Product Name: GARDASIL (41/30.1/0145)	Component: English Package Insert Regulation 9: 02 June 2015 Date Approved: 25 March 2015

SCHEDULING STATUS

S2

PROPRIETARY NAME AND DOSAGE FORM

GARDASIL® Injection

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

COMPOSITION

Each 0,5 ml dose contains approximately 20 mcg of Human Papillomavirus (HPV) 6 L1 protein, 40 mcg of HPV 11 L1 protein, 40 mcg of HPV 16 L1 protein, and 20 mcg of HPV 18 L1 protein.

Each 0,5 ml dose of the vaccine contains approximately 225 mcg of aluminium (as amorphous aluminium hydroxyphosphate sulphate adjuvant), 9,56 mg of sodium chloride, 0,78 mg of L-histidine, 50 mcg of polysorbate 80 and 35 mcg of sodium borate. The product does not contain a preservative or antibiotics.

PHARMACOLOGICAL CLASSIFICATION

A. 30.1 Biologicals - Antigens

PHARMACOLOGICAL ACTION

GARDASIL is a recombinant, quadrivalent vaccine that protects against cancer, pre-cancerous or dysplastic lesions, genital warts and human papillomavirus types targeted by the vaccine (i.e. HPV types 6, 11, 16 and 18).

Mechanism of Action

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

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

Clinical Studies

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

Vaccine Efficacy

The efficacy of GARDASIL was assessed in 5 placebo-controlled, double-blind, randomised Phase II and III clinical studies [Protocol 005, Protocol 007, FUTURE (Females United To Unilaterally Reduce Endo/Ectocervical Disease) I, II and III] that evaluated 24 358 women 16 through 45 years of age. The median duration of follow-up was 4,0, 3,0, 3,0, 3,0 and 4,0

years for Protocol 005, Protocol 007, FUTURE I, FUTURE II and FUTURE III, respectively. Efficacy, with respect to HPV types 6, 11, 16 and 18, were conducted in the PPE population that consisted of individuals who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, and were naïve to the relevant HPV type(s) prior to dose one and through 1 month Post-dose 3 (Month 7).

In women 16 through 26 years of age, the efficacy of GARDASIL against HPV 6, 11, 16 and 18-related persistent infection, procedures, and disease was as follows:

- 96,0 % (95 % CI: 92,3 %, 98,2 %) against HPV 6-, 11-, 16- or 18-related CIN (CIN 1, CIN 2/3) or AIS.
- 98,2 % (95 % CI: 93,5 %, 99,8 %) against HPV 16- or 18-related CIN 2/3 or AIS.
- 99,1 % (95 % CI: 96,8 %, 99,9 %) against HPV 6-, 11-, 16- or 18-related genital lesions (genital warts, VIN, VaIN, Vulvar Cancer and Vaginal Cancer).
- 99,0 % (95 % CI: 96,2 %, 99,9 %) against HPV 6- or 11-related genital warts.
- 95,8 % (95 % CI: 83,8 %, 99,5 %) against overall persistent infection or disease through Month 60.
- 92,4 % (95 % CI: 83,7 %, 97,0 %) and 96,9 % (95 % CI: 81,6 %, 99,9 %) against HPV 16-related and HPV 18-related Pap abnormalities (ASC-US HR positive, LSIL or worse), respectively.
- 21,8 %, 41,9 %, 43,7 %, and 49,3 % reduction in colposcopy with biopsy, definitive cervical therapy, genital biopsy and definitive genital therapy, respectively.

In addition, GARDASIL has demonstrated efficacy against non-vaccine HPV Types in women 16 through 26 years of age. Administration of GARDASIL to HPV-naïve Individuals has been shown to reduce the risk of acquiring CIN 1, CIN 2/3 and AIS caused by HPV

types 31, 33, 52, 56, 58 and 59. However, the efficacy against non-vaccine types was lower than the efficacy against vaccine types.

In women 24 through 45 years of age, the efficacy of GARDASIL against HPV 6, 11, 16 and 18-related persistent infection, procedures, and disease was as follows:

- 88,7 % (95 % CI: 78,1 %, 94,8 %) against HPV 6-, 11-, 16- or 18-related persistent infection, CIN (any grade) or EGL.
- 84,7 % (95 % CI: 67,5 %, 93,7 %) against HPV 16- or 18-related persistent infection, CIN (any grade) or EGL.
- 94,8 % (95 % CI: 79,9 %, 99,4 %) against HPV 6- or 11-related persistent infection, CIN (any grade) or EGL.
- 96,3 % (95 % CI: 77,7 %, 99,9 %) against a HPV 16/18-related Pap diagnosis of ASC-US positive for high-risk HPV.

