

Registration No.: 1C 50/60 (NBC)

Importer / Manufacturer: MSD (Thailand) Ltd. / Merck Sharp & Dohme Corp., West Point, Pennsylvania 19486 USA

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICAL PRODUCT

GARDASIL[®]9

[Human Papillomavirus 9-valent Vaccine, Recombinant]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GARDASIL 9 is a sterile preparation for intramuscular administration. 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, and 20 mcg of HPV 58 L1 protein.

3. PHARMACEUTICAL FORM

GARDASIL 9 is a recombinant vaccine that protects against 9 genotypes of Human Papillomavirus (HPV).

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

Prior to agitation, GARDASIL 9 may appear as a clear liquid with a white precipitate. After thorough agitation, GARDASIL 9 is a white, cloudy liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GARDASIL[®]9 is a vaccine indicated in girls and women from 9 through 26 years of age for the prevention of cervical, vulvar, vaginal, and anal cancer; precancerous or dysplastic lesions; genital warts; and persistent infections caused by Human Papillomavirus (HPV).

GARDASIL 9 is indicated to prevent the following diseases:

- Cervical, vulvar, vaginal, and 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 persistent infections 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
- VIN grade 1 and VaIN grade 1
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

GARDASIL 9 is indicated in boys and men from 9 through 26 years of age for the prevention of external genital lesions and persistent infections and the following diseases caused by 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 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.

4.2 Posology and method of administration

General

Dosage

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. However, in clinical studies, efficacy has been demonstrated in individuals who have received all 3 doses within a 1-year period. 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.

Method of Administration

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.

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.

If the decision is made to administer GARDASIL 9 after receiving 3 doses of GARDASIL, there should be an interval of at least 12 months between completion of vaccination with GARDASIL and the start of vaccination with GARDASIL 9.

Instruction of Use

The vaccine should be used as supplied; no dilution or reconstitution is necessary. The full recommended dose of the vaccine should be used.

Shake well before use. Thorough agitation immediately before administration is necessary to maintain suspension of the vaccine.

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

Single-dose Vial Use

For single-use vials a separate sterile syringe and needle must be used for each individual. Withdraw the 0.5-mL dose of vaccine from the single-dose vial using a sterile needle and syringe free of preservatives, antiseptics, and detergents. Once the single-dose vial has been penetrated, the withdrawn vaccine should be used promptly, and the vial must be discarded.

Prefilled Syringe Use

The prefilled syringe is for single use only and should not be used for more than one individual. Inject the entire contents of the syringe.

4.3 Contraindication

GARDASIL 9 is contraindicated in patients with hypersensitivity to either GARDASIL 9 or GARDASIL[®] or any of the inactive ingredients in either vaccine.

Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of GARDASIL 9 or GARDASIL should not receive further doses of GARDASIL 9.

4.4 Special warnings and precautions for use

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.

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.

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.

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.

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.

4.5 Interaction with other medical products and forms of interaction

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], 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)] (dTdap-IPV).

Use with Hormonal Contraceptives

In 7,269 women (16 through 26 years of age), 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 Steroids

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune responses to vaccines.

4.6 Pregnancy and lactation

Pregnancy

Studies in Female Rats

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.

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 gestation and possibly during lactation.

Clinical Studies in Humans

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.

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 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. 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.

Thus, there is no evidence to suggest that administration of GARDASIL 9 adversely affects fertility, pregnancy, or infant outcomes.

Lactation

GARDASIL 9 may be administered to lactating women.

It is not known whether vaccine antigens or antibodies induced by the vaccine are excreted in human milk.

A total of 86 women were breast feeding during the vaccination period of the clinical studies for GARDASIL 9. In these studies, vaccine immunogenicity was comparable between nursing women and women who did not nurse. In addition, the adverse experience profile for nursing women was comparable to that of the women in the overall safety population. There were no serious adverse experiences reported in infants who were nursing during the vaccination period.

NURSING MOTHERS

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It is not known whether vaccine antigens or antibodies induced by the vaccine are excreted in human milk.

A total of 86 women were breast feeding during the vaccination period of the clinical studies for GARDASIL 9. In these studies, vaccine immunogenicity was comparable between nursing women and women who did not nurse. In addition, the adverse experience profile for nursing women was comparable to that of the women in the overall safety population. There were no serious adverse experiences reported in infants who were nursing during the vaccination period.

