

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GARDASIL 9 safely and effectively. See full prescribing information for GARDASIL 9.

### GARDASIL<sup>®</sup> 9

(Human Papillomavirus 9-valent Vaccine, Recombinant)  
Suspension for intramuscular injection

Initial U.S. Approval: 2014

#### INDICATIONS AND USAGE

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

- Cervical, vulvar, vaginal, and anal cancer caused by Human Papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58. (1.1)
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11. (1.1)

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

- Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma *in situ* (AIS). (1.1)
- Cervical intraepithelial neoplasia (CIN) grade 1. (1.1)
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3. (1.1)
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3. (1.1)
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3. (1.1)

GARDASIL 9 is indicated in boys 9 through 15 years of age for the prevention of the following diseases:

- Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58. (1.2)
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11. (1.2)

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

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3. (1.2)

#### Limitations of Use and Effectiveness:

- GARDASIL 9 does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. (1.3, 17)
- Recipients of GARDASIL 9 should not discontinue anal cancer screening if it has been recommended by a health care provider. (1.3, 17)
- GARDASIL 9 has not been demonstrated to provide protection against disease from vaccine HPV types to which a person has previously been exposed through sexual activity. (1.3)
- GARDASIL 9 has not been demonstrated to protect against diseases due to HPV types other than 6, 11, 16, 18, 31, 33, 45, 52, and 58. (1.3)
- GARDASIL 9 is not a treatment for external genital lesions; cervical, vulvar, vaginal, and anal cancers; CIN; VIN; VaIN; or AIN. (1.3)
- Not all vulvar, vaginal, and anal cancers are caused by HPV, and GARDASIL 9 protects only against those vulvar, vaginal, and anal cancers caused by HPV 16, 18, 31, 33, 45, 52, and 58. (1.3)
- GARDASIL 9 does not protect against genital diseases not caused by HPV. (1.3)

- Vaccination with GARDASIL 9 may not result in protection in all vaccine recipients. (1.3)
- Safety and effectiveness of GARDASIL 9 have not been assessed in individuals older than 26 years of age. (1.3)

#### DOSAGE AND ADMINISTRATION

0.5-mL suspension for intramuscular injection at the following schedule: 0, 2 months, 6 months. (2.1)

#### DOSAGE FORMS AND STRENGTHS

0.5-mL suspension for injection as a single-dose vial and prefilled syringe. (3, 11)

#### CONTRAINDICATIONS

Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of GARDASIL 9 or GARDASIL<sup>®</sup>. (4, 11)

#### WARNINGS AND PRECAUTIONS

Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following HPV vaccination. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position. (5.1)

#### ADVERSE REACTIONS

- The most common ( $\geq 10\%$ ) local and systemic adverse reactions in females 16 through 26 years of age were injection-site pain (89.9%), injection-site swelling (40.0%), injection-site erythema (34.0%) and headache (14.6%). (6.1)
- The most common ( $\geq 10\%$ ) local and systemic reactions in girls 9 through 15 years of age were injection-site pain (89.3%), injection-site swelling (47.8%), injection-site erythema (34.1%) and headache (11.4%). (6.1)
- The most common ( $\geq 10\%$ ) local and systemic reactions in boys 9 through 15 years of age were injection-site pain (71.5%), injection-site swelling (26.9%), and injection-site erythema (24.9%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or VAERS at 1-800-822-7967 or [www.vaers.hhs.gov](http://www.vaers.hhs.gov).

#### USE IN SPECIFIC POPULATIONS

Safety and effectiveness of GARDASIL 9 have not been established in the following populations:

- Pregnant women. A pregnancy registry is available. Patients and health care providers are encouraged to register women exposed to GARDASIL 9 around the time of conception or during pregnancy by calling 1-800-986-8999. (8.1)
- Children below the age of 9 years. (8.4)
- Immunocompromised individuals. Response to GARDASIL 9 may be diminished. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2014

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Girls and Women

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

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

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

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

#### 1.2 Boys

GARDASIL 9 is indicated in boys 9 through 15 years of age for the prevention of the following diseases:

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

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

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

#### 1.3 Limitations of Use and Effectiveness

The health care provider should inform the patient, parent, or guardian that vaccination does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. Women who receive GARDASIL 9 should continue to undergo cervical cancer screening per standard of care. [See *Patient Counseling Information (17)*].

Recipients of GARDASIL 9 should not discontinue anal cancer screening if it has been recommended by a health care provider [see *Patient Counseling Information (17)*].

GARDASIL 9 has not been demonstrated to provide protection against disease from vaccine HPV types to which a person has previously been exposed through sexual activity.

GARDASIL 9 has not been demonstrated to protect against diseases due to HPV types other than 6, 11, 16, 18, 31, 33, 45, 52, and 58.

GARDASIL 9 is not a treatment for external genital lesions; cervical, vulvar, vaginal, and anal cancers; CIN; VIN; VaIN; or AIN.

Not all vulvar, vaginal, and anal cancers are caused by HPV, and GARDASIL 9 protects only against those vulvar, vaginal, and anal cancers caused by HPV 16, 18, 31, 33, 45, 52, and 58.

GARDASIL 9 does not protect against genital diseases not caused by HPV.

Vaccination with GARDASIL 9 may not result in protection in all vaccine recipients.

