Gardasil® 9 suspension for injection. Gardasil® 9 suspension for injection in a pre-filled syringe. Human Papillomavirus 9-valent Vaccine (Recombinant, adsorbed)

1. Name of the medicinal product

Gardasil® 9 suspension for injection.

2. Qualitative and quantitative composition

1 dose (0.5 ml) contains approximately:

| Human Papillomavirus Type 6 L1 protein | 30 micrograms |
| Human Papillomavirus Type 11 L1 protein | 40 micrograms |
| Human Papillomavirus Type 16 L1 protein | 60 micrograms |
| Human Papillomavirus Type 18 L1 protein | 40 micrograms |
| Human Papillomavirus Type 31 L1 protein | 20 micrograms |
| Human Papillomavirus Type 33 L1 protein | 20 micrograms |
| Human Papillomavirus Type 45 L1 protein | 20 micrograms |
| Human Papillomavirus Type 52 L1 protein | 20 micrograms |
| Human Papillomavirus Type 58 L1 protein | 20 micrograms |

1Human Papillomavirus = HPV.

2L1 protein in the form of virus-like particles produced in yeast cells (Saccharomyces cerevisiae CANADE 3C-5 (Strain 1895)) by recombinant DNA technology.

3Adsorbed on amorphous aluminium hydroxyphosphate sulphate adjuvant (0.5 milligrams Al).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Suspension for injection.

4. Clinical particulars

4.1 Therapeutic indications

Gardasil 9 is indicated for active immunisation of individuals from the age of 9 years against the following HPV diseases:

- Premalignant lesions and cancers affecting the cervix, vulva, vagina and anus caused by vaccine HPV types
- Genital warts (Condyloma acuminata) caused by specific HPV types.

See sections 4.4 and 5.1 for important information on the data that support these indications.

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

4.2 Posology and method of administration
Individuals with impaired immune responsiveness, due to either the use of potent immunosuppressive therapy, a genetic immunodeficiency virus (HIV) (see section 5.1). Individuals with impaired immune responsiveness, due to either the use of potent immunosuppressive therapy, a genetic immunodeficiency virus (HIV) (see section 5.1). Individuals with impaired immune responsiveness, due to either the use of potent immunosuppressive therapy, a genetic immunodeficiency virus (HIV) (see section 5.1). Individuals with impaired immune responsiveness, due to either the use of potent immunosuppressive therapy, a genetic immunodeficiency virus (HIV) (see section 5.1). Individuals with impaired immune responsiveness, due to either the use of potent immunosuppressive therapy, a genetic immunodeficiency virus (HIV) (see section 5.1). Individuals with impaired immune responsiveness, due to either the use of potent immunosuppressive therapy, a genetic immunodeficiency virus (HIV) (see section 5.1). 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Individuals with impaired immune responsiveness, due to either the use of potent immunosuppressive therapy, a genetic immunodeficiency virus (HIV) (see section 5.1).
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 interchangeability of Gardasil 9 with bivalent or quadrivalent HPV vaccines.

4.5 Interaction with other medicinal products and other forms of interaction

Safety and immunogenicity in individuals who have received immunoglobulin or blood-derived products during the 3 months prior to vaccination have not been studied in clinical trials.

Use with other vaccines

Gardasil 9 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. This is based on the results from a clinical trial in which a combined dTap-IPV vaccine was administered concomitantly with the first dose of Gardasil 9 (see section 4.8).

Use with hormonal contraceptives

In clinical studies, 60.2% of women aged 16 through 26 years who received Gardasil 9 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women (more than 1000 pregnancy outcomes) indicates no malformative nor foeto/neonatal toxicity of Gardasil 9 (see section 5.1).

Animal studies do not indicate reproductive toxicity (see section 5.3).

However, these data are considered insufficient to recommend use of Gardasil 9 during pregnancy. Vaccination should be postponed until completion of pregnancy (see section 5.1).

Breast-feeding

Gardasil 9 can be used during breast-feeding.

A total of 92 women were breast-feeding during the vaccination period of the clinical studies of Gardasil 9. In the studies, vaccine immunogenicity was comparable between breast-feeding women and women who did not breast-feed. In addition, the adverse experience profile for breast-feeding 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 breast-feeding during the vaccination period.

