PRODUCT MONOGRAPH

GARDASIL®9

[Human Papillomavirus 9-valent Vaccine, Recombinant]

Suspension for injection

Active Immunizing Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Intramuscular injection	Suspension for injection / Each 0.5 mL dose contains approximately: 30 mcg of HPV 6 L1 protein 40 mcg of HPV 11 L1 protein 60 mcg of HPV 16 L1 protein 40 mcg of HPV 18 L1 protein 20 mcg of HPV 31 L1 protein 20 mcg of HPV 33 L1 protein 20 mcg of HPV 45 L1 protein 20 mcg of HPV 52 L1 protein 20 mcg of HPV 58 L1 protein	*For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

GARDASIL®9, Human Papillomavirus 9-valent Vaccine, Recombinant, is a non-infectious recombinant 9-valent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The L1 proteins are produced by separate fermentations using recombinant *Saccharomyces cerevisiae* and self-assembled into VLPs. The fermentation process involves growth of *S. cerevisiae* on chemically-defined fermentation media which include vitamins, amino acids, mineral salts, and carbohydrates. The VLPs are released from the yeast cells by cell disruption and purified by a series of chemical and physical methods. The purified VLPs are adsorbed on preformed aluminum-containing adjuvant (Amorphous Aluminum Hydroxyphosphate Sulfate or AAHS). The 9-valent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of the aluminum-containing adjuvant and the final purification buffer.

INDICATIONS AND CLINICAL USE

Girls and Women

GARDASIL®9 is a vaccine indicated in girls and women 9 through 45 years of age for the prevention of infection caused by the Human Papillomavirus (HPV) types 6, 11, 16, 18, 31, 33, 45, 52 and 58 and the following diseases associated with the HPV types included in the vaccine:

- Cervical, vulvar, and vaginal 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:

- Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 2 and grade 3
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- Cervical intraepithelial neoplasia (CIN) grade 1

GARDASIL®9 is indicated in girls and women 9 through 26 years of age for the prevention of:

- Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3 caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Boys and Men

GARDASIL®9 is indicated in boys and men 9 through 26 years of age for the prevention of infection caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 and the following diseases associated with the HPV types included in the vaccine:

- 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 anal intraepithelial neoplasia (AIN) grades 1, 2, and 3 caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58.

CONTRAINDICATIONS

- Patients who are hypersensitive to either GARDASIL® or GARDASIL®9 or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of GARDASIL®9 or GARDASIL® should not receive further doses of GARDASIL®9.

WARNINGS AND PRECAUTIONS

General

As for any vaccine, vaccination with GARDASIL®9 may not result in protection in all vaccine recipients.

This vaccine is not intended to be used for treatment of active external genital lesions; cervical, vulvar, vaginal, or anal cancers; CIN, VIN, VaIN, or AIN.

This vaccine will not protect against diseases that are not caused by HPV.

GARDASIL®9 has not been shown to protect against diseases due to HPV types not contained in the vaccine.

As with all injectable vaccines, appropriate medical treatment should always be readily available in case of rare anaphylactic reactions following the administration of the vaccine.

Syncope (fainting) may follow any vaccination, especially in adolescents and young adults. Syncope, sometimes associated with falling, has occurred after HPV vaccination. Therefore, vaccinees should be carefully observed for approximately 15 minutes after administration of GARDASIL®9.

Routine monitoring and Pap test in women should continue to be performed as indicated, regardless of GARDASIL®9 administration. Recipients of GARDASIL®9 should not discontinue anal cancer screening if it has been recommended by a health care provider. Appropriate precautions against sexually transmitted diseases should continue to be used.

Febrile Illness

The decision to administer or delay vaccination because of a current or recent febrile illness depends largely on the severity of the symptoms and their etiology. Low-grade fever itself and mild upper respiratory infection are not generally contraindications to vaccination.

Immunocompromised individuals

Individuals with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, Human Immunodeficiency Virus (HIV) infection, or other causes, may have reduced antibody response to active immunization (see DRUG INTERACTIONS).

Individuals with Bleeding Disorders

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.

Special Populations

The safety, immunogenicity, and efficacy of GARDASIL®9 have not been evaluated in HIV-infected individuals

Geriatrics (> 65 years of age):
The safety and efficacy of GARDASIL®9 have not been evaluated in individuals aged 65 years and over.

Pediatrics (< 9 years of age):
The safety and efficacy of GARDASIL®9 have not been evaluated in children younger than 9 years.

Pregnant Women:
Reproduction studies have been performed in female rats at a dose approximately 240 times the human dose (mg/kg basis) and have revealed no evidence of impaired female fertility or harm to the fetus due to GARDASIL®9 (see TOXICOLOGY).

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, pregnancy should be avoided during the vaccination regimen for GARDASIL®9 (see TOXICOLOGY and ADVERSE REACTIONS).

Pregnant women exposed to GARDASIL®9 are encouraged to report their exposure or suspected adverse reactions by contacting Merck Canada Inc., at 1-800-567-2594 or the Vaccine Safety Section at Public Health Agency of Canada at 1-866-844-0018 or www.phac-aspc.gc.ca/im/vs-sv/index-eng.php.

Nursing Women:
It is not known whether vaccine antigens are excreted in human milk.

A total of 92 women were breast feeding during the vaccination period of the clinical studies for GARDASIL®9. There were no vaccine-related serious adverse experiences reported in infants who were nursing during the vaccination period.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Headache, fever, nausea, dizziness, fatigue, diarrhea, oropharyngeal pain, upper abdominal pain, and local injection site reactions (pain, swelling, erythema, pruritus, bruising, hematoma, mass, hemorrhage, induration) occurred after administration with GARDASIL®9.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of GARDASIL®9 was evaluated in 7 clinical studies (Protocols 001, 002, 003, 005, 006, 007, 009) that included 15,776 individuals who received at least one dose of GARDASIL®9 and had safety follow-up. Protocol 001 and Protocol 009 included 7,378 individuals who received at least one dose of GARDASIL® and had safety follow-up. The vaccines were administered on the day of enrollment and the subsequent doses administered 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 or GARDASIL®.

The individuals who were monitored using VRC-aided surveillance included 9,102 girls and women 16 through 26 years of age, 1,394 boys and men 16 through 26 years of age and 5,280 girls and boys 9 through 15 years of age (3,481 girls and 1,799 boys) at enrollment who received GARDASIL®9; and 7,078 girls and women 16 through 26 years of age and 300 girls 9 through 15 years of age at enrollment who received GARDASIL®. The race distribution of the integrated safety population for Protocols 001, 002, 005, 006, 007 and 009 for GARDASIL®9 was similar between women (56.2% White; 25.4% Other Races or Multiracial; 14.7% Asian; 3.7% Black) and girls and boys (61.2% White; 18.9% Other Races or Multiracial; 14.6% Asian; 5.3% Black). For Protocol 003, the race distribution for boys and men was 61.9% White; 22.7% Other Races or Multiracial; 9.8% Asian; 5.5% Black. The race distribution of the safety population for GARDASIL® was determined in two studies (Protocol 001 and Protocol 009) that had different profiles. In Protocol 001, the race distribution was similar to the integrated database for GARDASIL®9: 55.3% White; 26.9% Multiracial; 14.2% Asian; 3.3% Black; 0.2% Unknown; 0.1% American Indian or Alaskan Native; and 0.1% Native Hawaiian or other Pacific Islander. Protocol 009 race distribution was 98.0% White; 1.3% Multiracial; 0.3% Asian; and 0.3% Black.

Systemic and Injection-Site Adverse Reactions in Girls and Women

The vaccine-related adverse experiences that were observed among recipients of either GARDASIL®9 or GARDASIL® at a frequency of at least 1% are shown in Table 1. Few individuals (GARDASIL®9 = 0.1% vs. GARDASIL® < 0.1%) discontinued due to adverse experiences after receiving either vaccine.

Table 1: Injection-Site and Vaccine-Related Systemic Adverse Reactions Reported at a Frequency of ≥1% for GARDASIL®9 or GARDASIL® from Two Clinical Studies*

Adverse Reaction	Women 16 Through 26 Years of Age		Girls 9 Through 15 Years of Age	
	GARDASIL®9 (N=7071) %	GARDASIL® (N=7078) %	GARDASIL®9 (N=299) %	GARDASIL® (N=300) %
Injection-Site Adverse Reactions (1 to 5 Days Postvaccination)				
Pain†	89.9	83.5	89.3	88.3
Swelling†	40.0	28.8	47.8	36.0
Erythema†	34.0	25.6	34.1	29.3

Table 1: Injection-Site and Vaccine-Related Systemic Adverse Reactions Reported at a Frequency of ≥1% for GARDASIL®9 or GARDASIL® from Two Clinical Studies*

Adverse Reaction	Women 16 Through 26 Years of Age		Girls 9 Through 15 Years of Age	
	GARDASIL®9 (N=7071) %	GARDASIL® (N=7078) %	GARDASIL®9 (N=299) %	GARDASIL® (N=300) %
Pruritus	5.5	4.0	4.0	2.7
Bruising	1.9	1.9	‡	‡
Mass	1.3	0.6	‡	‡
Hemorrhage	1.0	0.7	1.0	2.0
Hematoma	0.9	0.6	3.7	4.7
Warmth	0.8	0.5	0.7	1.7
Induration	0.8	0.2	2.0	1.0
Reaction	0.6	0.6	0.3	1.0
Systemic Adverse Reactions (1 to 15 Days Postvaccination)				
Headache	14.6	13.7	11.4	11.3
Pyrexia	5.0	4.3	5.0	2.7
Nausea	4.4	3.7	3.0	3.7
Dizziness	3.0	2.8	0.7	0.7
Fatigue	2.3	2.1	0.0	2.7
Diarrhea	1.2	1.0	0.3	0.0
Myalgia	1.0	0.7	0.7	0.7
Oropharyngeal pain	1.0	0.6	2.7	0.7
Abdominal pain upper	0.7	0.8	1.7	1.3
Upper respiratory tract infection	0.1	0.1	0.3	1.0

*The data for women are from Protocol 001 and data for girls are from Protocol 009.
†Designates a solicited adverse reaction
‡There are no reports of injection-site bruising or mass for girls.
N=number of subjects vaccinated with safety follow-up.

Temperature and injection-site pain, swelling, and erythema were solicited using VRC-aided surveillance for 5 days after each injection of GARDASIL®9 during the clinical studies. The incidence and severity of solicited adverse reactions that occurred within 5 days following each dose of GARDASIL®9 are shown in Table 2.