Safety and effectiveness of GARDASIL 9 have not been assessed in individuals older than 26 years of age.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Dosage

Administer GARDASIL 9 intramuscularly as a 0.5-mL dose at the following schedule: 0, 2 months, 6 months.

#### 2.2 Method of 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, whenever solution and container permit. Do not use the product if particulates are present or if it appears discolored.

Administer GARDASIL 9 intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

Observe patients for 15 minutes after administration [see *Warnings and Precautions (5)*].

#### *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*

This package does not contain a needle. Shake well before use. Attach a needle by twisting in a clockwise direction until the needle fits securely on the syringe. Administer the entire dose as per standard protocol.

### **2.3 Administration of GARDASIL 9 in Individuals Who Have Been Previously Vaccinated with GARDASIL<sup>®</sup>**

Safety and immunogenicity of GARDASIL 9 were assessed in individuals who previously completed a three-dose vaccination series with GARDASIL [see *Adverse Reactions (6.1) and Clinical Studies (14.4)*]. Studies using a mixed regimen of HPV vaccines to assess interchangeability were not performed for GARDASIL 9.

## **3 DOSAGE FORMS AND STRENGTHS**

GARDASIL 9 is a suspension for intramuscular administration available in 0.5-mL single-dose vials and prefilled syringes. See *Description (11)* for the complete listing of ingredients.

## **4 CONTRAINDICATIONS**

Hypersensitivity, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of GARDASIL 9 or GARDASIL [see *Description (11)*].

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Syncope**

Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following HPV vaccination. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position.

### **5.2 Managing Allergic Reactions**

Appropriate medical treatment and supervision must be readily available in case of anaphylactic reactions following the administration of GARDASIL 9.

## **6 ADVERSE REACTIONS**

### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

The safety of GARDASIL 9 was evaluated in six clinical studies that included 13,234 individuals who received at least one dose of GARDASIL 9 and had safety follow-up. Study 1 and Study 3 also included 7,378 individuals who received at least one dose of GARDASIL as a control and had safety follow-up. The vaccines were administered on the day of enrollment and the subsequent doses administered approximately two and six 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 8,022 women 16 through 26 years of age and 5,212 girls and boys 9 through 15 years of age (3,436 girls and 1,776 boys) at enrollment who received GARDASIL 9 and 7,078 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 GARDASIL 9 was similar between women (56.3% White; 25.4% Other Races or Multiracial; 14.7% Asian; 3.7% Black) and girls and boys (62.0% White; 19.2% Other Races or Multiracial; 13.5% Asian; 5.4% Black). The race distribution of the safety population for GARDASIL was determined in two studies (Study 1 and Study 3) that had different profiles. In Study 1, 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. Study 3 race distribution was 98.0% White; 1.3% Multiracial; 0.3% Asian; and 0.3% Black.

#### *Solicited Injection-Site and Systemic Adverse Reactions*

Injection-site reactions (pain, swelling, and erythema) and oral temperature were solicited using VRC-aided surveillance for five days after each injection of GARDASIL 9 during the clinical studies. The rates and severity of these solicited adverse reactions that occurred within five days following each dose of GARDASIL 9 compared with GARDASIL in Study 1 (girls and women 16 through 26 years of age) and Study 3 (girls 9 through 15 years of age) are presented in Table 1. Among subjects who received GARDASIL 9, the rates of injection-site pain were approximately equal across the three reporting time periods. Rates of injection-site swelling and injection-site erythema increased following each successive dose of GARDASIL 9. Recipients of GARDASIL 9 had numerically higher rates of injection-site reactions compared with recipients of GARDASIL.

**Table 1: Rates (%) and Severity of Solicited Injection-Site and Systemic Adverse Reactions Occurring within Five Days of Each Vaccination with GARDASIL 9 Compared with GARDASIL (Studies 1 and 3)**

	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
<b>Girls and Women 16 through 26 Years of Age</b>								
<b>Injection-Site Adverse Reactions</b>	<b>N=7069</b>	<b>N=6997</b>	<b>N=6909</b>	<b>N=7071</b>	<b>N=7076</b>	<b>N=6992</b>	<b>N=6909</b>	<b>N=7078</b>
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
<b>Systemic Adverse Reactions</b>	<b>n=6995</b>	<b>n=6913</b>	<b>n=6743</b>	<b>n=7022</b>	<b>n=7003</b>	<b>n=6914</b>	<b>n=6725</b>	<b>n=7024</b>
Temperature $\geq 100^{\circ}\text{F}$	1.7	2.6	2.7	6.0	1.7	2.4	2.5	5.9
Temperature $\geq 102^{\circ}\text{F}$	0.3	0.3	0.4	1.0	0.2	0.3	0.3	0.8
<b>Girls 9 through 15 Years of Age</b>								
<b>Injection-Site Adverse Reactions</b>	<b>N=300</b>	<b>N=297</b>	<b>N=296</b>	<b>N=299</b>	<b>N=299</b>	<b>N=299</b>	<b>N=294</b>	<b>N=300</b>
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
<b>Systemic Adverse Reactions</b>	<b>n=300</b>	<b>n=294</b>	<b>n=295</b>	<b>n=299</b>	<b>n=299</b>	<b>n=297</b>	<b>n=291</b>	<b>n=300</b>
Temperature $\geq 100^{\circ}\text{F}$	2.3	1.7	3.0	6.7	1.7	1.7	0	3.3
Temperature $\geq 102^{\circ}\text{F}$	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 Study 1 (NCT00543543), and the data for girls 9 through 15 years of age are from Study 3 (NCT01304498).

