نشرة معتمدة طبقا لقرار اللجنة العلمية المتخصصة للمستحضرات الحيوية بدعوة أعضاء اللجنة العلمية المتخصصة لأمراض النساء والتوليد بجلستها في ٢٠٠٦/٦/٢٦ .

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Gardasil® suspension for injection.

Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml) contains approximately:

Human Papillomavirus[1] Type 6 L1 protein[2,3]	20 micrograms
Human Papillomavirus[1] Type 11 L1 protein[2,3]	40 micrograms
Human Papillomavirus[1] Type 16 L1 protein[2,3]	40 micrograms
Human Papillomavirus[1] Type 18 L1 protein[2,3]	20 micrograms.

[1]Human Papillomavirus = HPV.
[2]L1 protein in the form of virus-like particles produced in yeast cells (*Saccharomyces cerevisiae* CANADE 3C-5 (Strain 1895)) by recombinant DNA technology.
[3]adsorbed on amorphous aluminium hydroxyphosphate sulfate adjuvant (0.225 milligrams Al).

For a full list of excipients, see section 6.1.

هيئة الدواء المصرية
الإدارة المركزية للمستحضرات الحيوية والمبتكرة والدراسات الاكلينيكية
إدارة تسجيل المستحضرات الحيوية
نشرة معتمدة
تاريخ ٢٦ / ٦ / ٢٠٠٦

3. PHARMACEUTICAL FORM

Gardasil suspension for injection.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gardasil is a vaccine for use from the age of 9 years for the prevention of:
- premalignant genital lesions (cervical, vulvar and vaginal), premalignant anal lesions, cervical cancers and anal cancers causally related to certain oncogenic Human Papillomavirus (HPV) types
- genital warts (condyloma acuminata) causally related to specific HPV types.

See sections 4.4 and 5.1 for important information on the data that support this indication.

The use of Gardasil should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Individuals 9 to and including 13 years of age
Gardasil can be administered according to a 2-dose schedule (0.5 ml at 0, 6 months) (see section 5.1).

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.

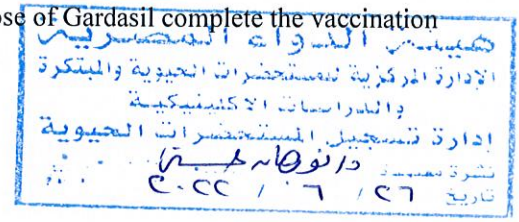
Individuals 14 years of age and older
Gardasil should be administered according to a 3-dose (0.5 ml at 0, 2, 6 months) schedule.

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.

The use of Gardasil should be in accordance with official recommendations.

Paediatric population
The safety and efficacy of Gardasil in children below 9 years of age have not been established. No data are available (see section 5.1).

It is recommended that individuals who receive a first dose of Gardasil complete the vaccination course with Gardasil (see section 4.4).



The need for a booster dose has not been established.

Method of administration

The vaccine should be administered by intramuscular injection. The preferred site is the deltoid area 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 (see section 6.6).

4.3 Contraindications

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

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

Administration of Gardasil should be postponed in individuals suffering from an acute severe febrile illness. However, the presence of a minor infection, such as a mild upper respiratory tract infection or low-grade fever, is not a contraindication for immunisation.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

The decision to vaccinate an individual should take into account the risk for previous HPV exposure and potential benefit from vaccination.

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), sometimes associated with falling, can occur following, or even before, any vaccination, especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia, and tonic-clonic limb movements during recovery. Therefore, vaccinees should be observed for approximately 15 minutes after vaccine administration. It is important that procedures are in place to avoid injury from faints.

As with any vaccine, vaccination with Gardasil may not result in protection in all vaccine recipients.

Gardasil will only protect against diseases that are caused by HPV types 6, 11, 16 and 18 and to a limited extent against diseases caused by certain related HPV types (see section 5.1). Therefore, appropriate precautions against sexually transmitted diseases should continue to be used.

Gardasil is for prophylactic use only and has no effect on active HPV infections or established clinical disease. Gardasil has not been shown to have a therapeutic effect. The vaccine is therefore, not indicated for treatment of cervical cancer, high-grade cervical, vulvar, and vaginal dysplastic lesions or genital warts. It is also not intended to prevent progression of other established HPV-related lesions.

Gardasil does not prevent lesions due to a vaccine HPV type in individuals infected with that HPV type at the time of vaccination (see section 5.1).

The use of Gardasil in adult women should take into consideration the variability of HPV type prevalence in different geographical areas.

Vaccination is not a substitute for routine cervical screening. Since no vaccine is 100 % effective and Gardasil will not provide protection against every HPV type, or against existing HPV infections, routine cervical screening remains critically important and should follow local recommendations.

Safety and immunogenicity of the vaccine have been assessed in individuals aged from 7 to 12 years who are known to be infected with human immunodeficiency virus (HIV) (see section 5.1). Individuals with impaired immune responsiveness, due to either the use of potent immunosuppressive therapy, a genetic defect, or other causes, may not respond to the vaccine.

This vaccine should be given with caution to individuals with thrombocytopaenia or any coagulation disorder because bleeding may occur following an intramuscular administration in these individuals.

Long-term follow-up studies were conducted to determine the duration of protection. (see section 5.1).

There are no safety, immunogenicity or efficacy data to support change during vaccination with Gardasil to other HPV vaccines which do not cover the same HPV types. Therefore, it is important that the same vaccine should be prescribed for the whole dose regimen.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

In all clinical trials, individuals who had received immunoglobulin or blood-derived products during the 6 months prior to the first vaccine dose were excluded.

Use with other vaccines

Administration of Gardasil at the same time (but, for injected vaccines, at a different injection site) as hepatitis B (recombinant) vaccine did not interfere with the immune response to the HPV types. The seroprotection rates (proportion of individuals reaching seroprotective level anti-HBs ≥10 mIU/ml) were unaffected (96.5 % for concomitant vaccination and 97.5 % for hepatitis B vaccine only). Anti-

HBs geometric mean antibody titres were lower on co-administration, but the clinical significance of this observation is not known.

