HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

5 March 2008

CERVARIX
suspension for injection, Human Papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) – pre-filled 0.5 mL syringe + needle (B/1)
(CIP: 381 642-3)

Applicant: GLAXOSMITHKLINE

List I

Marketing authorisation (MA) date: 20 September 2007 (centralised procedure)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance

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

L1 protein in the form of non-infectious virus-like particles (VLPs) produced by recombinant DNA technology are adsorbed onto hydrated aluminium hydroxide as is the AS04 adjuvant (containing 3-O-desacyl-4'- monophosphoryl lipid A)

1.2. Background

CERVARIX is a bivalent recombinant vaccine indicated for the prevention of high-grade Cervical Intraepithelial Neoplasia (CIN grades 2 and 3) and cervical cancer caused by Human Papillomavirus types 16 and 18.

1.3. Indication

"CERVARIX is indicated for the prevention of high-grade cervical intraepithelial neoplasia (CIN grades 2 and 3) and cervical cancer caused by Human Papillomavirus (HPV) types 16 and 18.

The indication is based on the demonstration of efficacy in youg women aged 15-25 vaccinated with Cervarix and on the immunogenicity of the vaccine in youg women aged 10-25 (see SPC)

Cervarix should be administered according to official guidelines.

1.4. Dosage

The recommended vaccination schedule consists of 3 doses given at 0, 1, and 6 months.
The need for a booster dose has not been established.

It is recommended that subjects who receive a first dose of Cervarix complete the three-dose vaccination course with Cervarix.

Girls under the age of 10: Cervarix is not recommended for use in girls under the age of 10 due to the lack of safety and immunogenicity data in this population.

Cervarix should be administered intramuscularly in the deltoid region.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2007)

Pharmaco-therapeutic group: J07BM02

J: General anti-infectives for systemic use
07:Vaccines
B: Viral vaccines
M: Papillomavirus vaccines
01: Papillomavirus (type 16, type 18)

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines

GARDASIL Human Papillomavirus Vaccine (types 6, 11, 16, 18)

The indications for GARDASIL are not identical to those of CERVARIX.
GARDASIL has obtained a wider range of indications: it is indicated in the prevention of

- high-grade cervical dysplasia (CIN 2/3), cervical cancers
- high-grade vulvar dysplasia (VIN 2/3)
- external genital warts (condyloma acuminata) caused by Human Papillomavirus types 6, 11, 16 and 18.

Unlike GARDASIL, CERVARIX is not indicated for the prevention of precancerous vulvar lesions of grade 2 or worse (VIN 2 orworse) and, because of its composition, it is not indicated for the prevention of lesions due to HPV genotypes 6 and 11 (particularly genital warts and CIN).

2.3. Medicines with a similar therapeutic aim

None

3 ANALYSIS OF AVAILABLE DATA

3-1 Efficacy

The preventative efficacy of Cervarix was assessed in two (phase II and phase III) controlled, double-blind, randomised, placebo-controlled clinical trials involving youg women aged 15 to 25.
In addition, retrospective analyses were joined to the clinical file.

3.1.1 Phase II study (HPV-001 study, involving 1,113 female subjects and HPV-001 follow-up study - HPV-007 - on 776 women)
This study assessed the efficacy of the vaccine, particularly in preventing incidental and persistent infection caused by Human Papillomavirus (HPV) type 16 and/or 18.

3.1.2 Phase III study (HPV-008, involving 18,644 vaccinated female subjects)
This study assessed the efficacy of the vaccine in preventing CIN lesions of grade 2 or worse: CIN 2 and CIN 3 (high-grade cervical intraepithelial neoplasias, AIS [adenocarcinoma *in situ]* and invasive cancer associated with Human Papillomavirus (HPV) type 16 and/or 18.

