ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Silgard, suspension for injection.
Silgard, suspension for injection in a pre-filled syringe.

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 sulphate adjuvant (0.225 milligrams Al).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Silgard, suspension for injection.
Silgard, suspension for injection in a pre-filled syringe.

Prior to agitation, Silgard 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

Silgard 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 Silgard should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Individuals 9 to and including 13 years of age
Silgard 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, Silgard 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
Silgard 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 Silgard should be in accordance with official recommendations.

Paediatric population
The safety and efficacy of Silgard 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 Silgard complete the vaccination course with Silgard (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.

Silgard 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 Silgard should not receive further doses of Silgard.

Administration of Silgard 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

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 Silgard may not result in protection in all vaccine recipients.

Silgard 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.

Silgard is for prophylactic use only and has no effect on active HPV infections or established clinical disease. Silgard 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.

Silgard 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 Silgard 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 Silgard 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 are currently ongoing to determine the duration of protection (see section 5.1).

There are no safety, immunogenicity or efficacy data to support change during vaccination with Silgard 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.

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 Silgard 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 $\geq$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.

Silgard 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 Silgard (see section 4.8).

The concomitant administration of Silgard 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 Silgard used hormonal contraceptives during the vaccination period. Use of hormonal contraceptives did not appear to affect the immune response to Silgard.

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 Silgard and placebo treated individuals. These data on pregnant women (more than 1000 exposed outcomes) indicate no malformative nor feto/ neonatal toxicity.

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

Breast-feeding

In breast-feeding mothers given Silgard 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 Silgard 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 Silgard 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 Silgard 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 Silgard 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 Silgard 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 Silgard 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 Silgard 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 Silgard 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 Silgard and 13,617 individuals who received placebo, there were 39 cases of non-specific arthritis/arthropathy reported, 24 in the Silgard 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 Silgard 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 the national reporting system listed in Appendix V.

4.9 Overdose

There have been reports of administration of higher than recommended doses of Silgard.

In general, the adverse event profile reported with overdose was comparable to recommended single doses of Silgard.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Viral Vaccine, ATC code: J07BM01

Mechanism of Action

Silgard 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 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 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 Silgard in females 16 to 45 years of age and in males 16 to 26 years of age and on the demonstration of immunogenicity of Silgard in 9- to 15-year old children and adolescents.

Clinical Studies

Efficacy in women 16 through 26 years

The efficacy of Silgard 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 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 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. Silgard 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 7 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, 2,084 women 16-23 years old during vaccination with Silgard 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 12 years. In this study, a durable protection was statistically demonstrated to approximately 10 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 Silgard was evaluated against HPV 16/18-related CIN 3 and AIS.

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

	Silgard	Placebo	% Efficacy at 2 years (95% CI)	Silgard	Placebo	% Efficacy*** at end of study (95% CI)
	Number of cases / Number of individuals*	Number of cases / Number of individuals*		Number of cases / Number of individuals*	Number of cases / Number of individuals*	
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 Silgard against HPV 6-, 11-, 16-, 18-related CIN 1 was 95.9 % (95% CI: 91.4, 98.4),
- the efficacy of Silgard 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 Silgard 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 Silgard against HPV 6-, 11-, 16-, 18-related genital warts was 99.0% (95% CI: 96.2, 99.9).

In Protocol 012 the efficacy of Silgard 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.

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

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.

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

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 Silgard in high grade cervical lesions in the modified ITT-population including women regardless of baseline HPV status

	Silgard	Placebo	% Efficacy** at 2 years (95% CI)	Silgard	Placebo	% Efficacy** at end of study (95% CI)
	Number of cases / Number of individuals*	Number of cases / Number of individuals*		Number of cases / Number of individuals*	Number of cases / Number of individuals*	
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 Silgard 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 Silgard 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 Silgard does not impact the course of infections or disease that are present at vaccination onset.