Gardasil may be administered concomitantly with a combined booster vaccine containing diphtheria (d) and tetanus (T) with either pertussis [acellular, component] (ap) and/or poliomyelitis [inactivated] (IPV) (dTap, dT-IPV, dTap-IPV vaccines) with no significant interference with antibody response to any of the components of either vaccine. However, a trend of lower anti-HPV GMTs was observed in the concomitant group. The clinical significance of this observation is not known. This is based on the results from a clinical trial in which a combined dTap-IPV vaccine was administered concomitantly with the first dose of Gardasil. (see section 4.8).

The concomitant administration of Gardasil with vaccines other than the ones above has not been studied.

Use with hormonal contraceptives

In clinical studies, 57.5 % of women aged 16 to 26 years and 31.2 % of women aged 24 to 45 years who received Gardasil used hormonal contraceptives during the vaccination period. Use of hormonal contraceptives did not appear to affect the immune response to Gardasil.

4.6 Fertility, pregnancy and lactation

Pregnancy

Specific studies of the vaccine in pregnant women were not conducted. During the clinical development program, 3,819 women (vaccine = 1,894 vs. placebo = 1,925) reported at least one pregnancy. There were no significant differences in types of anomalies or proportion of pregnancies with an adverse outcome in Gardasil and placebo treated individuals. These data on pregnant women (more than 1,000 exposed outcomes) indicate no malformative nor feto/ neonatal toxicity.

The data on Gardasil administered during pregnancy did not indicate any safety signal. However, these data are insufficient to recommend use of Gardasil during pregnancy. Vaccination should be postponed until completion of pregnancy.

Breast-feeding

In breast-feeding mothers given Gardasil or placebo during the vaccination period of the clinical trials the rates of adverse reactions in the mother and the breast-fed infant were comparable between the vaccination and the placebo groups. In addition, vaccine immunogenicity was comparable among breast-feeding mothers and women who did not breast-feed during the vaccine administration.

Therefore, Gardasil can be used during breast-feeding.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). No effects on male fertility were observed in rats (see section 5.3).

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

A. Summary of the safety profile

In 7 clinical trials (6 placebo-controlled), individuals were administered Gardasil or placebo on the

day of enrolment and approximately 2 and 6 months thereafter. Few individuals (0.2 %) discontinued due to adverse reactions. Safety was evaluated in either the entire study population (6 studies) or in a predefined subset (one study) of the study population 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 females 9 to 45 years of age and 3,093 males 9 to 26 years of age at enrolment) who received Gardasil and 7,995 individuals (5,692 females and 2,303 males) who received placebo.

The most common adverse reactions observed were injection-site adverse reactions (77.1 % of vaccinees within 5 days following any vaccination visit) and headache (16.6 % of the vaccinees). These adverse reactions usually were mild or moderate in intensity.

B. Tabulated summary of adverse reactions

Clinical Trials
Table 1 presents vaccine-related adverse reactions which were observed among recipients of Gardasil at a frequency of at least 1.0 % and also at a greater frequency than observed among placebo recipients. They are ranked under headings of frequency using the following convention:

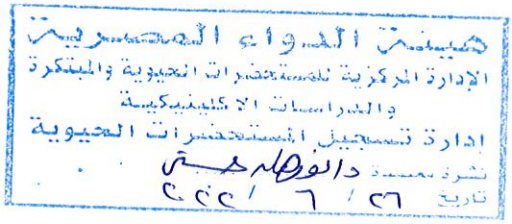
[Very Common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very Rare (<1/10,000)]

Post-Marketing Experience
Table 1 also includes additional adverse events which have been spontaneously reported during the post-marketing use of Gardasil worldwide. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Consequently, the frequency of these adverse events is qualified as "not known".

Table 1: Adverse Events Following Administration of Gardasil from Clinical Trials and Post-Marketing Surveillance

System Organ Class	Frequency	Adverse Events
Infections and infestations	Not known	Injection-site cellulitis *
Blood and lymphatic system disorders	Not known	Idiopathic thrombocytopenic purpura*, lymphadenopathy*
Immune system disorders	Not known	Hypersensitivity reactions including anaphylactic/anaphylactoid reactions*
Nervous system disorders	Very common	Headache
	Not known	Acute disseminated encephalomyelitis*, Dizziness[1] *, Guillain-Barré syndrome*, syncope sometimes accompanied by tonic-clonic movements*
Gastrointestinal disorders	Common	Nausea
	Not known	Vomiting*
Musculoskeletal and Connective Tissue Disorders	Common	Pain in extremity
	Not known	Arthralgia*, Myalgia*
General disorders and administration site conditions	Very common	At the injection site: erythema, pain, swelling
	Common	Pyrexia At the injection site: hematoma, pruritus
	Not known	Asthenia*, chills*, fatigue*, malaise*

* Post Marketing adverse events (frequency cannot be estimated from the available data).
[1] During clinical trials, dizziness was observed as a common adverse reaction in females. In males, dizziness was not observed at a greater frequency in vaccine recipients than in placebo recipients.



In addition, in clinical trials adverse reactions that were judged to be vaccine- or placebo-related by the study investigator were observed at frequencies lower than 1 %:

Respiratory, thoracic and mediastinal disorders:
Very rare: bronchospasm.

Skin and subcutaneous tissue disorders:
Rare: urticaria.
Nine cases (0.06 %) of urticaria were reported in the Gardasil group and 20 cases (0.15 %) were seen in the adjuvant-containing placebo group.

In the clinical studies, individuals in the Safety Population reported any new medical conditions during the follow-up. Among 15,706 individuals who received Gardasil and 13,617 individuals who received placebo, there were 39 cases of non-specific arthritis/arthropathy reported, 24 in the Gardasil group and 15 in the placebo group.

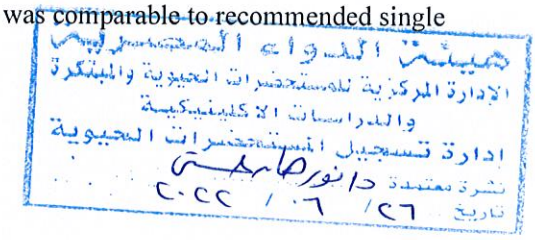
In a clinical trial of 843 healthy adolescent males and females 11-17 years of age, administration of the first dose of Gardasil concomitantly with a combined diphtheria, tetanus, pertussis [acellular, component] and poliomyelitis [inactivated] booster vaccine showed that there was more injection-site swelling and headache reported following concomitant administration. The differences observed were < 10 % and in the majority of subjects, the adverse events were reported as mild to moderate in intensity.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via e-mail: pv.followup@edaegypt.gov.eg.