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

### *Unsolicited Adverse Reactions*

Unsolicited injection-site and systemic adverse reactions (assessed as vaccine-related by the investigator) observed among recipients of either GARDASIL 9 or GARDASIL in Studies 1 and 3 at a frequency of at least 1% are shown in Table 2. Few individuals discontinued study participation due to adverse experiences after receiving either vaccine (GARDASIL 9 = 0.1% vs. GARDASIL <0.1%).

**Table 2: Rates (%) of Unsolicited Injection-Site and Systemic Adverse Reactions Occurring among ≥1.0% of Individuals after Any Vaccination with GARDASIL 9 Compared with GARDASIL (Studies 1 and 3)**

	Girls and 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
<b>Injection-Site Adverse Reactions (1 to 5 Days Post-Vaccination, Any Dose)</b>				
Pruritus	5.5	4.0	4.0	2.7
Bruising	1.9	1.9	0	0
Hematoma	0.9	0.6	3.7	4.7
Mass	1.3	0.6	0	0
Hemorrhage	1.0	0.7	1.0	2.0
Induration	0.8	0.2	2.0	1.0
Warmth	0.8	0.5	0.7	1.7
Reaction	0.6	0.6	0.3	1.0
<b>Systemic Adverse Reactions (1 to 15 Days Post-Vaccination, Any Dose)</b>				
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	2.7
Diarrhea	1.2	1.0	0.3	0
Oropharyngeal pain	1.0	0.6	2.7	0.7
Myalgia	1.0	0.7	0.7	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 girls and women 16 through 26 years of age are from Study 1 (NCT00543543), and the data for girls 9 through 15 years of age are from Study 3 (NCT01304498).

N=number of subjects vaccinated with safety follow-up

In an uncontrolled clinical trial with 639 boys and 1,878 girls 9 through 15 years of age (Study 2), the rates and severity of solicited adverse reactions following each dose of GARDASIL 9 were similar between boys and girls. Rates of unsolicited injection-site and systemic adverse reactions in boys 9 through 15 years of age were similar to those among girls 9 through 15 years of age. Solicited and unsolicited adverse reactions reported by boys 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 who Received Gardasil 9**

	GARDASIL 9 N=639
<b>Solicited Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)</b>	
Injection-Site Pain	71.5
Injection-Site Erythema	24.9
Injection-Site Swelling	26.9
Oral Temperature ≥100.0°F <sup>†</sup>	10.4
<b>Unsolicited Injection-Site Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)</b>	
Injection-Site Hematoma	1.3
Injection-Site Induration	1.1
<b>Unsolicited Systemic Adverse Reactions (1-15 Days Post-Vaccination, Any Dose)</b>	
Headache	9.4
Pyrexia	8.9
Nausea	1.3

The data for GARDASIL 9 are from Study 2 (NCT00943722).

\*Unsolicited adverse reactions reported by ≥1% of individuals

N=number of subjects vaccinated with safety follow-up

<sup>†</sup>For oral temperature: number of subjects with temperature data N=637

### *Serious Adverse Events in Clinical Studies*

Serious adverse events were collected throughout the entire study period (range one month to 48 months post-last dose) for the six integrated clinical studies for GARDASIL 9. Out of the 13,236 individuals who were administered GARDASIL 9 and had safety follow-up, 305 reported a serious adverse event; representing 2.3% of the population. As a comparison, of the 7,378 individuals who were administered GARDASIL and had safety follow-up, 185 reported a serious adverse event; representing

2.5% of the population. Five GARDASIL 9 recipients each reported at least one serious adverse event that was determined to be vaccine-related. The vaccine-related serious adverse reactions were pyrexia, allergy to vaccine, asthmatic crisis, headache, and tonsillitis.

#### *Deaths in the Entire Study Population*

Across the clinical studies, ten deaths occurred (five each in the GARDASIL 9 and GARDASIL groups); none were assessed as vaccine-related. Causes of death in the GARDASIL 9 group included one automobile accident, one suicide, one case of acute lymphocytic leukemia, one case of hypovolemic septic shock, and one unexplained sudden death 678 days following the last dose of GARDASIL 9. Causes of death in the GARDASIL control group included one automobile accident, one airplane crash, one cerebral hemorrhage, one gunshot wound, and one stomach adenocarcinoma.

#### *Systemic Autoimmune Disorders*

In all of the clinical trials with GARDASIL 9 subjects were evaluated for new medical conditions potentially indicative of a systemic autoimmune disorder. In total, 2.4% (321/13,234) of GARDASIL 9 recipients and 3.3% (240/7,378) of GARDASIL recipients reported new medical conditions potentially indicative of systemic autoimmune disorders, which were similar to rates reported following GARDASIL, AAHS control, or saline placebo in historical clinical trials.