Vaccine-induced Immunogenicity

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

The immunogenicity of GARDASIL was assessed in 23 951 9- through 45-year-old girls and women (GARDASIL n=12 634; placebo n=11 317) and 1 346 male (GARDASIL n=1 071; placebo n=275) adolescents 9 through 15 years of age.

Seropositivity at Month 7 (1 month post-dose 3) ranged from 96,4 % to 99,9 % across all 4 vaccine types and across populations defined by age range. Anti-HPV GMTs for all types

decreased with age. This finding is expected, as the immune responses to vaccines generally decrease with age at vaccination.

After peaking at Month 7, anti-GMTs for all HPV types decreased through Month 24 and then stabilised until at least Month 60 at levels above baseline. Seropositivity decreased at persistence time points and continued to decrease through end of study. The decline in the percent seropositivity for anti-HPV 18 responses was greater than the decline in the percent seropositivity for the other vaccine HPV types. Despite this decline in GMT and seropositivity, the efficacy of the vaccine remained high across all age groups. In the PPE population of the FUTURE I and FUTURE II studies, efficacy against HPV 18-related CIN 2/3 or AIS was 100,0% (95 % CI: 86,6 %, 100,0 %) and efficacy against HPV 18-related CIN (any grade) or AIS was 98,4 % (95 % CI: 90,6 %, 100,0 %). In the PPE population of the FUTURE III study, efficacy against HPV 18-related persistent infection or cervical, vulvar, and vaginal disease was 100,0 % (95 % CI: 67,4 %, 100,0 %).

In an additional study to evaluate the capacity to induce immune memory, individuals who received a 3-dose primary series of vaccine were given a challenge dose of GARDASIL 5 years after the onset of vaccination. These individuals exhibited a rapid and strong anamnestic response that exceeded the anti-HPV GMTs observed 1 month Post-dose 3 (Month 7).

Immune Responses to GARDASIL using a 2-dose schedule

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

2, 6 months). Duration of protection of a 2-dose schedule of GARDASIL has not been established.

INDICATIONS

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

GARDASIL is indicated to prevent the following diseases:

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

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

- Cervical intraepithelial neoplasia (CIN) grade 2 and 3 and Cervical adenocarcinoma *in situ* (AIS).
- Cervical intraepithelial neoplasia (CIN) grade 1.
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3.
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3.
- VIN grade 1 and VaIN grade 1.
- Anal intraepithelial neoplasia (AIN) grades 1, 2 and 3.

GARDASIL also provides protection in girls and women 9 through 26 years of age against HPV 31-, 33-, 52- and 58-related CIN grades.

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

- Anal cancer caused by HPV types 16 and 18.
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11.

And the following pre-cancerous or dysplastic lesions caused by HPV types 6, 11, 16 and 18:

- Anal intraepithelial neoplasia (AIN) grades 1, 2 and 3.

CONTRA-INDICATIONS

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

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

WARNINGS AND SPECIAL PREACUTIONS

This vaccine should not be used interchangeably with other Human Papillomavirus (HPV) vaccines (as such use has not been studied).

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

Appropriate medical treatment should always be readily available in case of anaphylactic reactions following the administration of GARDASIL.

General

Vaccination with GARDASIL may not result in protection in all vaccine recipients.

This vaccine is not intended to be used for treatment of active external genital lesions; cervical, vulvar, vaginal or anal cancers; CIN, VIN, VaIN or AIN.

GARDASIL will not protect against diseases that are not caused by HPV.

Syncope (fainting) may follow any vaccination, especially in adolescents and young adults. Syncope, sometimes associated with falling, has occurred after vaccination with GARDASIL. Therefore, vaccinees should be carefully observed for approximately 15 minutes after administration of GARDASIL (see **"SIDE EFFECTS, Post-Marketing Reports"**).

The decision to administer or delay vaccination, because of a current or recent febrile illness depends largely on the severity of the symptoms and their aetiology. Low-grade fever itself and mild upper respiratory infection are not generally contra-indications to vaccination.

Individuals with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, Human Immunodeficiency Virus (HIV) infection, or other causes, may have reduced antibody response to active immunisation (see **"INTERACTIONS"**).