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 is an adjuvanted non-infectious recombinant quadrivalent vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid L1 protein of HPV types 6, 11, 16 and 18. The VLPs contain no viral DNA, they cannot infect cells, reproduce or cause disease. HPV only infects humans, but animal studies with analogous papillomaviruses suggest that the efficacy of LI VLP vaccines is mediated by the development of a humoral immune response.

HPV 16 and HPV 18 are estimated to be responsible for approximately 70 % of cervical cancers and 75-80 % of anal cancers; 80 % of adenocarcinoma in situ (AIS); 45-70 % of high-grade cervical intraepithelial neoplasia (CIN 2/3); 25 % of low grade cervical intraepithelial neoplasia (CIN 1); approximately 70 % of HPV related high-grade vulvar (VIN 2/3) and vaginal (VaIN 2/3) intraepithelial neoplasia and 80 % of HPV related high-grade anal (AIN 2/3) intraepithelial neoplasia. HPV 6 and 1i are responsible for approximately 90 % of genital warts and 10 % of low grade cervical

intraepithelial neoplasia (CIN 1). CIN 3 and AIS have been accepted as immediate precursors of invasive cervical cancer.

The term "premalignant genital lesions" in section 4.1 corresponds to high-grade cervical intraepithelial neoplasia (CIN 2/3), high-grade vulvar intraepithelial neoplasia (VIN 2/3) and high-grade vaginal intraepithelial neoplasia (VaIN 2/3).

The term "premalignant anal lesions" in section 4.1 corresponds to high-grade anal intraepithelial neoplasia (AIN 2/3).

The indication is based on the demonstration of efficacy of Gardasil in females 16 to 45 years of age and in males 16 to 26 years of age and on the demonstration of immunogenicity of Gardasil in 9- to 15-year old children and adolescents.

Clinical Studies

Efficacy in women 16 through 26 years

The efficacy of Gardasil in 16- through 26 year-old women was assessed in 4 placebo-controlled, double-blind, randomised Phase II and III clinical studies including a total of 20,541 women, who were enrolled and vaccinated without pre-screening for the presence of HPV infection.

The primary efficacy endpoints included HPV 6-, 11-, 16-, or 18-related vulvar and vaginal lesions (genital warts, VIN, VaIN) and CIN of any grade and cervical cancers (Protocol 013, FUTURE I), HPV 16- or 18-related CIN 2/3 and AIS and cervical cancers (Protocol 015, FUTURE II), HPV 6-, 11-, 16-, or 18-related persistent infection and disease (Protocol 007), and HPV 16-related persistent infection (Protocol 005). The primary analyses of efficacy, with respect to vaccine HPV types (HPV 6, 11, 16, and 18), were conducted in the per-protocol efficacy (PPE) population (i.e. all 3 vaccinations within 1 year of enrollment, no major protocol deviations and naïve to the relevant HPV type(s) prior to dose 1 and through 1 month Postdose 3 (Month 7)).

Efficacy results are presented for the combined analysis of study protocols. The efficacy for HPV 16/18 related CIN 2/3 or AIS is based on data from protocols 005 (16-related endpoints only), 007, 013, and 015. The efficacy for all other endpoints is based on protocols 007, 013, and 015. The median duration of follow-up for these studies was 4.0, 3.0, 3.0, and 3.0 years for Protocol 005, Protocol 007, Protocol 013, and Protocol 015, respectively. The median duration of follow-up for the combined protocols (005, 007, 013, and 015) was 3.6 years. Results of individual studies support the results from the combined analysis. Gardasil was efficacious against HPV disease caused by each of the four vaccine HPV types. At end of study, individuals enrolled in the two Phase-III studies (Protocol-013 and Protocol-015), were followed for up to 4 years (median 3.7 years).

Cervical Intraepithelial Neoplasia (CIN) Grade 2/3 (moderate to high-grade dysplasia) and adenocarcinoma in situ (AIS) were used in the clinical trials as a surrogate marker for cervical cancer.

In the long-term extension study of Protocol 015, 2,536 women 16-23 years old during vaccination with Gardasil in the base study were followed. In the PPE population no cases of HPV diseases (HPV types 6/11/16/18 related high grade CIN) were observed up to approximately 14 years (median follow-up of 11.9 years). In this study, a durable protection was statistically demonstrated to approximately 12 years.

Efficacy in women naïve to the relevant vaccine HPV type(s)

Efficacy was measured starting after the Month 7 visit. Overall, 73 % of women were naïve (PCR negative and seronegative) to all 4 HPV types at enrolment.

The efficacy results for relevant endpoints analysed at 2 years post-enrolment and at end of study (median duration of follow-up = 3.6 years) in the per-protocol population are presented in the Table 2.

In a supplemental analysis, the efficacy of Gardasil was evaluated against HPV 16/18-related CIN 3 and AIS.

Table 2: Analysis of efficacy of Gardasil against high grade cervical lesions in the PPE population

	Gardasil Number of cases / Number of individuals*	Placebo Number of cases / Number of individuals*	% Efficacy at 2 years (95 % CI)	Gardasil Number of cases / Number of individuals*	Placebo Number of cases / Number of individuals*	% Efficacy*** at end of study (95 % CI)
HPV 16/18-related CIN 2/3 or AIS	0 / 8487	53 / 8460	100.0 (92.9, 100.0)	2** / 8493	112 / 8464	98.2 (93.5, 99.8)
HPV 16/18-related CIN 3	0 / 8487	29 / 8460	100 (86.5, 100.0)	2** / 8493	64 / 8464	96.9 (88.4, 99.6)
HPV 16/18-related AIS	0 / 8487	6 / 8460	100 (14.8, 100.0)	0 / 8493	7 / 8464	100 (30.6, 100.0)

*Number of individuals with at least one follow-up visit after Month 7
**Based on virologic evidence, the first CIN 3 case in a patient chronically infected with HPV 52 is likely to be causally related to HPV 52. In only 1 of 11 specimens HPV 16 was found (at Month 32.5) and was not detected in tissue excised during LEEP (Loop Electro-Excision Procedure). In the second CIN 3 case observed in a patient infected with HPV 51 at Day 1 (in 2 of 9 specimens); HPV 16 was detected at a Month 51 biopsy (in 1 of 9 specimens) and HPV 56 was detected in 3 of 9 specimens at Month 52 in tissue excised during LEEP.
***Patients were followed for up to 4 years (median 3.6 years)
Note: Point estimates and confidence intervals are adjusted for person-time of follow-up.