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

A clinical study (Study 4) evaluated the safety of GARDASIL 9 in 12- through 26-year-old girls and women who had previously been vaccinated with three 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 vaccination report card (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. Few (0.5%) individuals who received GARDASIL 9 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. Overall the safety profile was similar between individuals vaccinated with GARDASIL 9 who were previously vaccinated with GARDASIL and those who were naïve to HPV vaccination with the exception of numerically higher rates of injection-site swelling and erythema among individuals who were previously vaccinated with GARDASIL (Tables 1 and 4).

**Table 4: Rates (%) of Solicited and Unsolicited\* Injection-Site and Systemic Adverse Reactions among Individuals Previously Vaccinated with GARDASIL Who Received GARDASIL 9 or Saline Placebo (Girls and Women 12 through 26 Years of Age)**

	<b>GARDASIL 9 N=608</b>	<b>Saline Placebo N=305</b>
<b>Solicited Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)</b>		
Injection-Site Pain	90.3	38.0
Injection-Site Erythema	42.3	8.5
Injection-Site Swelling	49.0	5.9
Oral Temperature $\geq 100.0^{\circ}\text{F}^{\dagger}$	6.5	3.0
<b>Unsolicited Injection-Site Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)</b>		
Injection-Site Pruritus	7.7	1.3
Injection-Site Hematoma	4.8	2.3
Injection-Site Reaction	1.3	0.3
Injection-Site Mass	1.2	0.7
<b>Unsolicited Systemic Adverse Reactions (1-15 Days Post-Vaccination, Any Dose)</b>		
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 saline placebo are from Study 4 (NCT01047345).

\*Unsolicited adverse reactions reported by  $\geq 1\%$  of individuals

N=number of subjects vaccinated with safety follow-up

<sup>†</sup>For oral temperature: number of subjects with temperature data GARDASIL 9 N=604; Saline Placebo N=304

#### *Safety in Concomitant Use with Menactra and Adacel*

In Study 5, the safety of GARDASIL 9 when administered concomitantly 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)] was evaluated in a randomized study of 1,241 boys (n = 620) and girls (n = 621) with a mean age of 12.2 years [see *Clinical Studies (14.5)*].

Of the 1,237 boys and girls vaccinated, 1,220 had safety follow-up for injection-site adverse reactions. The rates of injection-site adverse reactions were similar between the concomitant group and non-concomitant group (vaccination with GARDASIL 9 separated from vaccination with Menactra and Adacel by 1 month) with the exception of an increased rate of swelling reported at the injection site for GARDASIL 9 in the concomitant group (14.4%) compared to the non-concomitant group (9.4%). The majority of injection-site swelling adverse reactions were reported as being mild to moderate in intensity.

## **6.2 Postmarketing Experience**

There is no post-marketing experience following administration of GARDASIL 9. However, the post-marketing safety experience with GARDASIL is relevant to GARDASIL 9 since the vaccines are manufactured similarly and contain the same antigens from HPV types 6, 11, 16, and 18. 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: Autoimmune diseases, hypersensitivity reactions including anaphylactic/anaphylactoid reactions, bronchospasm, and urticaria.

Musculoskeletal and connective tissue disorders: Arthralgia, myalgia.

Nervous system disorders: Acute disseminated encephalomyelitis, dizziness, Guillain-Barré syndrome, headache, motor neuron disease, paralysis, seizures, syncope (including syncope associated with tonic-



clonic movements and other seizure-like activity) sometimes resulting in falling with injury, transverse myelitis.

Infections and infestations: Cellulitis.

Vascular disorders: Deep venous thrombosis.

## **7 DRUG INTERACTIONS**

### **7.1 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 *Use in Specific Populations (8.6)*].

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

*Pregnancy Category B:*

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. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, GARDASIL 9 should be used during pregnancy only if clearly needed.

*Clinical Studies in Humans*

In clinical studies, women underwent serum or urine pregnancy testing prior to administration of each dose of GARDASIL 9. Women who were found to be pregnant before completion of a three-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 14.1% (145/1,028) in women who received GARDASIL 9 and 17.0% (168/991) 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, 20 and 21 cases of congenital anomaly were observed in women who have received GARDASIL 9 and GARDASIL, respectively. There was no clear pattern of anomaly types that differed from those occurring in pregnancies in the general population of the same age.

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.

*Pregnancy Registry for GARDASIL 9*

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., maintains a Pregnancy Registry to monitor fetal outcomes of pregnant women exposed to GARDASIL 9. Patients and health care providers are encouraged to register women exposed to GARDASIL 9 around the time of conception or during pregnancy by calling 1-800-986-8999.

### **8.3 Nursing Mothers**

It is not known whether GARDASIL 9 is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GARDASIL 9 is administered to a nursing woman.

## 8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients below 9 years of age.

## 8.5 Geriatric Use

The safety and effectiveness of GARDASIL 9 have not been evaluated in a geriatric population, defined as individuals aged 65 years and over.

## 8.6 Immunocompromised Individuals

The immunologic response to GARDASIL 9 may be diminished in immunocompromised individuals [see *Drug Interactions (7.1)*].

## 11 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.

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.

Each 0.5-mL dose of the vaccine also contains approximately 500 mcg of aluminum (provided as AAHS), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, <7 mcg yeast protein, and water for injection. The product does not contain a preservative or antibiotics.

