SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant
Suspension for intramuscular administration
0.5-mL single dose vials and prefilled syringes
Brand Name: GARDASIL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredients

Each 0.5-mL dose contains approximately:

Human Papillomavirus1 Type 6 L1 protein	20 micrograms
Human Papillomavirus1 Type 11 L1 protein	40 micrograms
Human Papillomavirus1 Type 16 L1 protein	40 micrograms
Human Papillomavirus1 Type 18 L1 protein	20 micrograms

Adsorbed on 225 mcg of aluminum (as amorphous aluminum hydroxyphosphate sulfate adjuvant)

Inactive Ingredients

Each 0.5-mL dose of the vaccine contains approximately:

Sodium chloride	9.56 mg of
L-histidine	0.78 mg
Polysorbate 80	50 mcg
Sodium borate	35 mcg
Water for injection	

The product does not contain a preservative or antibiotics.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GARADASIL is indicated in females aged 9 through 45 years "for prevention of cervical, vulvar, and vaginal cancer, precancerous or dysplastic lesions, genital warts (condyloma acuminata), and infection caused by Human Papillomavirus (HPV) Types 6, 11, 16 and 18 (which are included in the vaccine).

4.2 Posology and method of administration

Posology

Individuals 9 to 14 years of age

Gardasil can be administered according to a 2-dose schedule (0.5 ml at 0, 6 months).

If the second vaccine dose is administered earlier than 6 months after the first dose, a third dose should always be administered.

Alternatively, Gardasil can be administered according to a 3-dose (0.5 ml at 0, 2, 6 months) schedule. The second dose should be administered at least one month after the first dose and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period.

Individuals 15 years of age and older

Gardasil should be administered according to a 3-dose (0.5 ml at 0, 2, 6 months) schedule.

The second dose should be administered at least one month after the first dose and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period.

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.
For single-use vials a separate sterile syringe and needle must be used for each 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.

Single-dose Vial Use

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

Inject the entire contents of the syringe.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients of the vaccine including severe allergic reactions to yeast (a vaccine component).

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

4.4 Special warnings and precautions for use

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, or vaginal cancers; CIN, VIN, or VaIN.

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.

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 section 4.5 Interaction with other medicinal products and other forms of Interaction).

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.

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 vaccination with GARDASIL. 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.

4.5 Interaction with other medicinal products and other forms of Interaction

Use with Other Vaccines

Results from clinical studies indicate that GARDASIL may be administered concomitantly (at a separate injection site) with H-B-VAX II™* [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. 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. 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 section 4.4 Special warnings and precautions for use).

4.6 Pregnancy and lactation
Use in 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 DOSE, METHOD OF ADMINISTRATION AND USAGE).

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% (460/1,994) 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.

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.

Pediatric Use

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

Use in the Elderly

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

Use in other special populations

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

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects
Clinical Trials

In 6 clinical trials (5 placebo-controlled), subjects 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 subjects (≤0.3%) 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 6,995 girls and women 9 through 45 years of age at enrollment, who received GARDASIL and 5,692 individuals who received placebo.

The 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.

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, autoimmune hemolytic anemia, lymphadenopathy.

Respiratory, thoracic and mediastinal disorders: pulmonary embolus.

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.

Vascular Disorders: deep venous thrombosis.

Gastrointestinal disorders: nausea, pancreatitis, vomiting.

Musculoskeletal and connective tissue disorders: arthralgia, myalgia.

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.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Viral Vaccine, ATC code: J07BM01

Mechanism of Action

GARDASIL contains L1 VLPs, which are proteins that resemble wild-type virions. Because the virus-like particles contain no viral DNA, they cannot infect cells or reproduce.

In preclinical studies, induction of anti-papillomavirus antibodies with L1 VLP vaccines resulted in protection against infection. Administration of serum from vaccinated to unvaccinated animals resulted in the transfer of protection against HPV to the unvaccinated animals. These data suggest that the efficacy of L1 VLP vaccines is mediated by the development of humoral immune responses.

Clinical Studies

In female individuals, CIN 2/3 and AIS are the immediate precursors of invasive squamous cell carcinoma and invasive adenocarcinoma of the cervix, respectively. Their detection and removal has been shown to prevent invasive cancer (secondary prevention); thus, their primary prevention through vaccination will prevent invasive cancer.

Invasive cervical cancer cannot be used as an endpoint for efficacy studies of HPV vaccines because of the importance of employing secondary prevention measures. Therefore, the immediate precursors, CIN 2 (moderate-grade cervical dysplasia), CIN 3 (high-grade cervical dysplasia including carcinoma *in situ*), and AIS are the most appropriate endpoints for the demonstration of the prevention of cervical cancer by HPV vaccines.

