GARDASIL9 [Human Papillomavirus 9-valent Vaccine, Recombinant]
Suspension for Injection

1. NAME OF THE MEDICINAL PRODUCT

GARDASIL 9 suspension for injection
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 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

Girls and Women

GARDASIL 9 is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases:

- Cervical, vulvar, vaginal, and anal cancer caused by Human Papillomavirus (HPV) types 16, 18,31, 33, 45, 52, and 58
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma in situ (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 1
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

Boys and Men

GARDASIL 9 is indicated in boys and men 9 through 26 years of age for the prevention of the

following diseases:

- Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52,

and 58:

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

The use of GARDASIL 9 should be in accordance with official recommendations. Protection has been observed for up to 6 years (median duration of follow-up of 4 years) in a clinical study. There are no data on the efficacy of GARDASILI 9 beyond 6 years.

4.2 Posology and method of administration

Posology

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

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.

Alternatively, in individuals 9 through 14 years of age, GARDASIL 9 can be administered according to a 2-dose schedule. 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.

The need for a booster dose has not been established.

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

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).

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

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, vaccines 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 immunization.

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 (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 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.

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 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 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 enrollment 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 adolescents 9 through 15 years of age at enrollment) received GARDASIL 9. Few individuals (0.1%) discontinued due to adverse experiences.

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

Clinical Trials

Adverse reactions considered as being at least possibly related to vaccination have been categorised by frequency.

Frequencies are reported as:

- Very common (≥1/10)
- Common (≥1/100 to <1/10)

Table 1: Adverse reactions following administration of GARDASIL 9 occurring with a frequency of at least 1.0% from clinical trials

System Organ Class	Frequency	Adverse reactions
Nervous system disorders	Very common	Headache
	Common	Dizziness
Gastrointestinal disorders	Common	Nausea
General disorders and administration site conditions	Very common	At the injection site; pain, swelling, erythema
	Common	Pyrexia, fatigue, At the injection site: pruritus, bruising

In a clinical trial of 1,053 healthy adolescents 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).

Post-Marketing Experience

The post-marketing adverse experiences were reported voluntarily from a population of uncertain size, therefore, it is not possible to reliably estimate their frequency or to establish a causal relationship to vaccine exposure. The post-marketing adverse experience with qHPV vaccine is relevant to Gardasil 9 since the vaccines contain L1 HPV proteins of 4 of the same HPV types.

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GARDASIL 9

In addition to the adverse reactions reported in the clinical studies, the following adverse experiences have been spontaneously reported during post-approval use of GARDASIL 9:

Nervous system disorders: syncope sometimes accompanied by tonic-clonic movements.

Gastrointestinal disorders: vomiting.

GARDASIL

Additionally, the following post-marketing adverse experiences have been spontaneously reported for GARDASIL:

Infections and infestations: Injection-site cellulitis.

Blood and lymphatic system disorders: Idiopathic thrombocytopenic purpura, lymphadenopathy.

Immune system disorders: Hypersensitivity reactions including anaphylactic/anaphylactoid reactions, bronchospasm and urticaria.

Nervous system disorders: Acute disseminated encephalomyelitis, Guillain-Barré syndrome..

Musculoskeletal and connective tissue disorders: Arthralgia, myalgia.

General disorders and administration site conditions: Asthenia, chills, malaise.

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 to 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 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 enrollment 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 enrollment in the base study, PCR negative to the relevant HPV type(s) prior to dose 1 through one month postdose 3 (Month 7). 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 girls and women in the PPE population (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 in the PPE population. 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 in the PPE population (Table 2).