Impact on Definitive Cervical Therapy Procedures

The impact of Silgard 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), Silgard 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 Silgard 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 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	Silgard 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 Silgard 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 Silgard 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 Silgard 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 Silgard 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 Silgard 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 Silgard 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 Silgard 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 Silgard 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 (SILGARD = 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 also 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 Silgard against external genital lesions in the PPE population of 16-26 year old men*

Endpoint	**Silgard**		**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	1194	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 Silgard 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 Silgard against HPV 6-, 11-, 16-, 18-related external genital warts was 68.1% (95% CI: 48.8, 79.3).

The efficacy of Silgard 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 Silgard 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 Silgard 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 Silgard 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 Silgard 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), Silgard 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 Silgard was assessed in 20,132 (Silgard n = 10,723; placebo n = 9,409) girls and women 9 to 26 years of age, 3,417 (Silgard 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 (Silgard 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 Silgard 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 Silgard 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 Silgard 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 Silgard became anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 seropositive, respectively, by 1 month Postdose 3. Silgard 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 Silgard*).

Bridging the Efficacy of Silgard from Women to Girls

A clinical study (Protocol 016) compared the immunogenicity of Silgard 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 Silgard 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 Silgard 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 Silgard from Men to Boys

Three clinical studies (Protocols 016, 018 and 020) were used to compare the immunogenicity of Silgard 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 Silgard 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 Silgard 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 Silgard

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 exact duration of immunity following a 3-dose series has not been established and is currently being studied.

Girls and boys vaccinated with Silgard 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 Silgard at 16-23 years of age in Protocol 015 base study will be followed up to 14 years in an extension study. Nine years after vaccination, 94%, 96%, 99% and 60% were anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 seropositive in the cLIA, respectively, and 98%, 96%, 100% and 91% were anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 seropositive in the IgG LIA, respectively.

Women vaccinated with Silgard 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 Silgard 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 9 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 Silgard 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 Silgard has been performed in 126 HIV infected subjects aged from 7 to 12 years (of which 96 received Silgard). Seroconversion to all four antigens occurred in more than ninety-six percent of the subjects. The GMTs were somewhat lower than those 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 Silgard 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 Silgard (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 Silgard (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. A subset of the study participants from the 2-dose group (n=50) were followed 5-years post-vaccination (Month 60 Postdose 1). Among the girls receiving 2 doses of the vaccine, 96%, 100%, 100%, and 84% remained seropositive to anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18, respectively, in the cLIA.

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

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.

Silgard 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.

Silgard 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
L-histidine
Polysorbate 80
Sodium borate
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

Silgard, 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.

Silgard should be administered as soon as possible after being removed from the refrigerator.

Data from stability studies demonstrate that the vaccine components are stable for 72 hours when stored at temperatures from 8°C to 42°C. At the end of this period Silgard should be used or discarded. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

Silgard, suspension for injection in a pre-filled syringe:

Store in a refrigerator (2°C - 8°C).

Do not freeze. Keep the pre-filled syringe in the outer carton in order to protect from light.

Silgard should be administered as soon as possible after being removed from the refrigerator.

Data from stability studies demonstrate that the vaccine components are stable for 72 hours when stored at temperatures from 8°C to 42°C. At the end of this period Silgard should be used or discarded. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

6.5 Nature and contents of container

Silgard, 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.

Silgard, suspension for injection in a pre-filled syringe:

0.5 ml suspension in a pre-filled syringe (glass) with plunger stopper (siliconized FluroTec-coated bromobutyl elastomer or non-coated chlorobutyl elastomer) and a tip cap (bromobutyl) without needle or with one or two needle(s) - pack size of 1, 10 or 20.

Not all pack sizes are marketed.

6.6 Special precautions for disposal and other handling

Silgard, suspension for injection:

- Silgard 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.