CIN 3 and AIS are classified as Stage 0 cervical cancers according to FIGO (International Federation of Obstetrics and Gynaecology). VIN 2/3 and VaIN 2/3 are the immediate precursors to HPV-related vulvar and vaginal cancer, respectively.

The efficacy of GARDASIL in girls and women was assessed in 5 placebo-controlled, double-blind, randomized Phase II and III clinical studies. The first Phase II study evaluated the HPV 16 component of GARDASIL (Protocol 005, N = 2,391 girls and women) and the second evaluated all components of GARDASIL (Protocol 007, N = 551 girls and women). Three Phase III studies, termed FUTURE (Females United To Unilaterally Reduce Endo/Ectocervical Disease), evaluated GARDASIL in 5,442 (FUTURE I), 12,157 (FUTURE II), and 3,817 (FUTURE III) girls and women. Together, these studies evaluated 24,358 girls and women 16 through 45 years of age at enrollment. The median duration of follow-up was 4.0, 3.0, 3.0, 3.0 and 4.0 years for Protocol 005, Protocol 007, FUTURE I, FUTURE II, and FUTURE III respectively. Individuals received vaccine or placebo on the day of enrollment and 2 and 6 months thereafter. Efficacy was analyzed for each study individually and for all studies conducted in girls and women combined.

The studies did not have a screening phase. Thus, individuals who had been exposed to a vaccine HPV type prior to enrollment were included in the studies. Overall, 73% of 16- through 26-year-old girls and women and 67% of 24- through 45-year-old women were naive to all 4 vaccine HPV types at enrollment.

The naïve individuals continued to be at risk for infection and disease caused by all 4 vaccine HPV types. Among the 24- through 45-year-old women, only 0.4% had been exposed to all 4 vaccine HPV types.

Prophylactic Efficacy – HPV Types 6, 11, 16, and 18 in 16- Through 26-Year-Old Girls and Women

GARDASIL was highly efficacious in reducing the incidence of cervical, vulvar, and vaginal cancers; CIN (any grade); AIS; non-invasive cervical cancer (CIN 3 and AIS); and external genital lesions, including condyloma acuminata, VIN (any grade) and VaIN (any grade) caused by HPV types 6, 11, 16, and 18. Based on a pre-specified analysis of lesions evident beginning 30 days Postdose 1, there was evidence that the vaccine was already efficacious during the course of the 3-dose vaccination regimen.

The primary analyses of efficacy, with respect to HPV types 6, 11, 16, and 18, were conducted in the per-protocol efficacy (PPE) population, consisting of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve to the relevant HPV type(s) prior to dose one and through 1 month Postdose 3 (Month 7). Efficacy was measured starting after the Month 7 visit.

The efficacy of GARDASIL against HPV 16- or 18-related CIN 2/3 or AIS was 98.2% (95% CI: 93.5%, 99.8%) in the combined protocols. Analyses of individual protocols demonstrated the following results: 100% (95% CI: 65.1%, 100.0%) in Protocol 005, 100% (95% CI: <0.0%, 100.0%) in Protocol 007, 100% (95% CI: 89.2%, 100.0%) in FUTURE I and 96.9% (95% CI: 88.2%, 99.6%) in FUTURE II. There were two cases of CIN 3 that occurred in the group that received GARDASIL. In the first case HPV 16 and HPV 52 were detected. This individual was chronically infected with HPV 52 (infection at Day 1, and Months 32.5 and 33.6) in 8 of 11 specimens, including tissue that was excised during LEEP (Loop Electro-excision Procedure). HPV 16 was found in 1 of 11 specimens at Month 32.5. HPV 16 was not detected in tissue that was excised during LEEP. In the second case HPV 16, HPV 51, and HPV 56 were detected. This individual was infected with HPV 51 (infection detected by PCR at Day 1) in 2 of 9 specimens. HPV 56 was detected (in tissue excised during LEEP) in 3 of 9 specimens at Month 52. HPV 16 was detected in 1 of 9 specimens at a Month 51 biopsy. Given that these cases occurred in the context of mixed infection, with the dominant type being the non-vaccine HPV type, it is likely that the relevant vaccine HPV type was not the causal HPV type. Based on this assessment, it can be inferred that vaccine efficacy against HPV 16/18-related CIN 2/3 or AIS was 100%.

The efficacy of GARDASIL against HPV 16-related CIN 2/3 or AIS was 97.9% (95% CI: 92.3%, 99.8%) in the combined protocols. The efficacy of GARDASIL against HPV 18-related CIN 2/3 or AIS was 100.0% (95% CI: 86.6%, 100.0%) in the combined protocols.