Table 2: Rates (%) and Severity of Solicited Injection-Site and Systemic Adverse Reactions Occurring within Five Days of Each Vaccination with GARDASIL®9 Compared with GARDASIL® (Protocols 001 and 009)

	GARDASIL®9				GARDASIL®			
	Post-dose 1	Post-dose 2	Post-dose 3	Post any dose	Post-dose 1	Post-dose 2	Post-dose 3	Post any dose
Girls and Women 16 through 26 Years of Age								
Injection-Site Adverse Reactions	**N=7069**	**N=6997**	**N=6909**	**N=7071**	**N=7076**	**N=6992**	**N=6909**	**N=7078**
Pain, Any	70.7	73.5	71.6	89.9	58.2	62.2	62.6	83.5
Pain, Severe	0.7	1.7	2.6	4.3	0.4	1.0	1.7	2.6
Swelling, Any	12.5	23.3	28.3	40.0	9.3	14.6	18.7	28.8
Swelling, Severe	0.6	1.5	2.5	3.8	0.3	0.5	1.0	1.5
Erythema, Any	10.6	18.0	22.6	34.0	8.1	12.9	15.6	25.6
Erythema, Severe	0.2	0.5	1.1	1.6	0.2	0.2	0.4	0.8

Table 2: Rates (%) and Severity of Solicited Injection-Site and Systemic Adverse Reactions Occurring within Five Days of Each Vaccination with GARDASIL®9 Compared with GARDASIL® (Protocols 001 and 009)

	GARDASIL®9				GARDASIL®			
	Post-dose 1	Post-dose 2	Post-dose 3	Post any dose	Post-dose 1	Post-dose 2	Post-dose 3	Post any dose
Systemic Adverse Reactions	**n=6995**	**n=6913**	**n=6743**	**n=7022**	**n=7003**	**n=6914**	**n=6725**	**n=7024**
Temperature ≥37.8°C	1.7	2.6	2.7	6.0	1.7	2.4	2.5	5.9
Temperature ≥38.9°C	0.3	0.3	0.4	1.0	0.2	0.3	0.3	0.8
Girls 9 through 15 Years of Age								
Injection-Site Adverse Reactions	**N=300**	**N=297**	**N=296**	**N=299**	**N=299**	**N=299**	**N=294**	**N=300**
Pain, Any	71.7	71.0	74.3	89.3	66.2	66.2	69.4	88.3
Pain, Severe	0.7	2.0	3.0	5.7	0.7	1.3	1.7	3.3
Swelling, Any	14.0	23.9	36.1	47.8	10.4	17.7	25.2	36.0
Swelling, Severe	0.3	2.4	3.7	6.0	0.7	2.7	4.1	6.3
Erythema, Any	7.0	15.5	21.3	34.1	9.7	14.4	18.4	29.3
Erythema, Severe	0	0.3	1.4	1.7	0	0.3	1.7	2.0
Systemic Adverse Reactions	**n=300**	**n=294**	**n=295**	**n=299**	**n=299**	**n=297**	**n=291**	**n=300**
Temperature ≥37.8°C	2.3	1.7	3.0	6.7	1.7	1.7	0	3.3
Temperature ≥38.9°C	0	0.3	1.0	1.3	0.3	0.3	0	0.7

The data for girls and women 16 through 26 years of age are from P001, and the data for girls 9 through 15 years of age are from P009.
N=number of subjects vaccinated with safety follow-up
n=number of subjects with temperature data
Pain, Any=mild, moderate, severe or unknown intensity
Pain, Severe=incapacitating with inability to work or do usual activity
Swelling, Any=any size or size unknown
Swelling, Severe=maximum size greater than 2 inches
Erythema, Any=any size or size unknown
Erythema, Severe=maximum size greater than 2 inches

Systemic and Injection-Site Adverse Reactions in Boys and Men

An uncontrolled clinical trial with 662 boys and 1,923 girls 9 through 15 years of age (Protocol 002) was conducted. Solicited and unsolicited adverse reactions reported by boys in this study are shown in Table 3.

An uncontrolled clinical trial with 1,394 boys and men and 1,075 girls and women 16 through 26 years of age (Protocol 003) was also conducted. Solicited and unsolicited adverse reactions reported by boys and men 16 through 26 years of age in this study are shown in Table 3.

Table 3: Rates (%) of Solicited and Unsolicited* Injection-Site and Systemic Adverse Reactions among Boys 9 through 15 Years of Age and among Boys and Men 16 through 26 years of Age who Received Gardasil®9

	GARDASIL®9
Boys and Men 16 through 26 years of age	**N=1394**
Solicited Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)	
Injection-Site Pain	63.4
Injection-Site Erythema	20.7
Injection-Site Swelling	20.2
Oral Temperature ≥37.8°C†	4.4
Unsolicited Injection-Site Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)	

Table 3: Rates (%) of Solicited and Unsolicited* Injection-Site and Systemic Adverse Reactions among Boys 9 through 15 Years of Age and among Boys and Men 16 through 26 years of Age who Received Gardasil®9

	GARDASIL®9
Injection-Site Hypersensitivity	1.0
Injection-Site Pruritus	1.0
Unsolicited Systemic Adverse Reactions (1-15 Days Post-Vaccination, Any Dose)	
Headache	7.3
Pyrexia	2.4
Fatigue	1.4
Dizziness	1.1
Nausea	1.0
Boys 9 through 15 years of age	**N=662**
Solicited Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)	
Injection-Site Pain	70.2
Injection-Site Erythema	24.2
Injection-Site Swelling	26.0
Oral Temperature ≥37.8°C†	10.0
Unsolicited Injection-Site Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)	
Injection-Site Hematoma	1.2
Injection-Site Induration	1.1
Unsolicited Systemic Adverse Reactions (1-15 Days Post-Vaccination, Any Dose)	
Headache	9.1
Pyrexia	8.6
Nausea	1.2

The data for GARDASIL®9 boys 9 through 15 years of age are from Protocol 002. The data for boys and men 16 through 26 years of age for GARDASIL®9 are from Protocol 003.
*Unsolicited adverse reactions reported by ≥1% of individuals
N=number of subjects vaccinated with safety follow-up
†For oral temperature: number of subjects with temperature data for boys 9 through 15 years of age N=660; for boys and men 16 through 26 years of age N=1,386.

Serious Adverse Events in Clinical Studies of GARDASIL®9

Serious adverse events were collected throughout the entire study period for the seven integrated clinical studies for GARDASIL®9. Out of the 15,778 individuals who were administered GARDASIL®9 and had safety follow-up, 356 reported a serious adverse event; representing 2.3% of the population. Four individuals administered GARDASIL®9 reported at least one serious adverse event that was determined to be vaccine-related. The vaccine-related serious adverse events that occurred during the study period were pyrexia, allergy to vaccine, asthmatic crisis, and headache. No vaccine-related deaths were reported.

Clinical Trials Experience for GARDASIL®9 in Individuals Who Have Been Previously Vaccinated with GARDASIL®

A clinical study (Protocol 006) evaluated the safety of GARDASIL®9 in 12- through 26-year-old girls and women who had previously been vaccinated with 3 doses of GARDASIL®. The time interval between the last injection of GARDASIL® and the first injection of GARDASIL®9 ranged from approximately 12 to 36 months. Individuals were administered GARDASIL®9 or saline placebo and safety was evaluated using VRC-aided surveillance for 14 days after each injection of GARDASIL®9 or saline placebo in these individuals. The individuals who were monitored included 608 individuals who received GARDASIL®9 and 305 individuals who

received saline placebo. Three (0.5%) individuals who received GARDASIL®9 discontinued due to adverse reactions. No individuals who received placebo discontinued due to adverse reactions. The vaccine-related adverse experiences that were observed among recipients of GARDASIL®9 at a frequency of at least 1.0% and also at a greater frequency than that observed among saline placebo recipients are shown in Table 4.

Table 4: Injection-Site and Vaccine-Related Systemic Adverse Reactions Reported at a Frequency of ≥ 1% and Greater Than Saline Placebo for GARDASIL®9 in 12- through 26-year-old Girls and Women Who Have Been Previously Vaccinated with GARDASIL®*

Adverse Reaction	GARDASIL®9 (N=608) %	SALINE PLACEBO (N=305) %
Injection-Site Adverse Reactions (1 to 5 Days Postvaccination)		
Pain†	90.3	38.0
Swelling†	49.0	5.9
Erythema†	42.3	8.5
Pruritus	7.7	1.3
Hematoma	4.8	2.3
Reaction	1.3	0.3
Mass	1.2	0.7
Systemic Adverse Reactions (1 to 15 Days Postvaccination)		
Headache	19.6	18.0
Pyrexia	5.1	1.6
Nausea	3.9	2.0
Dizziness	3.0	1.6
Abdominal pain upper	1.5	0.7
Influenza	1.2	1.0

*The data for GARDASIL®9 and Placebo are from Protocol 006.
†Designates a solicited adverse reaction
N=number of subjects vaccinated with safety follow-up

Clinical Trials Experience for Concomitant Administration of GARDASIL®9 with Other Vaccines

The safety of GARDASIL®9 when administered concomitantly with other vaccines was evaluated in clinical studies.

There was an increase in injection-site swelling reported at the injection site for GARDASIL®9 when GARDASIL®9 was administered concomitantly with Repevax* [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content) (Tdap-IPV)]; or Adacel* [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] and Menactra* [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine], as compared to non-concomitant vaccination.

The majority of injection-site swelling seen with concomitant administration with other vaccines was reported as being mild to moderate in intensity.

Clinical Trials Experience of GARDASIL®9 in Pregnant Women

In clinical studies, women underwent serum or urine pregnancy testing prior to administration of GARDASIL®9. Women who were found to be pregnant before completion of a 3-dose regimen

of GARDASIL®9 were instructed to defer completion of their vaccination regimen until resolution of the pregnancy.

The overall proportion of pregnancies occurring at any time during the studies that resulted in an adverse outcome defined as the combined numbers of spontaneous abortion, late fetal death and congenital anomaly cases out of the total number of pregnancy outcomes for which an outcome was known (and excluding elective terminations), was 12.9% (174/1,353) in women who received GARDASIL®9 and 14.4% (187/1,303) in women who received GARDASIL®. The proportions of adverse outcomes observed were consistent with pregnancy outcomes observed in the general population.

Further sub-analyses were conducted to evaluate pregnancies with estimated onset within 30 days or more than 30 days from administration of a dose of GARDASIL®9 or GARDASIL®. For pregnancies with estimated onset within 30 days of vaccination, no cases of congenital anomaly were observed in women who have received GARDASIL®9 or GARDASIL®. In pregnancies with onset more than 30 days following vaccination, 30 and 23 cases of congenital anomaly were observed in women who have received GARDASIL®9 and GARDASIL®, respectively. The types of anomalies observed were consistent (regardless of when pregnancy occurred in relation to vaccination) with those generally observed in pregnancies in the general population.

For pregnancies with estimated onset within 30 days of vaccination, the proportion of pregnancies that resulted in a spontaneous abortion out of the total number of pregnancies with a known outcome (excluding elective terminations) was 27.4% (17/62) and 12.7% (7/55) in women who received GARDASIL®9 or GARDASIL®, respectively. For pregnancies with estimated onset more than 30 days following vaccination, that proportion was 10.9% (105/960) and 14.6% (136/933) in women who received GARDASIL®9 or GARDASIL®, respectively.

Postmarketing Adverse Drug Reaction

There are no post-marketing adverse experiences reported to date with GARDASIL®9. However, the post-marketing safety experience with GARDASIL® is relevant to GARDASIL®9 since the vaccines are similar in composition and contain 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 a causal relationship to vaccine exposure.