Table 2: Analysis of Efficacy of qHPV 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 16- or 18-related VIN 2/3	7772	0	7744	10	100.0 (67.2, 100.0)
HPV 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)
External HPV 6-, 11-, 16-, or 18-related Genital Warts***	1394	3	1404	28	89.3 (65.3, 97.9)
External HPV 6-, 11-, 16-, or 18-related PIN 1/2/3***	1394	0	1404	4	100.0 (-52.1, 100.0)
External 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 to 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 adolescents 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=2,084), no cases of HPV diseases (HPV types 6/11/16/18 related high grade CIN) were observed up to approximately 12 years. In this study, a durable protection was statistically demonstrated to approximately 10 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 post-dose 3 (Month 7)

In long term extensions of 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 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=684), 24-45 years of age at time of vaccination (median follow-up of 8.7 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 the three dose regimen of GARDASIL 9 were assessed in seven 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- through15-year-old girls	300 (273)	1679.4	300 (261)	1565.9	1.07	(0.93, 1.23)

		(1518.9, 1856.9)		(1412.2, 1736.3)		
16- through 26-year-old girls and women	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- through 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- through 26-year-old girls and women	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- through 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- through 26-year-old girls and women	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- through 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- through 26-year-old girls and women	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 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.

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 post-dose 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		GARDASIL 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 CIN 2	5949	1	5943	32	96.9 (81.5, 99.8)
HPV 31-, 33-, 45-, 52-, 58-related CIN 3	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	5883	37	5882	506	92.9

Positive or Worse Pap# Abnormality					(90.2, 95.1)
HPV 31-, 33-, 45-, 52-, 58-related cervical definitive therapy procedure‡	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)

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 11/6016 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- through 15-year-old girls	2805	2349	1744.6 (1684.7, 1806.7)
9- through 15-year-old boys	1239	1055	2085.3 (1984.2, 2191.6)
16- through 26-year-old women	7260	4321	893.7 (873.5, 914.3)
Anti-HPV 11			
9- through 15-year-old girls	2805	2350	1289.7 (1244.3, 1336.8)
9- through 15-year-old boys	1239	1055	1469.2 (1397.7, 1544.4)
16- through 26-year-old women	7260	4327	669.3 (653.6, 685.4)
Anti-HPV 16			
9- through 15-year-old girls	2805	2405	7159.9 (6919.7, 7408.5)

9- through 15-year-old boys	1239	1076	8444.9 (8054.2, 8854.5)
16- through 26-year-old women	7260	4361	3159.0 (3088.6, 3231.1)
Anti-HPV 18			
9- through 15-year-old girls	2805	2420	2085.5 (2002.2, 2172.3)
9- through 15-year-old boys	1239	1074	2620.4 (2474.3, 2775.2)
16- through 26-year-old women	7260	4884	809.9 (789.2, 831.1)
Anti-HPV 31			
9- through 15-year-old girls	2805	2397	1883.3 (1811.3, 1958.1)
9- through 15-year-old boys	1239	1069	2173.5 (2057.0, 2296.6)
16- through 26-year-old women	7260	4806	664.8 (647.4, 682.6)
Anti-HPV 33			
9- through 15-year-old girls	2805	2418	960.6 (927.5, 994.9)
9- through 15-year-old boys	1239	1076	1178.6 (1120.9, 1239.4)
16- through 26-year-old women	7260	5056	419.2 (409.6, 429.1)
Anti-HPV 45			
9- through 15-year-old girls	2805	2430	728.7 (697.6, 761.2)
9- through 15-year-old boys	1239	1079	841.7 (790.0, 896.7)
16- through 26-year-old women	7260	5160	254.1 (247.0, 261.5)
Anti-HPV 52			
9- through 15-year-old girls	2805	2426	978.2 (942.8, 1015.0)
9- through 15-year-old boys	1239	1077	1062.2 (1007.2, 1120.2)
16- through 26-year-old women	7260	4792	382.4 (373.0, 392.0)
Anti-HPV 58			
9- through 15-year-old girls	2805	2397	1306.0 (1259.8, 1354.0)
9- through 15-year-old boys	1239	1072	1545.8 (1470.6, 1624.8)
16- through 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 [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.

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.

Immune Responses to GARDASIL 9 Using a 2-dose Schedule in Individuals 9- through14 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- through 14 years old receiving 2 doses at a 6 month or 12-month interval (+/- 1 month); girls 9- through 14 years old receiving 3 doses (at 0, 2, 6 months); and women 16- through 26 years old receiving 3 doses (at 0, 2, 6 months).