The efficacy of GARDASIL against HPV 16- or 18-related VIN 2/3 was 100% (95% CI: 55.5%, 100.0%) in the combined protocols. Analyses of individual protocols demonstrated the following results: 100% (95% CI: 14.4%, 100.0%) in FUTURE I and 100% (95% CI: <0.0%, 100%) in FUTURE II.

The efficacy of GARDASIL against HPV 16- or 18-related VaIN 2/3 was 100% (95% CI: 49.5%, 100.0%) in the combined protocols. Analyses of individual protocols demonstrated the following results: 100% (95% CI: <0.0%, 100.0%) in FUTURE I and 100% (95% CI: <0.0%, 100%) in FUTURE II.

The efficacy of GARDASIL against HPV 6-, 11-, 16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS was 96.0% (95% CI: 92.3%, 98.2%) in the combined protocols. Analyses of individual protocols demonstrated the

following results: 100% (95% CI: <0.0%, 100.0%) in Protocol 007, 100% (95% CI: 95.1%, 100.0%) in FUTURE I, and 93.8% (95% CI: 88.0%, 97.2%) in FUTURE II.

The efficacy of GARDASIL against HPV 6-, 11-, 16-, or 18-related genital lesions (genital warts, VIN, VaIN, Vulvar Cancer, and Vaginal Cancer) was 99.1% (95% CI: 96.8%, 99.9%) in the combined protocols. Analyses of individual protocols demonstrated the following results: 100% (95% CI: <0.0%, 100.0%) in Protocol 007, 100% (95% CI: 94.9%, 100.0%) in FUTURE I and 98.7% (95% CI: 95.2%, 99.8%) in FUTURE II.

The efficacy of GARDASIL against HPV 6- or 11-related genital warts was 99.0% (95% CI: 96.2%, 99.9%) in the combined protocols.

Supplemental Analysis of Efficacy for Cancer Endpoints in 16- Through 26-Year-Old Girls and Women

In a supplemental analysis, the efficacy of GARDASIL was evaluated against HPV 16/18-related FIGO Stage 0 cervical cancer (CIN 3 and AIS) and for the immediate precursors to vulvar and vaginal cancer (VIN 2/3 or VaIN 2/3) in the per-protocol efficacy (PPE) population and a modified intention to treat-2 (MITT-2) population. The MITT-2 population consisted of individuals who were naïve to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1, received at least one dose of vaccine or placebo, and had at least one follow-up visit post- Day 30. The MITT-2 population differs from the PPE population in that it includes individuals with major protocol violations and who became infected with a vaccine HPV type during the vaccination period. Efficacy was measured starting 30 days Postdose 1 for the MITT-2 population.
The efficacy of GARDASIL against HPV 16/18-related disease was 96.9% (95% CI: 88.4%, 99.6%), 100% (95% CI: 30.6%, 100.0%), and 100% (95% CI: 78.6%, 100.0%) for CIN 3, AIS, and VIN 2/3 or VaIN 2/3, respectively, in the per-protocol population. Efficacy against HPV 16/18-related disease was 96.7% (95% CI: 90.2%, 99.3%), 100.0% (95% CI: 60.0%, 100.0%), and 97.0% (95% CI: 82.4%, 99.9%) for CIN 3, AIS, and VIN 2/3 or VaIN 2/3, respectively, in the MITT-2 population.

Prophylactic efficacy against overall persistent infection or disease in an extension phase of Protocol 007, that included data through Month 60, was 95.8% (95% CI: 83.8%, 99.5%). In the group that received GARDASIL, no cases due to waning immunity were observed.

GARDASIL was equally efficacious against HPV disease caused by HPV types 6, 11, 16, and 18.

Efficacy in 16- Through 26-Year-Old Girls and Women with Current or Prior Infection with HPV Types 6, 11, 16, or 18

Individuals who were already infected with one or more vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the remaining vaccine HPV types.

Individuals with evidence of a prior infection that had resolved by vaccination onset were protected from reacquisition or recurrence of infection leading to clinical disease.

Individuals who received GARDASIL, but had ongoing HPV infection at the time of vaccination had a 21.6% (95% CI: <0.0%, 42.1%) lower incidence of CIN (CIN 1 or CIN 2/3) or AIS resulting from this infection as compared with placebo. Ongoing infection was defined as infection with a vaccine HPV type at enrollment, but no evidence of immune response to it.