The following adverse experiences have been spontaneously reported during post-approval use of GARDASIL® and may also be seen in post-marketing experience with GARDASIL®9:

Blood and lymphatic system disorders:
Autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, lymphadenopathy

Respiratory, thoracic and mediastinal disorders:
Pulmonary embolus

Gastrointestinal disorders:
Nausea, pancreatitis, vomiting

General disorders and administration site conditions:
Asthenia, chills, death, fatigue, malaise

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

Musculoskeletal and connective tissue disorders:
Arthralgia, myalgia

Nervous system disorders:
Acute disseminated encephalomyelitis, dizziness, Guillain-Barré syndrome, headache, motor neuron disease, paralysis, syncope sometimes accompanied by tonic-clonic movements, transverse myelitis

Infections and infestations:
Cellulitis

DRUG INTERACTIONS

Use with Other Vaccines
Results from clinical studies indicate that GARDASIL®9 may be administered concomitantly (at a separate injection site) with Menactra* [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel* [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)], and Repevax* [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content) (Tdap-IPV)] (see CLINICAL TRIALS).

Use with Hormonal Contraceptives
In 7,269 women (aged 16 through 26 years, from Protocols 001 and 002), 60.2% 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.

Use with Systemic Immunosuppressive Medications
Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune responses to vaccines (see WARNINGS AND PRECAUTIONS, Special Populations).

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Administration of GARDASIL®9 in Individuals Who Have Been Previously Vaccinated with GARDASIL®

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

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

Safety and immunogenicity of GARDASIL®9 were assessed in individuals who previously completed a three-dose vaccination series with GARDASIL® (see ADVERSE REACTIONS and CLINICAL STUDIES).

Recommended Dose and Dosage Adjustment

GARDASIL®9 should be administered intramuscularly as 3 separate 0.5 mL doses according to the following schedule:

First dose: at elected date
Second dose: 2 months after the first dose
Third dose: 6 months after the first dose

Individuals are encouraged to adhere to the 0, 2, and 6 months vaccination schedule. The second dose should be administered at least 1 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 use of GARDASIL®9 should be in accordance with official recommendations.

Administration

For intramuscular use only.

Shake well before use. Thorough agitation immediately before administration is necessary to maintain suspension of the vaccine. GARDASIL®9 should not be diluted or mixed with other vaccines. After thorough agitation, GARDASIL®9 is a white, cloudy liquid. Parenteral drug

products should be inspected visually for particulate matter and discoloration prior to administration. Do not use the product if particulates are present or if it appears discolored.

GARDASIL®9 should be administered intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

GARDASIL®9 must not be injected intravascularly. Neither subcutaneous nor intradermal administration has been studied. These methods of administration are not recommended.

Instructions for Use

Single-Dose Vial Use
Withdraw the 0.5-mL dose of vaccine from the single-dose vial using a sterile needle and syringe and use promptly.

Prefilled Syringe Use
Shake well before use. 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.

Needles
A sterile 22 to 25 gauge needle, 1 to 1-½ inch (2.5 cm – 3.8 cm) length for IM injection should be used. It is important to use a separate sterile syringe and needle for each patient to prevent transmission of infectious agents from one individual to another.

OVERDOSAGE

There have been no reports of administration of higher than recommended doses of GARDASIL®9.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Disease Burden
HPV is estimated to infect over 550,000 Canadians each year.[1] Persistent infection with oncogenic HPV types is responsible for virtually all cases of invasive cervical cancer,[2] approximately 74% of vaginal cancers, and approximately 25% of vulvar cancers.[3,4] HPV is also associated with other malignancies, including oropharyngeal cancers (such as tonsillar cancer) and anal cancer. The proportion of tonsillar cancers in which HPV has been detected increased from 25% (1993 - 1999) to 62% (2006 – 2011) in Canada.[5] HPV has also been detected in 92% of anal cancer cases in one investigation, in Quebec.[6]

It is estimated that 1,400 Canadian women will be diagnosed with invasive cervical cancer each year, and approximately 380 will die from the disease in Canada.[7] Cervical cancer remains the 3rd most common cancer among Canadian women between 20 and 40 years of age.[8]

HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 (vs. types 6, 11, 16, and 18) cause approximately 90% (70%) of cervical cancers, 75-85% (50%) of cervical precancerous lesions, and 50-60% (30-35%) of low-grade cervical lesions. Among HPV-related cases, these HPV types also cause 85-90% (70-75%) of vulvar cancers, 80-85% (65%) of vaginal cancers, 90-95% (85-90%) of anal cancers, and at least 75% (60%) of these cancers' precursor lesions.[3, 4, 9, 10, 11, 12, 13]

HPV infection can also cause non-malignant lesions. HPV types 6 and 11 cause 90% of genital warts (condyloma acuminata) and 90% of recurrent respiratory papillomatosis (RRP) cases. These conditions rarely progress to cancer, but are associated with significant morbidity and psychosocial impacts, including a low health related quality of life.[14, 15, 16]

Mechanism of Action

HPV only infects human beings. Animal studies with analogous animal papillomaviruses suggest that the efficacy of L1 VLP vaccines may involve the development of humoral immune responses. Human beings develop a humoral immune response to the vaccine, although the exact mechanism of protection is unknown.

STORAGE AND STABILITY

Store refrigerated at 2° to 8°C. Do not freeze. Protect from light.

GARDASIL®9 should be administered as soon as possible after being removed from refrigeration. GARDASIL®9 can be administered provided total (cumulative multiple excursion) time out of refrigeration (at temperatures between 8°C and 25°C) does not exceed 72 hours. Cumulative multiple excursions between 0°C and 2°C are also permitted as long as the total time between 0°C and 2°C does not exceed 72 hours. These are not, however, recommendations for storage.

Discard the product if it is frozen, particulates are present, or if it appears discolored.

DOSAGE FORMS, COMPOSITION AND PACKAGING

GARDASIL®9 is a suspension for intramuscular administration available in 0.5-mL single-dose vials and prefilled syringes.

COMPOSITION

Active Ingredients
GARDASIL®9 is a sterile suspension for intramuscular administration. Each 0.5-mL dose contains approximately 30 mcg of HPV Type 6 L1 protein, 40 mcg of HPV Type 11 L1 protein, 60 mcg of HPV Type 16 L1 protein, 40 mcg of HPV Type 18 L1 protein, 20 mcg of HPV Type 31 L1 protein, 20 mcg of HPV Type 33 L1 protein, 20 mcg of HPV Type 45 L1 protein, 20 mcg of HPV Type 52 L1 protein, and 20 mcg of HPV Type 58 L1 protein.

Inactive Ingredients
Each 0.5-mL sterile dose of the vaccine contains approximately 500 mcg of aluminum (as Amorphous Aluminum Hydroxyphosphate Sulfate adjuvant), 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, 9.56 mg of sodium chloride, and water for injection.

The product does not contain a preservative or antibiotics.

PACKAGING

Vials
GARDASIL®9 is supplied in single-dose Type I glass vials containing 0.5 mL dose of liquid vaccine.

Available in packages of 10 single-dose vials.

Syringes
GARDASIL®9 is supplied in single-dose Type I glass prefilled Luer Lock syringes, containing 0.5 mL dose of liquid vaccine.

Available in a 1 single dose syringe package.

The components of the vials and prefilled syringes are latex free.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: [Human Papillomavirus 9-valent Vaccine, Recombinant]

Product Characteristics

GARDASIL®9, Human Papillomavirus 9-valent Vaccine, Recombinant, is a non-infectious recombinant 9-valent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The L1 proteins are produced by separate fermentations using recombinant *Saccharomyces cerevisiae* and self-assembled into VLPs. The fermentation process involves growth of *S. cerevisiae* on chemically-defined fermentation media which include vitamins, amino acids, mineral salts, and carbohydrates. The VLPs are released from the yeast cells by cell disruption and purified by a series of chemical and physical methods. The purified VLPs are adsorbed on preformed aluminum-containing adjuvant (Amorphous Aluminum Hydroxyphosphate Sulfate or AAHS). The 9-valent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of the aluminum-containing adjuvant and the final purification buffer.

After thorough agitation, GARDASIL®9 is a white, cloudy liquid.

CLINICAL TRIALS

Study demographics and trial design

Table 5: Summary of patient demographics for clinical trials in HPV Disease Efficacy, Immunogenicity, and Safety

Study #	Trial design	Vaccination Groups and Number of Subjects who Received at Least 1 Injection of the Correct Clinical Material (N)	Gender: Number of Randomized (N=number)	Mean age (Range)
001[17]	Randomized, double-blind, multicenter, international, controlled with GARDASIL®, dose-ranging safety, immunogenicity, and efficacy study of GARDASIL®9	(1) GARDASIL®9 (N=7099) (2) GARDASIL® (N=7105) Intramuscular injection 3 doses of 0.5 mL	Females N=14,215	Females: 21.9 years (16 to 26 years)
002	International, multicentered, immunogenicity, safety, and manufacturing consistency study of GARDASIL®9	All subjects received GARDASIL®9 N=3066 Intramuscular injection 3 doses of 0.5 mL	Females: 2405 Males: 669	Females: 11.6 years (9 to 15 years) Males: 11.7 years (9 to 15 years) Females: 21.3 years (16 to 26 years)
003	Open-label, international, multicenter, immunogenicity and tolerability of GARDASIL®9	All subjects received GARDASIL®9 N=2515 Intramuscular injection 3 doses of 0.5 mL	Females: 1101 Males: 1419 (HM: 1106; MSM: 313)	Females: 21.3 years (16 to 26 years) Males (HM and MSM): 21.1 years (16 to 26 years) 20.8 years (HM) (16 to 26 years) 22.2 years (MSM) (16 to 26 years)

Table 5: Summary of patient demographics for clinical trials in HPV Disease Efficacy, Immunogenicity, and Safety

Study #	Trial design	Vaccination Groups and Number of Subjects who Received at Least 1 Injection of the Correct Clinical Material (N)	Gender: Number of Randomized (N=number)	Mean age (Range)
005	Open-label, randomized, immunogenicity and safety study of GARDASIL®9 given concomitantly with Menactra* and Adacel*	All subjects received GARDASIL®9 (N=1237) Intramuscular injection 3 doses of 0.5 mL of GARDASIL®9	Females: 620 Males: 621	Females: 12.1 years (11 to 15 years) Males: 12.2 years (11 to 15 years)
006	Randomized, placebo-controlled, double-blind safety and immunogenicity study of GARDASIL®9 in prior GARDASIL® recipients	GARDASIL®9 (N=615) Placebo (N=306) Intramuscular injection 3 doses of 0.5 mL	Females: 924	Females: 19.0 years (12 to 26 years)
007	Open-label, randomized, immunogenicity and safety study of GARDASIL®9 given concomitantly with Repevax*	All subjects received GARDASIL®9 N=1053 Intramuscular injection 3 doses of 0.5 mL of GARDASIL®9	Females: 528 Males: 526	Females: 12.4 years (11 to 15 years) Males: 12.4 years (11 to 15 years)
009 /GDS01C	Randomized, GARDASIL®-controlled, double-blind immunogenicity and safety study of GARDASIL®9	GARDASIL®9 (N=300) GARDASIL® (N=300) Intramuscular injection 3 doses of 0.5 mL	Females: 600	Females: 12.6 years (9 to 15 years)
010	Open label, randomized, safety and immunogenicity of GARDASIL®9 (2-dose versus 3 dose)	All subjects received GARDASIL®9 N=1518 Intramuscular injection 3 doses of 0.5 mL of GARDASIL®9 2 doses of 0.5 mL of GARDASIL®9	Females: 1067 Males: 451	Females: 11.4 years (9 to 14 years) 21.0 years (16 to 26 years) Males: 11.5 (9 to 14 years)

HM = heterosexual men; MSM = men who have sex with men

Study results
GARDASIL®9 includes the same four HPV types contained in GARDASIL ® (HPV 6, 11, 16, 18) and five additional HPV types (31, 33, 45, 52, and 58).

