HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

18 April 2007

GARDASIL
suspension for injection, Human Papillomavirus [types 6, 11, 16, 18] vaccine (recombinant, adsorbed) – vial (glass) – 0.5 ml – Pack of 1 vial (CIP 377 143-6)

GARDASIL
suspension for injection in prefilled syringe, Human Papillomavirus [types 6, 11, 16, 18] vaccine
(recombinant, adsorbed) prefilled syringe (glass) – 0.5 ml – Pack of 1 prefilled syringe + 2 needles (CIP 377 130-1)

GARDASIL
suspension for injection in prefilled syringe, Human Papillomavirus [types 6, 11, 16, 18] vaccine
(recombinant, adsorbed) prefilled syringe (glass) – 0.5 ml – Pack of 1 prefilled syringe with needle guard device + 2 needles (CIP 377 133-0)

GARDASIL
suspension for injection in prefilled syringe, Human Papillomavirus [types 6, 11, 16, 18] vaccine
(recombinant, adsorbed) prefilled syringe (glass) – 0.5 ml – Pack of 10 prefilled syringes with needle guard device + 20 needles (CIP 570 100-3)

Applicant: SANOFI PASTEUR MSD

ATC code: J07BM01

List I

Marketing authorisation (MA) date: 29 September 2006

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals (pack of 1)
Inclusion on the list of medicines approved for use by hospitals (pack of 10)

Medical, Economic and Public Health Assessment Division.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

1 dose (0.5 ml) contains approximately:
Human Papillomavirus type 6 L1 Protein, 20 micrograms
Human Papillomavirus type 11 L1 Protein, 40 micrograms
Human Papillomavirus type 16 L1 Protein, 40 micrograms
Human Papillomavirus type 18 L1 Protein, 20 micrograms

L1 protein in the form of virus-like particles produced in yeast cells (*Saccharomyces cerevisiae* CANADE 3C-5 (Strain 1895)) by recombinant DNA technology, adsorbed on amorphous aluminium hydroxyphosphate sulphate adjuvant (225 micrograms Al).

1.2. Background

This is the first quadrivalent recombinant vaccine indicated in the prevention of high-grade cervical dysplasia (CIN 2/3), cervical carcinoma, high-grade vulvar dysplasia (VIN 2/3) and external genital warts (condyloma acuminata) due to Human Papillomavirus (HPV) types 6, 11, 16 and 18.
This vaccine is composed of virus-like particles (VLP) which induce an immune response.

1.3. Indication

GARDASIL is a vaccine for the prevention of high-grade cervical dysplasia (CIN 2/3), cervical carcinoma, high-grade vulvar dysplasia (VIN 2/3) and external genital warts (condyloma acuminata) due to Human Papillomavirus (HPV) types 6, 11, 16 and 18.

The indication is based on the demonstration of efficacy of GARDASIL® in adult females 16 to 26 years of age and on the demonstration of immunogenicity of GARDASIL® in 9- to 15-year-old children and adolescents. Protective efficacy has not been evaluated in males.

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

1.4. Dosage

The primary vaccination series consists of 3 separate 0.5 ml doses administered according to the following schedule: 0, 2, 6 months.

If an alternate vaccination schedule is necessary, the second dose should be administered at least one month after the first dose and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period.
The need for a booster dose has not been established.

Paediatric population: GARDASIL is not recommended for use in children below 9 years of age due to insufficient data on immunogenicity, safety and efficacy.

The vaccine should be administered by intramuscular injection. The vaccine should be injected preferably in the deltoid area of the upper arm or in the higher anterolateral area of the thigh.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2006)

J:	General anti-infectives for systemic use
J07:	Vaccines
J07B:	Viral vaccines
J07BM:	Papillomavirus vaccines
J07BM01:	Papillomavirus (types 6, 11, 16, 18), recombinant

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

No other vaccine has obtained these therapeutic indications

2.3. Medicines with a similar therapeutic aim

None

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

3.1.1. General (clinical development)

The efficacy of prevention was evaluated in 4 placebo-controlled, randomised, double-blind clinical studies on young women 16–26 years of age:

- .2 phase II studies (study 005 and study 007)
- .2 phase III studies (study 013 and study 015)

Primary endpoints:

The primary vaccine efficacy endpoints were the reduction compared with placebo of the risk of occurrence of:

- persistent infection due to HPV (Human Papillomavirus) type 16 (Study 005/phase II) (definition of persistent infection: presence of the same HPV type in 2 cervical specimens at least one year apart)
- persistent infection due to HPV types 6, 11, 16 or 18 (Study 007/phase II)
- cervical dysplasia (or cervical intraepithelial neoplasia) CIN 1/2/3, vulvar and vaginal dysplasia VIN 1/2/3 and VaIN 1/2/3 and genital warts due to HPV 6, 11, 16 or 18 (Study 007/phase II and Study 013/phase III)
- high-grade cervical dysplasia or cervical intraepithelial neoplasia (CIN 2/3) and histologically confirmed endocervical adenocarcinoma *in situ* (AIS) due to HPV 16 or 18 (Study 015/phase III).

Histologically confirmed high-grade cervical dysplasia (or cervical intraepithelial neoplasia) CIN 2/3 was used as a surrogate marker for cervical cancer.

Combined analysis
A combined analysis of the vaccine efficacy results of the phase II and phase III studies had been planned during clinical development to evaluate the efficacy of the vaccine in reducing the risk of occurrence of:

- high-grade cervical dysplasia (CIN 2/3) and endocervical adenocarcinoma *in situ* (AIS) due to HPV 16 or 18 (primary endpoint)
- grade 2/3 external genital lesions of the vulva (VIN 2/3) due to HPV 16 or 18 and condyloma acuminata due to HPV 6, 11, 16 or 18 (secondary endpoints).