GMTs were non-inferior in girls and boys who received 2 doses of GARDASIL 9 (at either 0, 6 months or 0, 12 months) to GMTs in 16 through 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 through 14 year old girls and boys is inferred. 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 (Table 12).

In the same study, in girls and boys 9 through 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 in girls 9 through 14 years old after a 3-dose schedule (HPV types 18, 31, 45, and 52 after 0, 6 months and HPV type 45 after 0, 12 months; Table 12). The clinical relevance of these findings is unknown.

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

Table 6. Summary of Anti-HPV cLIA Geometric Mean Titers in the PPI* Population at One Month After the Last Vaccine Dose Among Subjects Who Received 2 Doses† or 3 Doses† of GARDASIL 9

Population (Regimen)	N	n	GMT (95% CI) mMU§/mL
Anti-HPV 6			
9- through 14-year-old girls (0, 6)†	301	258	1657.9 (1479.6, 1857.6)
9- through 14-year-old boys (0, 6)†	301	263	1557.4 (1391.5, 1743.1)
9- through 14-year-old girls (0, 12)†	150	123	2685.7 (2274.6, 3171.2)
9- through 14-year-old boys (0, 12)†	150	134	2672.4 (2279.1, 3133.5)
9- through 14-year-old girls (0, 2, 6)†	300	254	1496.1 (1334.1, 1677.8)
16- through 26-year-old women (0, 2, 6)†	314	238	770.9 (684.8, 867.9)
Anti-HPV 11			
9- through 14-year-old girls (0, 6)†	301	258	1388.9 (1240.4, 1,555.3)
9- through 14-year-old boys (0, 6)†	301	264	1423.9 (1273.2, 1592.3)
9- through 14-year-old girls (0, 12)†	150	123	2915.9 (2475.1, 3435.1)
9- through 14-year-old boys (0, 12)†	150	134	2965.9 (2534.9, 3470.1)
9- through 14-year-old girls (0, 2, 6)†	300	254	1306.3 (1165.5, 1464.0)
16- through 26-year-old women (0, 2, 6)†	314	238	580.5 (516.0, 653.0)
Anti-HPV 16			
9- through 14-year-old girls (0, 6)†	301	272	8004.9 (7160.5, 8948.8)
9- through 14-year-old boys (0, 6)†	301	273	8474.8 (7582.4, 9472.3)
9- through 14-year-old girls (0, 12)†	150	129	13828.1 (11780.6, 16231.5)
9- through 14-year-old boys (0, 12)†	150	135	14825.2 (12675.7, 17339.3)
9- through 4-year-old girls (0, 2, 6)†	300	269	6996.0 (6254.1, 7825.8)
16- through 26-year-old women (0, 2, 6)†	314	249	3154.0 (2807.1, 3,543.7)
Anti-HPV 18			
9- through 14-year-old girls (0, 6)†	301	272	1872.8 (1651.6, 2123.6)
9- through 14-year-old boys (0, 6)†	301	272	1860.9 (1641.1, 2110.2)
9- through 14-year-old girls (0, 12)†	150	129	2696.0 (2252.4, 3227.0)
9- through 14-year-old boys (0, 12)†	150	137	2922.5 (2454.7, 3479.5)
9- through 14-year-old girls (0, 2, 6)†	300	270	2049.3 (1806.4, 2324.8)
16- through 26-year-old women (0, 2, 6)†	314	267	761.5 (670.8, 864.5)
Anti-HPV 31			
9- through 14-year-old girls (0, 6)†	301	272	1436.3 (1272.1, 1621.8)
9- through 14-year-old boys (0, 6)†	301	271	1498.2 (1326.5, 1692.0)
9- through 14-year-old girls (0, 12)†	150	132	2086.4 (1761.7, 2471.1)
9- through 14-year-old boys (0, 12)†	150	136	2148.1 (1818.3, 2537.7)
9- through 14-year-old girls (0, 2, 6)†	300	271	1748.3 (1548.1, 1974.5)
16- through 26-year-old women (0, 2, 6)†	314	264	572.1 (505.8, 647.2)
Anti-HPV 33			
9- through 14-year-old girls (0, 6)†	301	273	1030.0 (920.4, 1152.7)
9- through 14-year-old boys (0, 6)†	301	271	1040.0 (928.9, 1164.3)
9- through 14-year-old girls (0, 12)†	150	132	2037.4 (1737.6, 2389.0)
9- through 14-year-old boys (0, 12)†	150	137	2363.6 (2021.6, 2763.3)