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

## 12 CLINICAL PHARMACOLOGY

### 12.1 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. Efficacy of GARDASIL 9 against anogenital diseases related to the vaccine HPV types in human beings is thought to be mediated by humoral immune responses induced by the vaccine, although the exact mechanism of protection is unknown.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 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. Antibodies against all 9 HPV types were transferred to the offspring during gestation and lactation.

## 14 CLINICAL STUDIES

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. 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). The lower limits of quantification and serostatus cutoffs for each of the 9 vaccine HPV types are shown in Table 5 below. PCR positive is defined as DNA detected for a given HPV type. PCR negative is defined as DNA not detected for a given HPV type. The lower limit of detection for the multiplexed HPV PCR assays ranged from 5 to 34 copies per test across the 9 vaccine HPV types.

**Table 5: 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

### 14.1 Efficacy Data for GARDASIL

Efficacy of GARDASIL is relevant to GARDASIL 9 since the vaccines are manufactured similarly and contain four of the same HPV L1 VLPs.

*Females and males 16 through 26 years of age:* Efficacy of GARDASIL was assessed in six AAHS-controlled, double-blind, randomized clinical trials evaluating 24,596 individuals (20,541 girls and women 16 through 26 years of age, 4,055 boys and men 16 through 26 years of age).

The results of these trials are shown in Table 6 below.

**Table 6: Analysis of Efficacy of GARDASIL in the PPE\* Population for Vaccine HPV Types**

Disease Endpoints	GARDASIL		AAHS Control		% Efficacy (95% CI)
	N	Number of cases	N	Number of cases	
<b>16- through 26-Year-Old Girls and Women<sup>†</sup></b>					
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)
<b>16- through 26-Year-Old Boys and Men</b>					
<b>External Genital Lesions HPV 6-, 11-, 16-, or 18-related</b>					
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)
<b>HPV 6-, 11-, 16-, or 18-related Endpoint</b>					
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)
Condyloma Acuminatum	194	0	208	6	100.0 (8.2, 100.0)
Non-acuminate	194	4	208	11	60.4 (-33.5, 90.8)

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

<sup>†</sup>Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria.

N=Number of individuals with at least one 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: Table 6 does not include cases due to HPV types not covered by the vaccine.

AAHS = Amorphous Aluminum Hydroxyphosphate Sulfate, CIN = Cervical Intraepithelial Neoplasia, VIN = Vulvar Intraepithelial Neoplasia, VaIN=Vaginal Intraepithelial Neoplasia, PIN=Penile Intraepithelial Neoplasia, AIN=Anal Intraepithelial Neoplasia, AIS=Adenocarcinoma In Situ

In an extension study in females 16 through 26 years of age, prophylactic efficacy of GARDASIL through Month 60 against overall cervical and genital disease related to HPV 6, 11, 16, and 18 was 100% (95% CI: 12.3%, 100%).

*Females 27 through 45 years of age:* A clinical trial evaluated efficacy in 3,253 women 27 through 45 years of age, based on a combined endpoint of HPV 6-, 11-, 16- or 18-related persistent infection, genital warts, vulvar and vaginal dysplastic lesions of any grade, CIN of any grade, AIS, and cervical cancer. These women were randomized 1:1 to receive either GARDASIL or AAHS control. The efficacy estimate for the combined endpoint was driven primarily by prevention of persistent infection. No statistically significant efficacy was demonstrated for GARDASIL in prevention of cervical intraepithelial neoplasia grades 2 and 3 (CIN2/3), adenocarcinoma in situ (AIS) or cervical cancer related to HPV types 16 and 18.

#### 14.2 Clinical Trials for GARDASIL 9

Efficacy and/or immunogenicity of GARDASIL 9 were assessed in five clinical trials. Study 1 evaluated the efficacy of GARDASIL 9 to prevent HPV-related cervical, vulvar, and vaginal disease using GARDASIL as a comparator.

The analysis of efficacy for GARDASIL 9 was evaluated in the per-protocol efficacy (PPE) population of 16- through 26-year-old girls and women, who were naïve to the relevant HPV type(s) by serology and PCR of cervicovaginal specimens prior to dose one and who remained PCR negative for the relevant HPV type(s) through one month Post-dose 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 include cervical, vulvar and vaginal disease of any grade, persistent infection, cytological abnormalities and invasive procedures. For all endpoints, the efficacy against the HPV Types 31, 33, 45, 52 and 58 in GARDASIL 9 was evaluated compared with GARDASIL. Efficacy of GARDASIL 9 against anal lesions caused by HPV Types 31, 33, 45, 52, and 58 was not assessed due to low incidence. Effectiveness of GARDASIL 9 against anal lesions was inferred from the efficacy of GARDASIL against anal lesions caused by HPV types 6, 11, 16 and 18 in men and antibody responses elicited by GARDASIL 9 against the HPV types covered by the vaccine.

Effectiveness against disease caused by HPV Types 6, 11, 16, and 18 was assessed by comparison of geometric mean titers (GMTs) of type-specific antibodies following vaccination with GARDASIL 9 with those following vaccination with GARDASIL (Study 1 and Study 3). The effectiveness of GARDASIL 9 in girls and boys 9 through 15 years old was inferred for all clinical endpoints studied in 16- to 26-year-old girls and women by comparison between these two age groups of type-specific antibody GMTs following vaccination with GARDASIL 9. Immunogenicity analyses were performed in the per-protocol immunogenicity (PPI) population consisting of individuals who received all 3 vaccinations within one 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) prior to dose 1 and through Month 7.