Fertility

No human data on the effect of Gardasil 9 on fertility are available. Animal studies do not indicate harmful effects on fertility (see section 5.3).

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

A. Summary of the safety profile

In 7 clinical trials, individuals were administered Gardasil 9 on the day of enrolment and 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. A total of 15,776 individuals (10,495 subjects 16 through 26 years of age and 5,281 adolescents 9 through 15 years of age at enrolment) received Gardasil 9. Few individuals (0.1%) discontinued due to adverse experiences.

The most common adverse reactions observed with Gardasil 9 were injection-site adverse reactions (84.8% of vaccinees within 5 days following any vaccination visit) and headache (13.2% of the vaccinees within 15 days following any vaccination visit). These adverse reactions usually were mild or moderate in intensity.

B. Tabulated summary of adverse reactions

Clinical Trials

Adverse reactions considered as being at least possibly related to vaccination have been categorised by frequency. Frequencies are reported as:
- Very common (≥1/10)
- Common (≥1/100 to <1/10)

Table 1: Adverse reactions following administration of Gardasil 9 occurring with a frequency of at least 1.0% from clinical trials

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Very common</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Nausea</td>
</tr>
</tbody>
</table>
The qHPV vaccine was efficacious in reducing the incidence of anal intraepithelial neoplasia (AIN) in women 24 through 45 years of age. The qHPV vaccine was efficacious in reducing the incidence of CIN (any grade) in women 16 to 26 years of age and men 16 to 26 years of age, compared to girls and women 16 to 26 years of age.

Efficacy was assessed in 6 placebo-controlled, double-blind, randomized 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). The qHPV vaccine was efficacious in reducing the incidence of CIN (any grade including CIN 2/3; AIS; genital warts; VIN 2/3; and VaIN 2/3 related to vaccine HPV types 6, 11, 16, or 18 in those girls and women who were PCR negative and seronegative at baseline (Table 2). The qHPV vaccine was efficacious in reducing the incidence of genital warts related to vaccine HPV types 6 and 11 in boys and men who were PCR negative and seronegative at baseline. Efficacy against penile/perineal/perianal cancer was not demonstrated as the number of cases was too limited to reach statistical significance (Table 2). The qHPV vaccine was efficacious in reducing the incidence of anal intraepithelial neoplasia (AIN) grades 1/2/3 in women 16 to 26 years of age, women and men 16 to 26 years of age; consequently, efficacy for Gardasil 9 against persistent infection and disease related to HPV Types 6, 11, 16, or 18 can be inferred to be comparable to that of the qHPV vaccine.

The indication of Gardasil 9 is based on:

- non-inferior immunogenicity between Gardasil 9 and the qHPV vaccine for HPV Types 6, 11, 16 and 18 in girls 9 to 15 years of age, women and men 16 to 26 years of age; consequently, efficacy for Gardasil 9 against persistent infection and disease related to HPV Types 6, 11, 16, or 18 can be inferred to be comparable to that of the qHPV vaccine.
- demonstration of efficacy against persistent infection and disease related to HPV Types 31, 33, 45, 52 and 58 in girls and women 16 to 26 years of age, and
- demonstration of non-inferior immunogenicity against the Gardasil 9 HPV Types in boys and girls 9 to 15 years of age, women and men 16 to 26 years of age; consequently, efficacy for Gardasil 9 against persistent infection and disease related to HPV Types 31, 33, 45, 52 and 58 can be inferred to be comparable to that of the qHPV vaccine.

Clinical studies for qHPV vaccine

Efficacy in 16-26 year-old women and men

Efficacy was assessed in 6 placebo-controlled, double-blind, randomized 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). The qHPV vaccine was efficacious in reducing the incidence of CIN (any grade including CIN 2/3; AIS; genital warts; VIN 2/3; and VaIN 2/3 related to vaccine HPV types 6, 11, 16, or 18 in those girls and women who were PCR negative and seronegative at baseline (Table 2). The qHPV vaccine was efficacious in reducing the incidence of genital warts related to vaccine HPV types 6 and 11 in boys and men who were PCR negative and seronegative at baseline. Efficacy against penile/perineal/perianal cancer was not demonstrated as the number of cases was too limited to reach statistical significance (Table 2). The qHPV vaccine was efficacious in reducing the incidence of anal intraepithelial neoplasia (AIN)
grades 2 and 3 related to vaccine HPV types 6, 11, 16, and 18 in boys and men who were PCR negative and seronegative at baseline (Table 2).

