Applicant: MSD (Pty) Ltd
APPROVED PROFESSIONAL INFORMATION
GARDASIL 9 INJECTION

SCHEDULING STATUS

S2

1 NAME OF THE MEDICINE

GARDASIL® 9 Injection

[Human Papillomavirus 9-valent Vaccine, Recombinant]

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0,5 mL dose contains approximately 30 µg of HPV Type 6 L1 protein, 40 µg of HPV Type 11 L1 protein, 60 µg of HPV Type 16 L1 protein, 40 µg of HPV Type 18 L1 protein, 20 µg of HPV Type 31 L1 protein, 20 µg of HPV Type 33 L1 protein, 20 µg of HPV Type 45 L1 protein, 20 µg of HPV Type 52 L1 protein and 20 µg of HPV Type 58 L1 protein.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

GARDASIL 9 is an aqueous suspension that appears as a white cloudy liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

GARDASIL 9 is indicated to prevent the following diseases:

- Cervical, vulvar, vaginal and anal cancer caused by HPV types 16, 18, 31, 33, 45, 52 and 58
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11.

And persistent infections and the following pre-cancerous or dysplastic lesions caused by HPV types 6, 11, 16,18, 31, 33, 45, 52 and 58:

- Cervical intraepithelial neoplasia (CIN) grade 2/3 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 9 is indicated in boys and men from 9 years of age onward for the prevention of anal cancer, anal pre-cancerous or dysplastic lesions; external genital lesions (including genital warts) and persistent infections caused by HPV.

GARDASIL 9 is indicated to prevent the following diseases:

- Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52 and 58
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11.

And persistent infections and the following pre-cancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18, 31, 33, 45, 52 and 58:

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

4.2 Posology and method of administration

Posology

GARDASIL 9 should be administered as soon as possible after being removed from refrigeration.

GARDASIL 9 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 14 years of age, GARDASIL 9 can be administered according to a 2-dose schedule; the second dose should be administered between 5 and 13 months after the first dose. If the second vaccine dose is administered earlier than 5 months after the first dose, a third dose should always be administered.

The use of GARDASIL 9 should be in accordance with official recommendations.

It is recommended that individuals who receive a first dose of GARDASIL 9 complete the vaccination course with GARDASIL 9.

The need for a booster dose has not been established.

Administration of GARDASIL 9 in Individuals who have been Previously Vaccinated with GARDASIL

It is recommended that individuals who receive a first dose of GARDASIL 9 complete the vaccination course with GARDASIL 9 (see section 4.4).

Studies using a mixed regimen (interchangeability) of HPV vaccines were not performed for GARDASIL 9. If the decision is made to administer GARDASIL 9 after receiving 3 doses of GARDASIL, there should be

an interval of at least 12 months between completion of vaccination with GARDASIL and the start of vaccination with GARDASIL 9.

Paediatric population (children < 9 years of age)

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

Method of Administration

GARDASIL 9 should be administered intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

GARDASIL 9 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 9 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.

4.3 Contraindications

GARDASIL 9 is contraindicated in patients with hypersensitivity to either GARDASIL 9 or GARDASIL or any of the inactive ingredients in either vaccine.

Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of GARDASIL 9 or GARDASIL should not receive further doses of GARDASIL 9.

4.4 Special warnings and precautions for use

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 9.

General

Vaccination with GARDASIL 9 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 9 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 9 (See section 4.8).

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 contraindications to vaccination.

Individuals with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, Human Immunodeficiency Virus (HIV) infection or other causes, may have reduced antibody response to active immunisation (see section 4.5).

Paediatric Use

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

Use in Elderly

The safety and efficacy of GARDASIL 9 have not been evaluated in individuals aged 65 years and over.

Use in Other Special Populations

The safety, immunogenicity, and efficacy of GARDASIL 9 have not been fully evaluated in HIV-infected individuals.

