelial neoplasia (PIN) grades 1/2/3 or penile/perineal/perianal cancer was not demonstrated as the number of cases was too limited to reach statistical significance (Table 2). The qHPV vaccine was efficacious in reducing the incidence of anal intraepithelial neoplasia (AIN) grades 2 and 3 related to vaccine HPV types 6, 11, 16, and 18 in boys and men who were PCR negative and seronegative at baseline (Table 2).

Table 2: Analysis of Efficacy of qHPV vaccine in the PPE* Population for Vaccine HPV Types

Disease Endpoints	qHPV		Placebo Control		% Efficacy (95% CI)
	N	Number of cases	N	Number of cases	
16- Through 26-Year-Old Girls and Women[†]					
HPV 16- or 18-related CIN 2/3 or AIS**	8493	2	8464	112	98.2 (93.5, 99.8)
HPV 6-, 11-, 16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS	7864	9	7865	225	96.0 (92.3, 98.2)
HPV 6-, 11-, 16- or 18-related VIN 2/3	7772	0	7744	10	100.0 (67.2, 100.0)
HPV 6-, 11-, 16- or 18-related VaIN 2/3	7772	0	7744	9	100.0 (55.4, 100.0)
HPV 6-, 11-, 16-, or 18-related Genital Warts	7900	2	7902	193	99.0 (96.2, 99.9)
16- Through 26-Year-Old Boys and Men					
External HPV 6-, 11-, 16-, or 18-related Genital Lesions***	1394	3	1404	32	90.6 (70.1, 98.2)
HPV 6-, 11-, 16-, or 18-related Genital Warts***	1394	3	1404	28	89.3 (65.3, 97.9)
HPV 6-, 11-, 16-, or 18-related PIN 1/2/3***	1394	0	1404	4	100.0 (-52.1, 100.0)
HPV 6-, 11-, 16-, or 18-related AIN 2/3****	194	3	208	13	74.9 (8.8, 95.4)

*The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrolment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month postdose 3 (Month 7).

[†]Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria.

N=Number of individuals with at least 1 follow-up visit after Month 7.

CI=Confidence Interval.

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

***Median duration of follow-up 2.4 years

****Median duration of follow-up was 2.15 years

Efficacy in 24-45 year-old women

The efficacy of qHPV vaccine in 24- through 45-year-old women was assessed in 1 placebo-controlled, double-blind, randomized Phase III clinical study (Protocol 019, FUTURE III) including a total of 3,817 women.

In the PPE population, the efficacy of qHPV vaccine against the combined incidence of HPV 6-, 11-, 16-, or 18-related persistent infection, genital warts, vulvar and vaginal lesions, CIN of any grade, AIS, and cervical cancers was 88.7% (95% CI: 78.1, 94.8). The efficacy of qHPV vaccine against the combined incidence of HPV 16- or 18-related persistent infection, genital warts, vulvar and vaginal lesions, CIN of any grade, AIS, and cervical cancers was 84.7% (95% CI: 67.5, 93.7).

Long-term efficacy studies

A subset of subjects is currently being followed up for 10 to 14 years after qHPV vaccination for safety, immunogenicity and protection against clinical diseases related to HPV types 6/11/16/18.

Persistence of antibody response (postdose 3) has been observed for 10 years in girls and boys who were 9-15 years of age at time of vaccination; 9 years in women, 16-23 years of age at time of vaccination; 6 years in men, 16-26 years of age at time of vaccination; and 8 years in women, 24-45 years of age at time of vaccination.

In the long-term extension registry study for 16-23 year-old women vaccinated with qHPV vaccine in the base study (n=1,984), no cases of HPV diseases (HPV types 6/11/16/18 related high-grade CIN) were observed up to approximately 10 years. In this study, a durable protection was statistically demonstrated to approximately 8 years.