PEDIATRIC USE

The safety and efficacy of GARDASIL 9 have not been evaluated in children younger than 9 years.

GERIATRIC USE

The safety and efficacy of GARDASIL 9 have not been evaluated in individuals aged 65 years and over.

IMMUNOCOMPROMISED INDIVIDUALS

The immunologic response to GARDASIL 9 may be diminished in immunocompromised individuals.

4.7 Effects on the ability to drive and use machines

N/A

4.8 Undesirable effects

Clinical Trials Experience

Clinical Trials Experience with GARDASIL 9 and GARDASIL

The safety of GARDASIL 9 was evaluated in 6 clinical studies (Protocols 001, 002, 005, 006, 007, 009) that included 13,307 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 8,027 women 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 women 16 through 26 years of age and 300 girls 9 through 15 years of age at enrollment who received GARDASIL.

Systemic and Injection-Site Adverse Reactions in Clinical Trials of GARDASIL 9

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 Tables 3 and 4. Few individuals (GARDASIL 9 = 0.1% vs. GARDASIL <0.1%) discontinued due to adverse experiences after receiving either vaccine. The safety profile was similar between GARDASIL 9 and GARDASIL in women and girls and boys.

Table 3: Injection-Site and Vaccine-Related Systemic Adverse Reactions Reported at a Frequency of ≥1% in Individuals Who Received GARDASIL 9 from All Clinical Studies*

Adverse Reaction	Women 16 Through 26 Years of Age	Girls and Boys 9 Through 15 Years of Age
	GARDASIL 9 (N=8027) %	GARDASIL 9 (N=5280) %
Injection-Site Adverse Reactions (1 to 5 Days Postvaccination)		
Pain [†]	89.6	78.8
Swelling [†]	40.2	33.8
Erythema [†]	34.3	28.0
Pruritus	5.6	2.6
Bruising	1.7	0.0
Hematoma	1.3	2.0
Mass	1.2	0.2
Hemorrhage	0.9	1.0
Induration	0.7	1.1
Systemic Adverse Reactions (1 to 15 Days Postvaccination)		
Headache	14.7	12.7

Pyrexia	5.1	8.9
Nausea	4.2	2.2
Dizziness	2.9	1.6
Fatigue	2.3	1.3
Diarrhea	1.2	0.5
Oropharyngeal pain	1.0	0.8
Abdominal pain upper	0.7	1.3

*Data from Protocols 001,002, 005, 006, 007, 009

†Designates a solicited adverse reaction

N=number of subjects vaccinated

Table 4: Injection-Site and Vaccine-Related Systemic Adverse Reactions Reported at a Frequency of ≥1% for GARDASIL 9 Compared with 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
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

Solicited Systemic and Injection-Site Adverse Reactions in Clinical Trials of GARDASIL 9

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 5.

Table 5: Postdose Evaluation of Solicited Systemic and Injection-Site Adverse Reactions by Incidence and Severity from All Clinical Studies* (1 to 5 Days Postvaccination)

Solicited Systemic Adverse Reaction	Severity	Dose 1 N=13,174 %	Dose 2 N=12,913 %	Dose 3 N=12,741 %	Any Dose N=13,224 %
Temperature	< 37.8 °C (100.0 °F)	96.9	97.3	96.7	92.0
	≥ 37.8 °C (100.0 °F) < 38.9 °C (102.0 °F)	2.7	2.3	2.7	6.6
	≥ 38.9 °C (102.0 °F) < 39.9 °C (103.8 °F)	0.4	0.3	0.5	1.2
	≥ 39.9 °C (103.8 °F) < 40.9 °C (105.6 °F)	0.1	0.1	0.1	0.2
	≥ 40.9 °C (105.6 °F)	0.0	0.0	0.0	0.0

Solicited Injection-site Adverse Reaction	Severity	Dose 1 N=13,304	Dose 2 N=13,142	Dose 3 N=13,005	Any Dose N=13,307
Pain	Mild	53.5	47.6	45.3	51.1
	Moderate	11.5	16.3	17.8	30.3
	Severe	0.7	1.6	2.3	3.9
Swelling [†]	Mild	9.6	15.3	18.5	25.4
	Moderate	1.8	3.9	4.9	7.8
	Severe	0.8	1.7	2.7	4.3
Erythema [†]	Mild	8.6	14.0	16.6	25.3
	Moderate	0.9	2.0	2.7	4.6
	Severe	0.2	0.5	1.2	1.7

*Data from Protocols 001, 002, 005, 006, 007, 009

[†]Intensity of swelling and erythema was measured by size (inches): Mild = 0 to ≤1; Moderate = >1 to ≤2; Severe = >2.