Table 2: Analysis of Efficacy of qHPV vaccine in the PPE* Population for Vaccine HPV Types

<table>
<thead>
<tr>
<th>Disease Endpoints</th>
<th>qHPV</th>
<th>Placebo Control</th>
<th>% Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N</td>
<td>Number of cases</td>
<td>Number of cases</td>
</tr>
<tr>
<td>16- Through 26-Year-Old Girls and Women†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 16- or 18-related CIN 2/3 or AIS**</td>
<td>8493</td>
<td>2</td>
<td>8464 112</td>
</tr>
<tr>
<td>HPV 6-, 11-, 16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS</td>
<td>7864</td>
<td>9</td>
<td>7865 225</td>
</tr>
<tr>
<td>HPV 6-, 11-, 16- or 18-related VIN 2/3</td>
<td>7772</td>
<td>0</td>
<td>7744 10</td>
</tr>
<tr>
<td>HPV 6-, 11-, 16- or 18-related VaIN 2/3</td>
<td>7772</td>
<td>0</td>
<td>7744 9</td>
</tr>
<tr>
<td>HPV 6-, 11-, 16-, or 18-related Genital Warts</td>
<td>7900</td>
<td>2</td>
<td>7902 193</td>
</tr>
<tr>
<td>16- Through 26-Year-Old Boys and Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>External HPV 6-, 11-, 16-, or 18-related Genital Lesions***</td>
<td>1394</td>
<td>3</td>
<td>1404 32</td>
</tr>
<tr>
<td>HPV 6-, 11-, 16-, or 18-related Genital Warts***</td>
<td>1394</td>
<td>3</td>
<td>1404 28</td>
</tr>
<tr>
<td>HPV 6-, 11-, 16-, or 18-related PIN 1/2/3***</td>
<td>1394</td>
<td>0</td>
<td>1404 4</td>
</tr>
<tr>
<td>HPV 6-, 11-, 16-, or 18-related AIN 2/3***</td>
<td>194</td>
<td>3</td>
<td>208 13</td>
</tr>
</tbody>
</table>

*The PPE population consisted of individuals who received all 3 vaccinations within 1 year of enrolment, did not have major deviations from the study protocol, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month postdose 3 (Month 7).
†Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria.
N=Number of individuals with at least 1 follow-up visit after Month 7.
CI=Confidence Interval.
**Patients were followed for up to 4 years (median 3.6 years)
***Median duration of follow-up 2.4 years
****Median duration of follow-up was 2.15 years

Efficacy in 24-45 year-old women

The efficacy of qHPV vaccine in 24- through 45-year-old women was assessed in 1 placebo-controlled, double-blind, randomized Phase III clinical study (Protocol 019, FUTURE III) including a total of 3,817 women.

In the PPE population, the efficacy of qHPV vaccine 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 qHPV vaccine 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).

Long-term efficacy studies

A subset of subjects is currently being followed up for 10 to 14 years after qHPV vaccination for safety, immunogenicity and protection against clinical diseases related to HPV types 6/11/16/18.

Persistence of antibody response (postdose 3) has been observed for 10 years in adolescents who were 9-15 years of age at time of vaccination; 9 years in women, 16-23 years of age at time of vaccination; 6 years in men, 16-26 years of age at time of vaccination, and 8 years in women, 24-45 years of age at time of vaccination.

In the long-term extension registry study for 16-23 year old women vaccinated with qHPV vaccine in the base study (n=1,984), no cases of HPV diseases (HPV types 6/11/16/18 related high grade CIN) were observed up to approximately 10 years. In this study, a durable protection was statistically demonstrated to approximately 8 years.

In long-term extensions of clinical studies, protection has been observed postdose 3 in the PPE population. The PPE population consisted of individuals:
- who received all 3 vaccinations within 1 year of enrolment, did not have major deviations from the study protocol,
- were seronegative to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1, and among subjects 16 years and older at enrolment in the base study, were PCR negative to the relevant HPV type(s) prior to dose 1 through one month post-dose 3 (Month 7).