To perform the combined analysis of the 4 studies (005, 007, 013 and 015):

- at least 19 cases of cervical dysplasia CIN 2/3 due to HIV 16 or 18 in study 015, and
- at least 33 cases of cervical dysplasia CIN 2/3 due to HIV 16 or 18 in all 4 studies (005, 007, 013 and 015)

should have been observed in the per-protocol population.

Homogeneity tests were performed.

Populations analysed:
The women randomised in each 4 studies might or might not be infected by one or more of the papillomavirus types targeted by the vaccine. They must have no history of PAP-smear with squamous intraepithelial lesion (SIL) and/or biopsy-detected cervical dysplasia CIN (cervical intraepithelial neoplasia).
Tests performed on enrolment included a cervical smear (cytology), tests for HPV viral genome, and serology (antibodies).
Evaluation of the vaccine's efficacy was performed on different populations:

- Per-protocol population (PPE: Per-Protocol Efficacy population):

- population not infected on enrolment with one or more papillomavirus types targeted by the vaccine and for the 7 months following the first injection (HPV seronegative on day 1 and PCR negative: viral genome test by PCR (polymerase chain reaction) on day 1 and in the 7th month)
- had all 3 injections
- no major protocol violation observed.

- Different intention-to-treat populations were analysed:

- the MITT2 (Modified Intention-To-Treat 2) population corresponded to women not infected (HPV seronegative on day 1, PCR negative) with any of the papillomavirus types targeted by the vaccine and who had received at least 1 injection (1 dose) of the vaccine
- the MITT3 (Modified Intention-To-Treat 3) population corresponded to women infected or not with one or more of the papillomavirus types included in the vaccine (HPV seropositive or seronegative, and PCR positive or negative) and who had received at least 1 injection.

Analysis began 30 days after administration of the 1st dose.

Efficacy of the vaccine has not been evaluated in males.

3.1.2. Objectives and design of the various vaccine efficacy studies

(Studies 005, 007, 013 and 015)

Study 005 (phase II)
Objective: to evaluate the efficacy of the monovalent vaccine including type 16 (L1 VLP dosed at 40 µg) in preventing persistent infection due to papillomavirus 16.
Design:
- placebo-controlled, randomised, double-blind study (N=2409)
- baseline patient characteristics: young women 16–23 years of age

- intramuscular administration at the beginning of the study (day 1), at 2 months and at 6 months
- mean duration of follow-up: 44 months
- primary endpoint: - reduction in the risk of occurrence of persistent infection due to HPV type 16.

Study 007 (phase II)
Objective: to determine the optimal quantities of antigen for each of the 4 types contained in the vaccine
Design:
- placebo-controlled, randomised, double-blind study (N=1158)
- baseline patient characteristics: young women 16–23 years of age
- intramuscular administration at the beginning of the study (day 1), at 2 months and at 6 months
- women randomised into 5 treatment groups (with different antigen quantities for the types), 277 women randomised in the GARDASIL group and 277 in the placebo group
- mean duration of follow-up: 36 months
- primary endpoint: reduction in the risk of occurrence of:
    . persistent infections
    . cervical dysplasia of any grades (CIN 1–3), AIS, and/or cervical carcinoma
    . external genital lesions: external genital warts, vulvar dysplasia, vaginal dysplasia, and/or vaginal or vulvar carcinoma due to papillomavirus types 6, 11, 16 and/or 18.

Study 013 (phase III)
Objective: to evaluate the vaccine efficacy of GARDASIL vaccine in preventing the occurrence of:
- cervical dysplasia of grades CIN1, CIN2, CIN3 or AIS or cervical carcinoma due to papillomavirus type 6, 11, 16 and/or 18 infection
- vulvar and vaginal dysplasia VIN1, VIN2, VIN3, VaIN1, VaIN2, VaIN3, vulvar carcinoma, vaginal carcinoma or genital warts due to papillomavirus type 6, 11, 16 and/or 18 infection.

Design:
- placebo-controlled, randomised, double-blind clinical study on 5455 women
- baseline patient characteristics: young women 16–23 years of age
- intramuscular administration of 3 injections, at the beginning of the study (day 1), at 2 months and at 6 months
- follow-up visits: 3, 7, 12, 18, 24, 30, 36 and 48 months after the 1st visit
- mean duration of follow-up: 27 months
- primary endpoint: reduction in the risk of occurrence of:
    - cervical dysplasia of grades CIN1, CIN2, CIN3 or AIS or cervical carcinoma
    - vulvar and vaginal dysplasia VIN1, VIN2, VIN3, VaIN1, VaIN2, VaIN3, vulvar carcinoma, vaginal carcinoma or genital warts due to papillomavirus type 6, 11, 16 and/or 18 infection.

Study 015 (phase III)
Objective: to evaluate efficacy in the prevention of cervical carcinoma.
High-grade cervical dysplasia (CIN) grade 2 and grade 3 (moderate to high-grade dysplasia) was used as a surrogate marker for cervical cancer.

Design:
- placebo-controlled, randomised, double-blind clinical study on 12 167 women
- baseline patient characteristics: young women 16–26 years of age
- intramuscular administration of 3 injections, at the beginning of the study (day 1), at 2 months and at 6 months
- follow-up visits: 7, 12, 24, 36 and 48 months after the 1st visit

- mean duration of follow-up: 24 months
- planned duration: 4 years
- primary endpoint: reduction in the risk of occurrence of high-grade cervical dysplasia (CIN2, CIN3) or AIS or cervical carcinoma due to papillomavirus type 16 or 18 infection.

3.1.3. Vaccine efficacy results by study and combined analysis of results observed in preventing:

- high-grade cervical dysplasia CIN 2/3 or AIS
- high-grade vulvar dysplasia (VIN 2/3)
- external genital warts (condyloma acuminata).