Silgard, suspension for injection in a pre-filled syringe:

- Silgard may appear as a clear liquid with a white precipitate prior to agitation.
- Shake well before use, the pre-filled syringe, 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.
- Two needles of different lengths are provided in the pack, choose the appropriate needle to ensure an intramuscular (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.
- 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 Ltd,
Hertford Road,
Hoddesdon,
Hertfordshire, EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

Silgard, suspension for injection:

EU/1/06/358/001
EU/1/06/358/002
EU/1/06/358/018

Silgard, suspension for injection in a pre-filled syringe:

EU/1/06/358/003
EU/1/06/358/004
EU/1/06/358/005
EU/1/06/358/006
EU/1/06/358/007
EU/1/06/358/008
EU/1/06/358/019
EU/1/06/358/020
EU/1/06/358/021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2006
Date of latest renewal: 20 July 2011

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substances

Merck Sharp & Dohme Corp.
Sumneytown Pike
P.O.Box 4
West Point
PA 19486
USA

Merck Sharp & Dohme Corp.
2778 South East Side Highway
Elkton
Virginia 22827
USA

Name and address of the manufacturer responsible for batch release

Merck Sharp & Dohme BV
Waarderweg 39
2031 BN Haarlem
The Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirement for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON TEXT
Silgard, suspension for injection – single dose vial, pack of 1, 10, 20

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml) contains:
HPV Type 6 L1 protein 20 µg
HPV Type 11 L1 protein 40 µg
HPV Type 16 L1 protein 40 µg
HPV Type 18 L1 protein 20 µg

adsorbed on amorphous aluminium hydroxyphosphate sulphate (0.225 mg Al).

3. LIST OF EXCIPIENTS

Sodium chloride, L-histidine, polysorbate 80, sodium borate, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection.
1 dose vial, 0.5 ml.
10 single dose vials, 0.5 ml each.
20 single dose vials, 0.5 ml each.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular (IM) use.
Shake well before use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP MM/YYYY

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/358/001 – pack of 1
EU/1/06/358/002 – pack of 10
EU/1/06/358/018 – pack of 20

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL LABEL TEXT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Silgard, suspension for injection.
IM use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP MM/YYYY

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose, 0.5 ml.

6. OTHER

Merck Sharp & Dohme Ltd

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON TEXT
Silgard, suspension for injection – pre-filled syringe without needle, pack of 1, 10, 20

1. NAME OF THE MEDICINAL PRODUCT

Silgard, suspension for injection in a pre-filled syringe.
Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed).

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml) contains:
HPV Type 6 L1 protein 20 µg
HPV Type 11 L1 protein 40 µg
HPV Type 16 L1 protein 40 µg
HPV Type 18 L1 protein 20 µg

adsorbed on amorphous aluminium hydroxyphosphate sulphate (0.225 mg Al).

3. LIST OF EXCIPIENTS

Sodium chloride, L-histidine, polysorbate 80, sodium borate, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a pre-filled syringe.
1 dose, 0.5 ml pre-filled syringe without needle.
10 single doses, 0.5 ml pre-filled syringes without needles.
20 single doses, 0.5 ml pre-filled syringes without needles.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular (IM) use.
Shake well before use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/358/003 – pack of 1
EU/1/06/358/004 – pack of 10
EU/1/06/358/019 – pack of 20

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON TEXT
Silgard, suspension for injection – pre-filled syringe with 1 needle, pack of 1, 10, 20

1. NAME OF THE MEDICINAL PRODUCT

Silgard, suspension for injection in a pre-filled syringe.
Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed).

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml) contains:
HPV Type 6 L1 protein 20 µg
HPV Type 11 L1 protein 40 µg
HPV Type 16 L1 protein 40 µg
HPV Type 18 L1 protein 20 µg

adsorbed on amorphous aluminium hydroxyphosphate sulphate (0.225 mg Al).

3. LIST OF EXCIPIENTS

Sodium chloride, L-histidine, polysorbate 80, sodium borate, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a pre-filled syringe.
1 dose, 0.5 ml pre-filled syringe with 1 needle.
10 single doses, 0.5 ml pre-filled syringes with 1 needle each.
20 single doses, 0.5 ml pre-filled syringes with 1 needle each.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular (IM) use.
Shake well before use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/358/005 – pack of 1
EU/1/06/358/006 – pack of 10
EU/1/06/358/020 – pack of 20

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON TEXT
Silgard, suspension for injection – pre-filled syringe with 2 needles, pack of 1, 10, 20

1. NAME OF THE MEDICINAL PRODUCT

Silgard, suspension for injection in a pre-filled syringe.
Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed).