9- through 14-year-old girls (0, 2, 6)†	300	275	796.4 (712.0, 890.9)
16- through 26-year-old women (0, 2, 6)†	314	279	348.1 (311.5, 389.1)
Anti-HPV 45			
9- through 14-year-old girls (0, 6)†	301	274	357.6 (313.7, 407.6)
9- through 14-year-old boys (0, 6)†	301	273	352.3 (309.0, 401.7)
9- through 14-year-old girls (0, 12)†	150	132	439.6 (366.0, 528.0)
9- through 14-year-old boys (0, 12)†	150	136	397.6 (331.9, 476.2)
9- through 14-year-old girls (0, 2, 6)†	300	275	661.7 (580.6, 754.1)
16- through 26-year-old women (0, 2, 6)†	314	280	213.6 (187.7, 243.2)
Anti-HPV 52			
9- through 14-year-old girls (0, 6)†	301	272	581.1 (521.9, 647.1)
9- through 14-year-old boys (0, 6)†	301	273	640.4 (575.2, 713.0)
9- through 14-year-old girls (0, 12)†	150	131	1028.2 (885.0, 1194.7)
9- through 14-year-old boys (0, 12)†	150	137	1222.7 (1055.9, 1415.9)
9- through 14-year-old girls (0, 2, 6)†	300	275	909.9 (817.6, 1012.5)
16- through 26-year-old women (0, 2, 6)†	314	271	364.2 (327.0, 405.6)
Anti-HPV 58			
9- through 14-year-old girls (0, 6)†	301	270	1251.2 (1119.6, 1398.4)
9- through 14-year-old boys (0, 6)†	301	270	1325.7 (1186.2, 1481.6)
9- through14-year-old girls (0, 12)†	150	129	2244.7 (1919.2, 2625.3)
9- through 14-year-old boys (0, 12)†	150	136	2650.7 (2275.6, 3087.6)
9- through 14-year-old girls (0, 2, 6)†	300	273	1229.3 (1100.7, 1,373.0)
16- through 26-year-old women (0, 2, 6)†	314	261	491.1 (438.6, 549.8)

*The PPI population consisted of individuals who received all assigned vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the last vaccination dose and blood collection for immunogenicity assessment, and were seronegative to the relevant HPV type(s) (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) prior to dose 1.

†2-dose regimen (0, 6): vaccination at Day 1 and Month 6; 2-dose regimen (0, 12): vaccination at Day 1 and Month 12; 3-dose regimen (0, 2, 6): vaccination at Day 1, Month 2, and Month 6. The data are from Study 8 (NCT01984697).

§mMU=milli-Merck Units.

N = Number of individuals randomized to the respective vaccination group who received at least 1 injection. n = Number of individuals contributing to the analysis.

CI=confidence interval

cLIA=competitive Luminex immunoassay

GMT=Geometric Mean Titer

Persistence of immune response to GARDASIL 9

The persistence of antibody response following a complete 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 5 years; depending on HPV type, 90 to 99% of subjects were seropositive.

In 16-26 year-old women (Protocol 001), persistence of antibody response has been demonstrated for at least 5 years; depending on HPV type, 78-100% 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 individuals 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, 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.

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.