Prophylactic Efficacy in a Generally HPV-naïve Population and the General Study Population –HPV Types 31, 33, 45, 52, 56, 58 and 59 in 16- Through 26-Year-Old Girls and Women

The cross protective efficacy of GARDASIL was evaluated in the combined database of the FUTURE I and FUTURE II trials (N = 17,599). The primary endpoint of this analysis was the combined incidence of HPV 31- and HPV 45-related CIN (grades 1, 2, 3) or AIS. The secondary endpoint of this analysis was the combined incidence of HPV 31-, 33-, 45-, 52-, and 58-related CIN (grades 1, 2, 3) or AIS. Analyses were also conducted to evaluate efficacy with respect to CIN (grades 1, 2, 3) or AIS caused by non-vaccine HPV types individually. In individuals who were naïve to the relevant vaccine HPV types at Day 1 (MITT-2 population, n = 16,895 for the 31/45 composite endpoint and n = 16,969 for the 31/33/45/52/58 composite endpoint), a trend towards a reduction in the incidence of HPV 31- and 45-related and HPV 31-, 33-, 45-, 52-, and 58- related CIN (grades 1, 2, 3) or AIS was observed. Administration of GARDASIL reduced the incidence of HPV 31- and HPV 45-related CIN (grades 1, 2, 3) by 37.3% (95% CI: 17.0%, 52.8%) compared with placebo. Administration of GARDASIL reduced the incidence of HPV 31-, 33-, 45-, 52-, and 58-related CIN (grades 1, 2, 3) or AIS by 26.4% (95% CI: 12.9%, 37.8%), compared with placebo. Efficacy was driven by reductions in HPV 31-, 33-, 52-, and 58-related endpoints. There was no clear evidence of efficacy for HPV 45. In a post-hoc analysis, prophylactic administration of GARDASIL also reduced the incidence of HPV 56-related and HPV 59-related CIN (grades 1, 2, 3) or AIS, compared with placebo in this population.

Further post-hoc analyses considered efficacy in 2 clinically relevant populations: (1) an HPVnaïve population (negative to 14 common HPV types and had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1), approximating a population of sexually-naïve individuals plus individuals shortly after sexual debut; and (2) the general study population of individuals regardless of baseline HPV status, some of whom had HPV-related disease at vaccination onset. Administration of GARDASIL to HPV-naïve individuals reduced the incidences of HPV 31-, 33-, 52-, and 58-related CIN (grades 1, 2, 3) or AIS, HPV 56-related CIN (grades 1, 2, 3) or AIS, and HPV 59-related CIN (grades 1, 2, 3) or AIS. Reductions in the rates of these diseases were also observed in the general study population (which included HPV-naïve and HPV-infected individuals).

In the HPV-naïve population (n = 9,296), GARDASIL reduced the incidence of CIN (any grade) or AIS by 43.6% (95% CI: 12.9%, 64.1%) for HPV 31/45; 29.2% (95% CI: 8.3%, 45.5%) for HPV 31/33/45/52/58; 33.8% (95% CI: 13.4%, 49.6%) for HPV 31/33/52/58; 27.6% (95% CI: <0.0%, 49.3%) for HPV 56; and 22.3% (95% CI: <0.0%, 58.9%) for HPV 59.

In the general study population (n = 17,151), GARDASIL reduced the incidence of CIN (any grade) or AIS by 23.2% (95% CI: 5.6%, 37.7%) for HPV 31/45; 19.6% (95% CI: 8.2%, 29.6%) for HPV 31/33/45/52/58; 21.2% (95% CI: 9.6%,31.3%) for HPV 31/33/52/58: 16.8% (95% CI: <0.0%, 32.8%) for HPV 56; and 39.2% (95% CI: 8.1%, 60.3%) for HPV 59 .

Cross-protection efficacy analyses demonstrate that prophylactic administration of GARDASIL to individuals reduces the risk of acquiring CIN 1, CIN 2/3, and AIS caused by HPV types 31, 33, 52, 56, 58, and 59.

Protection Against the Overall Burden of Cervical, Vulvar, and Vaginal HPV Disease in 16- Through 26-Year-Old Girls and Women

The impact of GARDASIL against the overall risk for cervical, vulvar, and vaginal HPV disease (i.e., disease caused by any HPV type) was evaluated in a pre-specified analysis of 17,599 individuals enrolled in FUTURE I and FUTURE II. Among individuals who were naïve to at least one of 14 common HPV types and/or had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1 (MITT-2 population), administration of GARDASIL reduced the incidence of CIN 2/3 or AIS caused by vaccine- or non-vaccine HPV types by 33.8% (95% CI: 20.7%, 44.8%).

Further efficacy analyses were conducted in 2 clinically relevant populations: (1) an HPV-naïve population (negative to 14 common HPV types and had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1), approximating a population of sexually-naïve individuals plus individuals shortly after sexual debut; and (2) the general study population of individuals regardless of baseline HPV status, some of whom had HPV-related disease at vaccination onset.