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml) contains:
HPV Type 6 L1 protein 20 µg
HPV Type 11 L1 protein 40 µg
HPV Type 16 L1 protein 40 µg
HPV Type 18 L1 protein 20 µg

adsorbed on amorphous aluminium hydroxyphosphate sulphate (0.225 mg Al).

3. LIST OF EXCIPIENTS

Sodium chloride, L-histidine, polysorbate 80, sodium borate, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in a pre-filled syringe.
1 dose, 0.5 ml pre-filled syringe with 2 needles.
10 single doses, 0.5 ml pre-filled syringes with 2 needles each.
20 single doses, 0.5 ml pre-filled syringes with 2 needles each.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular (IM) use.
Shake well before use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/358/007 – pack of 1
EU/1/06/358/008 – pack of 10
EU/1/06/358/021 – pack of 20

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
Pre-filled syringe label text

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Silgard, suspension for injection in a pre-filled syringe.

IM use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP MM/YYYY

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose, 0.5 ml.

6. OTHER

Merck Sharp & Dohme Ltd

B. PACKAGE LEAFLET
(VIAL)

Package leaflet: Information for the user

Silgard, suspension for injection
Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed)

Read all of this leaflet carefully before you or your child are vaccinated.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist. See section 4.

What is in this leaflet

1. What Silgard is and what it is used for

Silgard is a vaccine. Vaccination with Silgard is intended to protect against diseases caused by Human Papillomavirus (HPV) types 6, 11, 16, and 18.

These diseases include pre-cancerous lesions of the female genitals (cervix, vulva, and vagina); pre-cancerous lesions of the anus and genital warts in males and females; cervical and anal cancers. HPV types 16 and 18 are responsible for approximately 70% of cervical cancer cases, 75-80% of anal cancer cases; 70% of HPV-related pre-cancerous lesions of the vulva and vagina; 75% of HPV related pre-cancerous lesions of the anus. HPV types 6 and 11 are responsible for approximately 90% of genital wart cases.

Silgard is intended to prevent these diseases. The vaccine is not used to treat HPV related diseases. Silgard does not have any effect in individuals who already have a persistent infection or disease associated with any of the HPV types in the vaccine. However, in individuals who are already infected with one or more of the vaccine HPV types, Silgard can still protect against diseases associated with the other HPV types in the vaccine.

Silgard cannot cause the diseases it protects against.

Silgard produces type-specific antibodies and has been shown in clinical trials to prevent HPV 6-, 11-, 16-, and 18-related diseases in women 16-45 years of age and in men 16-26 years of age. The vaccine also produces type-specific antibodies in 9- to 15-year-old children and adolescents.

Silgard should be used in accordance with official guidelines.

2. What you need to know before you receive Silgard

Do not receive Silgard if:
- you or your child is allergic (hypersensitive) to any of the active substances or any of the other ingredients of Silgard (listed under "other ingredients"– see section 6).
- you or your child developed an allergic reaction after receiving a dose of Silgard.
- you or your child suffer from an illness with high fever. However, a mild fever or upper respiratory infection (for example cold) itself is not a reason to delay vaccination.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before vaccination if you or your child
- has a bleeding disorder (a disease that makes you bleed more than normal), for example haemophilia
- has a weakened immune system, for example due to a genetic defect, HIV infection or medicines that affect the immune system.

Fainting, sometimes accompanied by falling, can occur (mostly in adolescents) following any needle injection. Therefore tell the doctor or nurse if you fainted with a previous injection.

As with any vaccine, Silgard may not fully protect 100% of those who get the vaccine.

Silgard will not protect against every type of Human Papillomavirus. Therefore appropriate precautions against sexually transmitted disease should continue to be used.

Silgard will not protect against other diseases that are not caused by Human Papillomavirus.

Vaccination is not a substitute for routine cervical screening**.** You should continue to follow your doctor's advice on cervical smear/Pap tests and preventative and protective measures.

What other important information should you or your child know about Silgard

The duration of protection is currently unknown. Longer term follow-up studies are ongoing to determine whether a booster dose is needed.

Other medicines or vaccines and Silgard
Silgard can be given with a Hepatitis B vaccine or 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) at a separate injection site (another part of your body, e.g. the other arm or leg) during the same visit.