3.1.3 Retrospective analyses:
. an unpublished analysis of pooled data from studies HPV-001/007 (phase II) and HPV-008 (phase III) evaluating the efficacy of the vaccine in preventing CIN 2 associated with HPV type 18
. an indirect comparative analysis of the cross-protection afforded by CERVARIX versus GARDASIL in terms of efficacy against oncogenic HPV type 45: the HPV-008 study versus FUTUR I and FUTUR II meta-analyses.

3-1-1 Phase II trial (HPV study 001/007)

Placebo-controlled, randomised, double-blind trial (study HPV-001) on youg women aged 15 to 25 and its follow-up study (study HPV-007).

Study HPV-001

Purpose
The purpose of this trial was to assess the efficacy of the vaccine (given in three doses at 0, 1 and 6 months) *versus* placebo (aluminium hydroxide) in preventing incident and persistent infections related to Human Papillomavirus (HPV) type 16 and/or 18 in 1,113 youg women aged 15 to 25 who were not infected with HPV at baseline.

The girls and young women included in the study (560 in the vaccine arm, and 553 in the placebo arm) had to:

- be seronegative for HPV-16 and 18 (ELISA test)
  - have a negative viral DNA test for oncogenic HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 (PCR test)
- have a normal cervical smear test result.

Tests carried out at baseline included:
- a cervical smear (for cytology and HPV viral genome testing: PCR test)
- serology (antibody testing): ELISA test
- a biopsy if any abnormality was detected on cytology.

Length of Study
The trial lasted 18 months. Follow-up continued until the 27th month.

Primary efficacy endpoint:
Prevention of incident infection[1] of the cervix with papillomavirus type 16 and/or 18 between the 6th month and the 18th month in female subjects who were not infected at baseline
(DNA test negative and seronegative)

Secondary endpoints, in particular:
Prevention of persistent infection[2] with papillomavirus type 16 and/or 18 between the 6th month and the 27th month

Results
Primary endpoint: Incident infection
Preventative efficacy, expressed as a reduction in the relative risk of occurrence of incident infection with HPV-16 and/or HPV-18, between month 6 and month 18 (per-protocol population)

	Type of HPV	**N/n**		**Efficacy**	
		Cervarix N = 366	**Placebo N = 355**	**% (95% CI)****	**p**
Incident infection	**16/18***	**2**	**23**	**91.6 (64.5 – 98)**	**< 0.001**
	16	0	18	**100** (79.4 – 100)	< 0.001
	18	2	7	72.3 (-32.5– 94.2)	NS

* protocol-specified endpoints
** expressed as relative risk reduction

The preventative efficacy of the vaccine was observed in terms of a reduction in the relative risk of occurrence of incident infection with papillomavirus type 16 and type 16 and 18.
It was not observed in terms of a reduction in the relative risk of occurrence of incident infection with papillomavirus type 18.

Secondary endpoint: Persistent infection (at 6 months)
Vaccine efficacy, expressed as a reduction in the relative risk of occurrence of persistent infection (at 6 months) with HPV-16 and/or HPV-18 between the 6th month and the 27th month (results for intention-to-treat [ITT] population).

	Type of HPV	**N/n**		**Efficacy**	
		Cervarix N = 560	**Placebo N = 553**	**% (95% CI)**	**p**
Persistent infection (at 6 months)	16/18	1	20	95.1 (63.5 – 99.3)	<0.001
	16	1	16	93.9 (53.2 – 99.2)	<0.001
	18	0	5	100.0 (24.4 – 100.0)	0.025

The preventative efficacy of the vaccine was observed in terms of a reduction in the relative risk of occurrence of persistent infection (at 6 months) caused by HPV-16 and/or 18, HPV 16 and HPV 18 between the 6th month and 27th month.