Efficacy Data for GARDASIL®
GARDASIL® was licensed in Canada in 2006. Efficacy was assessed in 6 AAHS-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, and 3817 women 24 through 45 years of age).

GARDASIL® was efficacious in reducing the incidence of CIN (any grade including CIN 2/3); AIS; genital warts; VIN (any grade); and VaIN (any grade) related to vaccine HPV types 6, 11, 16, or 18 in those girls and women who were PCR negative and seronegative at baseline (Table 6). In addition, girls and women who were already infected with 1 or more vaccine-related HPV types prior to vaccination appears to be protected from precancerous cervical lesions and external genital lesions caused by the other vaccine HPV types. Individuals who had prior infection that had been resolved before vaccination (PCR negative and seropositive at baseline) appears to be protected from reinfection or recurrence of infection leading to clinical disease with the same HPV type. There was no evidence of protection from disease caused by vaccine HPV types for which individuals were PCR positive and seropositive at baseline.

GARDASIL® 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 6). GARDASIL® was efficacious in reducing the incidence of anal intraepithelial neoplasia (AIN) grades 1 (both condyloma and non-acuminate), 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 6).

Table 6: Analysis of Efficacy of GARDASIL® in the PPE* Population of 16- through 26-Year-Old Subjects for Vaccine HPV Types

Disease Endpoints	GARDASIL®		AAHS 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 16- or 18-related VIN 2/3	7772	0	7744	10	100.0 (55.5, 100.0)
HPV 16- or 18-related VaIN 2/3	7772	0	7744	9	100.0 (49.5, 100.0)
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 Genital Warts	7900	2	7902	193	99.0 (96.2, 99.9)
HPV 6- and 11-related Genital Warts	6932	2	6856	189	99.0 (96.2, 99.9)
16- Through 26-Year-Old Boys and Men					
External Genital Lesions HPV 6-, 11-, 16-, or 18-related					
External Genital Lesions	1394	3	1404	32	90.6 (70.1, 98.2)
Condyloma	1394	3	1404	28	89.3 (65.3, 97.9)
PIN 1/2/3	1394	0	1404	4	100.0 (-52.1, 100.0)
HPV 6-, 11-, 16-, or 18-related Endpoint					
AIN 1/2/3	194	5	208	24	77.5 (39.6, 93.3)
AIN 2/3	194	3	208	13	74.9 (8.8, 95.4)
AIN 1	194	4	208	16	73.0 (16.3, 93.4)

*The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, 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
Note 1: Point estimates and confidence intervals are adjusted for person-time of follow-up.
Note 2: The first analysis in the table (i.e., HPV 16- or 18-related CIN 2/3, AIS or worse) was the primary endpoint of the vaccine development plan.
Note 3: Table 6 does not include cases due to non-vaccine HPV types.
AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate

Prophylactic efficacy against overall persistent infection or disease in an extension study, that included data through Month 60, was 95.8% (95% CI: 83.8%, 99.5%). In the group that received GARDASIL®, no cases due to waning immunity were observed.

In the long-term extension registry study for 16-23 year old women vaccinated with GARDASIL® in the base study (n=6082), a subset of subjects (n= 2650) is currently being followed-up for effectiveness for 14 years after GARDASIL® vaccination. In the PPE population (n= 1,902), no cases of HPV diseases (HPV types 6/11/16/18 related CIN [any grade], AIS, cervical cancer, vulvar cancer or vaginal cancer) were observed in the interim analysis with a median follow-up time of 6.7 years post-dose 1 (with a range of 2.8 to 8.4 years).

A minimum anti-HPV level that provides protection against HPV infection and disease has not been defined. Also, immune responses to vaccines are typically lower in older individuals

compared to younger individuals. Therefore, to confirm the utility of GARDASIL® to prevent cervical, vulvar, and vaginal cancers and related diseases caused by the types targeted by the vaccine in individuals up to and including age 45 years, an efficacy study was conducted.

GARDASIL® was highly efficacious in reducing the combined incidence of persistent infection; CIN (any grade); and external genital lesions (EGL) caused by HPV types 6, 11, 16, and 18, which was primarily driven by prevention of persistent infection (Table 7). The primary analyses of efficacy, with respect to HPV types 6, 11, 16, and 18, were conducted in the per-protocol efficacy (PPE) population. Efficacy was measured starting after the Month 7 visit (Table 7).

Table 7: Analysis of Efficacy of GARDASIL® in the PPE* Population of 24- Through 45-Year-Old Women for Vaccine HPV Types

Endpoint		GARDASIL®		AAHS Control		% Efficacy (95% CI)
		N	Number of cases	N	Number of cases	
HPV 6-, 11-, 16-, or 18-related Persistent Infection, CIN (any grade), or EGL		1601	10**	1599	86	88.7 (78.1, 94.8)
HPV 6-, 11-, 16-, or 18-related	Persistent Infection	1581	9	1586	85	89.6 (79.3, 95.4)
	CIN 1	1581	0	1584	15	100.0 (72.1, 100.0)
	CIN 2/3 or AIS	1581	1	1584	6	83.3 (-37.6, 99.6)
	Condyloma	1600	0	1599	7	100.0 (30.8, 100.0)
	VIN 1 or VaIN 1	1600	0	1599	1	100.0 (-3796.0, 100.0)
	VIN 2/3 or VaIN 2/3	1600	0	1599	0	not applicable
HPV 16- or 18-related Persistent Infection, CIN (any grade), or EGL		1587	8**	1571	51	84.7 (67.5, 93.7)

*The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, 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).
**There was 1 case of CIN 2 (HPV 16 and HPV 51 identified) in the PPE group. The CIN 2 case was positive for HPV types 16 and 51 at a Month 18 biopsy. The remaining 9 cases in the PPE group were persistent infection endpoints.
N = Number of individuals with at least 1 follow-up visit after Month 7.
CI = Confidence Interval.
AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate.

Clinical Trials 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 represents the standard of care for protection against HPV infection and disease in many countries. Therefore, the pivotal clinical study (Protocol 001) evaluated the efficacy of GARDASIL®9 to prevent HPV-related cervical, vulvar, and vaginal disease using GARDASIL® 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 GARDASIL® (Protocol 001, 002, and 009).

The analysis of efficacy for GARDASIL®9 was evaluated in the per-protocol efficacy population (PPE) of 16- through 26-year-old girls and women, who were naïve to the relevant HPV type(s)

prior to dose one and through 1 month Postdose 3 (Month 7). Overall, approximately 52% of subjects were negative to all vaccine HPV types by both PCR and serology at Day 1.

The primary analysis of efficacy against HPV Types 31, 33, 45, 52, and 58 is based on a combined endpoint of Cervical Intraepithelial Neoplasia (CIN) 2, CIN 3, Adenocarcinoma *in situ* (AIS), invasive cervical carcinoma, Vulvar Intraepithelial Neoplasia (VIN) 2/3, Vaginal Intraepithelial Neoplasia (VaIN) 2/3, vulvar cancer, or vaginal cancer. Other endpoints evaluated cervical, vulvar and vaginal disease of any grade, persistent infection, cytological abnormalities and invasive procedures. For all endpoints, the efficacy against the HPV Types in GARDASIL®9 (31, 33, 45, 52, and 58) was evaluated compared to GARDASIL®.

The efficacy is further extended to 9- through 15-year-old girls and boys and to 16- through 26-year-old boys and men, for all endpoints studied, using immunological bridging. The immunogenicity bridging analyses were performed in the per-protocol immunogenicity population consisting of individuals who received all 3 vaccinations within pre-defined day ranges, met pre-defined criteria for the interval between the Month 6 and Month 7 visit, did not have major deviations from the study protocol, and were naïve [PCR negative (in girls and women 16 through 26 years of age; Protocols 001 and 002) and seronegative (Protocols 001, 002, 003, 005, 007 and 009)] to the relevant HPV type(s) prior to dose 1 and through 1 month postdose 3 Month 7.

P001 evaluated immunogenicity of GARDASIL®9 and efficacy to prevent infection and disease caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in 16- through 26-year-old girls and women. P002 evaluated immunogenicity of GARDASIL®9 in girls and boys 9 through 15 years of age and women 16 through 26 years of age. P009 evaluated immunogenicity of GARDASIL®9 compared with GARDASIL® in girls 9 through 15 years of age. Protocol 003 evaluated immunogenicity of GARDASIL®9 in boys and men 16 through 26 years of age and in girls 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). P006 evaluated administration of GARDASIL®9 to girls and women 12 through 26 years of age previously vaccinated with GARDASIL®. P005 and P007 evaluated GARDASIL®9 concomitantly administered with Menactra* and Adacel*; or Repevax*, respectively, in girls and boys 11 through 15 years of age. Together, these seven clinical trials evaluated 15,875 individuals who received GARDASIL®9 (9,152 girls and women 16 through 26 years of age at enrollment with a mean age of 21.7 years; 3,498 girls 9 through 15 years of age at enrollment with a mean age of 12.0 years; 1,416 boys and men 16 through 26 years of age at enrollment with a mean age of 21.1 years; and 1,809 boys 9 through 15 years of age at enrollment with a mean age of 12.1 years. The race distribution of the 16- through 26-year-old girls and women in the clinical trials was as follows: 56.2% White; 25.4% Other; 14.7% Asian; and 3.7% Black. The race distribution of the 9- through 15-year-old girls in the clinical trials was as follows: 63.2% White; 16.2% Other; 14.6% Asian; and 5.9% Black. The race distribution of the 9- through 15-year-old boys in the clinical trials was as follows: 57.2% White; 24.0% Other; 14.6% Asian; and 4.1% Black. In Protocol 003, the race distribution was as follows: 16- through 26-year-old boys and men: 61.9% White; 22.7% Other; 9.8% Asian; and 5.5% Black; 16-through 26-year-old girls and women: 60.4% White; 23.7% Other; 10.0% Asian; and 5.9% Black.

One clinical trial (Protocol 010) assessed the two dose regimen of GARDASIL®9. 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). The mean age for the girls and boys 9 through 14 years of age was 11.5 years; the mean age for girls and women 16 through 26 years of age was 21.0 years.

Prophylactic Efficacy – HPV Types 31, 33, 45, 52 and 58 in Girls and Women 16 through 26 Years of Age

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; GARDASIL® = 7,105), who were enrolled and vaccinated without pre-screening for the presence of HPV infection. Subjects were followed up with a median duration of follow-up of 40 months post-dose 3 (range 0 to 64 months) after the last vaccination.

The primary efficacy was based on evaluation of a composite clinical endpoint of HPV 31-, 33-, 45-, 52-, and 58-related cervical cancer, vulvar cancer, vaginal cancer, CIN 2/3 or AIS, VIN 2/3, and VaIN 2/3. The efficacy is further supported by evaluation of HPV 31-, 33-, 45-, 52-, and 58-related CIN 1, vulvar and vaginal disease of any grade, and persistent infection. In addition, the study also evaluated the impact of GARDASIL®9 on the rates of HPV 31-, 33-, 45-, 52-, and 58-related abnormal Pap tests, cervical and external genital procedures (i.e., biopsies) and cervical definitive therapy procedures.