Silgard may not have an optimal effect if:
- used with medicines that suppress the immune system.

In clinical trials, oral or other contraceptives (e.g. the pill) did not reduce the protection obtained by Silgard.

Please tell your doctor or pharmacist if you or your child are taking or have taken recently any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
Silgard may be given to women who are breast-feeding or intend to breast-feed.

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

3. How Silgard is given

Silgard is given as an injection by your doctor. Silgard is intended for adolescents and adults from 9 years of age onwards.

If you are from 9 to and including 13 years of age
Silgard can be administered according to a 2-dose schedule:
- First injection: at chosen date
- Second injection: 6 months after first injection

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

Alternatively, Silgard can be administered according to a 3-dose schedule:
- First injection: at chosen date
- Second injection: 2 months after first injection
- Third injection: 6 months after first injection

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. Please speak to your doctor for more information.

If you are from 14 years of age
Silgard should be administered according to a 3-dose schedule:
- First injection: at chosen date
- Second injection: 2 months after first injection
- Third injection: 6 months after first injection

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. Please speak to your doctor for more information.

It is recommended that individuals who receive a first dose of Silgard complete the vaccination course with Silgard.

Silgard will be given as an injection through the skin into the muscle (preferably the muscle of the upper arm or thigh).

The vaccine should not be mixed in the same syringe with any other vaccines and solutions.

If you forget one dose of Silgard:

If you miss a scheduled injection, your doctor will decide when to give the missed dose.
It is important that you follow the instructions of your doctor or nurse regarding return visits for the follow-up doses. If you forget or are not able to go back to your doctor at the scheduled time, ask your doctor for advice. When Silgard is given as your first dose, the completion of the vaccination course should be done with Silgard, and not with another HPV vaccine.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist**.**

4. Possible side effects

Like all vaccines and medicines, Silgard can cause side effects, although not everybody gets them.

The following side effects can be seen after the use of Silgard:

Very commonly (more than 1 in 10 patients), side effects found at the injection site include: pain, swelling and redness. Headache was also seen.

Commonly (more than 1 in 100 patients), side effects found at the injection site include: bruising, itching, pain in extremity. Fever and nausea have also been reported.

Rarely (less than 1 in 1000 patients): hives (urticaria).

Very rarely (less than 1 in 10,000 patients), difficulty breathing (bronchospasm) has been reported.

When Silgard was given with a combined diphtheria, tetanus, pertussis [acellular, component] and poliomyelitis [inactivated] booster vaccine during the same visit, there was more headache and injection-site swelling.

Side effects that have been reported during marketed use include:

Fainting, sometimes accompanied by shaking or stiffening, has been reported. Although fainting episodes are uncommon, patients should be observed for 15 minutes after they receive HPV vaccine.

Allergic reactions that may include difficulty breathing, wheezing (bronchospasm), hives and rash have been reported. Some of these reactions have been severe.

As with other vaccines, side effects that have been reported during general use include: swollen glands (neck, armpit, or groin); muscle weakness, abnormal sensations, tingling in the arms, legs and upper body, or confusion (Guillain-Barré Syndrome, acute disseminated encephalomyelitis); dizziness, vomiting, joint pain, aching muscles, unusual tiredness or weakness, chills, generally feeling unwell, bleeding or bruising more easily than normal, and skin infection at the injection site.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Silgard

Keep this vaccine out of the sight and reach of children.

Do not use this vaccine after the expiry date which is stated on the vial label and the outer carton (after EXP). The expiry date refers to the last day of that month.
Store in a refrigerator (2ºC - 8ºC).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Silgard contains
The active substances are: highly purified non-infectious protein for each of the Human Papillomavirus types (6, 11, 16, and 18).

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 (0.225 milligrams Al).

The other ingredients in the vaccine suspension are:

Sodium chloride, L-histidine, polysorbate 80, sodium borate and water for injections.

What Silgard looks like and contents of the pack
1 dose of Silgard suspension for injection contains 0.5 ml.

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

Silgard is available in packs of 1, 10 or 20 vials.