In these extensions clinical studies, no cases of high-grade intraepithelial neoplasia and no cases of genital warts were observed in subjects who received qHPV vaccine in the base study:
- through 10.7 years in girls (n=369) and 10.6 years in boys (n=326), 9-15 years of age at time of vaccination (median follow-up of 10.0 years and 9.9 years, respectively);
Efficacy and/or immunogenicity of Gardasil 9 were assessed in eight 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 qHPV vaccine as a comparator. Efficacy against HPV Types 6, 11, 16, and 18 was primarily assessed using a bridging strategy that demonstrated comparable immunogenicity (as measured by Geometric Mean Titers [GMT]) of Gardasil 9 compared with qHPV vaccine (Protocol 001, GDS01C/Protocol 009 and GDS07C/Protocol 020).

In the pivotal study Protocol 001, the efficacy of Gardasil 9 against HPV Types 31, 33, 45, 52, and 58 was evaluated compared to qHPV vaccine in women 16 through 26 years of age (N=14,204; 7,099 receiving Gardasil 9; 7,105 receiving qHPV vaccine).

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 qHPV vaccine (N=921; 615 receiving Gardasil 9 and 306 receiving placebo).

GDS01C/Protocol 009 evaluated immunogenicity of Gardasil 9 in girls 9 through 15 years of age (N=600; 300 receiving Gardasil 9 and 300 receiving qHPV vaccine).

GDS07C/Protocol 020 evaluated immunogenicity of Gardasil 9 in men 16 through 26 years of age (N=500; 249 receiving Gardasil 9 and 251 receiving qHPV vaccine).

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 women 16 through 26 years of age (N=1,518; 753 girls; 451 boys and 314 women).

Studies supporting the efficacy of Gardasil 9 against HPV Types 6, 11, 18

Comparison of Gardasil 9 with qHPV vaccine 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, 9- through 15-year-old girls from GDS01C/Protocol 009 and 16- through 26-year-old men from GDS07C/Protocol 020.

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 (Table 3). 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.

Table 3: Comparison of immune responses (based on cLIA) between Gardasil 9 and qHPV vaccine for HPV Types 6, 11, 16, and 18 in the PPI* population of 9- through 15-year-old girls and 16- through 26-year-old women and men

<table>
<thead>
<tr>
<th>POPULATION</th>
<th>Gardasil 9</th>
<th>qHPV Vaccine</th>
<th>Gardasil 9/ qHPV Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GMT (95% CI) mMU/mL</td>
<td>GMT (95% CI) mMU/mL</td>
<td>GMT Ratio (95% CI)</td>
</tr>
<tr>
<td>Anti-HPV 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 to 15-years of age girls</td>
<td>300 (273)</td>
<td>1679.4 (1518.9, 1856.9)</td>
<td>1565.9 (1412.2, 1736.3)</td>
</tr>
<tr>
<td>16 to 26-years of age women</td>
<td>6792 (3993)</td>
<td>893.1 (871.7, 915.1)</td>
<td>875.2 (854.2, 896.8)</td>
</tr>
<tr>
<td>16 to 26-years of age men</td>
<td>249 (228)</td>
<td>758.3 (665.9, 863.4)</td>
<td>618.4 (554.0, 690.3)</td>
</tr>
<tr>
<td>Anti-HPV 11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 to 15-years of age girls</td>
<td>300 (273)</td>
<td>1315.6 (1183.8, 1462.0)</td>
<td>1417.3 (1274.2, 1576.5)</td>
</tr>
</tbody>
</table>

*PPI: Preferential Protection Index
**Anti-HPV 16**

<table>
<thead>
<tr>
<th>Disease Endpoint</th>
<th>Gardasil 9 N=7099</th>
<th>qHPV Vaccine N=7105</th>
<th>%Efficacy** (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, Vulvar Cancer, and Vaginal Cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 to 26-years of age women</td>
<td>6792 (3995)</td>
<td>666.3 (649.6, 683.4)</td>
<td>830.0 (809.2, 851.4)</td>
</tr>
<tr>
<td>16 to 26-years of age men</td>
<td>249 (228)</td>
<td>681.7 (608.9, 763.4)</td>
<td>769.1 (683.5, 865.3)</td>
</tr>
</tbody>
</table>