Efficacy was evaluated in the PPE population of 16- through 26-year-old women, who were naïve to the relevant HPV type(s) prior to dose one and through Month 7. Efficacy was measured starting after the Month 7 visit. GARDASIL®9 was efficacious in preventing HPV 31-, 33-, 45-, 52-, and 58-related persistent infection and disease (Table 8). GARDASIL®9 also reduced the incidence of HPV 31-, 33-, 45-, 52-, and 58-related Pap test abnormalities, cervical procedures (i.e., biopsies), and cervical definitive therapy procedures (including loop electrosurgical excision procedure [LEEP] or conization). See Table 8.

Table 8: 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	6016	1	6017	30	96.7[þ] (80.9, 99.8)
HPV 31-, 33-, 45-, 52-, 58-related CIN 1	5948	1	5943	69	98.6 (92.4, 99.9)
HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3 or AIS	5948	1	5943	27	96.3 (79.5, 99.8)
HPV 31-, 33-, 45-, 52-, 58-related Vulvar or Vaginal Disease	6009	1	6012	16	93.8 (61.5, 99.7)

Table 8: 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 Persistent Infection ≥6 Months§	5939	35	5953	810	96.0 (94.4, 97.2)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥12 Months¶	5939	21	5953	544	96.3 (94.4, 97.7)
HPV 31-, 33-, 45-, 52-, 58-related ASC-US HR-HPV Positive or Worse Pap# Abnormality	5881	35	5882	462	92.6 (89.7, 94.8)
HPV 31-, 33-, 45-, 52-, 58-related Biopsy	6016	7	6017	222	96.9 (93.6, 98.6)
HPV 31-, 33-, 45-, 52-, 58-related Definitive Therapy	6012	4	6014	32	87.5 (65.7, 96.0)

*The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 31, 33, 45, 52, and 58) prior to dose 1 who remained PCR negative to the relevant HPV type(s) and through 1 month postdose 3 (Month 7). The data are from Protocol 001.
†N=Number of individuals randomized to the respective vaccination group who received at least 1 injection
‡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
Þp-value<0.0001
CI=Confidence Interval
ASC-US=Atypical squamous cells of undetermined significance
HR=High Risk

At the end of study, efficacy analyses were conducted in the efficacy substudy cohort with a median follow-up time of 3.5 years post-dose 3 (with a range of 0.0 to 5.6 years). For the HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer, and Vaginal Cancer, there was 1 case in the GARDASIL®9 group and 38 cases in the GARDASIL® group representing an efficacy of 97.4%. With respect to 12 month persistent infection, there were 23 cases in the GARDASIL®9 group and 657 cases in the GARDASIL® group representing an efficacy of 96.7%. There were 37 cases in the GARDASIL®9 group and 506 cases in the GARDASIL® group of HPV31-, 33-, 45-, 52- and 58-related Pap test abnormalities representing an efficacy of 92.9%. There were 4 cases in the GARDASIL®9 group and 41 cases in the GARDASIL® group of HPV 31-, 33-, 45-, 52- and 58-related cervical definitive therapy representing an efficacy of 90.2%.

Immunogenicity

Assays to Measure Immune Response
The minimum anti-HPV titer that confers protective efficacy has not been determined.

Because there were few disease cases in individuals naïve (PCR negative and seronegative) to vaccine HPV types at baseline in the group that received GARDASIL®9 it has not been possible

to establish minimum antibody levels that protect against clinical disease caused by vaccine HPV types.

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.

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).

In these studies, seropositive is defined as anti-HPV titer greater than or equal to the pre-specified serostatus cutoff for a given HPV type. Seronegative is defined as anti-HPV titer less than the pre-specified serostatus cutoff for a given HPV type (Table 9). The serostatus cutoff is the antibody titer level above the assay's lower limit of quantification that reliably distinguishes sera samples classified by clinical likelihood of HPV infection and positive or negative status by previous versions of Competitive Luminex Immunoassay (cLIA).

Table 9: Competitive Luminex Immunoassay (cLIA) Limits of Quantification and Serostatus Cutoffs for GARDASIL®9 HPV Types

HPV Type	cLIA Lower Limit of Quantification (mMU*/mL)	cLIA Serostatus Cutoff (mMU*/mL)
HPV 6	16	30
HPV 11	6	16
HPV 16	12	20
HPV 18	8	24
HPV 31	4	10
HPV 33	4	8
HPV 45	3	8
HPV 52	3	8
HPV 58	4	8

*mMU=milli-Merck Units

Studies Supporting the Efficacy of GARDASIL®9 Against HPV Types 6, 11, 16, 18

GARDASIL®9 efficacy against HPV 6-, 11-, 16-, and 18-related infection and disease was inferred from comparative studies to the quadrivalent (Types 6, 11, 16 18) vaccine, GARDASIL®, in which GARDASIL®9 elicited immune responses as measured by GMT. These studies were designed to evaluate immunologic non-inferiority of GARDASIL®9 to GARDASIL®. Therefore, the efficacy findings from the pivotal clinical studies for GARDASIL® against HPV Type 6-, 11-, 16-, and 18-related disease were extended to GARDASIL®9 by demonstrating that the immune responses elicited by GARDASIL®9 were non-inferior to the immune responses elicited by GARDASIL®.

Comparison of GARDASIL®9 with GARDASIL® immunogenicity 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 (N=13,587) and 9- through 15-year-old girls from Protocol 009 (N=600). The primary analyses were conducted in the per-protocol population.

A statistical analysis of non-inferiority was performed base on 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® (Tables 10 and 11). Therefore, 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 GARDASIL®.

Table 10: Comparison of Immune Responses (Based on cLIA) Between GARDASIL®9 and GARDASIL® for HPV Types 6, 11, 16, and 18 in the PPI* Population of 9- through 15-Year-Old Girls

9- through15-year-old girls	GARDASIL®9			GARDASIL®			GARDASIL®9/ GARDASIL®	
	N† (n‡)	% Seropositive (95% CI)	GMT (95% CI) mMU§/mL	N† (n‡)	% Seropositive (95% CI)	GMT (95% CI) mMU§/mL	GMT Ratio	(95% CI)#
Anti-HPV 6	300 (273)	100 (98.7, 100)	1679.4 (1518.9, 1856.9)	300 (261)	100 (98.6, 100)	1565.9 (1412.2, 1736.3)	1.07	(0.93, 1.23)
Anti-HPV 11	300 (273)	100 (98.7, 100)	1315.6 (1183.8, 1462.0)	300 (261)	100 (98.6, 100)	1417.3 (1274.2, 1576.5)	0.93	(0.80, 1.08)
Anti-HPV 16	300 (276)	100 (98.7, 100)	6739.5 (6134.5, 7404.1)	300 (270)	100 (98.6, 100)	6887.4 (6220.8, 7625.5)	0.97	(0.85, 1.11)
Anti-HPV 18	300 (276)	100 (98.7, 100)	1956.6 (1737.3, 2203.7)	300 (269)	100 (98.6, 100)	1795.6 (1567.2, 2057.3)	1.08	(0.91, 1.29)

*The PPI population consisted of individuals who received all 3 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, and were seronegative to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1. The data for 9- through 15-year-old girls are from Protocol 009.
†N=Number of individuals randomized to the respective vaccination group who received at least 1 injection
‡Number of individuals contributing to the analysis
§mMU=milli-Merck units
#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

Table 11: Comparison of Immune Responses (Based on cLIA) Between GARDASIL®9 and GARDASIL® for HPV Types 6, 11, 16, and 18 in the PPI* Population of 16- through 26-Year-Old Girls and Women

16- through 26-year-old girls and women	GARDASIL®9			GARDASIL®			GARDASIL®9/ GARDASIL®	
	N† (n‡)	% Seropositive (95% CI)	GMT (95% CI) mMU§/mL	N† (n‡)	% Seropositive (95% CI)	GMT (95% CI) mMU§/mL	GMT Ratio	(95% CI)#
Anti-HPV 6	6792 (3993)	99.8 (99.6, 99.9)	893.1 (871.7, 915.1)	6795 (3975)	99.8 (99.7, 99.9)	875.2 (854.2, 896.8)	1.02	(0.99, 1.06)
Anti-HPV 11	6792 (3995)	100 (99.9, 100)	666.3 (649.6, 683.4)	6795 (3982)	99.9 (99.8, 100)	830.0 (809.2, 851.4)	0.80	(0.77, 0.83)
Anti-HPV 16	6792 (4032)	100 (99.9, 100)	3131.1 (3057.1, 3206.9)	6795 (4062)	100 (99.8, 100)	3156.6 (3082.3, 3232.7)	0.99	(0.96, 1.03)
Anti-HPV 18	6792 (4539)	99.8 (99.7, 99.9)	804.6 (782.7, 827.1)	6795 (4541)	99.7 (99.5, 99.8)	678.7 (660.2, 697.7)	1.19	(1.14, 1.23)

*The PPI population consisted of individuals who received all 3 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, and 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 were PCR negative to the relevant HPV type(s) through 1 month Postdose 3 (Month 7). The data for 16- through 26- year-old girls and women are from Protocol 001.
†N=Number of individuals randomized to the respective vaccination group who received at least 1 injection
‡Number of individuals contributing to the analysis
§mMU=milli-Merck units
#Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67

Table 11: Comparison of Immune Responses (Based on cLIA) Between GARDASIL®9 and GARDASIL® for HPV Types 6, 11, 16, and 18 in the PPI* Population of 16- through 26-Year-Old Girls and Women

16- through 26-year-old girls and women	GARDASIL®9			GARDASIL®			GARDASIL®9/ GARDASIL®	
	N† (n‡)	% Seropositive (95% CI)	GMT (95% CI) mMU§/mL	N† (n‡)	% Seropositive (95% CI)	GMT (95% CI) mMU§/mL	GMT Ratio	(95% CI)#
CI=Confidence Interval GMT=Geometric Mean Titers cLIA= Competitive Luminex Immunoassay								

Study Supporting the Effectiveness of GARDASIL®9 against Vaccine HPV Types in 9- through 15-Year-Old Girls and Boys

Effectiveness of GARDASIL®9 against persistent infection and disease related to vaccine HPV types in 9- through 15-year-old girls and boys was inferred from non-inferiority comparison in Protocol 2 of GMTs following vaccination with GARDASIL®9 among 9- to 15-year-old girls and boys with those among 16- through 26-year-old girls and women. The primary analyses were conducted in the per-protocol population. Anti-HPV GMTs at Month 7 among 9- through 15-year-old girls and boys were non-inferior to anti-HPV GMTs among 16- through 26-year-old girls and women (Table 12).