At end of study and in the combined protocols,

- the efficacy of Gardasil against HPV 6-, 11-, 16-, 18-related CIN 1 was 95.9 % (95 % CI: 91.4, 98.4),
- the efficacy of Gardasil against HPV 6-, 11-, 16-, 18-related CIN (1, 2, 3) or AIS was 96.0 % (95 % CI: 92.3, 98.2),
- the efficacy of Gardasil against HPV 6-, 11-, 16-, 18-related VIN2/3 and VaIN 2/3 was 100 % (95 % CI: 67.2, 100) and 100 % (95 % CI: 55.4, 100), respectively,
- the efficacy of Gardasil against HPV 6-, 11-, 16-, 18-related genital warts was 99.0 % (95 % CI: 96.2, 99.9).

In Protocol 012 the efficacy of Gardasil against the 6 month definition of persistent infection [samples positive on two or more consecutive visits 6 months apart (±1 month) or longer] related to HPV 16 was 98.7 % (95 % CI: 95.1, 99.8) and 100.0 % (95 % CI: 93.2, 100.0) for HPV 18 respectively, after a follow-up of up to 4 years (mean of 3.6 years). For the 12 month definition of persistent infection, efficacy against HPV 16 was 100.0 % (95 % CI: 93.9, 100.0) and 100.0 % (95 % CI: 79.9, 100.0) for HPV 18 respectively.

Efficacy in women with evidence of HPV 6, 11, 16, or 18 infection or disease at day 1

There was no evidence of protection from disease caused by vaccine HPV types for which women were PCR positive at day 1. Women 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.

Efficacy in women with and without prior infection or disease due to HPV 6, 11, 16, or 18

The modified intention to treat (ITT) population included women regardless of baseline HPV status at Day 1, who received at least one vaccination and in whom case counting started at 1 month Postdose 1. This population approximates to the general population of women with respect to prevalence of HPV infection or disease at enrolment. The results are summarised in Table 3.

Table 3: Efficacy of Gardasil in high grade cervical lesions in the modified ITT-population including women regardless of baseline HPV status

	Gardasil Number of cases / Number of individuals*	**Placebo** Number of cases / Number of individuals*	**% Efficacy** at 2 years (95 % CI)**	**Gardasil** Number of cases / Number of individuals*	**Placebo** Number of cases / Number of individuals*	**% Efficacy** at end of study (95 % CI)**
HPV 16- or HPV 18-related CIN 2/3 or AIS	122/9831	201/9896	39.0 (23.3, 51.7)	146/9836	303/9904	51.8 (41.1, 60.7)
HPV 16/18-related CIN 3	83/9831	127/9896	34.3 (12.7, 50.8)	103/9836	191/9904	46.0 (31.0, 57.9)
HPV 16/18-related AIS	5/9831	11/9896	54.3 (<0, 87.6)	6/9836	15/9904	60.0 (<0, 87.3)

*Number of individuals with at least one follow-up visit after 30 days after Day 1

**Percent efficacy is calculated from the combined protocols. The efficacy for HPV 16/18 related CIN 2/3 or AIS is based on data from protocols 005 (16-related endpoints only), 007, 013, and 015. Patients were followed for up to 4 years (median 3.6 years).

Note: point estimates and confidence intervals are adjusted for person-time of follow-up.

Efficacy against HPV 6-, 11-, 16-, 18-related VIN 2/3 was 73.3 % (95 % CI: 40.3, 89.4), against HPV 6-, 11-, 16-, 18-related VaIN 2/3 was 85.7 % (95 % CI: 37.6, 98.4), and against HPV 6-, 11-, 16-, 18-related genital warts was 80.3 % (95 % CI: 73.9, 85.3) in the combined protocols at end of study.

Overall 12 % of the combined study population had an abnormal Pap test suggestive of CIN at Day 1. Among women with an abnormal Pap test at Day 1 who were naïve to the relevant vaccine HPV types at Day 1, efficacy of the vaccine remained high. Among women with an abnormal Pap test at Day 1 who were already infected with the relevant vaccine HPV types at Day 1, no vaccine efficacy was observed.

Protection Against the Overall Burden of Cervical HPV disease in 16- Through 26-Year-Old Women

The impact of Gardasil against the overall risk for cervical, HPV disease (i.e., disease caused by any HPV type) was evaluated starting 30 days after the first dose in 17,599 individuals enrolled in the two Phase III efficacy trials (Protocols 013 and 015). Among women who were naïve to 14 common HPV types and had a negative Pap test at Day 1, administration of Gardasil reduced the incidence of CIN 2/3 or AIS caused by vaccine- or non-vaccine HPV types by 42.7 % (95 % CI: 23.7, 57.3) and of genital warts by 82.8 % (95 % CI: 74.3, 88.8) at end of study.

In the modified ITT population, the benefit of the vaccine with respect to the overall incidence of CIN 2/3 or AIS (caused by any HPV type) and of genital warts was much lower, with a reduction of 18.4 % (95 % CI: 7.0, 28.4) and 62.5 % (95 % CI: 54.0, 69.5), respectively, as Gardasil does not impact the course of infections or disease that are present at vaccination onset.

Impact on Definitive Cervical Therapy Procedures

The impact of Gardasil on rates of Definitive Cervical Therapy Procedures regardless of causal HPV types was evaluated in 18,150 individuals enrolled in Protocol 007, Protocols 013 and 015. In the HPV naïve population (naïve to 14 common HPV types and had a negative Pap test at Day 1), Gardasil reduced the proportion of women who experienced a definitive cervical therapy procedure (Loop Electro-Excision Procedure or Cold-Knife Conization) by 41.9 % (95 % CI: 27.7, 53.5) at end of study. In the ITT population the corresponding reduction was 23.9 % (95 % CI: 15.2, 31.7).

Cross-protective efficacy

The efficacy of Gardasil against CIN (any grade) and CIN 2/3 or AIS caused by 10 non-vaccine HPV types (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) structurally related to HPV 16 or HPV 18 was evaluated in the combined Phase III efficacy database (N = 17,599) after a median follow-up of 3.7 years (at end of study). Efficacy against disease endpoints caused by pre-specified combinations of non-vaccine HPV types was measured. The studies were not powered to assess efficacy against disease caused by individual HPV types.