The immunologic response to GARDASIL 9 may be diminished in immunocompromised individuals (see section 4.5)

Sodium

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

'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Use with Other Vaccines

Results from clinical studies indicate that GARDASIL 9 may be administered concomitantly (at a separate injection site) with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine], Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)], and Repevax [Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content)] (dTap-IPV).

No studies have been performed with OMZYTA (Measles, Mumps and Rubella) and yellow fever vaccines.

Use with Hormonal Contraceptives

In 7 269 women (16 through 26 years of age, from Protocols 001 and 002), 60,2 % used hormonal contraceptives during the vaccination period of the clinical studies. Use of hormonal contraceptives did not appear to affect the type specific immune responses to GARDASIL 9.

Use with Steroids

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune responses to vaccines (see section 4.4).

4.6 Fertility, pregnancy and lactation

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

Pregnancy

Studies in Female Rats

Reproduction studies have been performed in female rats at a dose approximately 240 times the human dose (mg/kg basis) and have revealed no evidence of impaired female fertility or harm to the foetus due to GARDASIL 9.

An evaluation of the effect of GARDASIL 9 on embryo-foetal, pre- and post-weaning development was conducted in studies using rats. No adverse effects on mating, fertility, pregnancy, parturition, lactation, embryo-foetal or pre- and post-weaning development were observed. There were no vaccine-related foetal malformations or other evidence of teratogenesis noted. In addition, there were no treatment-related effects on developmental signs, behaviour, reproductive performance or fertility of the offspring. GARDASIL 9 induced a specific antibody response against HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 in pregnant rats following one or multiple intramuscular injections. Antibodies against all 9-HPV types were transferred to the offspring during the period of gestation and lactation.

Clinical Studies in Humans

There are no adequate and well-controlled studies in pregnant women. Data from more than 1 000 pregnancy exposures to GARDASIL 9 in clinical studies and post-marketing experience do not demonstrate vaccine-associated increase in risk of major birth defects and miscarriages when GARDASIL 9 is administered during pregnancy. These pregnancies occurred in women who were pregnant at time of vaccination or became pregnant during the follow-up period in clinical studies. As a precautionary measure, the administration of GARDASIL 9 during pregnancy should be avoided. Women who become or plan to become pregnant during the vaccination series should be advised to interrupt or post-pone the vaccination regimen until completion of pregnancy.

In clinical studies, women underwent serum or urine pregnancy testing prior to administration of GARDASIL 9. Women who were found to be pregnant before completion of a 3-dose regimen of GARDASIL 9 were instructed to defer completion of their vaccination regimen until resolution of the

pregnancy.

The overall proportion of pregnancies occurring at any time during the studies 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), was 12,9 % (174/1 353) in women who received GARDASIL 9 and 14,4 % (187/1 303) in women who received GARDASIL. The proportions of adverse outcomes observed were consistent with pregnancy outcomes observed in the general population.

Further sub-analyses were conducted to evaluate pregnancies with estimated onset within 30 days or more than 30 days from administration of a dose of GARDASIL 9 or GARDASIL. For pregnancies with estimated onset within 30 days of vaccination, no cases of congenital anomaly were observed in women who have received GARDASIL 9 or GARDASIL. In pregnancies with onset more than 30 days following vaccination, 30 and 24 cases of congenital anomaly were observed in women who have received GARDASIL 9 and GARDASIL, respectively. The types of anomalies observed were consistent (regardless of when pregnancy occurred in relation to vaccination) with those generally observed in pregnancies in the general population.

A six-year pregnancy registry for GARDASIL 9 enrolled 185 women who were inadvertently exposed to GARDASIL 9 within one month prior to the last menstrual period (LMP) or at any time during pregnancy, 180 of whom were prospectively followed. After excluding elective terminations (n=1), ectopic pregnancies (n=0) and those lost to follow-up (n=110), there were 69 pregnancies with known outcomes. Frequencies of miscarriage and major birth defects were 4,3 % of pregnancies (3/69) and 4,5 % of live born infants (3/67), respectively. These frequencies of the assessed outcomes in the prospective population were consistent with estimated background frequencies.