Table 12: Comparison of Immune Responses (Based on cLIA) Between the PPI* Populations of 16- through 26-Year-Old, Girls and Women, 9- through 15-Year-Old Girls, and 9- through 15-Year-Old Boys for All GARDASIL®9 Vaccine HPV Types

Population	N†	n‡	% Seropositive (95% CI)	GMT (95% CI) mMU§/mL	GMT Ratio¶ relative to 16-through 26-year-old girls and women (95% CI)
Anti-HPV 6					
9- through 15-year-old girls	646	517	99.8 (98.9,100)	1715.4 (1595.1, 1844.7)	1.90 (1.70, 2.14)
9- through 15-year-old boys	666	559	99.8 (99.0, 100)	2084.7 (1944.0, 2235.7)	2.31 (2.07, 2.59)
16- through 26-year-old women	468	328	99.7 (98.3, 100)	900.8 (822.3, 986.9)	1
Anti-HPV 11					
9- through 15-year-old girls	646	517	100 (99.3, 100)	1295.1 (1204.1, 1393.0)	1.83 (1.63, 2.06)
9- through 15-year-old boys	666	559	100 (99.3, 100)	1487.1 (1386.5, 1595.0)	2.10 (1.88, 2.36)
16- through 26-year-old women	468	332	100 (98.9, 100)	706.6 (645.2, 773.8)	1
Anti-HPV 16					
9- through 15-year-old girls	646	529	100 (99.3, 100)	6979.8 (6508.1, 7485.8)	1.98 (1.77, 2.22)
9- through 15-year-old boys	666	569	100 (99.4, 100)	8628.9 (8065.9, 9231.3)	2.45 (2.19, 2.74)
16- through 26-year-old women	468	329	100 (98.9, 100)	3522.6 (3223.5, 3849.5)	1
Anti-HPV 18					
9- through 15-year-old girls	646	531	99.8 (99.0, 100)	2153.7 (1980.4, 2342.1)	2.44 (2.13, 2.80)
9- through 15-year-old boys	666	567	100 (99.4, 100)	2822.8 (2602.8, 3061.5)	3.20 (2.80, 3.65)
16- through 26-year-old women	468	345	99.7 (98.4, 100)	882.7 (795.4, 979.5)	1
Anti-HPV 31					
9- through 15-year-old girls	646	522	100 (99.3, 100)	1891.6 (1745.7, 2049.7)	2.51 (2.21, 2.85)
9- through 15-year-old boys	666	564	100 (99.3, 100)	2221.2 (2056.1, 2399.5)	2.95 (2.60, 3.34)
16- through 26-year-old women	468	340	99.7 (98.4, 100)	753.9 (682.5, 832.7)	1
Anti-HPV 33					
9- through 15-year-old girls	646	534	100 (99.3, 100)	980.4 (911.7, 1054.3)	2.10 (1.87, 2.36)
9- through 15-year-old boys	666	567	100 (99.4, 100)	1198.7 (1117.1, 1286.2)	2.57 (2.29, 2.88)
16- through 26-year-old women	468	354	99.7 (98.4, 100)	466.8 (426.9, 510.3)	1
Anti-HPV 45					
9- through 15-year-old girls	646	534	99.8 (99.0, 100)	714.4 (651.9, 782.8)	2.62 (2.27, 3.03)
9- through 15-year-old boys	666	570	100 (99.4, 100)	907.0 (830.2, 991.0)	3.33 (2.89, 3.84)
16- through 26-year-old women	468	368	99.5 (98.1, 99.9)	272.2 (243.8, 303.9)	1
Anti-HPV 52					
9- through 15-year-old girls	646	533	100 (99.3, 100)	932.9 (864.8, 1006.4)	2.22 (1.97, 2.51)
9- through 15-year-old boys	666	568	100 (99.4, 100)	1037.8 (964.4, 1116.9)	2.47 (2.19, 2.79)

Table 12: Comparison of Immune Responses (Based on cLIA) Between the PPI* Populations of 16- through 26-Year-Old, Girls and Women, 9- through 15-Year-Old Girls, and 9- through 15-Year-Old Boys for All GARDASIL®9 Vaccine HPV Types

Population	N†	n‡	% Seropositive (95% CI)	GMT (95% CI) mMU§/mL	GMT Ratio¶ relative to 16-through 26-year-old girls and women (95% CI)
16- through 26-year-old women	468	337	99.7 (98.4, 100)	419.6 (381.4, 461.5)	1
Anti-HPV 58					
9- through 15-year-old girls	646	531	100 (99.3, 100)	1286.7 (1195.7, 1384.6)	2.18 (1.93, 2.45)
9- through 15-year-old boys	666	566	100 (99.4, 100)	1567.7 (1460.2, 1683.1)	2.66 (2.37, 2.98)
16- through 26-year-old women	468	332	100 (98.9, 100)	590.5 (538.2, 647.9)	1

*The PPI population consisted of individuals who received all 3 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, and 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, 18, 31, 33, 45, 52 and 58) prior to dose 1 and [among 16- through 26-year-old girls and women] PCR negative to the relevant HPV type(s) through 1 month Postdose 3 (Month 7). The data are from Protocol 002.
†Number of individuals randomized to the respective vaccination group who received at least 1 injection
‡Number of individuals contributing to the analysis
§mMU=milli-Merck Units
¶Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67
cLIA=Competitive Luminex Immunoassay
CI=Confidence Interval
GMT=Geometric Mean Titers

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

Study Supporting the Effectiveness of GARDASIL®9 against Vaccine HPV Types in 16 -through 26-Year-Old Boys and Men

Effectiveness of GARDASIL®9 against persistent infection and disease related to vaccine HPV types in 16- through 26-year-old boys and men was inferred from non-inferiority comparison in Protocol 003 of GMTs following vaccination with GARDASIL®9 among 16- to 26-year-old boys and men with those among 16- through 26-year-old girls and women. The primary analyses were conducted in the per-protocol population. Anti-HPV GMTs at Month 7 among 16- through 26-year-old boys and men (HM) appeared non-inferior to anti-HPV GMTs among 16- through 26-year-old girls and women (Table 13). Anti-HPV GMTs at Month 7 among 16- through 26-year-old MSM (HIV-negative) were lower than in 16- through 26-year-old HM. The GMT fold difference in 16- through 26-year-old MSM relative to the HM was 0.6 to 0.8.

Table 13: Comparison of Immune Responses (Based on cLIA) Between the PPI* Populations of 16-through 26-Year-Old Girls and Women and 16- through 26-Year-Old Boys and Men for All GARDASIL®9 Vaccine HPV Types

	Comparison Group				Estimated Fold Difference Group A/ Group B (95% CI)
	16-26 year old males (HM) (Comparison Group A) (N = 1,103)		16-26 year old females (Comparison Group B) (N = 1,099)		
Assay (cLIA)	n	Estimated GMT (mMU/mL)	n	Estimated GMT (mMU/mL)	
Anti-HPV 6	847	782.0	708	703.9	1.11 (1.02, 1.21)
Anti-HPV 11	851	616.7	712	564.9	1.09 (1.00, 1.19)
Anti-HPV 16	899	3,346.0	781	2,788.3	1.20 (1.10, 1.30)
Anti-HPV 18	906	808.2	831	679.8	1.19 (1.08, 1.31)
Anti-HPV 31	908	708.5	826	570.1	1.24 (1.13, 1.37)

Table 13: Comparison of Immune Responses (Based on cLIA) Between the PPI* Populations of 16-through 26-Year-Old Girls and Women and 16- through 26-Year-Old Boys and Men for All GARDASIL®9 Vaccine HPV Types

	Comparison Group				Estimated Fold Difference Group A/ Group B (95% CI)
	16-26 year old males (HM) (Comparison Group A) (N = 1,103)		16-26 year old females (Comparison Group B) (N = 1,099)		
Assay (cLIA)	n	Estimated GMT (mMU/mL)	n	Estimated GMT (mMU/mL)	
Anti-HPV 33	901	384.8	853	322.0	1.19 (1.10, 1.30)
Anti-HPV 45	909	235.6	871	185.7	1.27 (1.14, 1.41)
Anti-HPV 52	907	386.8	849	335.2	1.15 (1.05, 1.26)
Anti-HPV 58	897	509.8	839	409.3	1.25 (1.14, 1.36)

*The PPI population consisted of individuals who, received all 3 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, and were seronegative to the relevant HPV type(s) (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) prior to dose 1. The data are from Protocol 003. ¶Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67
N = Number of subjects randomized to the respective vaccination group who received at least 1 injection.
n = Number of subjects contributing to the analysis.
CI = Confidence interval; GMT = Geometric mean titer; mMU = Milli Merck units; cLIA = 9 valent Competitive Luminex immunoassay.
HM = Heterosexual men.

On the basis of this immunogenicity bridging, the efficacy of GARDASIL®9 in 16- through 26-year-old boys and men is inferred.

Immune Responses to GARDASIL®9 Using a 2-dose Schedule in Individuals 9- through 14 Years of Age

Protocol 010 measured HPV antibody responses to the 9 HPV types after GARDASIL®9 vaccination in the following cohorts: girls and boys 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 14).

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 14. 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	GMT Ratio relative to 16- through 26-year-old girls and women (95 % CI)
Anti-HPV 6				
9- to 14-year-old girls (0, 6)†	301	258	1657.9 (1479.6, 1857.6)	2.15 (1.83, 2.53)§
9- to 14-year-old boys (0, 6)†	301	263	1557.4 (1391.5, 1743.1)	2.02 (1.73, 2.36)§
9- to 14-year-old girls and boys (0, 12)†	300	257	2678.8 (2390.2, 3002.1)	3.47 (2.93, 4.11)§
9- to 14-year-old girls (0, 2, 6)†	300	254	1496.1 (1334.1, 1677.8)	1.94 (1.65, 2.29)¶
16- to 26-year-old women (0, 2, 6)†	314	238	770.9 (684.8, 867.9)	1
Anti-HPV 11				
9- to 14-year-old girls (0, 6)†	301	258	1388.9 (1240.4, 1555.3)	2.39 (2.03, 2.82)§
9- to 14-year-old boys (0, 6)†	301	264	1423.9 (1273.2, 1592.3)	2.45 (2.09, 2.88)§
9- to 14-year-old girls and boys (0, 12)†	300	257	2941.8 (2626.6, 3294.9)	5.07 (4.32, 5.94)§
9- to 14-year-old girls (0, 2, 6)†	300	254	1306.3 (1165.5, 1464.0)	2.25 (1.90, 2.66)¶
16- to 26-year-old women (0, 2, 6)†	314	238	580.5 (516.0, 653.0)	1
Anti-HPV 16				
9- to 14-year-old girls (0, 6)†	301	272	8004.9 (7160.5, 8948.8)	2.54 (2.14, 3.00)§
9- to 14-year-old boys (0, 6)†	301	273	8474.8 (7582.4, 9472.3)	2.69 (2.29, 3.15)§
9- to 14-year-old girls and boys (0, 12)†	300	264	14329.3 (12796.4, 16045.9)	4.54 (3.84, 5.37)§
9- to 14-year-old girls (0, 2, 6)†	300	269	6996.0 (6254.1, 7825.8)	2.22 (1.89, 2.61)¶
16- to 26-year-old women (0, 2, 6)†	314	249	3154.0 (2807.1, 3543.7)	1
Anti-HPV 18				
9- to 14-year-old girls (0, 6)†	301	272	1872.8 (1651.6, 2123.6)	2.46 (2.05, 2.96)§
9- to 14-year-old boys (0, 6)†	301	272	1860.9 (1641.1, 2110.2)	2.44 (2.04, 2.92)§
9- to 14-year-old girls and boys (0, 12)†	300	266	2810.4 (2474.9, 3191.3)	3.69 (3.06, 4.45)§
9- to 14-year-old girls (0, 2, 6)†	300	270	2049.3 (1806.4, 2324.8)	2.69 (2.24, 3.24)¶
16- to 26-year-old women (0, 2, 6)†	314	267	761.5 (670.8, 864.5)	1
Anti-HPV 31				
9- to 14-year-old girls (0, 6)†	301	272	1436.3 (1272.1, 1621.8)	2.51 (2.10, 3.00)§
9- to 14-year-old boys (0, 6)†	301	271	1498.2 (1326.5, 1692.0)	2.62 (2.20, 3.12)§
9- to 14-year-old girls and boys (0, 12)†	300	268	2117.5 (1873.7, 2393.1)	3.70 (3.08, 4.45)§
9- to 14-year-old girls (0, 2, 6)†	300	271	1748.3 (1548.1, 1974.5)	3.06 (2.54, 3.67)¶
16- to 26-year-old women (0, 2, 6)†	314	264	572.1 (505.8, 647.2)	1
Anti-HPV 33				
9- to 14-year-old girls (0, 6)†	301	273	1030.0 (920.4, 1152.7)	2.96 (2.50, 3.50)§
9- to 14-year-old boys (0, 6)†	301	271	1040.0 (928.9, 1164.3)	2.99 (2.55, 3.50)§
9- to 14-year-old girls and boys (0, 12)†	300	269	2197.5 (1961.9, 2461.3)	6.31 (5.36, 7.43)§
9- to 14-year-old girls (0, 2, 6)†	300	275	796.4 (712.0, 890.9)	2.29 (1.95, 2.68)¶
16- to 26-year-old women (0, 2, 6)†	314	279	348.1 (311.5, 389.1)	1
Anti-HPV 45				
9- to 14-year-old girls (0, 6)†	301	274	357.6 (313.7, 407.6)	1.67 (1.38, 2.03)§
9- to 14-year-old boys (0, 6)†	301	273	352.3 (309.0, 401.7)	1.65 (1.37, 1.99)§
9- to 14-year-old girls and boys (0, 12)†	300	268	417.7 (365.9, 476.9)	1.96 (1.61, 2.37)§
9- to 14-year-old girls (0, 2, 6)†	300	275	661.7 (580.6, 754.1)	3.10 (2.54, 3.77)¶
16- to 26-year-old women (0, 2, 6)†	314	280	213.6 (187.7, 243.2)	1
Anti-HPV 52				
9- to 14-year-old girls (0, 6)†	301	272	581.1 (521.9, 647.1)	1.60 (1.36, 1.87)§
9- to 14-year-old boys (0, 6)†	301	273	640.4 (575.2, 713.0)	1.76 (1.51, 2.05)§
9- to 14-year-old girls and boys (0, 12)†	300	268	1123.4 (1008.1, 1251.9)	3.08 (2.64, 3.61)§
9- to 14-year-old girls (0, 2, 6)†	300	275	909.9 (817.6, 1012.5)	2.50 (2.12, 2.95)¶
16- to 26-year-old women (0, 2, 6)†	314	271	364.2 (327.0, 405.6)	1