The primary analysis was done in type-specific populations that required women to be negative for the type being analysed, but who could be positive for other HPV types (96 % of the overall population). The primary time point analysis after 3 years did not reach statistical significance for all pre-specified endpoints. The final end-of-study results for the combined incidence of CIN 2/3 or AIS in this population after a median follow-up of 3.7 years are shown in Table 4. For composite endpoints, statistically significant efficacy against disease was demonstrated against HPV types phylogenetically related to HPV 16 (primarily HPV 31) whereas no statistically significant efficacy was observed for HPV types phylogenetically related to HPV 18 (including HPV 45). For the 10 individual HPV types, statistical significance was only reached for HPV 31.

Table 4: Results for CIN 2/3 or AIS in Type-Specific HPV-Naïve Individuals† (end of study results)

Naïve to ≥ 1 HPV Type				
Composite Endpoint	Gardasil cases	Placebo cases	% Efficacy	95 % CI
(HPV 31/45)‡	34	60	43.2 %	12.1, 63.9
(HPV 31/33/45/52/58)§	111	150	25.8 %	4.6, 42.5
10 non-vaccine HPV Types‖	162	211	23.0 %	5.1, 37.7
HPV-16 related types (A9 species)	111	157	29.1 %	9.1, 44.9
HPV 31	23	52	55.6 %	26.2, 74.1†
HPV 33	29	36	19.1 %	<0, 52.1†
HPV 35	13	15	13.0 %	<0, 61.9†
HPV 52	44	52	14.7 %	<0, 44.2†
HPV 58	24	35	31.5 %	<0, 61.0†
HPV-18 related types (A7 species)	34	46	25.9 %	<0, 53.9
HPV 39	15	24	37.5 %	<0, 69.5†
HPV 45	11	11	0.0 %	<0, 60.7†
HPV 59	9	15	39.9 %	<0, 76.8†
A5 species (HPV 51)	34	41	16.3 %	<0, 48.5†
A6 species (HPV 56)	34	30	-13.7 %	<0, 32.5†

† The studies were not powered to assess efficacy against disease caused by individual HPV types.
‡ Efficacy was based on reductions in HPV 31-related CIN 2/3 or AIS
§ Efficacy was based on reductions in HPV 31-, 33-, 52-, and 58-related CIN 2/3 or AIS
‖ Includes assay-identified non-vaccine HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.

Efficacy in women 24 through 45 years

The efficacy of Gardasil in 24- through 45 year-old women was assessed in 1 placebo-controlled, double-blind, randomised Phase III clinical study (Protocol 019, FUTURE III) including a total of 3,817 women, who were enrolled and vaccinated without pre-screening for the presence of HPV infection.

The primary efficacy endpoints included the combined incidence of HPV 6-, 11-, 16- or 18-related and the combined incidence of HPV 16- or HPV 18-related persistent infection (6 month definition), genital warts, vulvar and vaginal lesions, CIN of any grade, AIS, and cervical cancers. The median duration of follow-up for this study was 4.0 years.

In the long-term extension study of Protocol 019, 685 women 24-45 years old during vaccination with Gardasil in the base study were followed. In the PPE population, no cases of HPV diseases (HPV types 6/11/16/18 related CIN any grade and Genital Warts) were observed through 10.1 years (median follow-up of 8.7 years).

Efficacy in women naïve to the relevant vaccine HPV type(s)

The primary analyses of efficacy were conducted in the per-protocol efficacy (PPE) population (i.e. all 3 vaccinations within 1 year of enrolment, no major protocol deviations and naïve to the relevant HPV type(s) prior to dose 1 and through 1 month Postdose 3 (Month 7)). Efficacy was measured starting after the Month 7 visit. Overall, 67 % of individuals were naïve (PCR negative and seronegative) to all 4 HPV types at enrolment.

The efficacy of Gardasil against the combined incidence of HPV 6-, 11-, 16-, or 18-related persistent infection, genital warts, vulvar and vaginal lesions, CIN of any grade, AIS, and cervical cancers was 88.7 % (95 % CI: 78.1, 94.8).

The efficacy of Gardasil against the combined incidence of HPV 16- or 18-related persistent infection, genital warts, vulvar and vaginal lesions, CIN of any grade, AIS, and cervical cancers was 84.7 % (95 % CI: 67.5, 93.7).

Efficacy in women with and without prior infection or disease due to HPV 6, 11, 16, or 18

The Full Analysis Set population (also known as the ITT population) included women regardless of baseline HPV status at Day 1, who received at least one vaccination and in whom case counting started at Day 1. This population approximates to the general population of women with respect to prevalence of HPV infection or disease at enrolment.

The efficacy of Gardasil against the combined incidence of HPV 6-, 11-, 16-, or 18-related persistent infection, genital warts, vulvar and vaginal lesions, CIN of any grade, AIS, and cervical cancers was 47.2 % (95 % CI: 33.5, 58.2).

The efficacy of Gardasil against the combined incidence of HPV 16- or 18-related persistent infection, genital warts, vulvar and vaginal lesions, CIN of any grade, AIS, and cervical cancers was 41.6 % (95 % CI: 24.3, 55.2).

Efficacy in women (16 to 45 years) with evidence of a prior infection with a vaccine HPV type (seropositive) that was no longer detectable at vaccination onset (PCR negative)

In post hoc analyses of individuals (who received at least one vaccination) with evidence of a prior infection with a vaccine HPV type (seropositive) no longer detectable (PCR negative) at vaccination onset, the efficacy of Gardasil to prevent conditions due to the recurrence of the same HPV type was 100 % (95 % CI: 62.8, 100.0; 0 vs. 12 cases [n = 2572 from pooled studies in young women]) against HPV 6-, 11-, 16-, and 18-related CIN 2/3, VIN 2/3, VaIN 2/3, and genital warts in women 16 to 26 years. Efficacy was 68.2 % (95 % CI: 17.9, 89.5; 6 vs. 20 cases [n = 832 from studies in young and

adult women combined]) against HPV 16- and 18-related persistent infection in women 16 to 45 years.

Efficacy in men 16 through 26 years

Efficacy was evaluated against HPV 6-, 11-, 16-, 18-related external genital warts, penile/perineal/perianal intraepithelial neoplasia (PIN) grades 1/2/3, and persistent infection.