N=Number of individuals with follow-up

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. 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 6. 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.

Table 6: 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

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 Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content) (dTdap-IPV) or Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap) and 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.

15.2 Post-marketing Experience

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. The post-marketing safety experience with GARDASIL is relevant to GARDASIL 9 since the vaccines are similar in composition and contain L1 HPV proteins of 4 of the same HPV types. Because these experiences 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.

Infections and infestations: cellulitis.

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

Nervous system disorders: acute disseminated encephalomyelitis, dizziness, Guillain-Barré syndrome, headache, syncope sometimes accompanied by tonic-clonic movements.

Gastrointestinal disorders: nausea, vomiting.

Musculoskeletal and connective tissue disorders: arthralgia, myalgia.

General disorders and administration site conditions: asthenia, chills, fatigue, malaise.

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

4.9 Overdose

Clinical Trials Experience with GARDASIL 9 and GARDASIL

The safety of GARDASIL 9 was evaluated in 6 clinical studies (Protocols 001, 002, 005, 006, 007, 009) that included 13,307 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 8,027 women 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 women 16 through 26 years of age and 300 girls 9 through 15 years of age at enrollment who received GARDASIL.

Systemic and Injection-Site Adverse Reactions in Clinical Trials of GARDASIL 9

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 Tables 3 and 4. Few individuals (GARDASIL 9 = 0.1% vs. GARDASIL <0.1%) discontinued due to adverse experiences after receiving either vaccine. The safety profile was similar between GARDASIL 9 and GARDASIL in women and girls and boys.

Table 3: Injection-Site and Vaccine-Related Systemic Adverse Reactions Reported at a Frequency of ≥1% in Individuals Who Received GARDASIL 9 from All Clinical Studies*

Adverse Reaction	Women 16 Through 26 Years of Age		Girls and Boys 9 Through 15 Years of Age	
	GARDASIL 9 (N=8027) %		GARDASIL 9 (N=5280) %	
Injection-Site Adverse Reactions (1 to 5 Days Postvaccination)				
Pain [†]	89.6		78.8	
Swelling [†]	40.2		33.8	
Erythema [†]	34.3		28.0	
Pruritus	5.6		2.6	
Bruising	1.7		0.0	
Hematoma	1.3		2.0	
Mass	1.2		0.2	
Hemorrhage	0.9		1.0	
Induration	0.7		1.1	
Systemic Adverse Reactions (1 to 15 Days Postvaccination)				
Headache	14.7		12.7	
Pyrexia	5.1		8.9	
Nausea	4.2		2.2	
Dizziness	2.9		1.6	
Fatigue	2.3		1.3	
Diarrhea	1.2		0.5	
Oropharyngeal pain	1.0		0.8	
Abdominal pain upper	0.7		1.3	

*Data from Protocols 001,002, 005, 006, 007, 009

[†]Designates a solicited adverse reaction

N=number of subjects vaccinated

Table 4: Injection-Site and Vaccine-Related Systemic Adverse Reactions Reported at a Frequency of ≥1% for GARDASIL 9 Compared with 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
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

Solicited Systemic and Injection-Site Adverse Reactions in Clinical Trials of GARDASIL 9

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 5.

Table 5: Postdose Evaluation of Solicited Systemic and Injection-Site Adverse Reactions by Incidence and Severity from All Clinical Studies* (1 to 5 Days Postvaccination)

Solicited Systemic Adverse Reaction	Severity	Dose 1 N=13,174 %	Dose 2 N=12,913 %	Dose 3 N=12,741 %	Any Dose N=13,224 %
Temperature	< 37.8 °C (100.0 °F)	96.9	97.3	96.7	92.0
	≥ 37.8 °C (100.0 °F) < 38.9 °C (102.0 °F)	2.7	2.3	2.7	6.6
	≥ 38.9 °C (102.0 °F) < 39.9 °C (103.8 °F)	0.4	0.3	0.5	1.2
	≥ 39.9 °C (103.8 °F) < 40.9 °C (105.6 °F)	0.1	0.1	0.1	0.2
	≥ 40.9 °C (105.6 °F)	0.0	0.0	0.0	0.0
Solicited Injection-site Adverse Reaction	Severity	Dose 1 N=13,304	Dose 2 N=13,142	Dose 3 N=13,005	Any Dose N=13,307
Pain	Mild	53.5	47.6	45.3	51.1
	Moderate	11.5	16.3	17.8	30.3
	Severe	0.7	1.6	2.3	3.9
Swelling [†]	Mild	9.6	15.3	18.5	25.4
	Moderate	1.8	3.9	4.9	7.8
	Severe	0.8	1.7	2.7	4.3
Erythema [†]	Mild	8.6	14.0	16.6	25.3
	Moderate	0.9	2.0	2.7	4.6
	Severe	0.2	0.5	1.2	1.7