Statistical test:
Vaccine efficacy was considered better than that of placebo if the lower limit of the 95% confidence interval for relative risk reduction was greater than:
- 0% (studies 005, 007 and 015)
- 20% (study 013)
- 25% (combined analysis of primary endpoint: CIN 2/3 due to HPV types 16 or 18)

Per-protocol population results of the various studies and combined analysis (Table 1) for women not infected on enrolment and for the 7 months following the first injection with one or several relevant papillomavirus types targeted by the vaccine, who were given all 3 injections without any major protocol violation.

Table 1: GARDASIL vaccine efficacy in terms of reduction of the relative risk of occurrence of CIN 2/3 or AIS due to HPV 16 or 18, or of VIN 2/3 and condyloma acuminata due to HPV 6, 11, 16 or 18 in the per-protocol population

	Gardasil		**Placebo**		**% vaccine efficacy (CI 95%)**
	N	**Number of cases**	**N**	**Number of cases**	
CIN 2/3 or AIS due to HPV 16 or 18					
Study 005*	755	0	750	12	100.0 (65.1 – 100.0)
Study 007**	231	0	230	1	100.0 (<0.0 – 100.0)
Study 013***	2200	0	2222	19	100.0 (78.5 – 100.0)
Study 015****	5301	0	5258	21	100.0 (80.9 – 100.0)
Combined analysis	8487	0	8460	53	**100.0 (92.9 – 100.0)°**
VIN 2/3 due to HPV 6, 11, 16 or 18					
Study 007	235	0	233	0	NA
Study 013	2261	0	2279	4	100 (<0.0 – 100)
Study 015	5401	0	5387	4	100 (<0.0 – 100)
Combined analysis (post hoc)	7897	0	7899	8	**100 (41.4 – 100)°**
Condyloma acuminata due to HPV 6, 11, 16 or 18ᵒᵒ					
Study 007	235	0	233	3	100.0 (<0 – 100.0)
Study 013	2261	0	2279	29	100.0 (86.4 – 100.0)
Study 015	5401	1	5387	59	98.3 (90.2 – 100.0)
Combined analysis	7897	1	7899	91	**98.9 (93.7 – 100.0)**

* duration 44 months ** duration 36 months *** duration 27 months **** 24 months

°homogeneity test: 1.00
ᵒᵒresults for VIN 2/3 due to HPV 16 or 18 alone no t available

The combined analysis of per-protocol results showed that vaccine efficacy was:
- 100% (CI 95%: 92.9 – 100.0) in terms of reducing the relative risk of occurrence of high-grade cervical dysplasia CIN 2/3 and adenocarcinoma *in situ* (AIS) due to papillomavirus 16 or 18
- 100% (CI 95%: 41.4 – 100) in terms of reducing the relative risk of occurrence of high-grade vulvar dysplasia VIN 2/3 due to papillomavirus 6,11,16 or 18
- 98.9% (CI 95%: 93.7 – 100.0) in terms of reducing the relative risk of occurrence of condyloma acuminata due to papillomavirus 6,11,16 or 18.

In the study 007 extension, maintenance of vaccine efficacy was observed for 4.5 years after full, 3-dose vaccination. Long-term follow-up studies are ongoing.

Results in the MITT2 intention-to-treat population (combined analysis):
in women not infected (HPV seronegative on day 1, PCR negative) with one or several of the relevant papillomavirus types targeted by the vaccine, who had received at least 1 injection.

The combined analysis showed that vaccine efficacy was:
- 98.8% (CI 95%: 92.9 – 100) in terms of reducing the relative risk of occurrence of high-grade cervical dysplasia CIN 2/3 and/or adenocarcinoma *in situ* (AIS) due to papillomavirus 16 or 18 (homogeneity test: 1.00)
- 100% (CI 95%: 78.5 – 100) in terms of reducing the relative risk of occurrence of high-grade vulvar dysplasia VIN 2/3 due to papillomavirus 6, 11, 16 or 18
- 93.4% (CI 95%: 87 – 97) in terms of reducing the relative risk of occurrence of condyloma acuminata due to papillomavirus 6, 11, 16 or 18
- 93.7% (CI 95%: 87.7 – 97.2) in terms of preventing CIN of any grades (1–3) or AIS due to HPV 6, 11, 16 and 18.

Results in the MITT3 intention-to-treat population, combined analysis (Table 2) in women infected or not (seropositive or seronegative and PCR positive or negative at the beginning of the study) with one or more of the papillomavirus types targeted by the vaccine, who had received at least 1 injection (73% had never been infected with any of the 4 types of HPV on enrolment, and 12% had an abnormal cervical smear suggesting CIN on day 1).

Table 2: Vaccine efficacy (in terms of reduction of the relative risk of occurrence) of CIN 2/3 or AIS due to HPV 16 or 18, VIN 2/3 and condyloma acuminata due to HPV 6, 11, 16 or 18 in the MITT3 population

Endpoints	**Gardasil or HPV 16 L1 VLP vaccine**		**Placebo**		**% Vaccine efficacy (CI 95%)**
	N	**Cases**	**N**	**Cases**	
CIN 2/3 or AIS due to HPV 16 or 18*	9831	122	9896	201	39.0 (23.3 - 51.7)°
VIN 2/3 due to HPV 16 or 18**	8954	7	8962	18	61.0 (2.1 - 86.2)
VIN 2/3 due to HPV 6, 11, 16 or 18** (*post hoc* analysis)	8954	7	8962	22	68.1 (22.7-88.5)
Condyloma acuminata due to HPV 6, 11, 16 or 18**	8954	58	8962	184	68.5 (57.5 -77.0)

* studies 005, 007, 013 and 015 ** studies 007, 013 and 015
study duration: 005 – 44 months; 007 – 36 months; 013 – 27 months; 015 – 24 months
°homogeneity test = 0.0543

The combined analysis showed that the vaccine efficacy results were lower than those obtained in the per-protocol combined analysis:
- 39% compared with 100% in preventing CIN 2/3 or AIS
- 61% and 68.1% compared with 100% in preventing VIN 2/3 due to HPV 16 and 18, and 6, 11, 16 and 18, respectively
- 68.5% compared with 98.9% in preventing condyloma acuminata.