In long-term extensions of clinical studies, protection has been observed postdose 3 in the PPE population. The PPE population consisted of individuals:

- who received all 3 vaccinations within 1 year of enrolment, did not have 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, were PCR negative to the relevant HPV type(s) prior to dose 1 through one month postdose 3 (Month 7).

In these extensions clinical studies, no cases of high-grade intraepithelial neoplasia and no cases of genital warts were observed in subjects who received qHPV vaccine in the base study:

- 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 9.6 years in men (n=918), 16-26 years of age at time of vaccination (median follow-up of 8.5 years); and
- through 8.4 years in women (n=684), 24-45 years of age at time of vaccination (median follow-up of 7.2 years).

Efficacy in HIV infected subjects

A study documenting safety and immunogenicity of qHPV vaccine has been performed in 126 HIV infected subjects aged from 7-12 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 Geometric Mean Titers (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.

Clinical studies for Gardasil 9

Efficacy and/or immunogenicity of Gardasil 9 were assessed in eight 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 Titers [GMT]) of Gardasil 9 compared with qHPV vaccine (Protocol 001 and GDS01C/Protocol 009).

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 16 through 26 years of age (N=14,204: 7,099 receiving Gardasil 9; 7,105 receiving qHPV vaccine).

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

Protocol 003 evaluated immunogenicity of Gardasil 9 in men 16 through 26 years of age and women 16 through 26 years of age (1,103 Heterosexual Men [HM]; 313 Men Who Have Sex with Men [MSM]; and 1,099 women receiving Gardasil 9).

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

Protocol 006 evaluated administration of Gardasil 9 to girls and women 12 through 26 years of age 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 9 through 15 years of age (N=600; 300 receiving Gardasil 9 and 300 receiving qHPV vaccine).

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

Studies supporting the efficacy of Gardasil 9 against 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 16- through 26-year-old women from Protocol 001 and 9- through 15-year-old girls from GDS01C/Protocol 009.

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 99.6% to 100% who received Gardasil 9 became seropositive for antibodies against all 9 vaccine types by Month 7 across all groups tested.

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* population of 9- through 26-year-old girls and women

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-years of age	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-years of age	6792 (3993)	893.1 (871.7, 915.1)	6795 (3975)	875.2 (854.2, 896.8)	1.02	(0.99, 1.06) [†]
Anti-HPV 11						
9 to 15-years of age	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-years of age	6792 (3995)	666.3 (649.6, 683.4)	6795 (3982)	830.0 (809.2, 851.4)	0.80	(0.77, 0.83) [†]
Anti-HPV 16						
9 to 15-years of age	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-years of age	6792 (4032)	3131.1 (3057.1, 3206.9)	6795 (4062)	3156.6 (3082.3, 3232.7)	0.99	(0.96, 1.03) [†]
Anti-HPV 18						
9 to 15-years of age	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-years of age	6792 (4539)	804.6 (782.7, 827.1)	6795 (4541)	678.7 (660.2, 697.7)	1.19	(1.14, 1.23) [†]

*The PPI population consisted of individuals who received all three vaccinations within pre-defined 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, were naïve (PCR negative [among 16- through 26-year-old girls and women] and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1, and among 16- through 26-year-old girls and women, were PCR negative to the relevant HPV type(s) 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 Titers.

cLIA= Competitive Luminex Immunoassay.

N= Number of individuals randomized 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 16- through 26-year-old women was assessed in an active comparator-controlled, double-blind, randomized 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 16- through 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 ^a	6016	1	6017	38	97.4 (85.0, 99.9)
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3 or AIS ^a	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 randomized 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)

^ano 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 11/6016 versus 262/6018 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 4/6016 versus 43/6018 cases.

Immunogenicity

The minimum anti-HPV titer 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 neutralizing 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 across all clinical studies

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 Titer (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 (Table 5). In clinical studies 99.6% 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 16- through 26-year-old women, and higher in boys than in girls and women.