*Data from Protocols 001, 002, 005, 006, 007, 009

†Intensity of swelling and erythema was measured by size (inches): Mild = 0 to ≤1; Moderate = >1 to ≤2; Severe = >2.

N=Number of individuals with follow-up

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. 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 6. 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.

Table 6: Injection-Site and Vaccine-Related Systemic Adverse Reactions Reported at a Frequency of \geq 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 (N=305) %	PLACEBO
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

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 Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content) (dTdap-IPV) or Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap) and 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.

15.2 Post-marketing Experience

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. The post-marketing safety experience with GARDASIL is relevant to GARDASIL 9 since the vaccines are similar in composition and contain L1 HPV proteins of 4 of the same HPV types. Because these experiences 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.

Infections and infestations: cellulitis.

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

Nervous system disorders: acute disseminated encephalomyelitis, dizziness, Guillain-Barré syndrome, headache, syncope sometimes accompanied by tonic-clonic movements.

Gastrointestinal disorders: nausea, vomiting.

Musculoskeletal and connective tissue disorders: arthralgia, myalgia.

General disorders and administration site conditions: asthenia, chills, fatigue, malaise.

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

4.12 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Viral Vaccine

ATC code: Not yet assigned

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.

CLINICAL STUDIES

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). In clinical studies conducted in girls and women, GARDASIL reduced the incidence of CIN (any grade including CIN 2/3); AIS; genital warts; VIN 2/3; and VaIN 2/3 related to vaccine HPV types 6, 11, 16, or 18.

Clinical Trials for GARDASIL 9

Efficacy and/or immunogenicity of GARDASIL 9 were assessed in six 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 demonstrates comparable immunogenicity (as measured by Geometric Mean Titers [GMT]) of GARDASIL 9 compared with GARDASIL (Protocols 001, 002, and 009).

In the pivotal study Protocol 001, the efficacy of GARDASIL 9 against HPV Types 31, 33, 45, 52 and 58 was evaluated compared to GARDASIL vaccine in women 16 through 26 years of age (N=14,204: 7,099 receiving GARDASIL 9; 7,105 receiving GARDASIL vaccine).

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

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

Protocol 006 evaluated administration of GARDASIL 9 to girls and women 12 through 26 years of age previously vaccinated with GARDASIL vaccine (N=921; 615 receiving GARDASIL 9 and 306 receiving placebo).

Protocol 009 evaluated immunogenicity of GARDASIL 9 in girls 9 through 15 years of age (N=600; 300 receiving GARDASIL 9 and 300 receiving GARDASIL vaccine).

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

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

Comparison of GARDASIL 9 with 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 and 9- through 15-year-old girls from Protocol 009. The primary analyses were conducted in the per-protocol immunogenicity population which included subjects 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; Protocol 001) and seronegative (Protocols 001 and 009) prior to dose one] to the relevant HPV type(s) and who remained PCR-negative (in girls and women 16 through 26 years of age; Protocol 001) to the relevant HPV types(s) through Month 7.

A statistical analysis of non-inferiority was performed based on Month 7 cLIA anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs between individuals administered GARDASIL 9 and individuals administered GARDASIL. Immune responses, measured by GMT, for GARDASIL 9 were non-inferior to immune responses for GARDASIL (Table 1). 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 1: Comparison of Immune Responses (Based on cLIA) Between GARDASIL 9 and GARDASIL for HPV Types 6, 11, 16, and 18 in the Per Protocol Immunogenicity (PPI)* Population of 9- Through 26-Year-Old Girls and Women

POPULATION	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								
9- through 15-year-old girls	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)
16- through 26-year-old girls and women	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								
9- through 15-year-old girls	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)
16- through 26-year-old girls and women	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								
9- through 15-year-old girls	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) ^{††}
16- through 26-year-old girls and women	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								
9- through 15-year-old girls	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) ^{††}
16- through 26-year-old girls and women	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, were naïve (PCR negative [among 16- through 26-year-old girls and women] and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1 and among 16- through 26-year old girls and women, were PCR negative to the relevant HPV type(s) through 1 month Postdose 3 (Month 7). The data for 16- through 26- year-old girls and women are from Protocol 001, and 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

[¶]p-value <0.001

[#] Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67

CI=Confidence Interval

GMT=Geometric Mean Titers

cLIA= Competitive Luminex Immunoassay

Studies Supporting 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 to Month 54 with a median duration of follow-up of 40 months.