The efficacy of Gardasil in 16- through 26 year-old men was assessed in 1 placebo-controlled, double-blind, randomised Phase III clinical study (Protocol 020) including a total of 4,055 men who were enrolled and vaccinated without pre-screening for the presence of HPV infection. The median duration of follow-up was 2.9 years.

In a subset of 598 men (GARDASIL = 299; placebo = 299) in Protocol 020 who self-identified as having sex with men (MSM) efficacy against anal intraepithelial neoplasia (AIN grades 1/2/3) and anal cancer, and intra-anal persistent infection was evaluated.

MSM are at higher risk of anal HPV infection compared to the general population; the absolute benefit of vaccination in terms of prevention of anal cancer in the general population is expected to be very low.

HIV infection was an exclusion criterion (see section 4.4).

Efficacy in Men naïve to the relevant vaccine HPV types

The primary analyses of efficacy, with respect to vaccine HPV types (HPV 6, 11, 16, 18), were conducted in the per-protocol efficacy (PPE) population (i.e. all 3 vaccinations within 1 year of enrolment, no major protocol deviations and naïve to the relevant HPV type(s) prior to dose 1 and through 1 month Postdose 3 (Month 7)). Efficacy was measured starting after the Month 7 visit. Overall, 83 % of men (87 % of heterosexual subjects and 61 % of MSM subjects) were naïve (PCR negative and seronegative) to all 4 HPV types at enrolment.

Anal Intraepithelial Neoplasia (AIN) Grade 2/3 (moderate to high-grade dysplasia) was used in the clinical trials as a surrogate marker for anal cancer.

The efficacy results for relevant endpoints analysed at end of study (median duration of follow-up 2.4 years) in the per-protocol population are presented in the Table 5. Efficacy against PIN grades 1/2/3 was not demonstrated.

Table 5: Efficacy of Gardasil against external genital lesions in the PPE population of 16-26 year old men*

Endpoint	Gardasil		Placebo		% Efficacy (95 %CI)
	N	Number of cases	N	Number of cases	
HPV 6/11/16/18-related external genital lesions					
External genital lesions	1394	3	1404	32	90.6 (70.1. 98.2)
Genital warts	1394	3	1404	28	89.3 (65.3, 97.9)
PIN1/2/3	1394	0	1404	4	100.0 (-52.1, 100.0)

*The individuals in the PPE population received all 3 vaccinations within 1 year of enrolment, had no major protocol deviations, and were naïve to the relevant HPV type(s) prior to dose 1 and through 1 month Postdose 3 (Month 7).

At end of study analysis for anal lesions in the MSM population (median duration of follow-up was 2.15 years), the preventive effect against HPV 6-, 11-, 16-, 18-related AIN 2/3 was 74.9 % (95 % CI: 8.8, 95.4; 3/194 versus 13/208) and against HPV 16- or 18-related AIN 2/3 86.6 % (95 % CI: 0.0, 99.7; 1/194 versus 8/208).

The duration of protection against anal cancer is currently unknown. In the long-term extension study

of Protocol 020, 917 men 16-26 years old during vaccination with Gardasil in the base study were followed. In the PPE population, no cases of HPV types 6/11 related genital warts, HPV 6/11/16/18 external genital lesions or HPV 6/11/16/18 high grade AIN in MSM were observed through 11.5 years (median follow-up of 9.5 years).

Efficacy in men with or without prior infection or disease due to HPV 6, 11, 16, or 18

The Full Analysis Set population included men regardless of baseline HPV status at Day 1, who received at least one vaccination and in whom case counting started at Day 1. This population approximates to the general population of men with respect to prevalence of HPV infection or disease at enrolment.

The efficacy of GARDASIL against HPV 6-, 11-, 16-, 18-related external genital warts was 68.1 % (95 % CI: 48.8, 79.3).

The efficacy of GARDASIL against HPV 6-, 11-, 16-, 18-related AIN 2/3 and HPV 16- or 18-related AIN 2/3, in the MSM substudy, was 54.2 % (95 % CI: 18.0, 75.3; 18/275 versus 39/276) and 57.5 % (95 % CI: -1.8, 83.9; 8/275 versus 19/276 cases), respectively.

Protection Against the Overall Burden of HPV disease in 16- Through 26-Year-Old Men

The impact of Gardasil against the overall risk for external genital lesions was evaluated after the first dose in 2,545 individuals enrolled in the Phase III efficacy trial (Protocol 020). Among men who were naïve to 14 common HPV types, administration of Gardasil reduced the incidence of external genital lesions caused by vaccine- or non-vaccine HPV types by 81.5 % (95 % CI: 58.0, 93.0). In the Full Analysis Set (FAS) population, the benefit of the vaccine with respect to the overall incidence of EGL was lower, with a reduction of 59.3 % (95 % CI: 40.0, 72.9), as Gardasil does not impact the course of infections or disease that are present at vaccination onset.

Impact on Biopsy and Definitive Therapy Procedures

The impact of Gardasil on rates of biopsy and treatment of EGL regardless of causal HPV types was evaluated in 2,545 individuals enrolled in Protocol 020. In the HPV naïve population (naïve to 14 common HPV types), Gardasil reduced the proportion of men who had a biopsy by 54.2 % (95 % CI: 28.3, 71.4) and who were treated by 47.7 % (95 % CI: 18.4, 67.1) at end of study. In the FAS population, the corresponding reduction was 45.7 % (95 % CI: 29.0, 58.7) and 38.1 % (95 % CI: 19.4, 52.6).

Immunogenicity

Assays to Measure Immune Response

No minimum antibody level associated with protection has been identified for HPV vaccines.

The immunogenicity of Gardasil was assessed in 20,132 (Gardasil n = 10,723; placebo n = 9,409) girls and women 9 to 26 years of age, 5,417 (Gardasil n = 3,109; placebo n = 2,308) boys and men 9 to 26 years of age and 3,819 women 24 to 45 years of age (Gardasil n = 1,911, placebo n = 1,908).

Type-specific immunoassays, competitive Luminex-based immunoassay (cLIA), with type-specific standards were used to assess immunogenicity to each vaccine type. This assay measures antibodies against a single neutralizing epitope for each individual HPV type.