Moreover, the efficacy of the vaccine in preventing CIN of any grades (1–3) or AIS due to HPV 6, 11, 16 and 18 was 46.4% (CI 95%: 35.2 – 55.7).

Subgroups analyses were performed *post hoc* for exploratory purposes:
- No efficacy was demonstrated against disease due to the vaccine HPV types in women already infected with the same types on enrolment (PCR test positive).
However, women who were already infected with one vaccine HPV type prior to vaccination were protected against clinical disease due to the remaining HPV types in the vaccine.
- Women who had an abnormal cervical smear on day 1 without being infected with one of the HPV types in the vaccine were protected against lesions due to the HPV types included in the vaccine.

3.1.4. <u>Vaccine efficacy results by study and combined analysis of results observed in preventing:</u>

- persistent infections
- low-grade cervical, vulvar and vaginal dysplasia: CIN1-VIN1-VaIN1 high-grade vaginal dysplasia VaIN 2/3.

These infections and lesions were not included in the marketing authorisation indications.

3.2. Immunogenicity

The immunogenicity of GARDASIL was assessed in 2 specific non-inferiority studies (study 016 and study 018). These studies compared the results obtained in a mixed group of young adolescent boys and girls 9–15 years of age and the results obtained in a group of young women 16–26 years of age (studies 013 and 015).

The immunogenicity of GARDASIL was assessed in:
- 8 915 women 18–26 years of age (GARDASIL N = 4 666; placebo N = 4 249)
- 3 400 girls (GARDASIL N = 1 471; placebo N = 583) and boys (GARDASIL N = 1 071; placebo N = 275) 9–15 years of age.

Type-specific cLIA (competitive Luminex-based immunoassay) tests with type-specific standards were used to assess immunogenicity to each vaccine HPV type.
The minimum level of protective antibodies was not defined for the HPV vaccines.

<u>Immune response (antibody induction)</u>
Overall, according to an integrated analysis of individuals who received GARDASIL:
- 99.9% developed anti-HPV 6 antibodies
- 99.8% developed anti-HPV 11 antibodies
- 99.8% developed anti-HPV 16 antibodies
- 99.6% developed anti-HPV 18 antibodies

by one month after the third dose in all age groups studied.

GARDASIL induced high geometric mean titres (GMTs) of anti-HPV antibodies by one month after the third dose in all age groups studied.

Immune response of young adult women compared with that of young adolescents:
The immunogenicity of GARDASIL was analysed in 2 non-inferiority studies (study 016 and study 018) in young adolescent boys and girls 9–15 years of age. The results of these 2 studies in terms of mean geometric antibody titres were compared with those of two groups of young women 16–26 years of age measured in the phase III studies (studies 013 and 015).

Study 016:
The study compared the immunogenicity of GARDASIL in 10–15-year-old boys and girls with that of 16–23-year-old young women (N = 2 545).
Study 018:
The study compared the immunogenicity of GARDASIL (secondary endpoint) in 9–15-year-old boys and in 9–15-year-old girls (N = 1 781).

Comparison of results (studies 016 and 018 and studies 013 and 015):
Geometric mean titres (GMT) of anti HPV 6, 11, 16 and 18 antibodies in 9–15-year-old boys and girls and in 16–26-year-old young women (per-protocol population) one month after the third dose.

	9–15-year-old boys (studies 016 and 018)		**9–15-year-old girls (studies 016 and 018)**		**16–26-year-old women (studies 013 and 015)**	
	N	GMT (CI 95%)	N	GMT (CI 95%)	N	GMT (CI 95%)
HPV 6	901	1038 [975; 1105]	927	931 [877; 989]	2827	542 [527; 559]
HPV 11	901	1392 [1304; 1485]	927	1306 [1226; 1390]	2827	766 [741; 793]
HPV 16	900	6091 [5640; 6579]	929	4945 [4584; 5335]	2707	2314 [2206; 2427]
HPV 18	905	1359 [1256; 1470]	932	1046 [971; 1127]	3040	461 [444; 478]
GMT – Geometric Mean Titre (mMU/ml)						

Anti-HPV GMT responses at month 7 among 9–15-year-old boys and girls were non-inferior to those observed in 16–26-year-old women for whom efficacy was established in the phase III studies.
Immunogenicity and safety were demonstrated in 9–15-year-old boys. Vaccine efficacy in 9–15-year-old girls was extrapolated from these immunogenicity data.

Persistence of immunity:
The observation period is currently limited to 2 years in the phase III studies on young women and to 18 months in the studies on adolescents.
The exact duration of the protection induced after the 3 doses planned in the vaccination schedule has not been established.

Evidence of an anamnestic (immune memory) response (SPC)
Evidence of an anamnestic response was shown in vaccinated individuals who were seropositive to one or more or the HPV types concerned prior to vaccination.
A subset of vaccinated individuals received a challenge dose of GARDASIL 5 years after the start of vaccination and developed a strong and rapid anamnestic response, with higher anti-HPV GMTs than the GMTs observed one month after the third dose.
Concomitant administration of GARDASIL and a hepatitis B vaccine (recombinant) did not modify the immune response to the HPV types.

3.3. Adverse effects

Tolerance was assessed in:

- the overall population of the 5 studies (007, 013, 015, 016 and 018): 11 813 individuals received GARDASIL and 9 701 received placebo
- a subset monitored by means of vaccination report cards for 14 days after each GARDASIL or placebo injection: 6 160 individuals received GARDASIL and 4 064 received placebo.

The vaccine-related adverse events in individuals who received GARDASIL are given below in order of frequency:
[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), including isolated cases]

General disorders and administration site conditions:
Very common: pyrexia.
Very common at the injection site: erythema, pain, swelling.
Common at the injection site: bleeding, pruritus.

Respiratory, thoracic and mediastinal disorders:
Very rare: bronchspasm.