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 prefilled 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 72 hours when stored at temperatures from 8°C to 25°C or 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 Nature and contents of container

Box, 1 pre-filled syringe @ 0.5 mL

6.6 Special precautions for disposal and other handling

pre-filled syringe

- GARDASIL 9 may appear as a clear liquid with a white precipitate prior to agitation.
- Shake well before use, the pre-filled syringe, 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.
- Two needles of different lengths are provided in the pack, choose the appropriate needle to ensure an intramuscular (IM) administration depending on your patient's size and weight.
- 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.

HARUS DENGAN RESEP DOKTER

Reg. No. DKI1863501043A1

Manufactured by:
Merck Sharp & Dohme Corp.
West Point, PA 19486, U.S.A.
Released by:
Merck Sharp & Dohme Haarlem BV/MVD – Holland, Haarlem,
Netherlands
Registered by:
PT. Merck Sharp Dohme Pharma Tbk
Pasuruan, Jawa Timur

Anda dapat melaporkan efek samping secara langsung melalui:

DPOC – PT Merck Sharp Dohme Pharma Tbk Email : dpoc.indonesia@merck.com Fax : 021 5789 7069
Pusat Farmakovigilans c.q Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotik, Psikotropik, Prekursor dan Zat Adiktif Badan Pengawas Obat dan Makanan Republik Indonesia Melalui pos: Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560 Email: pv-center@pom.go.id Tel: + 62-21-4244691 Ext: 1072 Faks: +62-21-42883485 Website: http//e-meso.pom.go.id/

Lembaran Paket: Informasi Untuk Pengguna

GARDASIL 9 suspensi untuk injeksi dalam *pre-filled syringe*
Human Papillomavirus 9-valent Vaccine (*Recombinant, adsorbed*)

Baca semua lembar informasi ini dengan hati-hati sebelum Anda atau anak Anda divaksinasi karena ini mengandung informasi penting untuk Anda dan anak Anda.
Simpan lembar informasi ini. Anda mungkin membutuhkannya untuk dibaca lagi.
- Jika Anda memiliki pertanyaan lain, silahkan bertanya pada dokter Anda, apoteker atau perawat.
- Jika Anda atau anak Anda mendapatkan efek samping apapun, hubungi dokter Anda, apoteker atau perawat Anda. Termasuk kemungkinan efek samping lainnya yang tidak tertera pada lembar informasi ini. Lihat bagian 4.

Apa saja yang terdapat di dalam leaflet ini

1. Apa itu GARDASIL 9 dan apa kegunaannya

GARDASIL 9 adalah vaksin untuk individu dari umur 9 sampai 26 tahun. Diberikan untuk melindungi dari penyakit yang disebabkan oleh *Human Papillomavirus* (HPV) tipe 6, 11, 16, 18, 31, 33, 45, 52 dan 58.

Penyakit ini termasuk lesi pre-kanker dan kanker pada alat kelamin wanita (serviks, vulva, dan vagina), lesi pre-kanker dan kanker anus dan kutil kelamin pada pria dan wanita.

GARDASIL 9 telah diteliti pada pria dan wanita dari umur 9 sampai 26 tahun.

GARDASIL 9 melindungi dari tipe HPV yang menjadi penyebab **utama** dari penyakit-penyakit tersebut.

GARDASIL 9 ditujukan untuk mencegah penyakit-penyakit tersebut. Vaksin ini tidak digunakan untuk mengobati penyakit terkait HPV. GARDASIL 9 tidak memiliki efek pada individu yang memiliki infeksi persisten atau penyakit yang berhubungan dengan tipe HPV manapun di vaksin ini. Namun, pada individu yang telah terinfeksi satu atau lebih oleh tipe HPV pada vaksin, GARDASIL 9 tetap memberikan perlindungan dari penyakit yang berhubungan dengan tipe HPV lain yang terdapat pada vaksin.

GARDASIL 9 tidak dapat menyebabkan penyakit terkait HPV.

Ketika seorang individu divaksinasi dengan GARDASIL 9, sistem imun (sistem pertahanan natural tubuh) merangsang produksi antibodi terhadap sembilan tipe HPV pada vaksin, untuk membantu melindungi terhadap penyakit yang disebabkan oleh virus tersebut.