The primary efficacy is 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 cervical, 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 2). GARDASIL 9 also reduced the incidence of HPV 31-, 33-, 45-, 52-, and 58- related Pap test abnormalities, cervical and external genital procedures (i.e., biopsies), and cervical definitive therapy procedures (Table 2).

Table 2: 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 (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 [§]	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 and through 1 month postdose 3 (Month 7).

[†]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 two or more consecutive visits over 12 months or longer

[#]Papanicolaou test

CI=Confidence Interval

ASC-US=Atypical squamous cells of undetermined significance

HR=High Risk

Immunogenicity of GARDASIL 9

Immune Response to GARDASIL 9 at Month 7 Across All Clinical Studies

Immunogenicity was measured by (1) the percentage of individuals who were seropositive for antibodies against the relevant vaccine HPV type, and (2) the Geometric Mean Titer (GMT).

GARDASIL 9 induced robust anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52, and anti-HPV 58 responses measured at Month 7. In clinical studies 99.6% to 100% who received GARDASIL 9 became seropositive for antibodies against all 9 vaccine types by Month 7 across all groups tested. GMTs were higher in girls and boys than in 16- through 26-year-old women and higher in boys than in girls and women.

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

Persistence of Immune Response to GARDASIL 9

The duration of immunity following a complete schedule of vaccination with GARDASIL 9 has not been established. Persistence of immunity has been demonstrated through Month 24.

Individuals who were seropositive to the relevant HPV type at baseline had substantially higher GMTs at Month 7, 12, and 24 than those who were seronegative to the same vaccine HPV type(s) at Day 1. In addition, persistence of efficacy has been demonstrated through Month 54 as evident by a low incidence of HPV-related disease and persistent infection in Protocol 001.

Administration of GARDASIL 9 to Individuals Previously Vaccinated with GARDASIL

Protocol 006 evaluated the immunogenicity of GARDASIL 9 in 921 girls and women (12 through 26 years of age) who had previously been vaccinated with GARDASIL. 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.

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 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 to 26-year-old girls and women who received 3 doses of GARDASIL 9 (at 0, 2, 6 months) for each of the 9 vaccine HPV types. On the basis of this immunogenicity bridging, the efficacy of a 2-dose regimen of GARDASIL 9 in 9 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.

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 (i.e. HPV types 18, 31, 45 and 52 after 0, 6 months and HPV types 45 after 0, 12 months). The clinical relevance of these findings is unknown.

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

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

N/A

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

N/A

6.2 Incompatibilities

N/A

6.3 Shelf life

36 months

6.4 Special precautions for storage

Precautions for Storage

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.

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

6.5 Nature and content of container

GARDASIL 9 is available in a single-dose 0.5 mL vial.

GARDASIL 9 is available in a single-dose 0.5 ml prefilled syringe with needle size 1 inch.

6.6 Special precautions for disposal and other handling

Single-dose Vial Use

For single-use vials a separate sterile syringe and needle must be used for each individual. Withdraw the 0.5-mL dose of vaccine from the single-dose vial using a sterile needle and syringe free of preservatives, antiseptics, and detergents. Once the single-dose vial has been penetrated, the withdrawn vaccine should be used promptly, and the vial must be discarded.

Prefilled Syringe Use

The prefilled syringe is for single use only and should not be used for more than one individual. Inject the entire contents of the syringe.

7. MARKETING AUTHORISATION HOLDER

MSD (Thailand) Ltd.
Bangkok, Thailand

8. MARKETING AUTHORISATION NUMBER(S)

1C 50/60 (NBC)

**9. DATE OF FIRST AUTHORAISATION/RENEWAL OF THE
AUTHORISATION**

29-Nov-2017

10. DATE OF REVISION OF THE TEXT

Nov-2017