Data for adverse pregnancy outcomes for GARDASIL are included below as they are relevant to GARDASIL 9 since the vaccines are similar in composition and contain HPV L1 proteins of 4 of the same

HPV types.

A five-year pregnancy registry for GARDASIL enrolled 2 942 women who were inadvertently exposed to GARDASIL within one month prior to the LMP or at any time during pregnancy, 2 566 of whom were prospectively followed. After excluding elective terminations (n=107), ectopic pregnancies (n=5) and those lost to follow-up (n=814), there were 1 640 pregnancies with known outcomes. Frequencies of miscarriage and major birth defects were 6,8 % of pregnancies (111/1,640) and 2,4 % of live born infants (37/1,527), respectively. These frequencies of the assessed outcomes in the prospective population were consistent with estimated background frequencies.

In two post-marketing studies of GARDASIL (one conducted in the U.S., and the other in Nordic countries), pregnancy outcomes among subjects who received GARDASIL within one month prior to the LMP or at any time during pregnancy were evaluated retrospectively. In the U.S. study database, 2 678 pregnancies were assessed for adverse pregnancy outcomes. Among GARDASIL exposed pregnancies with known outcomes (n=1 740), the estimated frequency of confirmed miscarriages was no greater than 8 %. The frequency of major birth defects was 3,6 % of live born infants (24/665).

In the Nordic registry study, 499 live born infants were assessed for major birth defects. The frequency of major birth defects was 5,4 % (27/499).

In both studies, frequencies of the assessed outcomes did not suggest an increased risk with the administration of GARDASIL within one month prior to the LMP or at any time during pregnancy.

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

Breastfeeding

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 9, is administered to a nursing woman.

GARDASIL 9 may be administered to lactating women.

A total of 92 women were breast feeding during the vaccination period of the clinical studies for GARDASIL 9. In these studies, vaccine immunogenicity was comparable between nursing women and women who did not nurse. In addition, the adverse experience profile for nursing women was comparable to that of the women in the overall safety population. There were no vaccine-related serious adverse experiences reported in infants who were nursing during the vaccination period.

4.7 Effects on ability to drive and use machines

GARDASIL 9 has no or negligible influence on the ability to drive or use machines. However, some of the effects mentioned under section 4.8 “Undesirable effects” may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

The safety of GARDASIL 9 was evaluated in 7 clinical studies (Protocols 001, 002, 003, 005, 006, 007, 009) that included 15 776 individuals who received at least one dose of GARDASIL 9 and had safety follow-up.

Protocol 001 and Protocol 009 included 7 378 individuals who received at least one dose of GARDASIL and had safety follow-up. The vaccines were administered on the day of enrolment and the subsequent doses administered approximately 2 and 6 months thereafter. Safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of GARDASIL 9 or GARDASIL.

The individuals who were monitored using VRC-aided surveillance included 9 102 girls and women 16 through 26 years of age, 1 394 boys and men 16 through 26 years of age and 5 280 girls and boys 9 through 15 years of age (3 481 girls and 1 799 boys) at enrolment who received GARDASIL 9; and 7 078 girls and women 16 through 26 years of age and 300 girls 9 through 15 years of age at enrolment who

received GARDASIL.

The vaccine-related adverse experiences that were observed among recipients of GARDASIL 9 at a frequency of at least 1,0 % 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)

Most injection site reactions were mild to moderate.

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, fatigue
Injection site reactions Most injection site reactions were mild to moderate.	Very common: Erythema, pain and swelling
	Common: Pruritus and haematoma

Few individuals (GARDASIL 9 = 0,1 % vs. GARDASIL < 0,1 %) discontinued due to adverse experiences after receiving either vaccine. The safety profile was similar between GARDASIL 9 and GARDASIL in women, men and girls and boys.