**Anti-HPV 18**

<table>
<thead>
<tr>
<th>Disease Endpoint</th>
<th>Gardasil 9 N=7099</th>
<th>qHPV Vaccine N=7105</th>
<th>%Efficacy** (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3 or AIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 to 26-years of age women</td>
<td>6792 (4032)</td>
<td>3131.1 (3057.1, 3206.9)</td>
<td>3156.6 (3082.3, 3232.7)</td>
</tr>
<tr>
<td>16 to 26-years of age men</td>
<td>249 (234)</td>
<td>3924.1 (3513.8, 4382.3)</td>
<td>3787.9 (3376.4, 4247.0)</td>
</tr>
</tbody>
</table>

*The PPI population consisted of individuals who received all three vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, seronegative to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1, and among 16- through 26-year-old women, were PCR negative to the relevant HPV type(s) prior to dose 1 through one month postdose 3 (Month 7).

$\text{mMU}=\text{milli-Merck units.}$

$p$-value <0.001.

Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67.

CI=Confidence Interval.

GMT=Geometric Mean Titers.

cLIA= Competitive Luminex Immunoassay.

N= Number of individuals randomized to the respective vaccination group who received at least one injection.

n= Number of individuals contributing to the analysis.

**Studies supporting the 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, randomized clinical study (Protocol 001) that included a total of 14,204 women (Gardasil 9 = 7,099; qHPV vaccine = 7,105). Subjects were followed up to 67 months postdose 3 with a median duration of 43 months postdose 3.

Gardasil 9 was efficacious in preventing HPV 31-, 33-, 45-, 52-, and 58-related persistent infection and disease (Table 4). Gardasil 9 also reduced the incidence of HPV 31-, 33-, 45-, 52-, and 58-related Pap test abnormalities, cervical and external genital procedures (i.e., biopsies), and cervical definitive therapy procedures (Table 4).

Table 4: Analysis of efficacy of Gardasil 9 against HPV Types 31, 33, 45, 52, and 58 in the PPE population 16- through 26-year-old women

<table>
<thead>
<tr>
<th>Disease Endpoint</th>
<th>Gardasil 9 N=7099</th>
<th>qHPV Vaccine N=7105</th>
<th>%Efficacy** (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3, AIS, Cervical Cancer, VIN 2/3, Vulvar Cancer, and Vaginal Cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 to 26-years of age women</td>
<td>6792 (3995)</td>
<td>666.3 (649.6, 683.4)</td>
<td>830.0 (809.2, 851.4)</td>
</tr>
<tr>
<td>16 to 26-years of age men</td>
<td>249 (228)</td>
<td>681.7 (608.9, 763.4)</td>
<td>769.1 (683.5, 865.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Endpoint</th>
<th>Gardasil 9 N=7099</th>
<th>qHPV Vaccine N=7105</th>
<th>%Efficacy** (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HPV 31-, 33-, 45-, 52-, 58-related CIN 2/3 or AIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 to 26-years of age women</td>
<td>6792 (4032)</td>
<td>3131.1 (3057.1, 3206.9)</td>
<td>3156.6 (3082.3, 3232.7)</td>
</tr>
<tr>
<td>16 to 26-years of age men</td>
<td>249 (234)</td>
<td>3924.1 (3513.8, 4382.3)</td>
<td>3787.9 (3376.4, 4247.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Endpoint</th>
<th>Gardasil 9 N=7099</th>
<th>qHPV Vaccine N=7105</th>
<th>%Efficacy** (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HPV 31-, 33-, 45-, 52-, 58-related CIN2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 to 26-years of age women</td>
<td>6792 (4032)</td>
<td>3131.1 (3057.1, 3206.9)</td>
<td>3156.6 (3082.3, 3232.7)</td>
</tr>
<tr>
<td>16 to 26-years of age men</td>
<td>249 (234)</td>
<td>3924.1 (3513.8, 4382.3)</td>
<td>3787.9 (3376.4, 4247.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Endpoint</th>
<th>Gardasil 9 N=7099</th>
<th>qHPV Vaccine N=7105</th>
<th>%Efficacy** (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HPV 31-, 33-, 45-, 52-, 58-related CIN3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 to 26-years of age women</td>
<td>6792 (4032)</td>
<td>3131.1 (3057.1, 3206.9)</td>
<td>3156.6 (3082.3, 3232.7)</td>
</tr>
<tr>
<td>16 to 26-years of age men</td>
<td>249 (234)</td>
<td>3924.1 (3513.8, 4382.3)</td>
<td>3787.9 (3376.4, 4247.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Endpoint</th>
<th>Gardasil 9 N=7099</th>
<th>qHPV Vaccine N=7105</th>
<th>%Efficacy** (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HPV 31-, 33-, 45-, 52-, 58-related VIN 2/3, VaIN 2/3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 to 26-years of age women</td>
<td>6792 (4032)</td>
<td>3131.1 (3057.1, 3206.9)</td>
<td>3156.6 (3082.3, 3232.7)</td>
</tr>
<tr>
<td>16 to 26-years of age men</td>
<td>249 (234)</td>
<td>3924.1 (3513.8, 4382.3)</td>
<td>3787.9 (3376.4, 4247.0)</td>
</tr>
</tbody>
</table>
Persistent infection detected in samples from two or more consecutive visits 6 months (±1 month visit windows) apart.