Study 1 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. Study 2 evaluated immunogenicity of GARDASIL 9 in girls and boys 9 through 15 years of age and women 16 through 26 years of age. Study 3 evaluated immunogenicity of GARDASIL 9 compared with GARDASIL in girls 9 through 15 years of age. Study 4 evaluated administration of GARDASIL 9 to girls and women 12 through 26 years of age previously vaccinated with GARDASIL. Study 5 evaluated GARDASIL 9 concomitantly administered with Menactra and Adacel in girls and boys 11 through 15 years of age. Together, these five clinical trials evaluated 12,233 individuals who received GARDASIL 9 (8,048 girls and women 16 through 26 years of age at enrollment with a mean age of 21.8 years; 2,927 girls 9 through 15 years of age at enrollment with a mean age of 11.9 years; and 1,258 boys 9 through 15 years of age at enrollment with a mean age of 11.9 years. The race distribution of the 16- through 26-year-old girls and women in the clinical trials was as follows: 56.3% 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: 60.3% White; 19.3% Other; 13.5% Asian; and 7.0% Black. The race distribution of the 9- through 15-year-old boys in the clinical trials was as follows: 46.6% White; 34.3% Other; 13.3% Asian; and 5.9% Black.

### **14.3 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 girls and women was assessed in an active comparator-controlled, double-blind, randomized clinical trial (Study 1) 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 40 months (range 0 to 64 months) after the last vaccination.

The primary efficacy evaluation was based on 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. Efficacy was evaluated in the PPE population of 16- through 26-year-old girls and women, who were naïve to the relevant HPV type(s) by serology and PCR of cervicovaginal specimens prior to dose one and who remained PCR negative to the relevant HPV type(s) through Month 7. Efficacy was further evaluated with the clinical endpoints 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 Papanicolaou (Pap) tests, cervical and external genital biopsy, and definitive therapy [including loop electrosurgical excision procedure (LEEP) and conization]. Efficacy for all endpoints was measured starting after the Month 7 visit.

GARDASIL 9 prevented HPV 31-, 33-, 45-, 52-, and 58-related persistent infection and disease and also reduced the incidence of HPV 31-, 33-, 45-, 52-, and 58-related Pap test abnormalities, cervical and external genital biopsy, and definitive therapy (Table 7).

**Table 7: Analysis of Efficacy of GARDASIL 9 against HPV Types 31, 33, 45, 52, and 58 in the PPE\* Population of 16- through 26-Year-old Girls and Women**

Disease Endpoint	GARDASIL 9 N <sup>†</sup> =7099		GARDASIL N <sup>†</sup> =7105		GARDASIL 9 Efficacy % (95% CI)
	n <sup>‡</sup>	Number of cases	n <sup>‡</sup>	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 (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)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥6 Months <sup>§</sup>	5939	26	5953	642	96.2 (94.4, 97.5)
HPV 31-, 33-, 45-, 52-, 58-related Persistent Infection ≥12 Months <sup>¶</sup>	5939	15	5953	375	96.1 (93.7, 97.9)
HPV 31-, 33-, 45-, 52-, 58-related ASC-US HR-HPV Positive or Worse Pap <sup>#</sup> 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 <sup>‡</sup>	6012	4	6014	32	87.5 (65.7, 96.0)

\*The PPE population consisted of individuals who received all 3 vaccinations within one year of enrollment, did not have major deviations from the study protocol, were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 31, 33, 45, 52, and 58) prior to dose 1, and who remained PCR negative to the relevant HPV type(s) through one month post-dose 3 (Month 7); data from Study 1 (NCT00543543).

<sup>†</sup>N=Number of individuals randomized to the respective vaccination group who received at least one injection

<sup>‡</sup>n=Number of individuals contributing to the analysis

<sup>§</sup>Persistent infection detected in samples from two or more consecutive visits at least six months apart

<sup>¶</sup>Persistent infection detected in samples from two or more consecutive visits over 12 months or longer

<sup>#</sup>Papanicolaou test

<sup>‡</sup>Including loop electrosurgical excision procedure (LEEP) and conization

CI=Confidence Interval

CIN=Cervical Intraepithelial Neoplasia, VIN=Vulvar Intraepithelial Neoplasia, VaIN=Vaginal Intraepithelial Neoplasia,

AIS=Adenocarcinoma In Situ, ASC-US=Atypical squamous cells of undetermined significance

HR=High Risk

#### 14.4 Immunogenicity

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

Type-specific immunoassays (i.e., cLIA) 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).

#### *Studies Supporting the Effectiveness of GARDASIL 9 against HPV Types 6, 11, 16, and 18*

Effectiveness of GARDASIL 9 against persistent infection and disease related to HPV Types 6, 11, 16, or 18 was inferred from non-inferiority comparisons in Study 1 (16- through 26-year-old girls and women) and Study 3 (9- through 15-year-old girls) of GMTs following vaccination with GARDASIL 9 with those following vaccination with GARDASIL. A low number of efficacy endpoint cases related to HPV types 6, 11, 16 and 18 in both vaccination groups precluded a meaningful assessment of efficacy using disease endpoints associated with these HPV types. The primary analyses were conducted in the per-protocol population, which included subjects who received all three vaccinations within 1 year of enrollment, did

not have major deviations from the study protocol, and were HPV-naïve. HPV-naïve individuals were defined as seronegative to the relevant HPV type(s) prior to dose 1 and among female subjects 16 through 26 years of age in Study 1 PCR negative to the relevant HPV type(s) in cervicovaginal specimens prior to dose 1 through Month 7.