Immune Responses to Gardasil at 1 month post dose 3

In the clinical studies in women 16 to 26 years of age, 99.8 %, 99.8 %, 99.8 %, and 99.5 % of individuals who received Gardasil became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18-seropositive, respectively, by 1 month Postdose 3. In the clinical study in women 24 to 45 years,

98.4 %, 98.1 %, 98.8 %, and 97.4 % of individuals who received Gardasil became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive, respectively, by 1 month Postdose 3. In the clinical study in men 16 to 26 years, 98.9 %, 99.2 %, 98.8 %, and 97.4 % of individuals who received Gardasil became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive, respectively, by 1 month Postdose 3. Gardasil induced high anti-HPV Geometric Mean Titres (GMTs) 1 month Postdose 3 in all age groups tested.

As expected for women 24 to 45 years of age (Protocol 019), the observed antibody titres were lower than that seen in women 16 to 26 years.

Anti-HPV levels in placebo individuals who had cleared an HPV infection (seropositive and PCR negative) were substantially lower than those induced by the vaccine. Furthermore, anti-HPV levels (GMTs) in vaccinated individuals remained at or above serostatus cut-off during the long-term follow-up of the Phase III studies (see below under *Persistence of Immune Response of Gardasil*).

Bridging the Efficacy of Gardasil from Women to Girls

A clinical study (Protocol 016) compared the immunogenicity of Gardasil in 10- to 15-year-old girls to those in 16- to 23 year old women. In the vaccine group, 99.1 to 100 % became seropositive to all vaccine serotypes by 1 month Postdose 3.

Table 6 compares the 1 month Postdose 3 anti-HPV 6, 11, 16, and 18 GMTs in 9- to 15 year-old girls with those in 16- to 26-year old women.

Table 6: Immunogenicity bridging between 9- to 15-year-old girls and 16- to 26-year-old women (per-protocol population) based on titres as measured by cLIA

	9- to 15-Year-Old Girls (Protocols 016 and 018)		**16- to 26-Year-Old Women (Protocols 013 and 015)**	
	n	**GMT (95 % CI)**	**n**	**GMT (95 % CI)**
HPV 6	915	929 (874, 987)	2631	543 (526, 560)
HPV 11	915	1303 (1223, 1388)	2655	762 (735, 789)
HPV 16	913	4909 (4548, 5300)	2570	2294 (2185, 2408)
HPV 18	920	1040 (965, 1120)	2796	462 (444, 480)

GMT- Geometric mean titre in mMU/ml (mMU = milli-Merck units)

Anti-HPV responses at Month 7 among 9- to 15-year-old girls were non-inferior to anti-HPV responses in 16- to 26-year-old women for whom efficacy was established in the Phase III studies. Immunogenicity was related to age and Month 7 anti-HPV levels were significantly higher in younger individuals below 12 years of age than in those above that age.

On the basis of this immunogenicity bridging, the efficacy of Gardasil in 9- to 15-year-old girls is inferred.

In the long-term extension study of Protocol 018, 369 girls 9-15 years old during vaccination with Gardasil in the base study were followed. In the PPE population, no cases of HPV diseases (HPV types 6/11/16/18 related CIN any grade and Genital Warts) were observed through 10.7 years (median follow-up of 10.0 years).

Bridging the Efficacy of Gardasil from Men to Boys

Three clinical studies (Protocols 016, 018 and 020) were used to compare the immunogenicity of Gardasil in 9- to 15-year-old boys to 16- to 26-year-old men. In the vaccine group, 97.4 to 99.9 % became seropositive to all vaccine serotypes by 1 month Postdose 3.

Table 7 compares the 1 month Postdose 3 anti-HPV 6, 11, 16, and 18 GMTs in 9- to 15-year-old boys with those in 16- to 26-year-old men.

Table 7: Immunogenicity bridging between 9- to 15-year-old boys and 16- to 26-year-old men (per-protocol population) based on titres as measured by cLIA

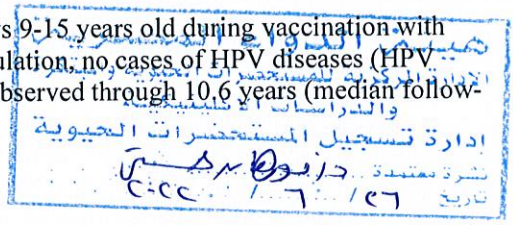
	9- to 15-Year-Old Boys		16- to 26-Year-Old Men	
	n	GMT (95 % CI)	n	GMT (95 % CI)
HPV 6	884	1038 (964, 1117)	1093	448 (419, 479)
HPV 11	885	1387 (1299, 1481)	1093	624 (588, 662)
HPV 16	882	6057 (5601, 6549)	1136	2403 (2243, 2575)
HPV 18	887	1357 (1249, 1475)	1175	403 (375, 433)

GMT- Geometric mean titre in mMU/ml (mMU = milli-Merck units)

Anti-HPV responses at Month 7 among 9- to 15-year-old boys were non-inferior to anti-HPV responses in 16- to 26-year-old men for whom efficacy was established in the Phase III studies. Immunogenicity was related to age and Month 7 anti-HPV levels were significantly higher in younger individuals.

On the basis of this immunogenicity bridging, the efficacy of Gardasil in 9- to 15-year-old boys is inferred.

In the long-term extension study of Protocol 018, 326 boys 9-15 years old during vaccination with Gardasil in the base study were followed. In the PPE population, no cases of HPV diseases (HPV types 6/11/16/18 related External Genital Lesions) were observed through 10.6 years (median follow-up of 9.9 years).



Persistence of Immune Response of Gardasil

A subset of individuals enrolled in the Phase III studies was followed up for a long-term period for safety, immunogenicity and effectiveness. Total IgG Luminex Immunoassay (IgG LIA) was used to assess the persistence of immune response in addition to cLIA.

In all populations (women 9 – 45 years, men 9 – 26 years), peak anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 GMTs cLIA were observed at Month 7. Afterwards, the GMTs declined through Month 24 - 48 and then generally stabilised. The duration of immunity following a 3-dose series has been observed for up to 14 years post-vaccination.

Girls and boys vaccinated with Gardasil at 9-15 years of age in Protocol 018 base study were followed up in an extension study. Depending on HPV type, 60-96 % and 78-98 % of subjects were seropositive by cLIA and IgG LIA respectively 10 years after vaccination (see Table 8).