Jika Anda atau anak Anda menerima dosis pertama GARDASIL 9, anda harus menyelesaikan rangkaian vaksinasi lengkap dengan GARDASIL 9.

Jika anda atau anak anda sudah menerima vaksin HPV, tanyakan pada dokter Anda jika GARDASIL 9 tepat untuk Anda.

GARDASIL 9 harus digunakan sesuai dengan pedoman resmi.

2. Apa yang perlu Anda ketahui sebelum Anda atau anak Anda menerima GARDASIL 9 Jangan

menerima GARDASIL 9 jika Anda atau anak Anda

- Alergi terhadap zat aktif atau kandungan apapun yang terdapat pada vaksin (terdapat dalam "kandungan lain", pada bagian 6).
- Timbul sebuah reaksi alergi setelah menerima satu dosis GARDASIL (HPV tipe 6, 11, 16, dan 18) atau GARDASIL 9.

Perhatian dan peringatan

Beritahu dokter Anda atau perawat jika Anda atau anak Anda:

- memiliki kelainan pendarahan (sebuah penyakit yang membuat anda berdarah lebih dari normal), contohnya hemofilia;
- memiliki sistem imun yang lemah, contohnya seperti yang disebabkan oleh cacat genetik, infeksi HIV atau obat-obatan yang mempengaruhi sistem imun ;
- menderita penyakit dengan demam tinggi. Namun, demam ringan atau infeksi pernapasan atas ringan (contohnya mengalami flu) bukan merupakan salah satu alasan untuk menunda vaksinasi.

Pingsan, terkadang diikuti dengan terjatuh, dapat terjadi (kebanyakan pada orang remaja) setelah injeksi dengan jarum. Oleh karena itu katakan pada dokter atau perawat jika terjadi pingsan pada penyuntikan sebelumnya .

Sama dengan vaksin lainnya, GARDASIL 9 mungkin tidak melindungi semua orang yang sudah divaksin.

GARDASIL 9 tidak akan melindungi dari setiap tipe *Human Papillomavirus*. Oleh karena itu, perhatian yang sesuai terhadap penyakit menular seksual harus selalu diterapkan.

Vaksinasi bukan merupakan pengganti untuk skrining serviks rutin. Jika Anda seorang wanita, **Anda harus melanjutkan untuk mengikuti saran dokter terhadap tes Pap/smear serviks dan tindakan pencegahan dan perlindungan.**

Apa informasi penting lainnya yang perlu anda atau anak anda ketahui tentang GARDASIL 9

Durasi untuk perlindungan belum diketahui pasti. Studi tindak lanjut jangka panjang sedang berlangsung untuk menentukan jika *booster* dibutuhkan atau tidak.

Obat lain dan GARDASIL 9

Beritahu dokter atau apoteker Anda jika Anda atau anak Anda sedang menggunakan, baru saja menggunakan atau ada kemungkinan menggunakan obat lain, termasuk obat yang didapatkan tanpa resep.

GARDASIL 9 dapat diberikan dengan vaksin *booster* kombinasi difteri (d) dan tetanus (T) bersama pertusis [komponen, *acellular*] (ap) dan/atau *poliomyelitis* [tidak aktif] (IPV) (vaksin dTap, dT-IPV, dTap-IPV) ditempat penyuntikkan yang berbeda (bagian lain dari tubuh Anda, seperti bagian lengan yang lain atau kaki) pada kunjungan yang sama.

GARDASIL 9 mungkin tidak memiliki efek yang maksimal jika digunakan dengan obat yang menekan sistem imun. Kontrasepsi hormonal (seperti pil) tidak mengurangi perlindungan yang dihasilkan oleh GARDASIL 9.

Kehamilan dan menyusui

Jika Anda hamil, atau merasa Anda mungkin hamil atau berencana memiliki anak, tanyakan pada dokter Anda untuk anjuran sebelum Anda menerima vaksin ini.