Clinical Trials Experience for Concomitant Administration of GARDASIL 9 with Other Vaccines

The safety of GARDASIL 9 when administered concomitantly with other vaccines was evaluated in clinical studies.

There was an increase in injection-site swelling reported at the injection site for GARDASIL 9 when GARDASIL 9 was administered concomitantly with Diphtheria, Tetanus, Pertussis (acellular, component) and Poliomyelitis (inactivated) Vaccine, (adsorbed, reduced antigen(s) content) (dTap-IPV) or Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap) and Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine as compared to non-concomitant vaccination. The majority of injection-site swelling seen with concomitant administration with other vaccines was reported as being mild to moderate in intensity.

Post-Marketing Reports

The post-marketing adverse experiences were reported voluntarily from a population of uncertain size, therefore, it is not possible to reliably estimate their frequency or to establish a causal relationship to vaccine exposure.

The safety profile of GARDASIL 9 and GARDASIL are similar. The post-marketing adverse experience with GARDASIL is relevant to GARDASIL 9 since the vaccines are similar in composition and contain HPV L1 proteins of 4 of the same HPV types.

GARDASIL 9

In addition to the adverse reactions reported in the clinical studies, the following adverse experiences have been spontaneously reported during post-approval use of GARDASIL 9:

System organ class	**Adverse reactions**
Nervous system disorders	Syncope sometimes accompanied by tonic-clonic movements
Gastrointestinal disorders	Vomiting
General disorders and administration site	Injection-site nodule

conditions	

GARDASIL

Additionally, the following post-marketing adverse experiences have been spontaneously reported for GARDASIL:

System organ class	**Adverse reactions**
Infections and infestations	Cellulitis
Blood and lymphatic system disorders	Idiopathic thrombocytopenic purpura, lymphadenopathy
Nervous system disorders	Acute disseminated encephalomyelitis, dizziness, Guillain-Barré syndrome
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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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4.9 OVERDOSE

There have been no reports of administration of higher than recommended doses of GARDASIL 9.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, Papillomavirus vaccines (A.30.1 Biologicals – Antigens), ATC code: J07BM03

PHARMACOLOGICAL ACTION

GARDASIL 9 is a recombinant vaccine that protects against 9 genotypes of Human Papillomavirus (HPV). GARDASIL 9, Human Papillomavirus 9-valent Vaccine, Recombinant, is a non-infectious recombinant 9-valent vaccine prepared from the purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52 and 58.

Mechanism of Action

HPV only infects human beings. Animal studies with analogous animal papillomaviruses suggest that the efficacy of L1 VLP vaccines may involve the development of humoral immune responses. Human beings develop a humoral immune response to the vaccine, although the exact mechanism of protection is unknown.

Clinical Studies

GARDASIL 9 includes the same four HPV types contained in GARDASIL (HPV 6, 11, 16, 18) and five additional HPV types (31, 33, 45, 52 and 58).

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Efficacy Data for GARDASIL

Efficacy was assessed in 6 placebo-controlled, double-blind, randomised Phase II and III clinical studies evaluating 28 413 individuals (20 541 girls and women 16 through 26 years of age, 4 055 boys and men 16 through 26 years of age, 3 817 women 24 through 45 years of age).

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 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.

GARDASIL was also efficacious in reducing the incidence of genital warts related to vaccine HPV types 6 and 11, and anal intraepithelial neoplasia (AIN) grades 2 and 3 related to vaccine HPV types 6, 11, 16, and 18 in boys and men 16 through 26 years of age.

Clinical Trials for GARDASIL 9

Efficacy and/or immunogenicity of 3-dose regimen of GARDASIL 9 were assessed in 8 clinical studies. Clinical studies evaluating the efficacy of GARDASIL 9 against placebo were not acceptable because HPV vaccination is recommended and implemented in many countries for protection against HPV infection and disease. Therefore, the pivotal clinical study (Protocol 001) evaluated the efficacy of GARDASIL 9 using GARDASIL as a comparator.