1 Incident infection: positive PCR viral DNA detection test on one cervical smear sample

2 Persistent infection: detection of viral DNA of the same viral serotype in two cervical smear samples taken 6 months apart (and at 12 months post-hoc)

HPV-007 Study (follow-up to HPV-001 Study)
A subset of women (N=776) who received the 3 doses of vaccine or placebo in study 001 was followed in study HPV-007 for an average of 5 years/60 months after the 1st dose (minimum 27 months in study 001 and 24 months in study 007).
N = 393 women in the vaccine arm
N = 383 women in the placebo arm

Results:
Primary endpoint: Incident infection
Long-term preventative efficacy of the vaccine against incident infection with HPV-16 and/or HPV-18 (ITT population).
Interim results no earlier than at 27 months in study 001 + 24 months in study HPV-007)

Incident infection	**Cervarix**		**Placebo**		**Efficacy % (95% CI)**	**p**
	N	**n**	**N**	**n**		
HPV-16/18*	**352**	2	**313**	50	**96.7 (87.6 – 99.6)**	**< 0.001**
HPV-16	353	2	322	38	95.5 (82.5 – 99.5)	< 0.001
HPV-18	356	0	332	20	100.0 (81.6 – 100.0)	< 0.001

* protocol-specified endpoints
N = number of subjects included in each arm n = number of cases
The preventative efficacy of the vaccine was observed in terms of a reduction in the relative risk of occurrence of incident infection caused by type HPV-16 and type HPV 16and HPV 18 at an average of 5 years after the first vaccine dose.

Secondary endpoints: Persistent infection (at 6 months and 12 months) and CIN 2+ (in particular)
Long-term preventative efficacy of the vaccine, expressed as a reduction in the relative risk of occurrence of persistent infection with HPV-16 and/or HPV-18 (ITT population)

Interim results no earlier than at 27 months in study 001 + 24 months in study HPV-007)

	Cervarix		**Placebo**		**Efficacy % (95% CI)**	**p**
	N	**n**	**N**	**n**		
Persistent infection (at 6 months)						
HPV-16/18	357	0	329	24	100.0 (85.4 – 100.0)	<0.001
HPV-16	357	0	331	20	100.0 (81.9 – 100.0)	<0.001
HPV-18	358	0	342	8	100.0 (44.6 – 100.0)	0.003
Persistent infection (at 12 months)						
HPV-16/18	357	0	340	12*	100.0 (66.5 - 100.0)	<0.001
HPV-16	357	0	341	10	100.0 (58.1 - 100.0)	<0.001
HPV-18	358	0	344	4	100 (-45.5 - 100.0)	NS

N = number of subjects included in each arm n = number of cases
* number of infections with HPV 16 and/or 18 may be lower than the number of infections with HPV-16 + HPV-18 if co-infection occurs (12 cases of HPV-16 and/or 18, with 10 cases of HPV-16 and 4 cases of HPV-18)
The preventative efficacy of the vaccine was observed as a reduction in the relative risk of occurrence of persistent infection (at 12 months) caused by HPV-16 and/or 18 and HPV 16 at an average of 5 years after the first vaccine dose. It was not observed in terms of a reduction of the relative risk of occurrence of persistent infection (at 12 months) caused by papillomavirus type 18.
The preventative efficacy of the vaccine in terms of risk of occurrence of high-grade cervical intraepithelial neoplasias (CIN 2+) associated with infection with papillomavirus type 16 and/or 18 at an average of 5 years after the first vaccine dose has not been established:
100% (95% CI: -45.3; 100) p: NS.

Incident and persistent infection were not included in the indications listed in the marketing authorisation.

3-1-2 Phase III trial (HPV-008 Study)

Randomised, double-blind, placebo-controlled (hepatitis A vaccine) clinical trial involving youg women aged 15-25

Purpose

The purpose of this study was to evaluate the preventative efficacy of the vaccine (in 3 doses at 0, 1 and 6 months) in preventing lesions of CIN 2+ : CIN 2 and CIN 3 (high-grade cervical intraepithelial neoplasia lesions), AIS (adenocarcinoma *in situ*) and invasive cancer caused by Human Papillomavirus (HPV) type 16 and/or type 18 in 18,644 girls and young women aged 15-25 by comparing the vaccine with a placebo.