GARDASIL 9 dapat diberikan kepada wanita yang sedang menyusui atau berencana untuk menyusui .

Mengemudi dan menjalankan mesin

GARDASIL 9 mungkin sedikit berpengaruh dan sementara terhadap kemampuan untuk menyetir atau menjalankan mesin (lihat bagian 4 “Efek samping yang memungkinkan”).

3. Bagaimana GARDASIL 9 diberikan

GARDASIL 9 diberikan sebagai injeksi oleh dokter anda. GARDASIL 9 ditujukan untuk individu dari

umur 9 sampai 26 tahun.

GARDASIL 9 harus diberikan berdasarkan jadwal 3-dosis:

- Injeksi pertama: waktu yang dipilih
- Injeksi kedua: 2 bulan setelah injeksi pertama (tidak lebih cepat dari satu bulan setelah dosis pertama)
- Injeksi ketiga: 6 bulan setelah injeksi pertama (tidak lebih cepat dari 3 bulan setelah mendapatkan dosis ke dua).

Ketiga dosis harus diberikan dalam jangka waktu 1 tahun. Mohon bicara dengan dokter anda untuk informasi lebih lanjut.

GARDASIL 9 dapat diberikan berdasarkan jadwal 2-dosis jika anda berusia 9 sampai dan masih berusia 14 tahun saat injeksi pertama diberikan

- Injeksi pertama: waktu yang dipilih
- Injeksi kedua: diberikan antara umur 5 dan 13 bulan setelah injeksi pertama

Jika dosis vaksin kedua diberikan lebih cepat dari 5 bulan setelah dosis pertama maka, dosis ke tiga harus selalu diberikan.

Ketiga dosis harus selalu diberikan dalam jangka waktu 1 tahun. Mohon bicara dengan dokter Anda untuk informasi lebih lanjut.

Seseorang yang telah menerima dosis pertama GARDASIL 9, direkomendasikan untuk menyelesaikan rangkaian vaksinasi dengan GARDASIL 9.

GARDASIL 9 akan diberikan sebagai injeksi dari kulit ke otot (yang lebih dipilih yakni otot di lengan atas atau paha).

Jika anda melupakan satu dosis dari GARDASIL 9

Jika salah satu jadwal injeksi terlewatkan, dokter anda akan memutuskan kapan diberikan dosis yang terlewat.

Penting untuk anda mengikuti instruksi dokter atau perawat Anda mengenai kunjungan selanjutnya untuk dosis-dosis selanjutnya. Jika Anda lupa atau tidak dapat mengunjungi dokter Anda pada jadwal yang ditentukan, mintalah anjuran dari dokter Anda. Ketika GARDASIL 9 diberikan sebagai dosis pertama Anda, penyelesaian rangkaian vaksinasi harus dilakukan dengan GARDASIL 9, dan bukan dengan vaksin HPV lainnya.

Jika kamu memiliki pertanyaan lainnya mengenai kegunaan vaksin ini, tanyakan kepada dokter atau apoteker Anda.

4. Efek samping yang memungkinkan

Seperti semua vaksin, vaksin ini dapat menyebabkan efek samping, meskipun tidak setiap orang mendapatkannya. Efek samping berikut dapat terlihat setelah menggunakan GARDASIL 9:

Sangat sering (dapat mempengaruhi lebih dari 1 dari 10 orang): efek samping yang ditemukan pada tempat injeksi (nyeri, pembengkakan, dan kemerahan) dan sakit kepala.

Sering (dapat mempengaruhi hingga 1 dari 10 orang): efek samping yang ditemukan pada tempat injeksi (memar, dan gatal), demam, kelelahan, pusing dan mual.

Ketika GARDASIL 9 diberikan dengan kombinasi *booster* vaksin difteri, tetanus, pertusis [*acellular*, komponen] dan *poliomyelitis* [tidak aktif] saat kunjungan yang bersamaan, terdapat pembengkakan di tempat injeksi yang berlebih.