Among HPV-naïve individuals and among the general study population (including individuals with HPV infection at vaccination onset), GARDASIL reduced the overall incidence of CIN 2/3 or AIS; of VIN 2/3 or VaIN 2/3; of CIN (any grade) or AIS; and of Genital Warts. These reductions were primarily due to reductions in lesions caused by HPV types 6, 11, 16, and 18. Among HPVnaïve individuals and the general study population, the benefit of the vaccine with respect to the overall incidence of CIN 2/3 or AIS (caused by any HPV type) became more apparent over time. This is because GARDASIL does not impact the course of infections that are present at vaccination onset. Such infected individuals may already have CIN 2/3 or AIS at vaccination onset, and some will develop CIN 2/3 or AIS during follow-up. GARDASIL reduces the incidence of CIN 2/3 or AIS caused by infections with HPV types 6, 11, 16, 18, 31, 33, 52, 56, 58 and 59 that occur after vaccination onset.

GARDASIL has not been shown to protect against the diseases caused by every HPV type, and will not treat existing disease. The overall efficacy of GARDASIL will vary with the baseline prevalence of HPV infection and disease, the incidence of infections against which GARDASIL has shown protection, and those infections against which GARDASIL has not been shown to protect.

Impact on the Rates of Pap Test Abnormalities and Cervical, Vulvar, and Vaginal Procedures in 16- Through 26-Year-Old Girls and Women

The impact of GARDASIL on rates of abnormal Pap tests and cervical procedures (colposcopic biopsy, definitive therapy) regardless of causal HPV types was evaluated in 18,150 individuals enrolled in Protocol 007, FUTURE I and FUTURE II. The impact of GARDASIL on rates of genital excisional procedures to treat lesions caused by any HPV type was evaluated in 5,442 individuals enrolled in FUTURE I. Two populations were considered: (1) an HPV-naïve population (negative to 14 common HPV types and had a Pap test that was negative for SIL [Squamous Intraepithelial Lesion] at Day 1), approximating a population of sexually-naïve individuals plus individuals shortly after sexual debut; and (2) the general study population of individuals regardless of baseline HPV status, some of whom had HPV-related disease at vaccination onset.

In both populations, GARDASIL reduced the proportions of individuals who experienced a Pap test abnormality suggestive of CIN, a colposcopic biopsy, a definitive cervical therapy procedure (Loop Electro-Excision Procedure or Cold-Knife Conization), a vulvar or vaginal biopsy, or a definitive excisional procedure of the vagina or vulva.

In addition, administration of GARDASIL to a generally HPV-naïve population of 16- through 26- year-old individuals reduced the incidence of HPV 16-related and HPV 18-related Pap abnormalities (ASC-US HR positive, LSIL, or worse) by 92.4% (95% CI: 83.7, 97.0) and 96.9% (95% CI: 81.6, 99.9) in the FUTURE I study.

Prophylactic Efficacy – HPV Types 6, 11, 16, and 18 in 24- Through 45-Year-Old Women

A minimum anti-HPV level that provides protection against HPV infection and disease has not been defined. Also, immune responses to vaccines are typically lower in older individuals compared to younger individuals. Therefore, to confirm the utility of GARDASIL to prevent cervical, vulvar, and vaginal cancers and related diseases caused by the types targeted by the vaccine in individuals up to and including age 45 years, an efficacy study (FUTURE III) was conducted.

GARDASIL was highly efficacious in reducing the incidence of persistent infection; CIN (any grade); and external genital lesions (EGL) caused by HPV types 6, 11, 16, and 18. GARDASIL was also highly efficacious in reducing the incidence of a HPV 16/18-related Pap Test diagnosis of ASC-US (Atypical Squamous Cells of Undetermined Significance) positive for high-risk HPV. The primary analyses of efficacy, with respect to HPV types 6, 11, 16, and 18, were conducted in the per-protocol efficacy (PPE) population. Efficacy was measured starting after the Month 7 visit.

The efficacy of GARDASIL against HPV 6-, 11-, 16- or 18-related persistent infection, CIN (any grade) or EGL was 88.7.5% (95% CI: 78.1%, 94.8%).

The efficacy of GARDASIL against HPV 16- or 18-related persistent infection, CIN (any grade), or EGL was 84.7% (95% CI: 67.5%, 93.7%).

