GARDASIL™, suspension for injection.

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

I. THERAPEUTIC CLASS

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

II. 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 sulphate adjuvant (225 micrograms Al).

List of excipients

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

III. PHARMACEUTICAL FORM

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.

IV. INDICATIONS

Gardasil is a vaccine indicated in girls and women 9 through 45 years of age for the prevention of cervical cancer, low grade and high grade cervical, vulvar and vaginal dysplasia; and external genital warts (condyloma acuminata) causally related to Human Papillomavirus (HPV) types 6, 11, 16 and 18.

Gardasil is indicated in boys and men 9 through 26 years of age for the prevention of external genital lesions including genital warts (condyloma acuminata), anal intraepithelial neoplasia (AIN 1/2/3), and infection caused by HPV types 6, 11, 16, and 18.

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

V. DOSAGE AND ADMINISTRATION

The primary vaccination series consists of 3 separate 0.5 ml doses administered according to the following schedule: 0, 2, 6 months.

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.

Alternatively, in individuals 9 through 13 years of age, Gardasil can be administered according to a 2-dose (0, 6 months) schedule.

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

The need for a booster dose has not been established.

Paediatric population: There is no experience with the use of Gardasil in children below 9 years of age (see section Pharmacodynamic properties).

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 Special precaution for disposal and other handling).

VI. CONTRAINDICATION

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 immunization.

VII. SPECIAL WARNINGS AND PRECAUTIONS

The decision to vaccinate an individual woman should take into account her risk for previous HPV exposure and her 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) may follow any vaccination, especially in adolescents and young adults. Syncope, sometimes associated with falling, has occurred after vaccination with Gardasil (See Undesirable Effects). Therefore, vaccines should be carefully observed for approximately 15 minutes after administration of Gardasil.

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. 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, anal intraepithelial neoplasia, 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 women infected with that HPV type at the time of vaccination (see section Pharmacodynamic properties).

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.

There are no data on the use of Gardasil in subjects with impaired immune responsiveness. Individuals with impaired immune responsiveness, whether due to the use of potent immunosuppressive therapy, a genetic defect, Human Immunodeficiency Virus (HIV) infection, 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.

The duration of protection is currently unknown. Sustained protective efficacy has been observed for 4.5 years after completion of the 3-dose series. Longer term follow-up studies are ongoing (see section Pharmacodynamic properties).

There are no safety, immunogenicity or efficacy data to support interchangeability of Gardasil with other HPV vaccines.

VIII. 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 Undesirable Effects).

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.

IX. PREGNANCY AND LACTATION

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.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/ foetal development, parturition or postnatal development (see section Preclinical safety data).

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, therefore, be postponed until after completion of pregnancy.

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

Therefore, Gardasil can be given to breastfeeding women.

X. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

XI. UNDESIRABLE EFFECTS

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 individual (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 enrollment) who received Gardasil and 7,995 individuals who received placebo.

The following vaccine-related adverse reactions 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, <1/10); Uncommon (≥ 1/1,000, <1/100); Rare (≥ 1/10,000, <1/1,000); Very Rare (<1/10,000), including isolated reports]

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.

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

Nervous system disorders
Common: headache

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

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

Most injection-site reactions were mild to moderate

In addition, in clinical trials that included the entire study population, 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 disorder:
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.

Post Marketing Experience

Post Marketing adverse events have been spontaneously reported for Gardasil and are not listed above.

Because these events were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish, for all events, a causal relationship to vaccine exposure.

Infections and infestations: cellulitis

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

Immune system disorders: hypersensitivity reactions including anaphylactic/anaphylactoid reactions.

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

Gastrointestinal disorders: nausea, vomiting.

Musculoskeletal and connective tissue disorders: arthralgia, myalgia.

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

XII. 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.

XIII. PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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; 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, 70% of HPV-related high grade anal intraepithelial neoplasia (AIN 2/3), HPV 6 and 11 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 indication is based on the demonstration of efficacy of Gardasil in females 16 to 45 years of age and and in males 16 to 26 years of age 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, randomized 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).