Reaksi alergi telah dilaporkan. Beberapa dari kasus ini menjadi parah. Gejala-gejalanya dapat termasuk kesulitan bernapas, bersin, gatal-gatal dan/atau ruam.

Sama seperti vaksin lain, efek samping lain yang telah dilaporkan selama penggunaan umum untuk GARDASIL 9 terlihat seperti dibawah. Efek samping yang telah dilaporkan selama penggunaan umum GARDASIL juga terlihat seperti dibawah. Efek samping pada GARDASIL dilaporkan karena kemungkinan relevan terhadap GARDASIL 9, karena veksin tersebut memiliki kesamaan pada komposisi.

GARDASIL 9:
Pingsan yang terkadang bersamaan dengan *seizure-like activity*
Muntah

Selain itu, efek samping berikut telah terlihat pada penggunaan umum GARDASIL.

GARDASIL:
pembengkakan kelenjar (leher, ketiak, atau paha atas); kelemahan otot, sensasi tidak normal , sensasi geli pada lengan, kaki dan tubuh bagian atas, atau kebingungan (Guillain-Barré syndrome, acute disseminated encephalomyelitis); nyeri sendi, sakit otot, atau kelemahan yang tidak biasa, menggigil, rasa tidak enak badan secara keseluruhan, pendarahan atau memar yang lebih mudah dari biasanya dan infeksi kulit pada tempat injeksi.

Pelaporan terhadap efek samping

Jika Anda atau anak Anda mendapatkan efek samping, beritahu dokter, apoteker atau perawat Anda. Ini termasuk kemungkinan efek samping apapun yang tidak terdapat pada lembar informasi ini. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi tambahan untuk keamanan vaksin ini.

5. Bagaimana cara penyimpanan GARDASIL 9

Simpan vaksin ini jauh dari pandangan dan jangkauan anak-anak.

Jangan gunakan vaksin ini setelah tanggal kadaluarsa yang tertera pada karton dan label *syringe*.

Simpan pada pendingin (2ºC - 8ºC). Jangan dibekukan. Simpan *syringe* di dalam karton pembungkus agar terlindung dari cahaya.

Jangan buang bagian manapun vaksin ini pada limbah cair atau limbah rumah tangga. Tanyakan kepada apoteker Anda tentang bagaimana cara membuang vaksin ini ketika sudah tidak digunakan. Langkah-langkah ini dapat membantu melindungi lingkungan.

6. Kandungan pada paket dan informasi lain

Apa kandungan GARDASIL 9

Zat aktifnya adalah: Protein *non-infectious* dengan kemurnian tinggi untuk setiap tipe *Human Papillomavirus* (6, 11, 16, 18, 31, 33, 45, 52, dan 58).

1 dosis (0.5 ml) mengandung:

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] Protein L1 dalam bentuk *virus like particles* diproduksi dalam sel ragi (*Saccharomyces cerevisiae CANADE 3C-5 (Strain 1895))* oleh teknologi DNA rekombinan.
[3] diadsorbsi oleh *amorphous aluminium hydroxyphosphate sulphate adjuvant* (0.5 milligrams Al).

Amorphous aluminium hydroxyphosphate sulphate dimasukkan dalam vaksin sebagai adjuvan. Adjuvan dimasukkan untuk meningkatkan respon sistem imun vaksin.

Kandungan lain dalam suspensi vaksin yaitu: *sodium chloride, L-histidine, polysorbate 80, sodium borate* dan *water for injections*.

Seperti apa bentuk GARDASIL 9 dan kandungan pada paket

1 dosis suspensi GARDASIL 9 untuk injeksi mengandung 0.5 ml.

Sebelum agitasi, GARDASIL 9 dapat terlihat seperti cairan jernih dengan endapan putih. Setelah agitasi lengkap, berupa cairan putih, berawan.

GARDASIL 9 tersedia dalam paket 1 *pre-filled syringe.*

HARUS DENGAN RESEP DOKTER

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Pendaftar dan Produsen

Pendaftar

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Pasuruan, Jawa Timur

Produsen

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