PRODUCT CIRCULAR

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GARDASIL™
[Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine]

I. THERAPEUTIC CLASS

GARDASIL is a recombinant, quadrivalent vaccine that protects against Human Papillomavirus (HPV).

II. INDICATIONS

GARDASIL is a vaccine indicated in girls and women 9 through 45 years for the prevention of cervical, vulvar, vaginal and anal cancer; precancerous or dysplastic lesions; genital warts; and infections caused by Human Papillomavirus (HPV).

GARDASIL is indicated to prevent the following diseases:

- Cervical, vulvar, vaginal, and anal cancer caused by HPV types 16 and 18
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11

And infections and the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18:

- 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 also provides protection in girls and women 9 through 26 years of age against HPV 31-, 33-, 52- and 58-related CIN (grades 1, 2, 3) or AIS.

GARDASIL is indicated in boys and men 9 through 26 years of age for the prevention of external genital lesions and infection and the following diseases caused by HPV types included in the vaccine:

- Anal cancer caused by HPV types 16 and 18
- 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, and 18:
Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3

III. DOSAGE AND ADMINISTRATION

GARDASIL is recommended for children and adolescents 9 through 17 years of age and women 18 through 45 years of age.

Dosage
GARDASIL 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. If an alternate vaccination schedule is necessary, 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.

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

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

The prefilled syringe is for single use only and should not be used for more than one individual.

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 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.

Prefilled Syringe Use
Inject the entire contents of the syringe.

IV. CONTRAINDICATIONS

Hypersensitivity to the active substances or to any of the excipients of the vaccine.

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

V. PRECAUTIONS

General
As for any vaccine, vaccination with GARDASIL 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, 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 vaccination with GARDASIL. Therefore, vaccinees should be carefully observed for approximately 15 minutes after administration of GARDASIL (See SIDE EFFECTS, *Post-Marketing Reports*).

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 (see DRUG INTERACTIONS).

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.

VI. PREGNANCY

Studies in Female Rats
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development. GARDASIL induced a specific antibody response against HPV types 6, 11, 16, and 18 in pregnant rats following one or multiple intramuscular injections. Antibodies against all 4 HPV types were transferred to the offspring during gestation and possibly during lactation.

Clinical Studies in Humans
There are, however, 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.

In clinical studies, women underwent urine pregnancy testing prior to administration of each dose of GARDASIL. Women who were found to be pregnant before completion of a 3-dose regimen of GARDASIL were instructed to defer completion of their vaccination regimen until

resolution of the pregnancy. Such non-standard regimens resulted in Postdose 3 anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses that were comparable to those observed in women who received a standard 0, 2, and 6 month vaccination regimen (see DOSAGE AND ADMINISTRATION).

During clinical trials, 3,819 women (vaccine N = 1,894 vs. placebo N = 1,925) reported at least one pregnancy. The overall proportions of pregnancies 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), were 22.6% (446/1,973) in individuals who received GARDASIL and 23.1% (460/1994) in individuals who received placebo.

Further sub-analyses were done to evaluate pregnancies with estimated onset within 30 days or more than 30 days from administration of a dose of GARDASIL or placebo. For pregnancies with estimated onset within 30 days of vaccination, 5 cases of congenital anomaly were observed in the group that received GARDASIL compared to 1 case of congenital anomaly in the group that received placebo. Conversely, in pregnancies with onset more than 30 days following vaccination, 40 cases of congenital anomaly were observed in the group that received GARDASIL compared with 33 cases of congenital anomaly in the group that received placebo. The types of anomalies observed were consistent (regardless of when pregnancy occurred in relation to vaccination) with those generally observed in pregnancies in women aged 16 through 45 years.

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

VII. NURSING MOTHERS

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

GARDASIL may be administered to lactating women.

GARDASIL or placebo were given to a total of 1,133 women who were breast feeding at any time during the relevant Phase III clinical studies. In these studies, the rates of adverse experiences in the mother and the nursing infant were comparable between vaccination groups. In addition, vaccine immunogenicity was comparable among nursing mothers and women who did not nurse during the vaccine administration.

VIII. PEDIATRIC USE

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

IX. USE IN ELDERLY

The safety and efficacy of GARDASIL have not been evaluated in adults above the age of 45 years.

X. USE IN OTHER SPECIAL POPULATIONS

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

XI. DRUG INTERACTIONS

Use with Other Vaccines
Results from clinical studies indicate that GARDASIL may be administered concomitantly (at a separate injection site) with hepatitis B vaccine (recombinant), 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)].

Use with Common Medications
In clinical studies for girls and women (aged 16 to 26 years), 11.9%, 9.5%, 6.9%, and 4.3% of individuals used analgesics, anti-inflammatory drugs, antibiotics, and vitamin preparations, respectively. In a clinical study in women (aged 24 to 45 years), 30.6%, 20.2%, 11.6%, and 7.5% of individuals used analgesics, anti-inflammatory drugs, antibiotics, and vitamin preparations, respectively. Conversely in a clinical study in boys and men (aged 16 to 26 years), 10.3%, 7.8%, 6.8%, 3.4% and 2.6% of individuals used analgesics, anti-inflammatory drugs, antibiotics, antihistamines, and vitamin preparations, respectively. The efficacy, immunogenicity, and safety of the vaccine were not impacted by the use of these medications.