Persistent infection detected in samples from three or more consecutive visits 6 months (±1 month visit windows) apart.

Papanicolaou test.

CI=Confidence Interval.

ASC-US=Atypical squamous cells of undetermined significance.

HR=High Risk.

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 qHPV vaccine 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 qHPV vaccine was 100% (95% CI 46.3; 100.0) with 0/5,952 versus 8/5,947 cases.

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 qHPV vaccine was 95.9% (95% CI 92.7; 97.9) with 11/6016 versus 262/6018 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 qHPV vaccine was 90.7% (95% CI 76.3; 97.0) with 4/6016 versus 43/6018 cases.

Immunogenicity

The minimum anti-HPV titer 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 neutralizing 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 Titer (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 GDS01C/Protocol 009 (Table 5). In clinical studies 99.6% 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 16- through 26-year-old women, and higher in boys than in girls and women.

Table 5: Summary of month 7 Anti-HPV cLIA Geometric Mean Titers in the PPI* population

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>n</th>
<th>GMT (95% CI) mMU⁹/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HPV 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 to 15-year-old girls</td>
<td>2805</td>
<td>2349</td>
<td>1744.6 (1684.7, 1806.7)</td>
</tr>
<tr>
<td>9 to 15-year-old boys</td>
<td>1239</td>
<td>1055</td>
<td>2065.3 (1984.2, 2191.6)</td>
</tr>
<tr>
<td>Anti-HPV</td>
<td>9 to 15-year-old girls</td>
<td>9 to 15-year-old boys</td>
<td>16 to 26-year-old women</td>
</tr>
<tr>
<td>----------</td>
<td>------------------------</td>
<td>-----------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>11</td>
<td>2805</td>
<td>1239</td>
<td>7260</td>
</tr>
<tr>
<td>16</td>
<td>2805</td>
<td>1239</td>
<td>7260</td>
</tr>
<tr>
<td>18</td>
<td>2805</td>
<td>1239</td>
<td>7260</td>
</tr>
<tr>
<td>31</td>
<td>2805</td>
<td>1239</td>
<td>7260</td>
</tr>
<tr>
<td>33</td>
<td>2805</td>
<td>1239</td>
<td>7260</td>
</tr>
<tr>
<td>45</td>
<td>2805</td>
<td>1239</td>
<td>7260</td>
</tr>
<tr>
<td>52</td>
<td>2805</td>
<td>1239</td>
<td>7260</td>
</tr>
<tr>
<td>58</td>
<td>2805</td>
<td>1239</td>
<td>7260</td>
</tr>
</tbody>
</table>

*The PPI population consisted of individuals who received all three vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, were seronegative to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1, and among 16- through 26-year-old women, were PCR negative to the relevant HPV type(s) prior to dose 1 through one month postdose 3 (Month 7).

 governo=milli-Merck units.
 cLIA=Competitive Luminex Immunoassay.
 CI=Confidence Interval.
 GMT=Geometric Mean Titers.
 N= Number of individuals randomized to the respective vaccination group who received at least one injection.
 n= Number of individuals contributing to the analysis.

Anti-HPV responses at Month 7 among 9- through 15-year-old girls/boys were comparable to anti-HPV responses in 16-through 26-year-old women in the combined database of immunogenicity studies for Gardasil 9.