Table 8: Long-term immunogenicity data (per-protocol population) based on percentage of seropositive subjects as measured by cLIA and IgG LIA (Protocol 018) at 10 years, in girls and boys 9-15 years of age

	cLIA		IgG LIA	
	n	% of seropositive subjects	n	% of seropositive subjects
HPV 6	409	89 %	430	93 %
HPV 11	409	89 %	430	90 %
HPV 16	403	96 %	426	98 %
HPV 18	408	60 %	429	78 %

Women vaccinated with Gardasil at 16-23 years of age in Protocol 015 base were followed up in an extension study. Fourteen years after vaccination, 91 %, 91 %, 98 % and 52 % were anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 seropositive in the cLIA, respectively, and 98 %, 98 %, 100 % and 94 % were anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 seropositive in the IgG LIA,

respectively.

Women vaccinated with Gardasil at 24-45 years of age in Protocol 019 base study were followed up in an extension study. Ten years after vaccination, 79 %, 85 %, 94 %, and 36 % were anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 seropositive in the cLIA, respectively, and 86 %, 79 %, 100 % and 83 % were anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 seropositive in the IgG LIA, respectively.

Men vaccinated with Gardasil at 16-26 years of age in Protocol 020 base study were followed up in an extension study. Ten years after vaccination, 79 %, 80 %, 95 % and 40 % were anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 seropositive in the cLIA, respectively, and 92 %, 92 %, 100 % and 92 % were anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 seropositive in the IgG LIA, respectively.

In these studies, individuals who were seronegative for anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 in the cLIA were still protected against clinical disease after a follow-up of 14 years for 16-23 year-old women, 10 years for 24-45 year-old women, and 10 years for 16-26 year-old men.

Evidence of Anamnestic (Immune Memory) Response

Evidence of an anamnestic response was seen in vaccinated women who were seropositive to relevant HPV type(s) prior to vaccination. In addition, a subset of vaccinated women who received a challenge dose of Gardasil 5 years after the onset of vaccination, exhibited a rapid and strong anamnestic response that exceeded the anti-HPV GMTs observed 1 month Postdose 3.

HIV infected subjects

An academic study documenting safety and immunogenicity of Gardasil has been performed in 126 HIV infected subjects aged from 7-12 years (of which 96 received Gardasil). Seroconversion to all four antigens occurred in more than ninety-six percent of the subjects. The GMTs were somewhat lower than reported in non-HIV infected subjects of the same age in other studies. The clinical relevance of the lower response is unknown. The safety profile was similar to non-HIV infected subjects in other studies. The CD4 % or plasma HIV RNA was not affected by vaccination.

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 (3 doses, 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.

Post hoc analyses were conducted at 120-month follow-up in girls (2 doses, n = 35; 3 doses, n = 38) and women (3 doses, n = 30). The GMT ratios (girls who received 2 doses / women who received 3 doses) ranged from 0.99 to 2.02 for all 4 HPV types. The GMT ratios (girls who received 2 doses / girls who received 3 doses) ranged from 0.72 to 1.21 for all 4 HPV types. The lower bound of the

95 % CI of all the GMT ratios remained > 0.5 through month 120 (except for HPV 18 in girls who received 2 doses / girls who received 3 doses).

Seropositivity rates in girls and women were > 95 % for HPV 6, 11, and 16, and seropositivity rates for HPV 18 were > 80 % in girls who received.2 doses, > 90 % in girls who received 3 doses, and > 60 % in women who received 3 doses, in the cLIA.

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.

GARDASIL administered to male rats at the full human dose (120 mcg total protein) had no effects on reproductive performance including fertility, sperm count, and sperm motility, and there were no vaccine-related gross or histomorphologic changes on the testes and no effects on testes weights.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Histidine
Polysorbate 80
Borax
Water for injections

For adjuvant, see section 2.

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Gardasil suspension for injection:

Store in a refrigerator (2°C - 8°C).

Do not freeze. Keep the vial in the outer carton in order to protect from light.

Gardasil should be administered as soon as possible after being removed from the refrigerator. GARDASIL can be out of refrigeration (at temperatures at or below 25°C), for a total time of not more

than 72 hours.

6.5 Nature and contents of container

Gardasil suspension for injection:

0.5 ml suspension in a vial (glass) with stopper (FluroTec-coated or Teflon-coated chlorobutyl elastomer) and flip-off plastic cap (aluminium crimp band) in a pack size of 1, 10 or 20.

Not all pack sizes are marketed.

6.6 Special precautions for disposal and other handling

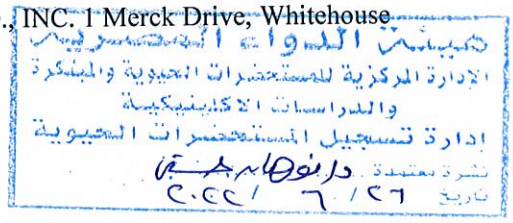
Gardasil suspension for injection:

- Gardasil may appear as a clear liquid with a white precipitate prior to agitation.
- Shake well before use to make a suspension. After thorough agitation, it is a white, cloudy liquid.
- Inspect the suspension visually for particulate matter and discolouration prior to administration. Discard the vaccine if particulates are present and/or if it appears discoloured.
- Withdraw the 0.5 ml dose of vaccine from the single-dose vial using a sterile needle and syringe.
- Inject immediately using the intramuscular (IM) route, preferably in the deltoid area of the upper arm or in the higher anterolateral area of the thigh.
- The vaccine should be used as supplied. The full recommended dose of the vaccine should be used.

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

7. MARKETING AUTHORISATION HOLDER:

Merck Sharp & Dohme Corp., a subsidiary of MERCK & CO., INC. 1 Merck Drive, Whitehouse Station, NJ 08889, USA



8. Released by:

Merck Sharp & Dohme B.V. – Waarderweg 39,
2031 BN Haarlem - The Netherlands

9. DATE OF REVISION OF THE TEXT

This leaflet was last revised in January 2022

(THIS IS A MEDICAMENT)
-Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
-Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament.
-The doctor and the pharmacist are experts in medicine, its benefits and risks.
-Do not by yourself interrupt the period of treatment prescribed for you.
-Do not repeat the same prescription without consulting your doctor.
Keep medicament out of reach of children
Council of Arab Health Ministers
Union of Arab Pharmacists