Skin and subcutaneous tissue disorders:
Rare: urticaria.

The following adverse events were more common in the GARDASIL group:

In the study population subset monitored by means of vaccination report cards:

- the incidence of local injection-site reactions was 82.9% in the GARDASIL group and 73.3% in the placebo group, including 4.5% severe reactions in the GARDASIL group and 1.9% in the placebo group
- the incidence of pyrexia was 11.4% in the GARDASIL group and 9.7% in the placebo group.

In the population of all 5 studies (007, 013, 015, 016 and 018):

- arthritis: there were 8 cases of non-specific arthritis reported (6 in the GARDASIL group and 2 in the placebo group) and 1 case of juvenile arthritis in the GARDASIL group
- bronchspasm: there were 5 cases of bronchospasm reported (4 in the GARDASIL group and 1 in the placebo group).

Specific studies in pregnant women were not conducted. However, during the clinical development programme, 2 266 women reported at least one pregnancy (1 115 in the GARDASIL group and 1 151 in the placebo group).
For pregnancies with estimated onset within 30 days after vaccination, 5 cases of congenital abnormality were observed in the GARDASIL group compared to 0 case in the placebo group.
For pregnancies with onset more than 30 days after vaccination, 10 cases of congenital abnormality were observed in the GARDASIL group compared to 16 cases in the placebo group. The congenital abnormalities observed were similar in nature to those generally observed in women aged 16–26 years.

No signal relating to the safety of the vaccine was detected when GARDASIL was administered during pregnancy. However, these data are insufficient to recommend use of this vaccine during pregnancy. Vaccination should be postponed until after the end of pregnancy.

3.4. Conclusion (efficacy, immunogenicity and tolerance)

In the clinical studies on adult women 16 to 23 or 26 years of age not infected at enrolment with the papillomavirus types targeted by the vaccine, the vaccine efficacy of GARDASIL (in a 3-dose schedule) was established in:

- preventing high-grade cervical dysplasia (CIN 2/3 or AIS): such dysplasia was used as a surrogate marker for cervical cancer
- preventing high-grade vulvar dysplasia (VIN 2/3)
- preventing external genital warts (condyloma acuminata)
- due to papillomavirus 6, 11, 16 and 18.

- For women not infected on enrolment and for the 7 months following the first injection with any of the papillomavirus types targeted by the vaccine, the per-protocol vaccine efficacy was:
    - 100% (CI 95%: 92.9 – 100.0) in high-grade cervical dysplasia CIN 2/3 and adenocarcinoma *in situ* (AIS) due to papillomavirus 16 or 18
    - 100% (CI 95%: 41.4 – 100) in high-grade vulvar dysplasia VIN 2/3 due to papillomavirus 6, 11, 16 or 18
    - 98.9% (CI 95%: 93.7 – 100.0) in condyloma acuminata due to papillomavirus 6, 11, 16 or 18.

- For women infected or not with any of the human papillomavirus types targeted by the vaccine at the time of the first vaccine injection, the vaccine efficacy was lower than that achieved in women not infected at enrolment (MITT3 intention-to-treat analysis):
    - 39% in preventing CIN 2/3 or AIS
    - 61% and 68.1% in preventing VIN 2/3 due to HPV 16 and 18, and 6, 11, 16 and 18, respectively
    - 68.5% in preventing condyloma acuminata.

- For women already infected (PCR positive and/or seropositive) at enrolment, there was no evidence of protection against disease due to the types of human papillomavirus targeted by the vaccine.

- Efficacy of the vaccine has not been evaluated in males.

The immune responses at month 7 among 9–15-year-old boys and girls were similar to those observed in 16–26-year-old women for whom efficacy was established in studies 013 and 015 (phase III).
On the basis of the immune responses observed in the studies, the vaccine efficacy data for GARDASIL observed in young adult women may be extrapolated to girls aged 9–15.

In the current state of the dossier, the following data have not been established:

- maintenance of vaccine efficacy beyond 5 years
- efficacy in terms of preventing cervical cancer
- immunogenicity in immunocompromised populations at high risk of progressive HPV infection
- possible interaction with vaccines other than hepatitis B vaccine in cases of simultaneous administration.

Safety data are limited at present to the results of the clinical studies (study duration 24–44 months). These data have shown a satisfactory safety profile. Local injection-site reactions and some cases of transient pyrexia were observed more commonly than in the placebo group. Few individuals (0.2%) withdraw from the study because of an adverse event.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

GARDASIL is a vaccine against human papillomavirus 6, 11, 16 and 18 for:
- the prevention of high-grade dysplasia of the uterine cervix (CIN 2/3) and vulva (VIN 2/3) and cervical cancer, which may be life threatening
- the prevention of external genital warts (condyloma acuminata), which are benign, recurrent, non-life-threatening tumours.

This medicinal product is a preventive therapy (primary prevention).

The vaccine efficacy/safety ratio is important.

Public health benefit

Cervical cancer causes significant mortality in France. The public health burden caused by this cancer and by vulvar cancer and external genital warts is considerable.

Reducing the incidence of cervical cancer is a public health need (a priority identified by the National Technical Group for Defining Public Health Objectives (GTNDO) and the Public Health Act). Vaccination against oncogenic human papillomavirus (HPV) may help to meet this need, in combination with improvements in screening throughout France.

In view of the results of studies demonstrating the vaccine efficacy of GARDASIL in high-grade cervical dysplasia, high-grade vulvar dysplasia and external genital warts associated with papillomavirus types 6, 11, 16 or 18, GARDASIL is expected to have a considerable impact in reducing morbidity in the short term.

There is no guarantee that these data may be transposable to the long term, since:

- 30% of cervical cancer cases are associated with other types of oncogenic HPV than those contained in GARDASIL. If vaccinated women were to be screened less often, the risk of an increase in the incidence of and mortality from such cancer could not be ruled out.
- the duration of the protection provided by the vaccine beyond 5 years is as yet unknown.