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

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 in 16- through 26-year-old MSM was also observed, although lower than in HM, similarly to qHPV.
In Protocol 020/GDS07C, 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 boys and men (HM) administered with the qHPV vaccine for HPV 6, 11, 16 and 18. 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 qHPV vaccine in women 16- through 45 years of age and (2) comparable immunogenicity of Gardasil 9 and qHPV vaccine 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 9-15 year-old boys and girls (Protocol 002), persistence of antibody response has been demonstrated for at least 3 years; depending on HPV type, 93 to 99% of subjects were seropositive.

In 16-26 year-old women (Protocol 001), persistence of antibody response has been demonstrated for at least 3.5 years; depending on HPV type, 78-98% 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 postdose 3; median follow-up duration of 43 months postdose 3).

GMTs for HPV-6, -11, -16 and -18 were numerically comparable in subjects who received qHPV vaccine or Gardasil 9 for at least 3.5 years.

**Administration of Gardasil 9 to individuals previously vaccinated with qHPV vaccine**

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 qHPV vaccine. For subjects receiving Gardasil 9 after receiving 3 doses of qHPV vaccine, there was an interval of at least 12 months between completion of vaccination with qHPV vaccine 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 qHPV vaccine 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 old receiving 2 doses at a 6 month or 12-month interval (+/- 1 month); girls 9 to 14 years old receiving 3 doses (at 0, 2, 6 months); and women 16 to 26 years old 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 to 14 years old, 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.**

**Pregnancy**

Specific studies of Gardasil 9 in pregnant women were not conducted. The qHPV vaccine was used as an active control during the clinical development program for Gardasil 9.

During the clinical development of Gardasil 9; 2,586 women (1,347 in the Gardasil 9 group vs. 1,239 in the qHPV vaccine group) reported at least one pregnancy. The types of anomalies or proportion of pregnancies with an adverse outcome in individuals who received Gardasil 9 or qHPV vaccine were comparable and consistent with the general population.

**5.2 Pharmacokinetic properties**

Not applicable.

**5.3 Preclinical safety data**

A repeat dose toxicity study in rats, which included an evaluation of single-dose toxicity and local tolerance, revealed no special hazards to humans.

Gardasil 9 administered to female rats had no effects on mating performance, fertility, or embryonic/foetal development.

Gardasil 9 administered to female rats had no effects on development, behaviour, reproductive performance or fertility of the offspring. Antibodies against all 9 HPV types were transferred to the offspring during gestation and lactation.

**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
Gardasil 9 suspension for injection:
Store in a refrigerator (2°C - 8°C).
Do not freeze. Keep the vial in the outer carton in order to protect from light.
Gardasil 9 should be administered as soon as possible after being removed from the refrigerator.
Stability data indicate that the vaccine components are stable for 72 hours when stored at temperatures from 8°C to 25°C or from 0°C to 2°C. At the end of this period Gardasil 9 should be used or discarded. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

Gardasil 9 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.
Gardasil 9 should be administered as soon as possible after being removed from the refrigerator.
Stability data indicate that the vaccine components are stable for 72 hours when stored at temperatures from 8°C to 25°C or from 0°C to 2°C. At the end of this period Gardasil 9 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
Gardasil 9 suspension for injection:
0.5 ml suspension in a vial (glass) with stopper (halobutyl) and a flip-off plastic cap (aluminium crimp band) in a pack size of 1.

Gardasil 9 suspension for injection in a pre-filled syringe:
0.5 ml suspension in a pre-filled syringe (glass) with plunger stopper (siliconized FluroTec-laminated bromobutyl elastomer) and a tip cap (synthetic isoprene-bromobutyl blend) with two needles in pack size of 1 or 10. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Gardasil 9 suspension for injection:
• Gardasil 9 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.

Gardasil 9 suspension for injection in a pre-filled syringe:
• Gardasil 9 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
MSD VACCINS
162 avenue Jean Jaurès
69007 Lyon
France

8. Marketing authorisation number(s)

EU/1/15/1007/001
EU/1/15/1007/002
EU/1/15/1007/003

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 10 June 2015

10. Date of revision of the text

27 January 2017

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

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SPC.GRD9.PFS.17.UK.4993-IA(MSD Vaccins)