There were 3 cases of HPV 16 infection and 1 case of CIN 2 (HPV 16 and HPV 51 identified) in the PPE group. All 4 cases occurred early in the follow-up period. Two of the 3 cases of persistent infection had antibody levels to HPV 16 at Month 7 that were very high and suggestive of an anamnestic response to a previous infection. The third persistent infection case had anti-HPV 16 levels that were higher than the anti-HPV 16 GMT among individuals who received HPV vaccine within the PPI population of Protocol 019. HPV 16 infection was detected in Month 18 and Month 24 swabs. The CIN 2 case was positive for HPV types 16 and 51 at a Month 18 biopsy.

The efficacy of GARDASIL against HPV 6-or 11-related persistent infection, CIN (any grade) or EGL was 94.8% (95% CI: 79.9%, 99.4%).

The efficacy of GARDASIL against a HPV 16/18-related Pap diagnosis of ASC-US positive for high-risk HPV was 96.3% (95% CI: 77.7%, 99.9%).

On the basis of these efficacy findings, the efficacy of GARDASIL with respect to prevention of cervical, vulvar, and vaginal cancers and related diseases in individuals up to and including age 45 years can be inferred.

Immunogenicity

Assays to Measure Immune Response

Type-specific assays 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, rather

than the total antibodies directed at the VLPs in the vaccine. The scales for these assays are unique to each HPV type; thus, comparisons across types and to other assays are not meaningful. The assays used to measure the immune responses to GARDASIL were demonstrated to correlate with the capacity to neutralize live HPV virions.

Because of the very high efficacy of GARDASIL in clinical trials, it has not been possible to establish minimum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 antibody levels that protect against clinical HPV disease.

The immunogenicity of GARDASIL was assessed in 23,951 9- through 45-year-old girls and women (GARDASIL N = 12,634; placebo N = 11,317).

The primary immunogenicity analyses were conducted in a per-protocol immunogenicity (PPI) population. This population consisted of individuals who were seronegative and Polymerase Chain Reaction (PCR) negative to the relevant HPV type(s) at enrollment, remained HPV PCR negative to the relevant HPV type(s) through 1 month Post dose 3 (Month 7), received all 3 vaccinations, and did not deviate from the study protocol in ways that could interfere with the effects of the vaccine.

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).

Immune Response to GARDASIL at Month 7 in 9- Through 45-Year-Old Girls and Women (Time Point Approximating Peak Immunogenicity)

In the per-protocol immunogenicity population of 9- through 45-year-olds, seropositivity at Month 7 ranged from 96.4% to 99.9% across all 4 vaccine types and across populations defined by age range. Anti-HPV GMTs for all types decreased with age. This finding is expected, as the immune responses to vaccines generally decrease with age at vaccination. The efficacy of GARDASIL remained high despite the observed age-related decrease in anti- HPV GMTs.

Bridging the Efficacy of GARDASIL from Adults to Adolescents

A clinical study compared anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses in 10- through 15-year-old adolescent girls with responses in 16- through 23-year-old girls and women. Among the girls and women who received GARDASIL, 99.1% to 100% became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive by 1 month Postdose 3. Anti-HPV responses in 10- through 15-year-old adolescent girls were significantly superior to those observed in 16- through 23-year-old girls and women.

Similar outcomes were observed in a comparison of the anti-HPV responses 1 month Postdose 3 among 9- through 15-year-old adolescent girls with anti-HPV responses in 16- through 26-year-old girls and women in the combined database of immunogenicity studies for GARDASIL.