Paediatric Use

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

Use in Elderly

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

Use in Other Special Populations

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

INTERACTIONS

Use with Other Vaccines

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

Use with Common Medications

In clinical studies for girls and women (aged 16 to 26 years), 11,9 %, 9,5 %, 6,9 %, and 4,3 % of individuals used analgesics, anti-inflammatory drugs, antibiotics and vitamin preparations, respectively. In a clinical study in women (aged 24 to 45 years), 30,6 %, 20,2 %, 11,6 %, and 7,5 % of individuals used analgesics, anti-inflammatory drugs, antibiotics, and vitamin preparations, respectively. Conversely in a clinical study in boys and men (aged 16 to 26 years), 10,3 %, 7,8 %, 6,8 %, 3,4 % and 2,6 % of individuals used analgesics, anti-inflammatory drugs, antibiotics, antihistamines, and vitamin preparations, respectively. The

efficacy, immunogenicity, and safety of the vaccine were not impacted by the use of these medications.

Use with Hormonal Contraceptives

In clinical studies, 50,2 % of women (aged 16 to 45 years) who received GARDASIL used hormonal contraceptives during the vaccination period. Use of hormonal contraceptives did not appear to affect the immune responses to GARDASIL.

Use with Steroids

In clinical studies for girls and women (aged 16 to 26 years), 1,7 % (n=158), 0,6 % (n=56), and 1,0 % (n=89) of individuals used inhaled, topical, and parenteral immunosuppressants, respectively. In a clinical study in women (aged 24 to 45 years), 1,4 % (n=27) used corticosteroids for systemic use. In a clinical study in boys and men (aged 16 to 26 years), 1,0 % (n=21) used corticosteroids for systemic use. The corticosteroids for all individuals were administered close to the time of administration of a dose of GARDASIL. These medicines did not appear to affect the immune responses to GARDASIL. Very few individuals in the clinical studies were taking steroids, and the amount of immunosuppression is presumed to have been low.

Use with Systemic Immunosuppressive Medications

There are no data on the concomitant use of potent immunosuppressants with GARDASIL. Individuals receiving therapy with immunosuppressive agents (systemic doses of corticosteroids, anti-metabolites, alkylating agents, cytotoxic agents) may not respond to active immunisation (see **"WARNINGS AND SPECIAL PRECAUTIONS, General"**).

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established in well-controlled clinical studies.

Pregnancy

Studies in Female Rats

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development. GARDASIL induced a specific antibody response against HPV Types 6, 11, 16 and 18 in pregnant rats, and antibodies against all 4 HPV types were transferred to the offspring during gestation and possibly during lactation.

Clinical Studies in Humans

There are however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, pregnancy should be avoided during the vaccination regimen for GARDASIL. Women who are found to be pregnant before completion of a 3-dose regimen of GARDASIL should be instructed to defer completion of their vaccination regimen until resolution of the pregnancy.

During clinical trials, 3 819 women (vaccine n=1 894 vs. placebo n=1 925) reported at least one pregnancy. The overall proportions of pregnancies that resulted in an adverse outcome defined as the combined numbers of spontaneous abortion, late foetal death and congenital anomaly cases out of the total number of pregnancy outcomes for which an outcome was known (and excluding elective terminations), were 22,6 % (446/1 973) in individuals who received GARDASIL and 23,1 % (460/1 994) in individuals who received placebo.

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

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

Lactation

It is not known whether vaccine antigens or antibodies induced by the vaccine are excreted in human milk. Because many pharmaceutical products are excreted in human milk, caution should be exercised when GARDASIL is administered to a nursing woman.

GARDASIL may be administered to lactating women.

GARDASIL or placebo were given to a total of 1 133 women who were breastfeeding at any time during the relevant Phase III clinical studies. In these studies, the rates of adverse experiences in the mother and the nursing infant were comparable between vaccination

groups. In addition, vaccine immunogenicity was comparable among nursing mothers and women who did not nurse during the vaccine administration.

DOSAGE AND DIRECTIONS FOR USE

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

Dosage

GARDASIL should be administered intramuscularly as 3 separate 0,5 ml doses according to the following schedule:

First dose: At elected date.

Second dose: 2 months after the first dose.

Third dose: 6 months after the first dose.

Individuals are encouraged to adhere to the 0, 2, and 6 months vaccination schedule. However in clinical studies, efficacy has been demonstrated in individuals who have received all 3 doses within a 1-year period. The second dose should be administered at least 1 month after the first dose, and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period.

Alternatively, in individuals 9 through 13 years of age, GARDASIL can be administered according to a 2-dose (0, 6 months or 0, 12 months) schedule.

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

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

The need for a booster dose has not been established.

Method of Administration

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

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

The pre-filled syringe is for single use only and should not be used for more than one individual. For single-use vials, a separate sterile syringe and needle must be used for each individual.

The vaccine should be used as supplied; no dilution or reconstitution is necessary. The full recommended dose of the vaccine should be used.

Shake well before use. Thorough agitation immediately before administration is necessary to maintain suspension of the vaccine.