The study included women who had not been pre-screened, who were infected or uninfected with HPV and who had a normal or low-grade cervical smear (N = 18,644: 9,319 in the vaccine arm and 9,325 in the placebo arm).

The girls and young women who were included:
- had a negative or positive PCR test (a test to detect the DNA of high-risk oncogenic HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68; types 31, 33, 35, 52 and 58 are phylogenetically similar to HPV-16, and types 45 and 59 are phylogenetically similar to HPV-18)
- had to have a normal or low-grade CIN 1 cervical smear (women with high-grade cytological abnormalities were excluded).

At baseline, current and/or prior infection was detected in approximately 26% of women.
- 20% of women had evidence of prior infection (i.e. HPV-16 and/or HPV-18 seropositive).
- 7% percent of women were infected at the time of vaccination (i.e. DNA test positive for HPV-16 and/or HPV-18 DNA) and only 0.5% of these women had positive DNA tests for both types.

Tests carried out at baseline included:
- a cervical smear (cytology - testing for HPV viral genome: PCR test)
- serology (antibody testing): ELISA test
- a biopsy if abnormalities were detected on cytology.

Study duration:

The final analysis will be carried out after confirming 36 cases of CIN 2+ caused by HPV 16/18.
An interim analysis, as specified in the protocol, was carried out after 23 cases of CIN 2+ were confirmed. This was carried out after an average follow-up period of 15 months after the first vaccine dose.

Definition of the population to be included in the interim analysis

1 – The interim analysis, which was done after an average 15-month follow-up period, was performed on a limited population of female subjects who, at baseline, had no current infection, no anti-HPV-16 or 18 antibodies, no HPV-16 or 18 DNA and normal or low-grade (CIN 1) cytology.
This interim analysis was carried out on 15,626 female subjects (7,788 in the vaccine arm and 7,838 in the placebo arm/TVC-1 population) who had:
- a negative PCR test to detect HPV DNA and were seronegative for HPV type 16 or type 18 (ELISA test)
- normal or low-grade cytology
- received at least one dose of vaccine or placebo.

A further planned analysis (TVC-2) was carried out, which excluded women with low-grade abnormal cytology (CIN 1).

2—An additional interim analysis (average follow-up period 15 months) was carried out to only include those female subjects within the TVC-1 population who had cervical intraepithelial neoplasia (CIN 2+) linked solely to HPV-16 or HPV-18, and exclude cervical intraepithelial neoplasia (CIN 2+) attributable to other HPV types.

Primary endpoint:
Prevention of high-grade cervical intraepithelial neoplasias (CIN 2+) caused by infection with Human Papillomavirus type 16 and/or 18 in female subjects who are HPV DNA negative and HPV-16/18 seronegative.

Grade 2 and 3 Cervical Intraepithelial Neoplasias (CIN) were used as surrogate markers for cervical cancer.

The evaluation of the primary endpoint was supported by biopsies that revealed cervical intraepithelial neoplasias (CIN 2+) and the presence of HPV-16 and/or HPV-18. A CIN 2+ lesion with the presence of HPV-16 and/or HPV-18, was counted, regardless of whether these types of HPV actually caused the lesion.
At the time of the interim analysis (month 15), cases of co-infection involving one or more types of oncogenic HPV that were not contained in the vaccine were observed (14 of the 23 cases of lesions of grade CIN 2+).
As a result, an additional interim analysis was carried out at 15 months with the aim of determining whether HPV-16 and/or HPV-18 did in fact cause these lesions.

Secondary endpoints, in particular:
- Prevention of persistent infection (at 12 months) with papillomavirus 16/18 in HPV DNA negative and seronegative female subjects
- Prevention of persistent infection (at 6 and 12 months) associated with oncogenic Human Papillomavirus types 16, 18 and other oncogenic HPV types 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 in females who were HPV DNA negative and seronegative for oncogenic HPV types.