Table 5: Summary of month 7 Anti-HPV cLIA Geometric Mean Titers in the PPI* population

Population	N	n	GMT (95% CI) mMU [§] /mL
Anti-HPV 6			
9 to 15-year-old girls	2805	2349	1744.6 (1684.7, 1806.7)
9 to 15-year-old boys	1239	1055	2085.3 (1984.2, 2191.6)
16 to 26-year-old women	7260	4321	893.7 (873.5, 914.3)
Anti-HPV 11			
9 to 15-year-old girls	2805	2350	1289.7 (1244.3, 1336.8)
9 to 15-year-old boys	1239	1055	1469.2 (1397.7, 1544.4)
16 to 26-year-old women	7260	4327	669.3 (653.6, 685.4)
Anti-HPV 16			
9 to 15-year-old girls	2805	2405	7159.9 (6919.7, 7408.5)
9 to 15-year-old boys	1239	1076	8444.9 (8054.2, 8854.5)
16 to 26-year-old women	7260	4361	3159.0 (3088.6, 3231.1)
Anti-HPV 18			
9 to 15-year-old girls	2805	2420	2085.5 (2002.2, 2172.3)
9 to 15-year-old boys	1239	1074	2620.4 (2474.3, 2775.2)
16 to 26-year-old women	7260	4884	809.9 (789.2, 831.1)
Anti-HPV 31			
9 to 15-year-old girls	2805	2397	1883.3 (1811.3, 1958.1)
9 to 15-year-old boys	1239	1069	2173.5 (2057.0, 2296.6)
16 to 26-year-old women	7260	4806	664.8 (647.4, 682.6)
Anti-HPV 33			
9 to 15-year-old girls	2805	2418	960.6 (927.5, 994.9)
9 to 15-year-old boys	1239	1076	1178.6 (1120.9, 1239.4)
16 to 26-year-old women	7260	5056	419.2 (409.6, 429.1)
Anti-HPV 45			
9 to 15-year-old girls	2805	2430	728.7 (697.6, 761.2)
9 to 15-year-old boys	1239	1079	841.7 (790.0, 896.7)
16 to 26-year-old women	7260	5160	254.1 (247.0, 261.5)
Anti-HPV 52			
9 to 15-year-old girls	2805	2426	978.2 (942.8, 1015.0)
9 to 15-year-old boys	1239	1077	1062.2 (1007.2, 1120.2)
16 to 26-year-old women	7260	4792	382.4 (373.0, 392.0)
Anti-HPV 58			
9 to 15-year-old girls	2805	2397	1306.0 (1259.8, 1354.0)
9 to 15-year-old boys	1239	1072	1545.8 (1470.6, 1624.8)
16 to 26-year-old women	7260	4818	489.2 (477.5, 501.2)

*The PPI population consisted of individuals who received all three vaccinations within pre-defined 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, were naïve (PCR negative and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1, and among 16- through 26-year-old girls and women, were PCR negative to the relevant HPV type(s) through one month postdose 3 (Month 7).

[§]mMU=milli-Merck Units.

cLIA=Competitive Luminex Immunoassay.

CI=Confidence Interval.

GMT=Geometric Mean Titers.

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

n= Number of individuals contributing to the analysis.

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

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

Anti-HPV antibody GMTs at Month 7 among 16- through 26-year-old boys and men (HM) were comparable to anti-HPV antibody GMTs among 16- through 26-year-old girls and women. High immunogenicity in 16- through 26-year-old MSM was also observed, although lower than in HM, similarly to qHPV vaccine. These results support the efficacy of Gardasil 9 in the male population.

No studies have been conducted in women older than 26 years of age. In women 27- through 45 years of age, efficacy of Gardasil 9 for the 4 original types is expected based on (1) high efficacy of qHPV vaccine in women 16- through 45 years of age and (2) comparable immunogenicity of Gardasil 9 and qHPV vaccine in girls and women 9- through 26 years of age.