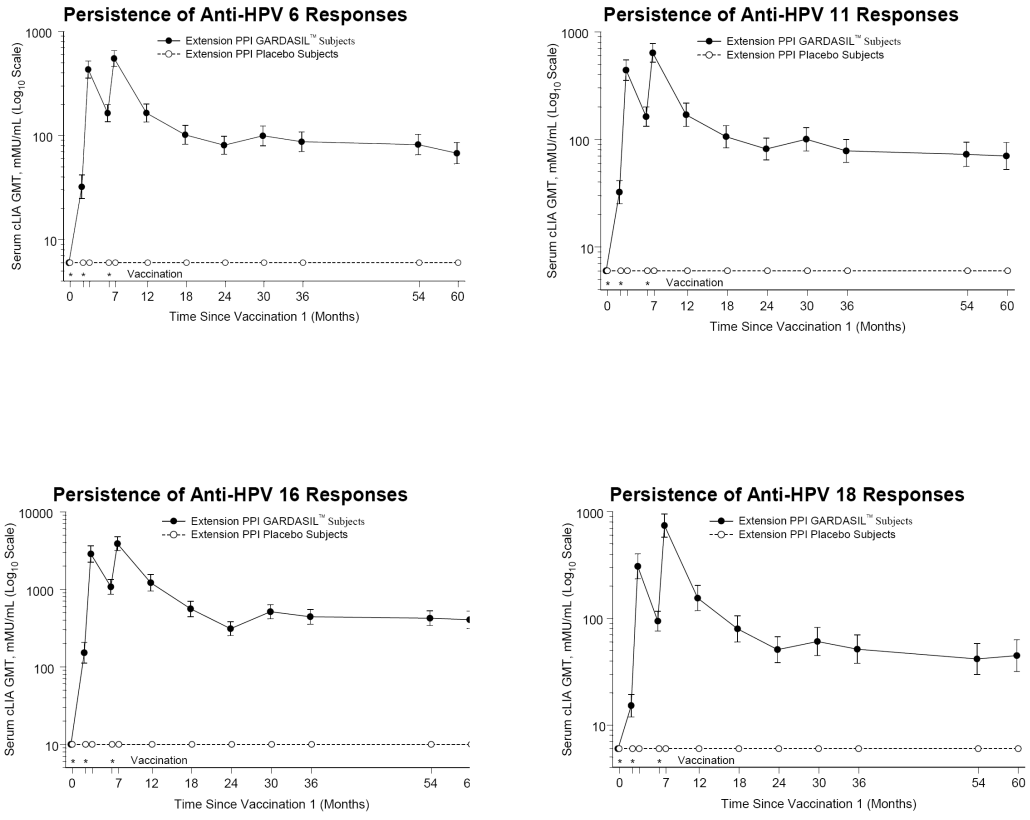
On the basis of this immunogenicity bridging, the efficacy of GARDASIL in 9- through 15-year-old adolescent girls is comparable to the efficacy of GARDASIL observed in 16- through 26-year-old girls and women.

Persistence of The Immune Response to GARDASIL

The duration of immunity following a complete schedule of immunization with GARDASIL has not been established. After peaking at Month 7, anti-GMTs for all HPV types decreased through Month 24 and then stabilized at levels above baseline.

In Protocol 007, peak anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs were observed at Month 7. The GMTs decreased through Month 24 and then stabilized until at least Month 60 (see Figure 1).

Figure 1
Persistence of Anti-HPV Responses Following a 3-Dose Regimen of GARDASIL



Evidence of Anamnestic (Immune Memory) Response

Evidence of an anamnestic response was seen in vaccinated individuals who were seropositive to relevant HPV type(s) prior to vaccination.

In a study to evaluate the capacity to induce immune memory, individuals who received a 3- dose primary series of vaccine were given a challenge dose of GARDASIL 5 years after the onset of vaccination. These individuals exhibited a rapid and strong anamnestic response that exceeded the anti-HPV GMTs observed 1 month Postdose 3 (Month 7). The GMTs 1 week post-challenge dose were 0.9-, 2.2-, 1.2-, and 1.4-fold higher than the Postdose 3 GMTs for types 6, 11, 16, and 18, respectively. The

GMTs 1 month post-challenge dose were 1.3-, 4.2-, 1.5-, and 1.7-fold higher than the Postdose 3 GMTs for types 6, 11, 16, and 18, respectively. At 1 week post-challenge dose, 87.2%, 94.9%, 86.4% and 95.2% of individuals had anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs higher than those detected at Month 60.

In addition, a subset of individuals that received a 3-dose primary series of vaccine became nominally anti-HPV 18 seronegative by Month 60. Although these individuals were nominally anti-HPV 18 seronegative, no cases of HPV 18-related disease were detected among these individuals. They also showed immune memory: when these individuals were given a challenge dose of GARDASIL (at Month 60), 93% and 97% became anti-HPV 18 seropositive by 1 week and 1 month post-challenge, respectively; 73% had anti-HPV 18 levels at 1 month post challenge that were higher than their Month 7 (1 month Postdose 3) anti-HPV 18 level.

Persistence of Immune Response in Phase III Studies of 9- Through 45-Year-Old Girls and Women for GARDASIL

Anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositivity was highest at Month 7, and then declined at persistence time points. At Month 24, anti-HPV seropositivity was highest among 9- through 17-year-olds and lowest among 35- through 45-year-olds.

The decline in the percent seropositivity for anti-HPV 18 responses was greater than the decline in the percent seropositivity for anti-HPV 6, anti-HPV 11, and anti-HPV 16 responses. Despite this decline, the efficacy of the vaccine remained high, across all age groups. In the PPE population of the FUTURE I and FUTURE II studies, efficacy against HPV 18-related CIN 2/3 or AIS was 100.0% (95% CI: 86.6%, 100.0%) and efficacy against HPV 18-related CIN (any grade) or AIS was 98.4% (95% CI: 90.6%, 100.0%). In the PPE population of the FUTURE III study, efficacy against HPV 18-related persistent infection or cervical, vulvar, and vaginal disease was 100.0% (95% CI: 67.4%, 100.0%).