As a result, GARDASIL is expected to provide a moderate benefit to public health, subject to there being optimal coverage of the populations concerned by screening programmes for precancerous and cancerous lesions of the cervix.

There is no alternative vaccine.
Screening based on a cytological test – a cervical smear – is an effective secondary means of prevention of cervical cancer.
There is no means of screening for vulvar dysplasia.
There is no means of preventing external genital warts.

The actual benefit of this vaccine is substantial.

4.2. Improvement in actual benefit

GARDASIL is a primary means of prevention designed in the short and medium terms to prevent morbidity associated with high-grade cervical and vulvar dysplasia. It will also prevent external genital warts.

Its preventive effect on the occurrence of cervical cancer, which has not yet been demonstrated and must be limited to approximately 70% of cases (since human papillomavirus types 16 and 18 are only involved in 70% of cervical cancer cases), will only be shown over the long term, since it is estimated that some 15–25 years elapse between infection with human papillomavirus and the appearance of invasive cancer.
A vaccination campaign must be accompanied by an organized screening programme for precancerous and cancerous cervical lesions (secondary prevention) by means of cervical smears.

Bearing in mind on the one hand:
- that GARDASIL is the first vaccine against human papillomavirus 6, 11, 16 and 18
- the efficacy of this vaccine in preventing precancerous cervical lesions (high-grade cervical dysplasia (CIN 2/3), high-grade vulvar dysplasia (VIN 2/3) and external genital warts due to Human Papillomavirus types 6, 11, 16 and 18

and on the other hand:
- the absence of data on the duration of the protection provided by the vaccine beyond 5 years
- the safety profile to be confirmed under actual conditions of use
- the potentially damaging effects that may be induced by vaccination:
    - a reduction in condom use, since the vaccine may be perceived as protection against all sexually transmitted diseases
    - reduced take-up of screening for cervical cancer, with the risk of seeing a rise in the number of cases of cervical cancer due to oncogenic HPV types other than 16 and 18
    - a shift in the incidence of cervical cancer to an older age group if a booster were to prove necessary and if some women failed to have it
    - the selection of other oncogenic HPV types.

The Committee considers that the GARDASIL vaccine provides a moderate (level III) improvement in actual benefit within the strategy of preventing precancerous and cancerous cervical lesions, high-grade vulvar dysplasia and external genital warts in the populations recommended by the Technical Committee on Vaccinations and the French High Council for Public Health (opinion of 9 March 2007).

In any case, the Committee believes that a nationwide programme of screening for precancerous and cancerous cervical lesions by means of cervical smears (secondary prevention) ought to be organised and implemented before a vaccination campaign is introduced for oncogenic human papillomavirus.

It also points out that the explanations to be given to girls and young women by the doctor prior to vaccination should be compiled in writing in a document validated by the competent authorities.

4.3. Therapeutic use

The Committee takes note of the opinion of the Technical Committee on Vaccinations and the French High Council for Public Health. The opinion is as follows:

MINISTRY OF HEALTH AND SOCIAL WELFARE
DIRECTORATE GENERAL FOR HEALTH

OPINION OF THE TECHNICAL COMMITTEE ON VACCINATIONS and of the FRENCH HIGH COUNCIL FOR PUBLIC HEALTH TRANSMISSIBLE DISEASES SECTION

Re: vaccination against human papillomavirus 6, 11, 16 and 18 (meetings of 9 March 2007)

Having noted the report of the *ad hoc* working group;

Having regard to:
♦ The opinion on vaccination against papillomavirus types 16 and 18 issued by the French High Council for Public Health at its meeting on 5 December 2006;

Whereas:
♦ Certain human papillomaviruses (HPV) are found in 99.7% of cervical cancer cases[1];
♦ It is currently accepted that certain HPV are the cause of cervical cancer[1]
♦ In France, cervical cancer is the 8th most common type of cancer in women and the 15th most common cause of death by cancer[2]
♦ The incidence of cervical cancer peaks at about the age of 40[2]
♦ The median age at which this cancer is discovered in France is 51[2]
♦ The annual number of deaths associated with this cancer fell between 1980 and 2000, according to cancer register data, from 1941 deaths in 1980 to 1004 deaths in 2000[3] in 2002 the number was estimated at 904 deaths;
♦ The incidence of cervical cancer has fallen in parallel with these figures;
♦ Squamous cancers are preceded by precancerous lesions; the estimated incidence of CIN[a] 2/3 in metropolitan France in 2004 was between 20 000 and 30 000[4]
♦ These lesions do not systematically develop into cancer[5]
♦ Invasive cancer develops some 15–20 years after acquisition of HPV infection[5]
♦ HPVs are also responsible for genital warts (condyloma);
♦ The annual incidence of genital warts in France has been estimated at 10[7] per 100 000 inhabitants, and women account for approximately 40% of these cases[6]
♦ These warts have a major impact on the person's psycho-affective life[7]
♦ HPV is transmitted by cutaneo-mucosal means, most often through sexual relations, and condom use only partly prevents HPV infection[8]
♦ Infection is usually acquired at the beginning of a person's sexual life[9]
♦ Approximately 3% of girls have their first sexual intercourse before the age of 15, and 9% before the age of 16;
♦ There are approximately 120 HPV genotypes, 40 of which infect the genital epithelium; some HPV types are oncogenic (particularly HPV 16 and HPV 18) and may cause cancers of the cervix, vulva and anus, while others are not oncogenic and may cause condyloma or genital warts (HPV6 and HPV11 in particular)[11]
♦ In Western Europe, genotypes 16 and 18 are involved in approximately 73% of cases of cervical cancer, 57% of high-grade lesions and 24% of low-grade lesions[12,13]