Efficacy against HPV Types 6, 11, 16 and 18 was primarily assessed using a bridging strategy that demonstrates comparable immunogenicity (as measured by Geometric Mean Titres [GMT]) of GARDASIL 9 compared with GARDASIL (Protocols 001 and 009).

In the pivotal study Protocol 001, the efficacy of GARDASIL 9 against HPV types 31, 33, 45, 52 and 58 was evaluated compared to GARDASIL in women 16 through 26 years of age (n=14 204: 7 099 receiving GARDASIL 9; 7 105 receiving GARDASIL). Protocol 002 evaluated immunogenicity of GARDASIL 9 in girls and boys 9 through 15 years of age and women 16 through 26 years of age (n=3 066: 1 932 girls, 666 boys and 468 women receiving GARDASIL 9). Protocol 003 evaluated immunogenicity of GARDASIL 9 in men 16 through 26 years of age and women 16 through 26 years of age (1 103 Heterosexual Men [HM], 313 Men Who Have Sex with Men [MSM] and 1 099 women receiving GARDASIL 9). Protocols 005 and 007 evaluated GARDASIL 9 concomitantly administered with vaccines

recommended routinely in girls and boys 11 through 15 years of age (n=2 295). Protocol 006 evaluated administration of GARDASIL 9 to girls and women 12 through 26 years of age previously vaccinated with GARDASIL (n=921, 615 receiving GARDASIL 9 and 306 receiving placebo). Protocol 009 evaluated immunogenicity in girls 9 through 15 years of age (n=600, 300 receiving GARDASIL 9 and 300 receiving GARDASIL).

GARDASIL in women 16 through 26 years of age (n=14 204: 7 099 receiving GARDASIL 9; 7 105 receiving GARDASIL). Protocol 002 evaluated immunogenicity of GARDASIL 9 in girls and boys 9 through 15 years of age and women 16 through 26 years of age (n=3 066: 1 932 girls, 666 boys and 468 women receiving GARDASIL 9). Protocol 003 evaluated immunogenicity of GARDASIL 9 in men 16 through 26 years of age and women 16 through 26 years of age (N=2,515: 1 103 Heterosexual Men [HM], 313 Men Who Have Sex with Men [MSM] and 1 099 women receiving GARDASIL 9). Protocols 005 and 007 evaluated GARDASIL 9 concomitantly administered with vaccines recommended routinely in girls and boys 11 through 15 years of age (n=2 295). Protocol 006 evaluated administration of GARDASIL 9 to girls and women 12 through 26 years of age previously vaccinated with GARDASIL (n=921, 615 receiving GARDASIL 9 and 306 receiving placebo). Protocol 009 evaluated immunogenicity in girls 9 through 15 years of age (n=600, 300 receiving GARDASIL 9 and 300 receiving GARDASIL). Protocol 010 evaluated the immunogenicity of 2 doses of GARDASIL 9 in girls and boys 9 through 14 years of age and 3 doses of GARDASIL 9 in girls 9 through 14 years of age and girls and women 16 through 26 years of age (n=1 516, 751 girls, 451 boys and 314 women).

Studies Supporting the Efficacy of GARDASIL 9 Against HPV Types 6, 11, 16, 18

Comparison of GARDASIL 9 with GARDASIL immunogenicity with respect to HPV types 6, 11, 16 and 18 were conducted in a population of 16 through 26-year-old women from Protocol 001, and 9 through 15-year-old girls from Protocol 009.