Anti-HPV 6, 11, 16 and 18 GMTs at Month 7 for GARDASIL 9 among girls 9 through 15 years of age and young women 16 to 26 years of age were non-inferior to those among the corresponding populations for GARDASIL (Table 8). At least 99.7% of individuals included in the analyses for each HPV type became seropositive by Month 7.

**Table 8: 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 26-Year-Old Girls and Women**

POPULATION	GARDASIL 9		GARDASIL		GARDASIL 9/ GARDASIL	
	N† (n‡)	GMT mMU§/mL	N† (n‡)	GMT mMU§/mL	GMT Ratio	(95% CI)¶
<b>Anti-HPV 6</b>						
9- through 15-year-old girls	300 (273)	1679.4	300 (261)	1565.9	1.07	(0.93, 1.23)
16- through 26-year-old girls and women	6792 (3993)	893.1	6795 (3975)	875.2	1.02	(0.99, 1.06)
<b>Anti-HPV 11</b>						
9- through 15-year-old girls	300 (273)	1315.6	300 (261)	1417.3	0.93	(0.80, 1.08)
16- through 26-year-old girls and women	6792 (3995)	666.3	6795 (3982)	830.0	0.80	(0.77, 0.83)
<b>Anti-HPV 16</b>						
9- through 15-year-old girls	300 (276)	6739.5	300 (270)	6887.4	0.97	(0.85, 1.11)
16- through 26-year-old girls and women	6792 (4032)	3131.1	6795 (4062)	3156.6	0.99	(0.96, 1.03)
<b>Anti-HPV 18</b>						
9- through 15-year-old girls	300 (276)	1956.6	300 (269)	1795.6	1.08	(0.91, 1.29)
16- through 26-year-old girls and women	6792 (4539)	804.6	6795 (4541)	678.7	1.19	(1.14, 1.23)

\*The PPI population consisted of individuals who received all three vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, were naïve (PCR negative and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1, and among 16- through 26-year-old girls and women PCR negative to the relevant HPV type(s) through one month Post-dose 3 (Month 7). The data for 16- through 26-year-old girls and women are from Study 1 (NCT00543543), and the data for 9- through 15-year-old girls are from Study 3 (NCT01304498).

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

‡n=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

### *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 Study 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, which included subjects who received all three vaccinations within one year of enrollment, did not have major deviations from the study protocol, and were HPV-naïve. HPV-naïve individuals were defined as seronegative to the relevant HPV type(s) prior to dose 1 and among female subjects 16 through 26 years of age PCR negative to the relevant HPV type(s) in cervicovaginal specimens prior to dose 1 through Month 7. 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 9).

**Table 9: 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 <sup>†</sup>	n <sup>‡</sup>	GMT (95% CI) mMU <sup>§</sup> /mL	GMT Ratio relative to 16- through 26-year-old women (95% CI) <sup>¶</sup>
<b>Anti-HPV 6</b>				
9- through 15-year-old girls	630	503	1703.1	1.89 (1.68, 2.12)
9- through 15-year-old boys	641	537	2083.4	2.31 (2.06, 2.60)
16- through 26-year-old girls and women	463	328	900.8	1
<b>Anti-HPV 11</b>				
9- through 15-year-old girls	630	503	1291.5	1.83 (1.63, 2.05)
9- through 15-year-old boys	641	537	1486.3	2.10 (1.88, 2.36)
16- through 26-year-old girls and women	463	332	706.6	1
<b>Anti-HPV 16</b>				
9- through 15-year-old girls	630	513	6933.9	1.97 (1.75, 2.21)
9- through 15-year-old boys	641	546	8683.0	2.46 (2.20, 2.76)
16- through 26-year-old girls and women	463	329	3522.6	1
<b>Anti-HPV 18</b>				
9- through 15-year-old girls	630	516	2148.3	2.43 (2.12, 2.79)
9- through 15-year-old boys	641	544	2855.4	3.23 (2.83, 3.70)
16- through 26-year-old girls and women	463	345	882.7	1
<b>Anti-HPV 31</b>				
9- through 15-year-old girls	630	506	1894.7	2.51 (2.21, 2.86)
9- through 15-year-old boys	641	543	2255.3	2.99 (2.63, 3.40)
16- through 26-year-old girls and women	463	340	753.9	1
<b>Anti-HPV 33</b>				
9- through 15-year-old girls	630	518	985.8	2.11 (1.88, 2.37)
9- through 15-year-old boys	641	544	1207.4	2.59 (2.31, 2.90)
16- through 26-year-old girls and women	463	354	466.8	1
<b>Anti-HPV 45</b>				
9- through 15-year-old girls	630	518	707.7	2.60 (2.25, 3.00)
9- through 15-year-old boys	641	547	912.1	3.35 (2.90, 3.87)
16- through 26-year-old girls and women	463	368	272.2	1
<b>Anti-HPV 52</b>				
9- through 15-year-old girls	630	517	962.2	2.21 (1.96, 2.49)
9- through 15-year-old boys	641	545	1055.5	2.52 (2.22, 2.84)
16- through 26-year-old girls and women	463	337	419.6	1
<b>Anti-HPV 58</b>				
9- through 15-year-old girls	630	516	1288.0	2.18 (1.94, 2.46)
9- through 15-year-old boys	641	544	1593.3	2.70 (2.40, 3.03)
16- through 26-year-old girls and women	463	332	590.5	1