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, 2536 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)

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

The efficacy results for relevant endpoints analysed at 2 years post-enrollment and at end of study (median duration of follow-up = 3.6 years) in the per-protocol population are presented in the Table 1.

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

Table 1: Analysis of efficacy of Gardasil against high grade cervical lesions in the PPE population

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

*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 enrollment. The results are summarised in Table 2.

Table 2: Efficacy of Gardasil in high grade cervical lesions in the modified ITT-population including women regardless of baseline HPV status

	Gardasil	Placebo	%	Gardasil	Placebo	%
	Number of cases	Number of cases	Efficacy** at 2 years (95% CI)	Number of cases	Number of cases	Efficacy** at end of study (95% CI)
	Number of individuals*	Number of individuals*		Number of individuals*	Number of individuals*	
HPV 16- or HPV 18-related CIN 2/3 or AIS	122 / 9831	210 / 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 analyzed, 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 3. 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 3: 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, randomized 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, one case of HPV 16/18 related CIN 2 or worse was observed day 1 up to year 4 and no cases of HPV diseases (HPV types 6/11/16/18 related CIN any grade and Genital Warts) were observed in year 4 until year 10.

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 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 was measured starting after the Month 7 visit. Overall, 67% of individuals were naïve (PCR negative and seronegative) to all 4 HPV types at enrollment.

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 enrollment.

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.

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

The efficacy of Gardasil in 16- through 26-year-old men was assessed in 1 placebo-controlled, double-blind, randomized 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.

Efficacy was evaluated using the following endpoints: external genital warts; penile/perineal/perianal intraepithelial neoplasia (PIN) grades 1/2/3 or penile/perineal/perianal cancer; and persistent infection. High grade PIN is associated with certain types of penile/perineal/perianal cancers. Persistent infection is a predictor of clinical disease.

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

Gardasil was efficacious in reducing the incidence of external genital lesions (Condyloma and PIN grades 1/2/3) and persistent infection related to vaccine HPV types 6, 11, 16, or 18 in those who were PCR negative and seronegative at baseline (Table 4).

Table 4: Analysis of Efficacy of Gardasil in the PPE Population of 16- Through 26-Year-Old Boys and Men for Vaccine HPV Types

Endpoint	Gardasil		AAHS Control		% Efficacy (95% CI)
	N	Number of cases	N	Number of cases	
External Genital Lesion HPV 6-, 11-, 16- or 18- related					
External Genital Lesions	1394	3	1404	32	90.6 (70.1, 98.2)
Condyloma	1394	3	1404	28	89.3 (65.3, 97.9)

PIN 1/2/3	1394	0	1404	4	100 (<0.0, 100.0)
Persistent Infection					
HPV 6, 11, 16, or 18-related	1390	21	1402	140	85.5 (77.0, 91.3)
HPV 6-related	1238	5	1242	50	90.1 (75.3, 96.9)
HPV 11-related	1238	1	1242	18	94.4 (64.7, 99.9)
HPV 16-related	1288	13	1268	61	79.3 (61.9, 89.6)
HPV 18-related	1327	2	1350	33	93.9 (76.3, 99.3)

N= Number of individuals with at least 1 follow-up visit after Months 7

CI = Confidence Interval

AAHS Control = Amorphus Aluminum Hydroxyphosphate Sulfate

Prophylactic Efficacy – Anal Disease Caused by HPV Types 6, 11, 16, and 18 in Boys and Men 16 Through 26 Years of Age in the MSM Sub-study

A sub-study of Protocol 020 evaluated the efficacy of Gardasil against anal disease (anal intraepithelial neoplasia and anal cancer) in a population of 598 (Gardasil = 299; placebo = 299) men who self-identified as having sex with men (MSM population). The median duration of follow-up was 2.9 years. In this sub-study, cases of anal intraepithelial neoplasia (AIN 2/3) were the efficacy endpoints used to assess prevention of HPV-related anal cancer. The primary analyses of efficacy were conducted in the PPE-population of Protocol 020.