Table 14. 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	GMT Ratio relative to 16- through 26-year-old girls and women (95 % CI)
Anti-HPV 58				
9- to 14-year-old girls (0, 6)†	301	270	1251.2 (1119.6, 1398.4)	2.55 (2.15, 3.01)§
9- to 14-year-old boys (0, 6)†	301	270	1325.7 (1186.2, 1481.6)	2.70 (2.30, 3.16)§
9- to 14-year-old girls and boys (0, 12)†	300	265	2444.6 (2185.2, 2734.9)	4.98 (4.23, 5.86)§
9- to 14-year-old girls (0, 2, 6)†	300	273	1229.3 (1100.7, 1,373.0)	2.50 (2.11, 2.97)¶
16- to 26-year-old women (0, 2, 6)†	314	261	491.1 (438.6, 549.8)	1

*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.
§Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67
¶Exploratory analysis; criterion for non-inferiority was not pre-specified
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

Variation in Dosing Regimen in 16- through 26-Year-Old Women

All individuals evaluated for efficacy in the PPE population of Study 1 received all 3 vaccinations within a 1-year period, regardless of the time interval between doses. An analysis of immune response data suggests that flexibility of ±1 month for Dose 2 (i.e., Month 1 to Month 3 in the vaccination regimen) and flexibility of ±2 months for Dose 3 (i.e., Month 4 to Month 8 in the vaccination regimen) do not substantially impact the immune responses to GARDASIL®9 (see DOSAGE AND ADMINISTRATION).

Persistence of Immune Response to GARDASIL®9

The persistence of antibody response following a complete schedule of vaccination with GARDASIL®9 was studied in two Protocols, Protocol 001 and Protocol 002. In both studies, Anti-HPV cLIA GMTs were highest at 1 month postdose 3 (Month 7) and decreased by approximately 70% at Month 12. In 16-26 year-old girls and women (Protocol 001), at Month 42, GMTs were approximately 10-20% of Month 7 GMTs and 78-98% of subjects were seropositive for each of the 9 vaccine HPV types. In 9-15 year-old boys and girls (Protocol 002), at Month 36, GMTs were approximately 10-20% of Month 7 GMTs and 93-99% of subjects were seropositive for each of the 9 vaccine HPV types.

Administration of GARDASIL®9 to Individuals Previously Vaccinated with GARDASIL®

Protocol 006 evaluated administration of GARDASIL®9 to girls and women 12 through 26 years of age previously vaccinated with GARDASIL® (N=921; 615 receiving GARDASIL®9 and 306 receiving placebo). Prior to enrollment in the study, over 99% of subjects had received 3 injections of GARDASIL® within a one year period. The time interval between the last injection of GARDASIL® and the first injection of GARDASIL®9 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 31, 33, 45, 52 and 58 were lower than in the population who had not previously received GARDASIL® in Protocols 001, 002, 005, 007 and 009. Efficacy of GARDASIL®9 in preventing infection and disease related to HPV Types 31, 33, 45, 52, and 58 in individuals previously vaccinated with GARDASIL® has not been assessed.

Studies with Menactra* [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel* [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)]

In Protocol 005, the safety and immunogenicity of co-administration of GARDASIL®9 with Menactra* [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel* [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] (same visit, injections at separate sites) were evaluated in 1,237 boys and girls 11 through 15 years of age at enrollment. The race distribution of the study subjects was as follows: 47.4% White; 35.0% Multiracial; 9.6% American Indian or Alaska Native; 6.4% Black; 1.1% Asian; and 0.6% Native Hawaiian or Other Pacific Islander.

One group received GARDASIL®9 in one limb and both Menactra* and Adacel*, as separate injections, in the opposite limb concomitantly on Day 1 (n = 619). The second group received the first dose of GARDASIL®9 on Day 1 in one limb then Menactra* and Adacel*, as separate injections, at Month 1 in the opposite limb (n = 618). Subjects in both vaccination groups received the second dose of GARDASIL®9 at Month 2 and the third dose at Month 6. Immunogenicity was assessed for all vaccines 1 month post completion of the vaccination series (1 dose for Menactra* and Adacel* and 3 doses for GARDASIL®9).

Concomitant administration of GARDASIL®9 with Menactra* and Adacel* did not interfere with the antibody response to any of the vaccine antigens when GARDASIL®9 was given concomitantly with Menactra* and Adacel* or separately.

Repevax* [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content) (Tdap-IPV)]

In Protocol 007, the safety and immunogenicity of co-administration of GARDASIL®9 with Repevax* [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content) (Tdap-IPV)] (same visit, injections at separate sites) were evaluated in a study of 1053 boys and girls 11 through 15 years of age at enrollment.

One group received GARDASIL®9 in one limb and Repevax* in the opposite limb concomitantly on Day 1 (n = 525). The second group received the first dose of GARDASIL®9 on Day 1 in one limb then Repevax* at Month 1 in the opposite limb (n = 528). Subjects in both vaccination groups received the second dose of GARDASIL®9 at Month 2 and the third dose at Month 6. Immunogenicity was assessed for all vaccines 1 month post completion of the vaccination series (1 dose for Repevax* and 3 doses for GARDASIL®9).

Concomitant administration of GARDASIL®9 with Repevax* did not interfere with the antibody response to any of the vaccine antigens when GARDASIL®9 was given concomitantly with Repevax* or separately.

TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

GARDASIL®9 has not been evaluated for the potential to cause carcinogenicity or genotoxicity.

Reproduction

GARDASIL®9 administered to female rats at a dose approximately 240 times the human dose (mg/kg basis) had no effects on mating performance, fertility, or embryonic/fetal survival.

Development

GARDASIL®9 administered to female rats at a dose approximately 160 times the human dose (mg/kg basis) had no effects on development, behavior, reproductive performance or fertility of the offspring.

An evaluation of the effect of GARDASIL®9 on embryo-fetal, pre- and postweaning development was conducted in studies using rats. No adverse effects on mating, fertility, pregnancy, parturition, lactation, embryo-fetal or pre- and postweaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis noted. In addition, there were no treatment-related effects on developmental signs, behavior, reproductive performance, or fertility of the offspring. GARDASIL®9 induced a specific antibody response against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in pregnant rats following one or multiple intramuscular injections. Antibodies against all 9 HPV types were transferred to the offspring during the period of gestation and lactation.

Repeat Dose Toxicity and Local Tolerance

A repeat dose toxicity study has been performed in rats at a dose approximately 250 times the human dose (mg/kg basis) and revealed no special hazards to humans.

REFERENCES

1. Money DM, Roy M. Preamble – HPV Guidelines Committee Chairs: JOGC 2007;29(8):S3.
2. Braaten KP, Laufer MR. Human Papillomavirus (HPV), HPV-Related Disease, and the HPV Vaccine. Reviews Obst & Gynecol 2008;1(1):2-10.
3. De sanjose S, Alemany A, Ordi J, Tous S, Alejo M, Bigby SM, et al. Worldwide Human Papillomavirus Genotypes Attribution in over 2000 Cases of intraepithelial and Invasive Lesions of the Vulva. Eur J Cancer 2013;49:3450-67.
4. Alemany L, Saunier M, Tinoco L, Quiros b, Alvarado-Cabrero I, Alejo M, et al. Large Contribution of Human Papillomavirus in Vaginal Neoplastic Lesions: A Worldwide Study in 597 Samples. Eur J Cancer 2014;50: 2846-54.
5. Nicols AC, Palma DA, Dhaliwal SS, Tan S, Theuer J, Chow W, et al. The Epidemic of Human Papillomavirus and oropharyngeal Cancer in a Canadian Population. Curr Oncol. 2013;20(4):212-9.
6. Ouhoummane N, Steben M, Coutlée F, Vuong T, Forest P, Rodier C, et al. Squamous anal cancer: Patient characteristics and HPV Type Distribution. Cancer Epidemiol 2013;37:807-12.
7. Cervical Cancer Screening in Canada - Monitoring Program Performance 2006–2008. Canadian Partnership Against Cancer, 2011.
8. Cervical Cancer Screening in Canada: 1998 Surveillance Report. Public Health Agency of Canada, 1998.
9. Coutlée F, Ratnam S, Ramanakumar AV, Insinga RR, Bentley J, Escott N, et al. Distribution of Human Papillomavirus Genotypes in Cervical Intraepithelial Neoplasia and Invasive Cervical Cancer in Canada. J Med Virol 2011;83;1034-41.
10. De Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, et al. Human Papillomavirus Genotype Attribution in Invasive Cervical Cancer: A Retrospective Cross-Sectional Worldwide Study. Lancet Oncol 2010;11:1048-56.
11. Alemany l, de Sanjose S, Tous S, Quint W, Vallejos C, Shin HR, et al. Time Trends of Human Papillomavirus Types in Invasive Cervical Cancer, From 1040-2007. Int J Cancer 2013;135:88-95.
12. Bosch FX, Broker TR, Forman D, Moscicki AB, Gillison ML, Doorbar J, et al. Comprehensive Control of Human Papillomavirus Infections and related Diseases. Vaccine 2013;S31:H1-31.
13. Serrano B, Alemany L, Tous S, Bruni L, Clifford GM, Weiss T, et al. Potential Impact of a nine-Valent vaccine in Human Papillomavirus Related Cervical Disease. Infect Dis & Cancer 2012;7(38):1-13.
14. Drolet M, Brisson M, Maunsell E, Franco EL, Coutléee F, Ferenczy A, et al. The Impact of anogenital Warts on Health-Related Quality of Life: a 6-Month Prospective Study. Sex Trans Dis 2011;38(10);949-56.