After thorough agitation, GARDASIL is a white, cloudy liquid. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the product if particulates are present or if it appears discoloured.

Single-dose Vial Use

Withdraw the 0,5 ml dose of vaccine from the single-dose vial using a sterile needle and syringe free, of preservatives, antiseptics and detergents. Once the single-dose vial has been penetrated, the withdrawn vaccine should be used promptly, and the vial must be discarded.

Pre-filled Syringe Use

Inject the entire contents of the syringe.

Instructions for using the pre-filled single-dose syringes pre-assembled with needle guard (safety) device

NOTE: Please use the enclosed needle for administration. If a different needle is chosen, it should fit securely on the syringe and be no longer than 2,5 cm (1 inch) to ensure proper functioning of the needle guard device. Two detachable labels are provided which can be removed after the needle is guarded.

At any of the following steps, avoid contact with the trigger fingers to keep from activating the safety device prematurely.

Remove syringe tip cap and needle cap. Attach Luer needle by pressing both anti-rotation tabs to secure syringe and attach Luer needle by twisting the Luer needle in a clockwise direction until secured to the syringe. Remove needle sheath. Administer injection per standard protocol as stated above under **"DOSAGE AND DIRECTIONS FOR USE"**. Depress the plunger while grasping the finger flange until the entire dose has been given.

The needle guard device will **NOT** activate to cover and protect the needle unless the **ENTIRE** dose has been given. While the plunger is still depressed, remove needle from the vaccine recipient. Slowly release the plunger and allow syringe to move up until the entire needle is guarded. For documentation of vaccination, remove detachable labels by pulling slowly on them. Dispose in approved sharps container.

SIDE EFFECTS

In 7 clinical trials (6 placebo-controlled), individuals were administered GARDASIL or placebo on the day of enrollment, and approximately 2 and 6 months thereafter. Few individuals (0,2 %) discontinued due to adverse experiences. In all except one of the clinical trials, safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of GARDASIL or placebo. The individuals who were monitored using VRC-aided surveillance, included 10 088 individuals (6 995 females 9 through 45 years of age and 3 093 boys and men 9 through 26 years of age at enrollment) who received GARDASIL, and 7 995 individuals who received placebo.

The vaccine-related adverse experiences that were observed among recipients of GARDASIL at a frequency of at least 1,0 %, and also at a greater frequency than that observed among placebo recipients are listed according to frequency and system organ class.

The frequency classifications are as follows:

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

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

Nervous system disorders

Very common: Headache

Common: Dizziness

Gastrointestinal disorders

Common: Nausea

Musculoskeletal and connective tissue disorders

Common: Pain in extremity

General disorders and administration site conditions

Common: Pyrexia

Injection site reactions

Very common: Erythema, pain and swelling.

Common: Pruritus and haematoma

Most injection site reactions were mild to moderate.

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

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

Nervous system disorders

Common: Headache

General disorders and administration site conditions:

Common: Pyrexia

Injection site reactions

Very common: Erythema, pain and swelling.

Common: Haematoma

Most injection site reactions were mild to moderate.

The safety of GARDASIL when administered concomitantly with hepatitis B vaccine (recombinant) was evaluated in a placebo-controlled study. The frequency of adverse experiences observed with concomitant administration was similar to the frequency when GARDASIL was administered alone.

Post-Marketing Reports

The following adverse experiences have been spontaneously reported during post-approval use of GARDASIL. Because these experiences were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish a causal relationship to vaccine exposure.

Infections and infestations: *C*ellulitis.

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

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

Gastrointestinal disorders: Nausea, vomiting.

Musculoskeletal and connective tissue disorders: Arthralgia, myalgia.

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

Immune system disorders: Hypersensitivity reactions including anaphylactic/anaphylactoid reactions, bronchospasm and urticaria.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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

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

IDENTIFICATION

GARDASIL is a white, cloudy liquid.

PRESENTATION

GARDASIL is supplied in a 3 ml glass vial or 1,5 ml glass syringe. 1 or 10 syringes or vials are packed into labelled cartons.

STORAGE INSTRUCTIONS

Store refrigerated at 2 to 8 °C. Protect from light. GARDASIL remains stable for up to 72 hours at 25 °C.

DO NOT FREEZE. DISCARD IF THE VACCINE HAS BEEN FROZEN.

Do not remove from carton until required for use.

Keep out of reach of children.

REGISTRATION NUMBER

41/30.1/0145

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

MSD (Pty) Ltd

117 16th Road

Halfway House

South Africa

1685

DATE OF PUBLICATION OF THE PACKAGE INSERT

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