Gardasil was efficacious in reducing the incidence of anal intraepithelial neoplasia (AIN) grades 1 (both condyloma and non-acuminate), 2, and 3 related to vaccine HPV types 6, 11, 16, and 18 in those boys and men who were PCR negative and seronegative at baseline (Table 5).

Table 5 Analysis of Efficacy of Gardasil for Anal Disease in the PPE Population of 16- Through 26-Year-Old Boys and Men in the MSM Sub-study for Vaccine HPV Types

HPV 6, 11, 16, or 18- related Endpoint	Gardasil		AAHS Control		% Efficacy (95% CI)
	N	Number of cases	N	Number of cases	
AIN 1/2/3	194	5	208	24	77.5 (39.6, 93.3)
AIN 2/3	194	3	208	13	74.9 (8.8, 95.4)
AIN 1	194	4	208	16	73.0 (16.3, 93.4)

N = Number of individuals with at least 1 follow-up visit after Month 7

CI = Confidence Interval

AAHS Control = Amorphous Aluminum Hydroxyphosphate Sulfate"

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 related external genital lesions or HPV 6/11/16/18 related high grade AIN in MSM were observed through 11.5 years (median follow-up of 9.5 years).

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 in Clinical Studies*).

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 and 326 boys 9-15 years old during vaccination with Gardasil in the base study were followed. In the PPE population.

- In girls, 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 years.
- in boys, 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).

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)

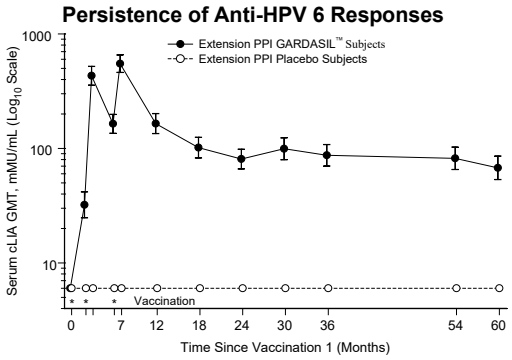
GMT- Geometric mean titre in mMU/ml (mMU = milli-Merck units)

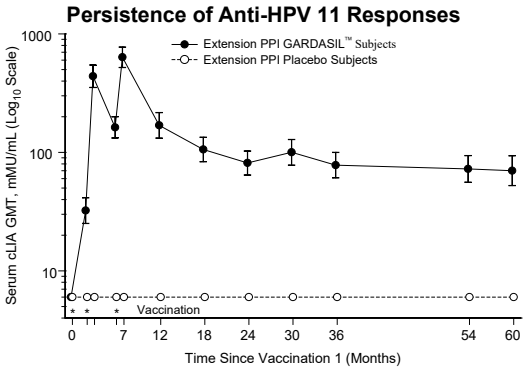
Anti-HPV responses at Month 7 among 9- to 15-year-old boys were non-inferior to anti-HPV responses in 16- to 26-year-old men for whom efficacy was established in the Phase III studies. Immunogenicity was related to age and Month 7 anti-HPV levels were significantly higher in younger individuals.

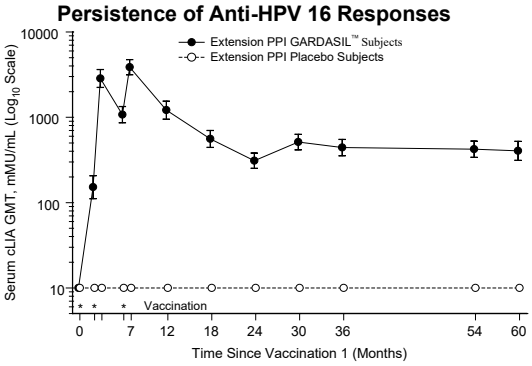
On the basis of this immunogenicity bridging, the efficacy of Gardasil in 9- to 15-year-old boys is inferred.
In the long-term extension study of Protocol 018 for 9-15 year old boys vaccinated with Gardasil in the base study, no cases of HPV diseases (HPV types 6/11/16/18 related External Genital Lesions) were observed after a median follow-up of approximately 6.5 years.