Whereas in addition:
♦ There is a screening test for lesions that may lead to cervical cancer: the cervical smear;
♦ The introduction of organised screening in certain countries in Northern Europe has led to an 80% reduction in the incidence of and mortality from cervical cancer[14]
♦ In metropolitan France, screening for cervical cancer is currently performed on an individual basis, with the recommendation that women aged between 25 and 65 have a smear every 3 years if the first 2 smears performed one year apart are normal (ANAES);
♦ Treatment for CIN 2/3 has an efficacy of almost 100%[15]

♦ Treatment for genital warts, whether chemical, physical or surgical, does not always eradicate them and they recur in 20–30% of cases[16]
♦ There is a vaccine, Gardasil®, against genotypes 6, 11, 16 and 18;
♦ The 2-year efficacy of this vaccine on high-grade cervical lesions (CIN 2/3) and cervical cancer *in situ* associated with HPV 16 and 18 infection is in the order of 95%; 2 phase III studies[17] with this vaccine have in fact been conducted on women aged 16–23[b] in Asia, Australasia, the Americas and Europe;

- these women received either injections of vaccine in month 0, month 2 and month 6, or 3 injections of placebo according to the same schedule
- approximately 17 000 women received at least one injection of either vaccine or placebo
- in the roughly 16 000 women who received three injections of vaccine or placebo and who were not infected and remained uninfected[c] until the 3rd injection, the efficacy of the vaccine in preventing cases of CIN 2/3 and cancer *in situ* associated with HPV 16 and 18 infection that were diagnosed at least one month after the 3rd injection was 100%
- in the roughly 17 000 women who received at least one vaccine or placebo injection and who were not infected on the day of the first injection, the efficacy of the vaccine in preventing cases of CIN 2/3 and cancer *in situ* associated with HPV 16 and 18 infection that were diagnosed at least one month after the 1st injection was in the order of **95%, a figure that may be taken as the efficacy of this vaccine in the situation in which it will be used**
- in the roughly 17 000 women who received at least one injection of vaccine or placebo, whether they were infected or not, the efficacy of the vaccine in preventing cases of CIN 2/3 and cancer *in situ* associated with HPV 16 and 18 infection that were diagnosed at least one month after the 1st injection was in the order of 40%;

♦ In these same studies, the efficacy of this vaccine on vulvar condyloma associated with HPV 6, 11, 16 and 18 infection was in the order of 95%[17]

- in the roughly 16 000 women who received three injections of vaccine or placebo and who were not infected and remained uninfected until the 3rd injection, the efficacy of the vaccine in preventing cases of vulvar condyloma associated with HPV 6, 11, 16 and 18 infection that were diagnosed at least one month after the 3rd injection was in the order of 99%

- in the roughly 17 000 women who received at least one vaccine or placebo injection and who were not infected on the day of the first injection, the efficacy of the vaccine in preventing cases of vulvar condyloma associated with HPV 6, 11, 16 and 18 infection that were diagnosed at least one month after the 1st injection was in the order of **95%, a figure that may be taken as the efficacy of this vaccine in the situation in which it will be used**
- in the roughly 17 000 women who received at least one injection of vaccine or placebo, whether they were infected or not, the efficacy of the vaccine in preventing cases of vulvar condyloma associated with HPV 6, 11, 16 and 18 infection that were diagnosed at least one month after the 1st injection was in the order of 70%;

b Fewer than 100 women 24–26 years of age were included in one of the studies
c Seronegative and PCR negative for HPV 6, 11, 16 and 18.

♦ The mean number of sexual partners was 2 and less than or equal to 4 for 99% of the women who took part in the study;
♦ The safety of this vaccine was satisfactory, but the sample sizes were insufficient to detect any adverse event with an incidence of less than 1/4000;

♦ In the women who became pregnant in the month following vaccination, 5 congenital malformations were observed compared with 0 in the placebo group; although this difference is not significant, a note on this point was included in the summary of product characteristics;
♦ The immunological data collected during these trials show a higher antibody titre than that observed after natural infection and suggest that strong, prolonged protection will be provided;
♦ The analysis performed to compare at a population level the epidemiological and economic impact of organising screening and vaccination of 14-year-old adolescent girls shows that:

- priority should be given to the organisation of a screening programme
- nevertheless, vaccination would have a significant extra epidemiological impact: in the first 70 years, a screening programme and a screening programme combined with vaccination would cut the number of diagnosed cancer cases by 16% and 34%, respectively
- at the current price of the vaccine, the estimated cost/efficacy ratio from the viewpoint of the National Health Insurance scheme for vaccination combined with a screening programme would be between € 17,500 and € 35,400 per year of life gained, according to the discount rate used to update benefits, without taking the impact of vaccination on condyloma into account;

Whereas furthermore:
♦ The percentage of women in France who had not had a smear in 6 years was in the order of 34% in 2000, with some regional disparities[18]
♦ In the trial screening programme organised in Bas-Rhin, coverage was 72% after 3 years and 82% after 5 years[19]
♦ Screening is a secondary method for preventing cervical cancer;
♦ The vaccine is a primary method for preventing precancerous and cancerous cervical lesions as well as genital warts;
♦ The treatment of any lesions can have physical and psychological consequences;
♦ The impact of the vaccine on the incidence of and mortality from cervical cancer will only become apparent in the long term, in 15–25 years' time;
♦ The short- and medium-term benefit of this vaccine lies in reducing the potentially traumatic situations of discovering and treating cervical lesions and of discovering and treating vulvar condyloma
♦ There is a possibility that, if vaccinated women were to attend for screening less often, the incidence of and more especially the mortality caused by cervical cancer would rise, since the vaccine is not effective against approximately 30% of cancer cases
♦ It cannot be ruled out that the effect of the vaccine may be only transient because other oncogenic genotypes of HPV may emerge to take the place of genotypes 16 and 18
♦ The duration of the protection provided by the vaccine, as assessed based on a restricted population of roughly 100 women and on immunological data, is at least 5 years, but the long-term duration of protection cannot yet be known
♦ If a booster were to prove necessary and if some women failed to have it, there would be a risk of a shift in the incidence of cervical cancer to an older age group.