Persistence of immune response to Gardasil 9 using a 3-dose schedule

The persistence of antibody response following a 3-dose schedule of vaccination with Gardasil 9 is being studied in a subset of individuals who will be followed up for at least 10 years after vaccination for safety, immunogenicity and effectiveness.

In 9-15 year-old boys and girls (Protocol 002), persistence of antibody response has been demonstrated for at least 3 years; depending on HPV type, 93 to 99% of subjects were seropositive.

In 16-26 year-old women (Protocol 001), persistence of antibody response has been demonstrated for at least 3.5 years; depending on HPV type, 78-98% of subjects were seropositive. 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).

GMTs for HPV-6, -11, -16 and -18 were numerically comparable in subjects who received qHPV vaccine or Gardasil 9 for at least 3.5 years.

Administration of Gardasil 9 to girls and women previously vaccinated with qHPV vaccine

Protocol 006 evaluated the immunogenicity of Gardasil 9 in 921 girls and women (12 through 26 years of age) 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 HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 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.

Immune Responses to Gardasil 9 using a 2-dose schedule in girls and boys 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 9 to 14 years old receiving 2 doses at a 6 month or 12-month interval (+/- 1 month); girls 9 to 14 years old receiving 3 doses (at 0, 2, 6 months); and women 16 to 26 years old 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 16 to 26-year-old girls and women 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 9 to 14-year-old girls and boys is inferred.

In the same study, in girls and boys 9 to 14 years old, 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.

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 versus 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 women who received Gardasil 9 or qHPV vaccine were comparable and consistent with the general population.

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.

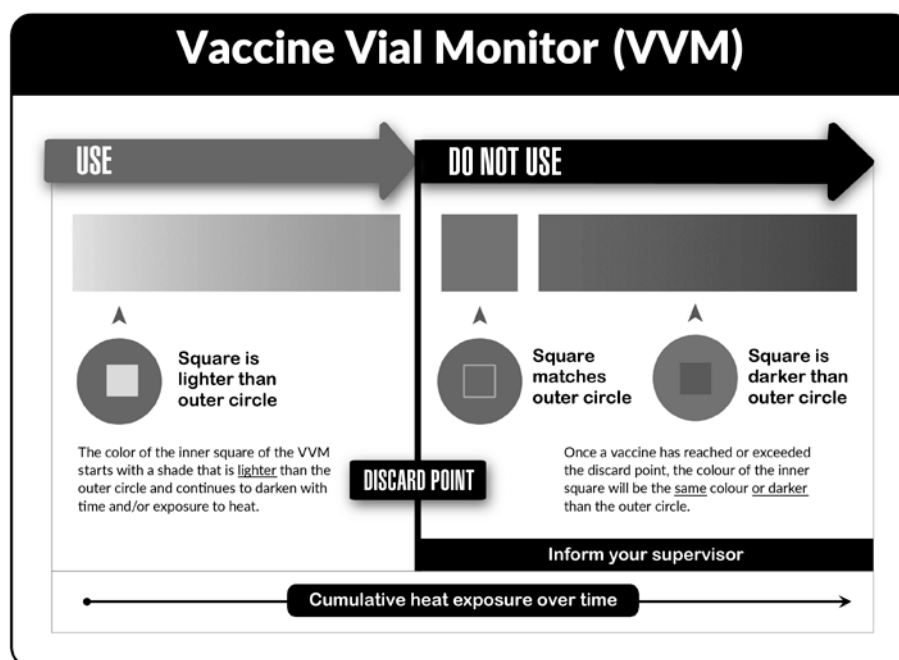
Stability data indicate that the vaccine components are stable for 96 hours when stored at temperatures from 8°C to 40°C or for 72 hours when stored at temperatures from 0°C to 2°C. At the end of this period Gardasil 9 should be used or discarded. These data are intended to guide healthcare professionals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