Not all pack sizes are marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Merck Sharp and Dohme Ltd
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

Manufacturer
Merck Sharp & Dohme BV
Waarderweg 39
2031 BN Haarlem
The Netherlands

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for medical or healthcare professionals only:

The vaccine should be used as supplied; no dilution or reconstitution is necessary. The full recommended dose of the vaccine should be used. Any unused product or waste material should be disposed of in accordance with local requirements.

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 discoloration prior to administration. Discard the product if particulates are present or if it appears discolored.

B. PACKAGE LEAFLET
(PREFILLED SYRINGE)

PACKAGE LEAFLET: INFORMATION FOR THE USER

Silgard, suspension for injection in a pre-filled syringe
Human Papillomavirus Vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed)

Read all of this leaflet carefully before you or your child are vaccinated.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist. See section 4.

What is in this leaflet

1. What Silgard is and what it is used for

Silgard is a vaccine. Vaccination with Silgard is intended to protect against diseases caused by Human Papillomavirus (HPV) types 6, 11, 16, and 18.

These diseases include pre-cancerous lesions of the female genitals (cervix, vulva, and vagina); pre-cancerous lesions of the anus and genital warts in males and females; cervical and anal cancers. HPV types 16 and 18 are responsible for approximately 70% of cervical cancer cases, 75-80% of anal cancer cases; 70% of HPV-related pre-cancerous lesions of the vulva and vagina; 75% of HPV related pre-cancerous lesions of the anus. HPV types 6 and 11 are responsible for approximately 90% of genital wart cases.

Silgard is intended to prevent these diseases. The vaccine is not used to treat HPV related diseases. Silgard does not have any effect in individuals who already have a persistent infection or disease associated with any of the HPV types in the vaccine. However, in individuals who are already infected with one or more of the vaccine HPV types, Silgard can still protect against diseases associated with the other HPV types in the vaccine.

Silgard cannot cause the diseases it protects against.

Silgard produces type-specific antibodies and has been shown in clinical trials to prevent HPV 6-, 11-, 16-, and 18-related diseases in women 16-45 years of age and in men 16-26 years of age. The vaccine also produces type-specific antibodies in 9- to 15-year-old children and adolescents.

Silgard should be used in accordance with official guidelines.

2. What you need to know before you receive Silgard

Do not receive Silgard if:
- you or your child is allergic (hypersensitive) to any of the active substances or any of the other ingredients of Silgard (listed under "other ingredients"– see section 6).
- you or your child developed an allergic reaction after receiving a dose of Silgard.
- you or your child suffer from an illness with high fever. However, a mild fever or upper respiratory infection (for example cold) itself is not a reason to delay vaccination.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before vaccination if you or your child
- has a bleeding disorder (a disease that makes you bleed more than normal), for example haemophilia
- has a weakened immune system, for example due to a genetic defect, HIV infection or medicines that affect the immune system.

Fainting, sometimes accompanied by falling, can occur (mostly in adolescents) following any needle injection. Therefore tell the doctor or nurse if you fainted with a previous injection.

As with any vaccine, Silgard may not fully protect 100% of those who get the vaccine.

Silgard will not protect against every type of Human Papillomavirus. Therefore appropriate precautions against sexually transmitted disease should continue to be used.

Silgard will not protect against other diseases that are not caused by Human Papillomavirus.

Vaccination is not a substitute for routine cervical screening**.** You should continue to follow your doctor's advice on cervical smear/Pap tests and preventative and protective measures.

What other important information should you or your child know about Silgard

The duration of protection is currently unknown. Longer term follow-up studies are ongoing to determine whether a booster dose is needed.

Other medicines or vaccines and Silgard
Silgard can be given with a Hepatitis B vaccine or 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) at a separate injection site (another part of your body, e.g. the other arm or leg) during the same visit.

Silgard may not have an optimal effect if:
- used with medicines that suppress the immune system.

In clinical trials, oral or other contraceptives (e.g. the pill) did not reduce the protection obtained by Silgard.

Please tell your doctor or pharmacist if you or your child are taking or have taken recently any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
Silgard may be given to women who are breast-feeding or intend to breast-feed.

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

3. How Silgard is given

Silgard is given as an injection by your doctor. Silgard is intended for adolescents and adults from 9 years of age onwards.