Schedule flexibility

All individuals evaluated in the PPE populations of the Phase II and III studies received the 3-dose regimen of GARDASIL within a 1-year period, regardless of the interval between doses. An analysis of immune response data suggests that flexibility of ±1 month for Dose 2 (i.e., Month 1 to Month 3 in the vaccination regimen) and flexibility of ±2 months for Dose 3 (i.e., Month 4 to Month 8 in the vaccination regimen) do not substantially impact the immune responses to GARDASIL (see DOSE, METHOD OF ADMINISTRATION AND USAGE).

Immune Responses to GARDASIL using a 2-dose schedule in individuals 9-13 years of age
A clinical trial showed that among girls who received 2 doses of HPV vaccine 6 months apart, antibody responses to the 4 HPV types, one month after the last dose were non-inferior to those among young women who received 3 doses of the vaccine within 6 months.

At Month 7, in the Per Protocol population, the immune response in girls aged 9-13 years (n=241) who received 2 doses of Gardasil (at 0, 6 months) was non–inferior and numerically higher to the immune response in women aged 16-26 years (n=246) who received 3 doses of Gardasil (at 0, 2, 6 months).

At 36 month follow-up, the GMT in girls (2 doses, n=86) remained non-inferior to the GMT in women (3doses, n=86) for all 4 HPV types.

In the same study, in girls aged 9-13 years, the immune response after a 2-dose schedule was numerically lower than after a 3-dose schedule (n=248 at Month 7; n=82 at Month 36). The clinical relevance of these findings is unknown. Duration of protection of a 2-dose schedule of Gardasil has not been established.

A clinical study done in India of 17729 girls supported these findings.

Studies with Other Vaccines

H-B-VAX II [hepatitis B vaccine (recombinant)]
The safety and immunogenicity of co-administration of GARDASIL with H-B-VAX II [hepatitis B vaccine (recombinant)] (same visit, injections at separate sites) were evaluated in a randomized study of 1,871 women aged 16 through 24 years at enrollment. Immune response and safety profile to both H-B-VAX II [hepatitis B vaccine (recombinant)] and GARDASIL were similar whether they were administered at the same visit or at a different visit.

Repevax [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content)]
The safety and immunogenicity of co-administration of GARDASIL with Repevax [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content)] (same visit, injections at separate sites) were evaluated in a randomized study of 843 boys and girls 11 through 17 years of age at enrollment. Concomitant administration of GARDASIL with Repevax [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content)] does not interfere with the antibody response to any of the components of either vaccine. In addition, the safety profile was generally similar (See Undesirable Effects, *Concomitant Administration with Other Vaccines).*

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)]
The safety and immunogenicity of co-administration of GARDASIL 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 a randomized study of 1040 boys and girls 11 through 17 years of age at enrollment. Concomitant administration of GARDASIL 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)] does not interfere with the antibody response to any of the components of any of the vaccines. In addition, the safety profile was generally similar (See Undesirable Effects, *Concomitant Administration with Other Vaccines).*

5.2 Pharmacokinetic properties
Not applicable.

5.3 Preclinical safety data
Single-dose and repeated-dose toxicity and local tolerance studies revealed no special hazards to humans.

Gardasil induced specific antibody responses against HPV types 6, 11, 16, and 18 in pregnant rats, following one or multiple intramuscular injections. Antibodies against all four HPV types were transferred to the offspring during gestation and possibly during lactation. There were no treatment-related effects on developmental signs, behaviour, reproductive performance, or fertility of the offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
L-histidine
Polysorbate 80
Sodium borate
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store refrigerated at 2 to 8°C (36 to 46°F). Do not freeze. Protect from light.

GARDASIL should be administered as soon as possible after being removed from refrigeration.

GARDASIL can be out of refrigeration (at temperatures at or below 25°C/77°F), for a total time of not more than 72 hours.

6.5 Nature and contents of container

GARDASIL is supplied in vials and prefilled syringes:
Carton of one 0.5-mL single-dose vials
Carton of ten 0.5-mL single-dose vials
Carton of one 0.5-mL single-dose pre-filled Luer-Lok syringes with tip caps with needle(s)
Carton of ten 0.5-mL single-dose prefilled Luer-Lok syringes with tip caps with or without with needle(s)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused vaccine or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION/ PREQUALIFICATION HOLDER

MSD Pharmaceuticals Pvt. Ltd.,
Gala No. 1B, Building No. B-3,
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8. MARKETING>AUTHORISATION NUMBER(S)

Import Permission No.: Import-722/08

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorization (Form 45): 04 July 2008

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