Use with Hormonal Contraceptives
In clinical studies, 50.2% of women (aged 16 to 45 years) who received GARDASIL used hormonal contraceptives. Use of hormonal contraceptives did not appear to affect the immune responses to GARDASIL.

Use with Steroids
In clinical studies for girls and women (aged 16 to 26 years), 1.7% (n = 158), 0.6% (n = 56), and 1.0% (n = 89) of individuals used inhaled, topical, and parenteral immunosuppressants, respectively.. In a clinical study in women (aged 24 to 45 years), 1.4% (n = 27) used corticosteroids for systemic use. In a clinical study in boys and men (aged 16 to 26 years), 1.0% (n = 21) used corticosteroids for systemic use. The corticosteroids for all individuals were administered close to the time of administration of a dose of GARDASIL. These medicines did not appear to affect the immune responses to GARDASIL. Very few individuals in the clinical studies were taking steroids, and the amount of immunosuppression is presumed to have been low.

Use with Systemic Immunosuppressive Medications
There are no data on the concomitant use of potent immunosuppressants with GARDASIL. Individuals receiving therapy with immunosuppressive agents (systemic doses of corticosteroids, antimetabolites, alkylating agents, cytotoxic agents) may not respond optimally to active immunization (see PRECAUTIONS, *General*).

XII. SIDE EFFECTS

Clinical Trials
In 7 clinical trials (6 placebo-controlled), individuals were administered GARDASIL or placebo on the day of enrollment and approximately 2 and 6 months thereafter. GARDASIL demonstrated a favorable safety profile when compared with placebo (aluminum or non-aluminum containing). Few individuals (0.2%) discontinued due to adverse experiences. In all except one of the clinical trials, safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of GARDASIL or placebo. The individuals who were monitored using VRC-aided surveillance included 10,088 individuals (6,995 girls and women 9 through 45 years of age and 3,093 males boys and men 9 through 26 years of age at enrollment) who received GARDASIL and 7,995 individuals who received placebo.

The following vaccine-related adverse experiences that were observed among recipients of GARDASIL at a frequency of at least 1.0% and also at a greater frequency than that observed among placebo recipients are listed according to frequency and system organ class.

The frequency classifications are as follows:
Very Common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1,000, <1/100); Rare (≥1/10,000, <1/1,000); Very Rare (<1/10,000)

Vaccine-Related Clinical Adverse Experiences in 9- Through 45-Year-Old Girls and Women

Nervous system disorders
Very Common: *headache*
Common: *dizziness*

Gastrointestinal disorders
Common: *nausea*

Musculoskeletal and connective tissue disorders
Common: *pain in extremity*

General disorders and administration site conditions
Very Common: *pyrexia*

The following injection-site reactions occurred at a greater incidence in the group that received GARDASIL compared with either the amorphous aluminum hydroxyphosphate sulfate adjuvant-containing or the saline placebo group: Very common: *erythema, pain, and swelling*. Common: *pruritus, and hematoma*.

Most injection-site reactions were mild to moderate.

In addition, bronchospasm was reported very rarely as a serious adverse experience.

Vaccine-Related Clinical Adverse Experiences in 9- Through 26-Year-Old Boys and Men

Nervous system disorders
Common: *headache*

General disorders and administration site conditions
Common: *pyrexia*

The following injection-site reactions occurred at a greater incidence in the group that received GARDASIL compared with either the amorphous aluminum hydroxyphosphate sulfate adjuvant-containing or the saline placebo group: Very common: *erythema, pain, and swelling*.

The following injection-site reaction occurred at a greater incidence in the group that received GARDASIL compared with the amorphous aluminum hydroxyphosphate sulfate adjuvant-containing placebo group: Common: *hematoma*.

Most injection-site reactions were mild to moderate.

Concomitant Administration with Other Vaccines
The safety of GARDASIL when administered concomitantly with other vaccines was evaluated in clinical studies.

The frequency of adverse experiences observed with concomitant administration with hepatitis B vaccine (recombinant) was similar to the frequency when GARDASIL was administered alone.

There was an increase in headache and injection-site swelling when GARDASIL was given concomitantly with Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content).

There was an increase in injection-site swelling when GARDASIL was given concomitantly with Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine and Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap).

The majority of these adverse experiences seen with concomitant administration with other vaccines were reported as being mild to moderate in intensity.

Post-Marketing Reports
The following adverse experiences have been spontaneously reported during post-approval use of GARDASIL. 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.

XIII. OVERDOSAGE

There have been reports of administration of higher than recommended doses of GARDASIL. In general, the adverse event profile reported with overdose was comparable to recommended single doses of GARDASIL.

XIV. AVAILABILITY

One single dose pre-filled syringe of 0.5 ml.