Results (average follow-up period: 15 months after the first vaccine dose)

Primary endpoint (cervical intraepithelial neoplasia: CIN 2+)

1 - Interim analysis of female subjects with a negative PCR DNA test, HPV 16 and HPV-18 seronegativity (ELISA test) and normal or low-grade cytology at baseline (intention-to-treat population)

Preventative efficacy, expressed as a reduction in the relative risk of occurrence of cervical intraepithelial neoplasia (CIN 2+) associated with HPV 16/18, HPV 16 or HPV 18

HPV-008 Study	**Cervarix**		**Placebo**		**Efficacy (97.9% CI)**	**p**
	N	**n**	**N**	**n**		
CIN 2+ (primary efficacy endpoint)						
HPV-16 and/or 18*	7788	2	7838	21	90.4 (53.4; 99.3)	p<0,0001
HPV 16	6701	1	6717	15	93.3 (47.0; 99.9)	p<0,0005
HPV 18	7221	1	7258	6	83.3 (<0.0; 99.9)	NS
N = number of subjects included in each arm n = number of cases * protocol-specified endpoints						

The preventative efficacy of the vaccine was observed in terms of reduction of the relative risk of occurrence of cervical intraepithelial neoplasias (CIN 2+) associated with papillomavirus type 16 and/or 18 and type 16.
It was not observed in terms of reduction of the relative risk of occurrence of cervical intraepithelial neoplasias (CIN 2+) associated with papillomavirus type 18.

2 – An additional interim analysis on cases considered to be caused solely by HPV-16 and HPV-18 infection acquired during the study.
Several of the CIN 2 or worse lesions contained multiple oncogenic types (including HPV types other than those contained in the vaccine). An additional analysis was carried out to determine the efficacy of the vaccine against lesions likely to be caused exclusively by Human Papillomavirus type 16 and/or type 18.
This post-hoc analysis (clinical case assignment) attributed a causal relationship of a given HPV type with the lesion based on the presence of this HPV type in cervical samples prior to detecting the lesion.

Based on this case assignment, the analysis excluded three CIN 2+ cases (two in the vaccine group and one in the control group), which were not considered to be caused by HPV-16 or HPV-18 infections acquired during the trial.

Based on this analysis, the vaccine's efficacy was:
- 100% (95% CI 74.2%-100%; p<0.0001) for CIN 2+ caused by HPV 16 and/or HPV-18
- 100% (95% CI 64.5 %-100%; p<0.0001) for CIN 2+ caused by HPV 16
- 100% (95% CI - 49.5 %-100%; p=NS) for CIN 2+ caused by HPV 18

Secondary endpoints:
In female subjects who have a negative PCR DNA test, HPV 16 and HPV-18 seronegativity (ELISA test) and normal or low-grade cytology (CIN 1)

Persistent infection (at 12 months) with papillomavirus 16/18:
Preventative efficacy expressed as a reduction in the relative risk of occurrence of persistent infection with papillomavirus 16/18 at 12 months:

Study HPV-008	**Cervarix**		**Placebo**		**Efficacy (97.9% CI)**	**p**
	N	**n**	**N**	**n**		
12-month persistent infection (secondary endpoint)						
HPV-16 and/or 18*	3386	11	3437	46	75.9 (47.7;90.2)	p<0,0001
HPV 16	2945	7	2972	35	79.9 (48.3;93.8)	p<0,0001
HPV 18	3143	4	3190	12	66.2 (<0.0; 94.9)	NS
N = number of subjects included in each arm of the TVC-1 cohort n = number of cases * protocol-specified endpoints						

The preventative efficacy of the vaccine was observed in terms of reduction of the relative risk of occurrence of persistent infection with Human Papillomavirus type 16 and/or 18 and type 16. It was not observed in terms of relative risk of occurrence of persistent infection with papillomavirus type 18.