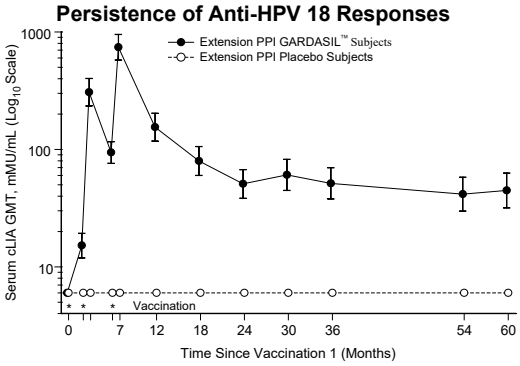
Persistence of Immune Response of Gardasil in Clinical Studies

Figure 1
Persistence of Anti-HPV Responses Following a 3-Dose Regimen 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 stabilized. 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 8 years, in girls and boys 9- 15 years of age

	cLIA		IgG LIA	
	n	% of seropositive subjects	n	% of seropositive subjects
HPV 6	439	88%	387	94%
HPV 11	439	89%	387	89%
HPV 16	436	97%	382	100%
HPV 18	440	64%	385	89%

Women vaccinated with Gardasil at 16-23 years of age in Protocol 015 base study 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-HPV6, 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-HPV6, 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-HPV6, 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 individuals who were seropositive to relevant HPV type(s) prior to vaccination. In addition, a subset of vaccinated individuals 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.

Immune Responses to Gardasil using a 2-dose schedule

A clinical trial showed that, at Month 7, the immune response in girls aged 9-13 years (n=259) who received 2 doses of Gardasil (at 0, 6 months) was not inferior to the immune response in women aged 16-26 years (n=310) who received 3 doses of Gardasil (at 0, 2, 6 months).

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

The duration of immunity following a 2-dose schedule has been observed for up to 10 years post-vaccination. At 120 month follow-up, the GMT in girls (2 doses, n = 35) remained non-inferior to the GMT in women (3 doses, n = 30) for all 4 HPV types. Among the girls receiving 2 doses of the vaccine, seropositivity rates were >95% for HPV6, 11, and 16, and >80% for HPV 18, in the cLIA.

Pharmacokinetic properties

Evaluation of pharmacokinetic studies is not required for vaccines.

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 a dose of 120 mcg total protein, which corresponds to approximately 200-fold excess relative to the projected human dose, 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.

XIV. PHARMACEUTICAL PARTICULARS

Incompatibilities

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

Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze. Keep the vial in the outer carton in order to protect from light.

Special precautions for disposal and other handling

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.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. Discard the product if particulates are present or if it appears discoloured.

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.

Disposal

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

Pre-filled syringe use

NOTE: Please use one of the enclosed needles for administration. Choose the appropriate needle to ensure an IM administration depending on your patient's size and weight. Attach the needle by twisting in a clockwise direction until the needle fits securely on the syringe. Administer the entire dose as per standard protocol. Two detachable labels containing details of the batch number, expiry date and product name are provided.

Disposal

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

HARUS DENGAN RESEP DOKTER

Shelf life: 36 months

Manufactured by:
Merck Sharp & Dohme Corp.
West Point, PA 19486, U.S.A.

Released by:
Merck Sharp & Dohme Haarlem BV/MVD – Holland, Haarlem,
Netherlands

Registered by:
PT. Organon Pharma Indonesia Tbk
Pasuruan, Jawa Timur

Distributed by:
PT Merck Sharp & Dohme Indonesia
Jakarta, Indonesia

Box, 1 syringe @ 0.5 mL	- Reg. No.: DKI1063602143A1
Box, 1 vial @ 0.5 mL	- Reg. No.: DKI1563500743A1
Box, 10 vial @ 0.5 mL	- Reg. No.: DKI1563500743A1

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