If you are from 9 to and including 13 years of age
Silgard can be administered according to a 2-dose schedule:
- First injection: at chosen date
- Second injection: 6 months after first injection

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

Alternatively, Silgard can be administered according to a 3-dose schedule:
- First injection: at chosen date
- Second injection: 2 months after first injection
- Third injection: 6 months after first injection

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. Please speak to your doctor for more information.

If you are from 14 years of age
Silgard should be administered according to a 3-dose schedule:
- First injection: at chosen date
- Second injection: 2 months after first injection
- Third injection: 6 months after first injection

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. Please speak to your doctor for more information.

It is recommended that individuals who receive a first dose of Silgard complete the vaccination course with Silgard.

Silgard will be given as an injection through the skin into the muscle (preferably the muscle of the upper arm or thigh).

The vaccine should not be mixed in the same syringe with any other vaccines and solutions.

If you forget one dose of Silgard:

If you miss a scheduled injection, your doctor will decide when to give the missed dose.
It is important that you follow the instructions of your doctor or nurse regarding return visits for the follow-up doses. If you forget or are not able to go back to your doctor at the scheduled time, ask your doctor for advice. When Silgard is given as your first dose, the completion of the vaccination course should be done with Silgard, and not with another HPV vaccine.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist**.**

4. Possible side effects

Like all vaccines and medicines, Silgard can cause side effects, although not everybody gets them.

The following side effects can be seen after the use of Silgard:

Very commonly (more than 1 in 10 patients), side effects found at the injection site include: pain, swelling and redness. Headache was also seen.

Commonly (more than 1 in 100 patients), side effects found at the injection site include: bruising, itching, pain in extremity. Fever and nausea have also been reported.

Rarely (less than 1 in 1000 patients): hives (urticaria).

Very rarely (less than 1 in 10,000 patients), difficulty breathing (bronchospasm) has been reported.

When Silgard was given with a combined diphtheria, tetanus, pertussis [acellular, component] and poliomyelitis [inactivated] booster vaccine during the same visit, there was more headache and injection-site swelling.

Side effects that have been reported during marketed use include:

Fainting, sometimes accompanied by shaking or stiffening, has been reported. Although fainting episodes are uncommon, patients should be observed for 15 minutes after they receive HPV vaccine.

Allergic reactions that may include difficulty breathing, wheezing (bronchospasm), hives and rash have been reported. Some of these reactions have been severe.

As with other vaccines, side effects that have been reported during general use include: swollen glands (neck, armpit, or groin); muscle weakness, abnormal sensations, tingling in the arms, legs and upper body, or confusion (Guillain-Barré Syndrome, acute disseminated encephalomyelitis); dizziness, vomiting, joint pain, aching muscles, unusual tiredness or weakness, chills, generally feeling unwell, bleeding or bruising more easily than normal, and skin infection at the injection site.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Silgard

Keep this vaccine out of the sight and reach of children.

Do not use this vaccine after the expiry date which is stated on the syringe label and the outer carton (after EXP). The expiry date refers to the last day of that month.
Store in a refrigerator (2ºC - 8ºC).
Do not freeze.
Keep the syringe in the outer carton in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Silgard contains
The active substances are: highly purified non-infectious protein for each of the Human Papillomavirus types (6, 11, 16, and 18).

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 (0.225 milligrams Al).

The other ingredients in the vaccine suspension are:

Sodium chloride, L-histidine, polysorbate 80, sodium borate and water for injections.

What Silgard looks like and contents of the pack
1 dose of Silgard suspension for injection contains 0.5 ml.

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

Silgard is available in packs of 1, 10 or 20 pre-filled syringes.

Not all pack sizes are marketed.

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This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for medical or healthcare professionals only:

- Silgard is available in a pre-filled syringe ready to use for intramuscular injection (IM), preferably in the deltoid area of the upper arm.
- If 2 needles of different lengths are provided in the pack, choose the appropriate needle to ensure an IM administration depending on your patient's size and weight.
- 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. Any unused product or waste material should be disposed of in accordance with local requirements.

Shake well before use. 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.