\*The PPI population consisted of individuals who received all three vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, were naïve seronegative to the relevant HPV type(s) prior to dose 1 and among 16- to 26-year-old girls and women PCR negative to the relevant HPV types prior to dose 1 through one month Post-dose 3 (Month 7). The data are from Study 2 (NCT00943722).

<sup>†</sup>N=Number of individuals randomized to the respective vaccination group who received at least one injection

<sup>‡</sup>n=Number of individuals contributing to the analysis

<sup>§</sup>mMU=milli-Merck Units

<sup>¶</sup>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



#### *Immune Response to GARDASIL 9 Across All Clinical Trials*

Across all clinical trials, at least 99.5% of individuals included in the analyses for each of the nine vaccine HPV types became seropositive by Month 7. Anti-HPV GMTs at Month 7 among 9- through 15-year-old girls and boys were comparable to anti-HPV responses among 16- through 26-year-old girls and women in the combined database of immunogenicity studies for GARDASIL 9.

#### *Persistence of Immune Response to GARDASIL 9*

The duration of immunity following a complete schedule of vaccination with GARDASIL 9 has not been established. The peak anti-HPV GMTs for each vaccine HPV type occurred at Month 7. Proportions of individuals who remained seropositive to each vaccine HPV type at Month 24 were similar to the corresponding seropositive proportions at Month 7.

#### *Administration of GARDASIL 9 to Individuals Previously Vaccinated with GARDASIL*

Study 4 evaluated the immunogenicity of GARDASIL 9 in 921 girls and women (12 through 26 years of age) who had previously been vaccinated with GARDASIL. Prior to enrollment in the study, over 99% of subjects had received three 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 anti-HPV 31, 33, 45, 52 and 58 GMTs for the population previously vaccinated with GARDASIL were 25-63% of the GMTs in the combined populations from Studies 1, 2, 3, and 5, who had not previously received GARDASIL, although the clinical relevance of these differences is unknown. 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.

#### *Concomitant Use of Hormonal Contraceptives*

Among 7,269 female recipients of GARDASIL 9 (16 through 26 years of age), 60.2% used hormonal contraceptives during the vaccination period of clinical studies 1 and 2. Use of hormonal contraceptives did not appear to affect the type specific immune responses to GARDASIL 9.

### **14.5 Studies with Menactra and Adacel**

In Study 5, 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.

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 one month post vaccination (one dose for Menactra and Adacel and three doses for GARDASIL 9).

Assessments of post-vaccination immune responses included type-specific antibody GMTs for each of the vaccine HPV types at four weeks following the last dose of GARDASIL 9; GMTs for anti-filamentous hemagglutinin, anti-pertactin, and anti-fimbrial antibodies at four weeks following Adacel; percentage of subjects with anti-tetanus toxin and anti-diphtheria toxin antibody concentrations  $\geq 0.1$  IU/mL at four weeks following Adacel; and percentage of subjects with  $\geq 4$ -fold rise from pre-vaccination baseline in antibody titers against *N. meningitidis* serogroups A, C, Y, and W-135 at four weeks following Menactra. Based on these measures, concomitant administration of GARDASIL 9 with Menactra and Adacel did not interfere with the antibody responses to any of the vaccines when compared with non-concomitant administration of GARDASIL 9 with Menactra and Adacel.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

GARDASIL 9 is supplied in vials and syringes.

Carton of one 0.5-mL single-dose vial. NDC 0006-4119-02

Carton of ten 0.5-mL single-dose vials. NDC 0006-4119-03

Carton of ten 0.5-mL single-dose prefilled Luer Lock syringes with tip caps. NDC 0006-4121-02

Store refrigerated at 2 to 8°C (36 to 46°F). 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.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform the patient, parent, or guardian:

- Vaccination does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening. Women who receive GARDASIL 9 should continue to undergo cervical cancer screening per standard of care.
  - Recipients of GARDASIL 9 should not discontinue anal cancer screening if it has been recommended by a health care provider.
  - GARDASIL 9 has not been demonstrated to provide protection against disease from vaccine and non-vaccine HPV types to which a person has previously been exposed through sexual activity.
  - Since syncope has been reported following HPV vaccination sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended.
  - Vaccine information is required to be given with each vaccination to the patient, parent, or guardian.
  - Provide information regarding benefits and risks associated with vaccination.
  - Safety and effectiveness of GARDASIL 9 have not been established in pregnant women. A pregnancy registry is available. Women exposed to GARDASIL 9 around the time of conception or during pregnancy are encouraged to register by calling 1-800-986-8999.
  - It is important to complete the full vaccination series unless contraindicated.
  - Report any adverse reactions to their health care provider.
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