The Technical Committee on Vaccinations and the French High Council on Public Health, Transmissible Diseases Section:
♦ **Reiterate their recommendation to organise screening for precancerous and cancerous cervical lesions by means of cervical smears throughout France,** since vaccination against papillomavirus 16 and 18 is not a substitute for it;
♦ **Reiterate their recommendation that information and training measures** be developed for healthcare professionals regarding the complementary nature of vaccination and screening, and on how to address the subject of sex with their young female patients;
♦ **Reiterate their recommendation that a communication campaign to promote screening** for cervical cancer and to emphasise the value of screening, directed at both vaccinated women and non-vaccinated women, be set up by the health authorities;

♦ **Recommend, with a view to the prevention of precancerous and cancerous cervical lesions and the prevention of vulvar condyloma, the vaccination of 14-year-old girls**, in order to protect girls before they are exposed to the risk of HPV infection;
♦ **Recommend that the vaccine also be offered to girls and women aged 15–23** before sexual debut or, at the latest, within the year following the onset of sexual activity, an offer that could be made at the time of an initial prescription for contraception, a request for the morning-after pill, or a medical consultation on any other matter;
♦ **Recommend the expansion of existing arrangements** to permit the funding of vaccination for adolescents who wish to be vaccinated without their parents' approval;
♦ **Recommend that prior to vaccination the doctor should explain** the need for screening, its procedures, the vaccination schedule, the fact that it is preferable not to become pregnant during the month following each injection, the lack of efficacy in preventing approximately 30% of cancer cases, the possibility that a booster dose may become necessary, and that a written document will be sent stating the date on which the person should first attend for screening;
♦ **Recommend that it be made mandatory for companies** that produce or come to produce a vaccine against HPV to promote both the use of this vaccine and screening for cervical lesions in their communications and to mention the lack of efficacy in preventing approximately 30% of cancer cases;
♦ **Request that public health impact studies** be carried out in the following areas: safety; surveillance of congenital malformations in the children born to women who have been vaccinated by mistake during pregnancy or who started a pregnancy immediately after vaccination; duration of protection; incidence of cancerous and precancerous lesions; emergence of new oncogenic HPV genotypes and ecology of HPV genotypes; cross-protection with other genotypes than 16 and 18; impact of vaccination on screening; and impact of vaccination on behaviour regarding the prevention of sexually transmitted infections;
♦ **Call for the establishment of a national reference centre** for papillomavirus;
♦ **Request** that studies be conducted specifically on vaccination in immunocompromised girls and young women;
♦ **Recall** that condom use plays a part in preventing other sexually transmitted infections and therefore the permanence of campaigns promoting the use of condoms must be guaranteed.

References (see Appendix)

4.4. Target population

The target population for vaccination against human papillomavirus 6, 11, 16 and 18 is specified by the Technical Committee on Vaccinations and the French High Council for Public Health in their opinion of 9 March 2007. It corresponds to:

- girls 14 years of age
- girls and young women 15–23 years of age who before sexual debut or at the latest during the year following the onset of sexual activity.

- Population of girls 14 years of age

This corresponds to the complete cohort of girls 14 years of age, or roughly 370 000 girls every year (INSEE data at 1 January 2007: 350 769 individuals)

- Population of girls and young women 15–23 years of age (catch-up population) who have not had sexual intercourse or at the latest during the year following the onset of sexual activity

A study carried out by INPES (The National Prevention and Health Education Institute)[1] provides *inter alia* the proportion (%) of young women who have never had sexual relations in each age group.

In order to estimate the population by age group of girls and young women 15–23 years of age who have not had sexual intercourse or at the latest during the year following the onset of sexual activity (i.e. sexually active for less than a year), the percentages of young women who have never had sexual relations for each age group are applied to the age group cohort for the following year.

1 Guilbert P, Gautier A. Baromètre Santé 2005. INPES

Estimation of the target catch-up population of girls and young women who have never had sexual relations or who have been sexually active for less than a year:

Age group	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**
Total population of age group in question (INSEE population)	367 163	375 262	379 760	384 785	386 634	387 793	392 342	385 647	383 282
Percentage of girls who have never had sexual relations	84.2	65.1	49.8	39.2	25.9	21.0	19.2	12.0	14.7
Percentage of girls and young women 15–23 years of age who have never had sexual relations or who have been sexually active for less than a year (INPES)	**98.4**	**84.2**	**65.1**	**49.8**	**39.2**	**25.9**	**21.0**	**19.2**	**12.0**
Target catch-up population by age group	**381 288**	**315 971**	**247 224**	**191 623**	**151 561**	**100 438**	**82 392**	**74 044**	**45 994**

From the INSEE and INPES data, the population of girls and young women 15–23 years of age who have never had sexual intercourse or who have been sexually active for less than a year is estimated to be approximately 1 570 000 individuals in 2007.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the populations recommended in the opinion of the Technical Committee on Vaccinations and the French High Council for Public Health on vaccination against human papillomavirus 6, 11, 16 and 18 (meeting of 9 March 2007).

4.5.1. Packaging

The packaging is appropriate to prescription requirements.

4.5.2. Reimbursement rate: 65 %

The Transparency Committee considers it is essential that all the public health impact studies mentioned in the opinion of the Technical Committee on Vaccinations and the French High Council for Public Health on vaccination against human papillomavirus 6, 11, 16 and 18 (opinion of 9 March 2007) be carried out.
To the extent that planned or ongoing studies, particularly in the context of the European Risk Management Plan for GARDASIL, may not answer all the questions raised in the opinion of the Technical Committee on Vaccinations and the French High Council for Public Health, specific studies should be carried out.

APPENDIX

References attached to the opinion of the Technical Committee on Vaccinations and the French High Council for Public Health on vaccination against human papillomavirus 6, 11, 16 and 18 (opinion of 9 March 2007).

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