15. Forman D, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, et al. Global Burden of Human Papillomavirus and Related Diseases. Vaccine 2012;30(S5):F12-23.

16. Gillison ML, Alemany L, Snijders PJF, Chaturvedi A, Steinberg BM, Schwartz S, et al. Human Papillomavirus and Diseases of the Upper Airway: Head and Neck Cancer and Respiratory Papillomatosis. Vaccine 2012;30(S5):F34–54.

17. Joura E, Giuliano A, Iversen OE, et al. 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med 2015;372(8):711–723.

PART III: CONSUMER INFORMATION

GARDASIL®9

[Human Papillomavirus 9-valent Vaccine, Recombinant]

This leaflet is part III of a three-part "Product Monograph" published when GARDASIL®9 was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about GARDASIL®9. Contact your doctor or pharmacist if you have any questions about the vaccine.

ABOUT THIS VACCINE

What the vaccine is used for:
GARDASIL®9 is a vaccine (injection/shot) that helps protect against some diseases caused by some types of Human Papillomavirus (HPV). GARDASIL®9 contains the same 4 HPV types (6, 11, 16, 18) as in GARDASIL® with 5 additional HPV types (31, 33, 45, 52, 58).

Girls and Women
GARDASIL®9 is a vaccine (injection/shot) that helps protect girls and women 9 through 45 years of age against the following diseases caused by an infection with Human Papillomavirus (HPV) types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Cervical cancer (cancer of the lower end of the uterus or womb) caused by HPV types 16, 18, 31, 33, 45, 52, and 58
- Vulvar (the outside of the female genital area) and vaginal cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11
- Abnormal and precancerous cervical lesions (changes in cells of the cervix that have a risk of turning into cancer) as found in a Pap test caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58
- Abnormal and precancerous vaginal and vulvar lesions (outside of the female genital area) caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58

GARDASIL®9 helps protect girls and women 9 through 26 years of age against:

- Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58
- Abnormal and precancerous anal lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Boys and Men
GARDASIL®9 helps protect boys and men 9 through 26 years of age against infection caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 and the following diseases caused by HPV:

- Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58
- Genital warts caused by HPV types 6 and 11
- Abnormal and precancerous anal lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

These diseases have many causes. Most of the time, these diseases are caused by nine types of HPV: HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. GARDASIL®9 only protects against diseases caused by these nine types of HPV.

People cannot get HPV or any of these diseases from GARDASIL®9.

What it does not:
GARDASIL®9:

- Does not remove the need for cervical cancer screening; women should still get routine cervical cancer screening.
- Does not protect the person getting GARDASIL®9 from a disease that is caused by other types of HPV, other viruses or bacteria.
- Does not treat HPV infection.
- Does not protect the person getting GARDASIL®9 from HPV types that he/she may already have; but most people do not have all types contained in the vaccine.

GARDASIL®9 may not fully protect each person who gets it.

How does GARDASIL®9 work?
When an individual receives the GARDASIL®9 vaccine, his/her immune system produces antibodies against the 9 HPV types contained in the vaccine. If that individual is exposed to one of these types, the antibodies may help defend against developing infection and related diseases.

About HPV
Human Papillomavirus (HPV) is a common virus. Without vaccination, the majority of sexually active people will catch HPV during their lifetime. While most infected people clear the virus, those who do not can develop HPV-related cancers and precancers, or genital warts. Many people who have HPV may not show any signs or symptoms. This means that they can transmit (pass on) the virus to others without knowing it.

HPV causes nearly 100% of cervical cancers. HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 specifically cause approximately 90% of cervical cancers and 75-85% of cervical precancers. These 9 types of HPV also cause at least 75% of HPV-related vulvar, vaginal and anal cancers, and precancers. Over 90% of genital warts are caused by HPV types 6 and 11.

Will GARDASIL®9 help me if I already have Human Papillomavirus?
GARDASIL®9 helps prevent the diseases caused by some types of papillomavirus but will not treat them. If you are already infected with one type of HPV contained in the vaccine, GARDASIL®9 will help protect you against the

other eight types. Talk to your health-care provider for more information.

Use in children
GARDASIL®9 can be used in children as young as 9 years of age.

Use in pregnancy
It is not known whether the vaccine is harmful to an unborn baby when administered to a pregnant woman. If you are pregnant, you should be vaccinated with GARDASIL®9 only if your doctor or health care professional decides it is clearly needed.

Women who become pregnant before completion of the vaccine series should complete their vaccination schedule after childbirth.

Pregnant women exposed to GARDASIL®9 are encouraged to report their exposure or suspected adverse reactions by contacting Merck Canada Inc., at 1-800-567-2594 or the Vaccine Safety Section at Public Health Agency of Canada at 1-866-844-0018 or www.phac-aspc.gc.ca/im/vs-sv/index-eng.php.

Use in breast-feeding
It is not known whether GARDASIL®9 is excreted in human milk. If you are breast-feeding, talk to your doctor or health care professional to see if you should be vaccinated with GARDASIL®9.

Use in geriatrics
GARDASIL®9 has not been studied in the elderly.

When it should not be used:
Anyone with an allergic reaction to:
- A previous dose of GARDASIL®9
- A previous dose of GARDASIL®
- Any of the ingredients in the vaccine (listed in "What the important non-medicinal ingredients are" section).

What the medicinal ingredient is:
The main ingredients are highly purified inactive proteins (L1) that come from HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

What the important non-medicinal ingredients are:
It also contains amorphous aluminum hydroxyphosphate sulfate (AAHS Adjuvant), L-histidine, polysorbate 80, sodium borate, sodium chloride, and water for injection.

What dosage forms it comes in:
GARDASIL®9 is supplied as:
- 0.5 mL single-dose vials
- 0.5 mL single-dose prefilled syringes

WARNINGS AND PRECAUTIONS

It is very important to tell your healthcare professional if you or your child (the person getting GARDASIL®9):
- Are pregnant or planning to get pregnant. GARDASIL®9 is not recommended for use in pregnant women.
- Have immune problems, like HIV or cancer.
- Take medicines that affect the immune system.
- Have any illness with a fever over 37.8°C.
- Had an allergic reaction to a previous dose of GARDASIL®9 or GARDASIL®.
- Have a bleeding disorder and cannot receive injections in the arm.
- Take any medicines, even those you can buy over the counter.

The healthcare professional will help decide if you or your child should get the vaccine.

INTERACTIONS WITH THIS VACCINE

Can you get GARDASIL®9 if you have already gotten GARDASIL®?
Talk to your health care professional to see if GARDASIL®9 is right for you.

Can you get GARDASIL®9 with other vaccines?
GARDASIL®9 can be given at the same time as:
- Menactra* [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine]
- Adacel* [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)]
- Repevax* [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content) (Tdap-IPV)]

PROPER USE OF THIS VACCINE

Usual dose:
GARDASIL®9 is a shot that is usually given in the arm muscle.

You or your child (the person getting GARDASIL®9) will receive 3 doses of the vaccine. Ideally the doses are given as:
- First dose: at a date you and your health-care provider choose
- Second dose: 2 months after the first dose (not earlier than one month after the first dose)
- Third dose: 6 months after the first dose (not earlier than 3 months after the second dose)

All three doses should be given within a 1-year period. Talk to your doctor for more information.

Alternatively, individuals 9 through 14 years of age may receive 2 doses of the vaccine.

- Dose 1: at a date you and your doctor or health care professional choose
- Dose 2: given between 5 and 13 months after first dose.

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

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

Missed dose:
Make sure the person getting GARDASIL®9 gets the complete vaccine series. This allows you or your child to get the full benefits of GARDASIL®9. If the person getting GARDASIL®9 misses a dose, tell the doctor or health care professional. Your doctor or health care professional will decide when to give the missed dose.

It is important that you follow the instructions of your doctor or health care professional regarding return visits for follow-up doses.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects seen with GARDASIL®9 are:

- pain, swelling, redness, itching, bruising, bleeding, and a lump where you got the shot
- headache, fever, nausea, dizziness, tiredness, diarrhea, abdominal pain, sore throat

Fainting can happen after getting a HPV vaccine. Sometimes people who faint can fall and hurt themselves. For this reason, the health care professional may ask the person getting GARDASIL®9 to sit or lie down for 15 minutes after getting the vaccine. Some people who faint might shake or become stiff. The health care professional may need to treat the person getting GARDASIL®9.

Studies show that there was more swelling where the shot was given when GARDASIL®9 was given at the same time as Repevax*, or Menactra* and Adacel*.

Tell the doctor or health care professional if you or your child has these problems because these may be signs of an allergic reaction:

- difficulty breathing
- wheezing (bronchospasm)
- hives
- rash

As with other vaccines, side effects have been reported during general use. The following side effects have been reported with GARDASIL® and may also be seen after getting GARDASIL®9:

- swollen glands (neck, armpit, or groin), Guillain-Barré syndrome, headache, joint pain, aching muscles, unusual tiredness, weakness, or confusion, chills, bad stomach ache, muscle weakness, shortness of breath, generally feeling unwell, bleeding or bruising more easily than normal, and skin infection.

This is not a complete list of side effects. For any unexpected effects while taking GARDASIL®9, contact your doctor or pharmacist.

HOW TO STORE IT

Store refrigerated at 2°C to 8°C. Do not freeze. Protect from light.

Keep out of reach of children.

Reporting Suspected Vaccine Adverse Events

For the general public:
If you suspect you have had a serious or unexpected event following receipt of a vaccine, please ask your healthcare professional to complete the Adverse Events Following Immunization (AEFI) Form and send it to your local health unit in your province/territory.

For healthcare professionals:
If a patient experiences an adverse event following immunization, please complete the Adverse Events Following Immunization (AEFI) Form and send it to your local health unit in your province/territory.

If you have any questions or have difficulty contacting your local health unit, please contact Vaccine Safety Section at Public Health Agency of Canada:

Toll-free telephone: 1-866-844-0018
Toll-free fax: 1-866-844-5931
By email: caefi@phac-aspc.gc.ca

NOTE: Should you require information related to the management of the adverse events, please contact your health professional before notifying the Public Health Agency of Canada. The Public Health Agency of Canada does not provide medical advice.

MORE INFORMATION

If you want more information about GARDASIL®9:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website or Merck Canada web site www.merck.ca or by calling Merck Canada at 1-800-567-2594.

To report an adverse event related to GARDASIL®9, please contact 1-800-567-2594.

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