A statistical analysis of non-inferiority was performed at Month 7 comparing cLIA anti-HPV 6, anti-HPV 11, anti-HPV 16 and anti-HPV 18 GMTs between individuals administered GARDASIL 9 and individuals administered GARDASIL. Immune responses, measured by GMT, for GARDASIL 9 were non-inferior to immune responses for GARDASIL. In clinical studies 98,2 % to 100 % who received GARDASIL 9 became seropositive for antibodies against all 9 vaccine types by Month 7 across all groups tested. These results support the efficacy of GARDASIL 9 against HPV types 6, 11, 16 and 18.

Studies Supporting Efficacy of GARDASIL 9 Against HPV Types 31, 33, 45, 52 and 58

The efficacy of GARDASIL 9 in 16 through 26-year-old women was assessed in an active comparator-controlled, double-blind, randomised clinical study (Protocol 001) that included a total of 14 204 women (GARDASIL 9=7 099; GARDASIL=7 105). Subjects were followed up to 67 months post-dose 3, with a median duration of 43 months.

In women, 16 through 26 years of age, the efficacy of GARDASIL 9 against HPV Types 31, 33, 45, 52 and 58- related persistent infection, disease, Pap test abnormalities and procedures was as follows:

- 97,4 % (95 % CI: 85,0 %, 99,9 %) against HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, VaIN 2/3, Vulvar Cancer and Vaginal Cancer
    - no cases of cervical cancer, VIN2/3, vulvar and vaginal cancer were diagnosed in the PPE population.
- 97,1 % (95 % CI: 83,5 %, 99,9 %) against HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3 or AIS
    - 96,9 % (95 % CI: 81,5 %, 99,8 %) against HPV 31-, 33-, 45-, 52-, 58-related CIN 2
    - 100 % (95 % CI: 39,4 %, 100 %) against HPV 31-, 33-, 45-, 52-, 58-related CIN 3
- 100,0 % (95 % CI: -71,5 %, 100,0 %) against HPV 31-, 33-, 45-, 52-, 58-related VIN 2/3, VaIN 2/3
- 96,0 % (95 % CI: 94,6 %, 97,1 %) against HPV 31-, 33-, 45-, 52-, 58-related persistent infection of ≥ 6 months duration

- 96,7 % (95 % CI: 95,1 %, 97,9 %) against HPV 31-, 33-, 45-, 52-, 58-related persistent infection of ≥ 12 months duration
- 92,9 % (95 % CI: 90,2 %, 95,1 %) against HPV 31-, 33-, 45-, 52-, 58-related ASC-US HR-HPV positive or worse Pap test abnormalities
- 90,2 % (95 % CI: 75,0 %, 96,8 %) against HPV 31-, 33-, 45-, 52-, 58-related cervical definitive therapy procedures.

Additional Efficacy Evaluation of GARDASIL 9 Against HPV Types 6, 11, 16, 18, 31, 33, 45, 52 and 58

Since the efficacy of GARDASIL 9 could not be evaluated against placebo, the following exploratory analyses were conducted.

Efficacy Evaluation of GARDASIL 9 Against Cervical High Grade Diseases Caused by HPV Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 in the PPE

The efficacy of GARDASIL 9 against CIN 2 and worse related to HPV Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 compared to GARDASIL was 94,4 % (95 % CI 78,8; 99,0) with 2/5 952 versus 36/5 947 cases. The efficacy of GARDASIL 9 against CIN 3 related to HPV Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 compared to GARDASIL was 100 % (95 % CI 46,3; 100,0) with 0/5 952 versus 8/5 947 cases. These results reflect efficacy of GARDASIL 9 versus GARDASIL against disease caused by HPV types 31, 33, 45, 52 and 58 since both vaccines are efficacious in preventing disease related to HPV types 6, 11, 16, 18.

Impact of GARDASIL 9 Against Cervical Biopsy and Definite Therapy Related to HPV Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 in the PPE

The efficacy of GARDASIL 9 against cervical biopsy related to HPV Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 compared to GARDASIL was 95,9 % (95 % CI 92,7; 97,9) with 11/6 016 versus 262/6 018 cases.

