



## INFORMATION FOR HEALTH PROFESSIONALS

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### Data Sheet

## GARDASIL®

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

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## DESCRIPTION

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GARDASIL® is a recombinant, quadrivalent vaccine

The quadrivalent Human Papillomavirus Virus-Like Particle vaccine (HPV VLP vaccine) is a sterile liquid suspension prepared from the highly purified virus-like particles (VLPs) of the recombinant major capsid (L1) protein of HPV Types 6, 11, 16, and 18. The L1 proteins are produced by separate fermentations in recombinant *Saccharomyces cerevisiae* CANADE 3C-5 (Strain 1895) and self-assembled into VLPs. The VLPs for each type are purified and adsorbed on aluminum-containing adjuvant (amorphous aluminum hydroxyphosphate sulfate). The quadrivalent HPV VLP vaccine is prepared by combining the adsorbed VLPs of each HPV type, the aluminum-containing adjuvant formulation, and a buffer.

GARDASIL is a sterile preparation for intramuscular administration. Each 0.5-mL dose contains approximately 20 mcg of 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 aluminum (as amorphous aluminum hydroxyphosphate sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 mcg of polysorbate 80, 35 mcg of sodium borate, and water for injection. The product does not contain a preservative or antibiotics.

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## PHARMACOLOGY

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### *Mechanism of Action*

GARDASIL contains HPV 6,11,16 and 18 L1 VLPs. Each VLP is composed of a unique recombinant L1 major capsid protein for the respective HPV type. Because the virus-like particles contain no viral DNA, they cannot infect cells or reproduce.

Pre-clinical data suggests that the efficacy of L1 VLP vaccines is mediated by the development of humoral immune responses. 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.

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## CLINICAL STUDIES

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CIN 2/3 and AIS are the immediate precursors of invasive squamous cell carcinoma and invasive adenocarcinoma of the cervix, respectively. Their detection and removal has been shown to prevent invasive cancer (secondary prevention); thus, their primary prevention through vaccination will prevent invasive cancer.

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 immunization (see DRUG INTERACTIONS).

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

### ***Carcinogenicity***

GARDASIL has not been evaluated for carcinogenic potential.

### ***Genotoxicity***

GARDASIL has not been evaluated for genotoxic potential

### ***Effects on Fertility***

Female rats were given the clinical dose of GARDASIL (500mcL) intramuscularly twice (during early gestation and one week postnatal) or four times (five and two weeks prior to mating, during early gestation, and one week postnatal). Mating performance and fertility of the dams or their offspring were not affected. The effect of GARDASIL administration on male fertility has not been studied.

### ***Use in Pregnancy (Category B2)***

Female rats were given the clinical dose of GARDASIL (500mcL) intramuscularly twice (during early gestation and one week postnatal) or four times (five and two weeks prior to mating, during early gestation, and one week postnatal). Maternal toxicity or adverse effects on offspring were not observed. High titers of HPV-type specific antibodies were detected in maternal blood during gestation, in near-term fetal blood, and in blood of offspring at weaning and at 11 weeks postnatal, indicative of transplacental and lactational transfer of antibodies (see Use in Lactation). The effect of GARDASIL administration of vaccine-treated males on offspring has not been studied.

In clinical studies, women underwent urine pregnancy testing prior to administration of each dose of GARDASIL. Women who were found to be pregnant before completion of a 3-dose regimen of GARDASIL were instructed to defer completion of their vaccination regimen until resolution of the pregnancy. Such non-standard regimens resulted in Postdose 3 anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 responses that were comparable to those observed in women who received a standard 0, 2, and 6 month vaccination regimen (see DOSAGE AND ADMINISTRATION).

During clinical trials, 2,832 women (vaccine = 1,396 vs. placebo = 1,436) reported at least one pregnancy. Overall, the proportions of pregnancies with an adverse outcome were comparable in subjects who received GARDASIL and subjects 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 0 cases of congenital anomaly in the group that received placebo. Conversely, in pregnancies with onset more than 30 days following vaccination, 20 cases of congenital anomaly were observed in the group that received GARDASIL compared with 22 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 16 through 26 years of age.

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

### ***Use in Lactation***

Female rats were given the clinical dose of GARDASIL (500mcL) intramuscularly twice (during early gestation and one week postnatal) or four times (five and two weeks prior to mating, during early gestation, and one week postnatal). Maternal toxicity or adverse effects on offspring were not observed. Offspring of dams receiving the two doses had higher serum titres of HPV-type specific antibodies at weaning than near term

fetuses, suggesting transfer of antibodies in milk as well as via the placenta (see Use in Pregnancy). Antibodies were still present in offspring at postnatal week 11 when they were last measured.

It is not known whether vaccine antigens or antibodies induced by the vaccine are excreted in human milk.

GARDASIL may be administered to lactating women.

A total of 995 nursing mothers were given GARDASIL or placebo during the vaccination period of the clinical trials. 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.

### ***Paediatric Use***

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

### ***Use in the Elderly***

The safety and efficacy of GARDASIL have not been evaluated in the elderly population.

### ***Use in other special populations***

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

### ***Drug 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). GARDASIL has not been studied in clinical trials with other vaccines.

#### **Use with Common Medications**

In clinical studies, 11.9%, 9.5%, 6.9%, and 4.3% of individuals used analgesics, anti-inflammatory drugs, antibiotics, 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 57.5% of women (16 to 26 years of age), who received GARDASIL, used hormonal contraceptives. Use of hormonal contraceptives did not appear to affect the immune responses to GARDASIL.

#### **Use with Steroids**

In clinical studies, 1.7% (n = 158), 0.6% (n = 56), and 1.0% (n = 89) of individuals used inhaled, topical, and parenteral immunosuppressants, respectively, 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 subjects 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, antimetabolites, alkylating agents, cytotoxic agents) may not respond optimally to active immunization (see PRECAUTIONS, General).

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**Medicine Classification**

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Prescription Medicine

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**Date of Preparation**

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14 March 2008

This product information was approved by the Therapeutic Goods Administration on 14 March 2008