The efficacy of GARDASIL 9 against cervical definitive therapy (including loop electrosurgical excision procedure [LEEP] or conisation) related to HPV Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 compared to GARDASIL was 90,7 % (95 % CI 76,3; 97,0) with 4/6 016 versus 43/6 018 cases. These results reflect efficacy of GARDASIL 9 versus GARDASIL against procedures associated with HPV types 31, 33, 45, 52 and 58 since both vaccines are efficacious in preventing disease related to HPV types 6, 11, 16, 18.

Long-term effectiveness studies

A subset of subjects who received 3 doses is being followed up for 10 to 14 years after GARDASIL 9 vaccination for safety, immunogenicity and effectiveness against clinical diseases related to the HPV types 6/11/16/18/31/33/45/52/58.

Clinical protection has been observed in all subjects in the long-term extension of Protocol 001 registry study in the PPE population. No cases of high-grade CIN were observed through 13,6 years post-dose 3 (median duration of follow-up of 10.4 years) in girls and women who were 16 through 26 years of age at time of vaccination.

Immunogenicity

The minimum anti-HPV titre that confers protective efficacy has not been determined.

Type-specific immunoassays with type-specific standards were used to assess immunogenicity to each vaccine HPV type. These assays measured antibodies against neutralising epitopes for each HPV type. The scales for these assays are unique to each HPV type; thus, comparisons across types and to other assays are not appropriate.

Immune Response to GARDASIL 9 at Month 7

Immunogenicity was measured by (1) the percentage of individuals who were seropositive for antibodies

against the relevant vaccine HPV type and (2) the Geometric Mean Titre (GMT).

GARDASIL 9 induced robust anti-HPV 6, anti-HPV 11, anti-HPV 16, anti-HPV 18, anti-HPV 31, anti-HPV 33, anti-HPV 45, anti-HPV 52 and anti-HPV 58 responses measured at Month 7 in Protocols 001, 002, 005, 007 and Protocol 009. In clinical studies 99,2 % to 100 % who received GARDASIL 9 became seropositive for antibodies against all 9 vaccine types by Month 7 across all groups tested. GMTs were higher in girls and boys than in women 16 through 26 years of age, and higher in boys than in girls and women.

In Protocol 003, anti-HPV antibody GMTs at Month 7 among 16 through 26-year-old boys and men (HM) were comparable to anti-HPV antibody GMTs among 16 through 26 year old girls and women for HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58. High immunogenicity in16 through 26 year old MSM was also observed, although lower than in HM similarly to GARDASIL. These results support the efficacy of GARDASIL 9 in the male population.

No studies have been conducted in women older than 26 years of age. In women 27 through 45 years of age, efficacy of GARDASIL 9 for the 4 original types is expected based on (1) high efficacy of GARDASIL in women 16 through 45 years of age and (2) comparable immunogenicity of GARDASIL 9 and GARDASIL in girls and women 9 through 26 years of age.

Persistence of Immune Response to GARDASIL 9

The persistence of antibody response following a complete schedule of vaccination with GARDASIL 9 is being studied in a subset of individuals who will be followed up for at least 10 years after vaccination for safety, immunogenicity and effectiveness.

In 9- to 15-year-old boys and girls (Protocol 002), persistence of antibody response has been demonstrated for at least 10 years; depending on HPV type, 93 to 99 % of subjects were seropositive.

In 16- to 26-year-old girls and women (Protocol 001), persistence of antibody response has been

demonstrated for at least 5 years; depending on HPV type, 78 to 100 % of subjects were seropositive. Efficacy was maintained in all subjects regardless of seropositivity status for any vaccine HPV type through the end of the study (up to 67 months post-dose 3; median follow-up duration of 43 months). GMTs for HPV-6, -11, -16 and -18 were numerically comparable in subjects who received GARDASIL-or GARDASIL 9 for at least 3,5 years.

Administration of GARDASIL 9 to Individuals Previously Vaccinated with GARDASIL

Protocol 006 evaluated the immunogenicity of GARDASIL 9 in 921 girls and women (12 through 26 years of age) who had previously been vaccinated with GARDASIL. For subjects receiving GARDASIL 9 after receiving 3 doses of GARDASIL, there was an interval of at least 12 months between completion of vaccination with GARDASIL and the start of vaccination with GARDASIL 9 with a 3 dose regimen (the time interval ranged from approximately 12 to 36 months).

Seropositivity to HPV Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 in the per protocol population ranged from 98,3 to 100 % by Month 7 in individuals who received GARDASIL 9. The GMTs to HPV Types 6, 11, 16, 18 were higher than in the population who had not previously received GARDASIL in other studies whereas the GMTs to HPV Types 31, 33, 45, 52 and 58 were lower. The clinical significance of this observation is not known.

Immune Responses to GARDASIL 9 using a 2-dose schedule in individuals 9 through 14 years of age

Protocol 010 measured HPV antibody responses to the 9 HPV types after GARDASIL 9 vaccination in the following cohorts: girls and boys 9 to 14 years of age receiving 2 doses at a 6 month or 12 month interval (+/- 1 month); girls 9 to 14 years of age receiving 3 doses (at 0, 2, 6 months) and women 16 to 26 years of age receiving 3 doses (at 0, 2, 6 months).

One month following the last dose of the assigned regimen, between 97,9 % and 100 % of subjects across all groups became seropositive for antibodies against the 9 vaccine HPV types. GMTs were higher in girls and boys who received 2 doses of GARDASIL 9 (at either 0, 6 months or 0, 12 months) than 16- to 26-year-old girls and women who received 3 doses of GARDASIL 9 (at 0, 2, 6 months) for each of the 9 vaccine HPV types. On the basis of this immunogenicity bridging, the efficacy of a 2 dose regimen of GARDASIL 9 in 9 to 14 year old girls and boys is inferred.

In the same study, in girls and boys 9 to14 years of age, GMTs at one month after the last vaccine dose were numerically lower for some vaccine types after a 2-dose schedule than after a 3 dose schedule (i.e. HPV types 18, 31, 45 and 52 after 0, 6 months and HPV type 45 after 0, 12 months). The clinical relevance of these findings is unknown.

Duration of protection of a 2 dose schedule of GARDASIL 9 has not been established.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each 0,5 mL dose of the vaccine also contains approximately 500 µg of aluminium (provided as AAHS), 9,56 mg of sodium chloride, 0,78 mg of L-histidine, 50 µg of polysorbate 80, 35 µg of sodium borate and water for injection.

The product does not contain a preservative or antibiotics.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store refrigerated at 2 to 8 °C. Protect from light. GARDASIL 9 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.

6.5 Nature and contents of container

Syringe

1,5 mL Type 1 glass syringe with a grey plunger stopper (bromobutyl elastomer) and brown syringe plunger rod.

Vial

3 mL clear Type 1 borosilicate glass vial with a grey stopper (chlorobutyl elastomer) and a brown plastic flip-off cap.

Carton

1,5 mL syringe or 3 mL vial are packed together in a cardboard carton with the professional information and patient information leaflet.

Pack sizes of 1 or 10 syringes or vials.

Not all pack sizes may be marketed.

7 HOLDER OF CERTIFICATE OF REGISTRATION

MSD (Pty) Ltd, 117 16th Road, Halfway House 1685, South Africa

8 REGISTRATION NUMBER

51/30.1/0264

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 11 June 2018

Applicant: MSD (Pty) Ltd
APPROVED PROFESSIONAL INFORMATION
GARDASIL 9 INJECTION

Date of renewal: 03 March 2025

10 DATE OF REVISION OF THETEXT

18 August 2025