In a further protocol-specified analysis (TVC-2) excluding females with low-grade abnormal cytology (CIN 1) at baseline, the preventative efficacy of the vaccine was observed in terms of reduction in relative risk of occurrence of persistent infection with HPV 18.
One case was observed in the vaccine arm, compared to 10 cases in the control arm:
[89.9% (CI 97.9%: 11.3; 99.9)] p=0.0117

Persistent infection (at 6 and 12 months) with oncogenic Human Papillomavirus other than types 16 and 18:
The protective efficacy of the vaccine against persistent infection (at 6 and 12 months) with different high-risk HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 (TVC-1 population)

Type of HPV	**Cervarix**		**Placebo**		**Efficacy % (97.9% CI)**	**p**
	N	**n**	**N**	**n**		
Persistent infection (at 6 months) (subjects negative for DNA and seronegative for virus type being analysed)						
45	**6 724**	**10**	**6 747**	**25**	**59,9 (2,6 – 85,2)**	**0,0165**
31	6 615	47	6 667	74	36,1 (0,5 – 59,5)	0,0173
52	6 532	79	6 573	116	31,6 (3,5 – 51,9)	0,0093
Persistent infection (at 12 months) (subjects negative for DNA and seronegative for virus type being analysed)						
HPV-wHR*	3 611	100	3 632	137	27,1 (0,5 – 46,8)	0,0174

* High-risk HPV excluding types 16/18: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68

Persistent infection and lesions involving types of oncogenic HPV other than 16 and 18 were not included in the indications listed in the marketing authorisation.

Prophylactic efficacy in women with current or prior infection

There was no evidence of protection from disease caused by the HPV types for which subjects were HPV DNA-positive at study entry. However, individuals already infected with one of the vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the remaining HPV type.

3.1.3 Retrospective analyses

. An unpublished analysis of pooled data from studies HPV-001/007 (phase II) and HPV-008 (phase III) evaluating the efficacy of the vaccine in the prevention of CIN 2 associated with HPV type 18

The evidence provided by these results is of low quality. The HPV-008 results that are under consideration here come from an interim analysis carried out at 15 months (average follow-up period duration) and study HPV-001/07 does not use CIN 2 as a primary endpoint.

. an unpublished indirect comparative analysis of the cross-protection afforded by CERVARIX versus GARDASIL in terms of efficacy against oncogenic HPV type 45: the HPV-008 study viewed alongside a pooled analysis of the FUTUR I and FUTUR II studies

This document groups disparate data sets coming from the HPV-001/007 studies and the HPV-008 study with the FUTUR I and FUTUR II studies, and does not use an methodology appropriate for carrying-out indirect comparisons.

3-2 Immunogenicity

For the HPV vaccines, there has been no determination of a minimum level of antibodies that protect against grade 2 or 3 CIN or against persistent infection caused by the vaccine HPV types.
The anti HPV-16 and anti HPV-18 antibody responses were measured using an ELISA test specific for each genotype and known for being correlated with the pseudovirion-based neutralisation assay.
The immunogenicity induced by three doses of Cervarix was evaluated in 5,303 female subjects aged 10 to 55.
In the clinical trials, 99.9% of initially seronegative subjects seroconverted for both HPV types 16 and 18 after the third dose.

Vaccine-induced IgG Geometric Mean Titres (GMT) were well above the titres observed in women who had been previously infected but who had cleared HPV infection (natural infection). Initially seropositive and seronegative subjects reached similar levels after vaccination.

001/007 Study (phase II)

Study 001/007, which included youg women aged 15 to 25 at the time of vaccination, evaluated the immune response to HPV 16 and HPV 18 at up to 64 months after the first dose.
The IgG Geometric Mean Titres (GMT) for HPV-16 and HPV-18 peaked at month 7 and then declined to reach a plateau extending from month 18 up to the end of month 64.
At the end of the follow-up period, GMTs for both HPV-16 and HPV-18 were still at least 11 times higher than titres observed in previously infected women who had cleared the virus. More than 98% of the women were still seropositive for both antigens.

HPV 008 Study (phase III)

In study 008, immunogenicity was similar to what was observed in study 001.

HPV 014 Study (phase III: female subjects aged 26-55 and youg women aged 15-25)
In this clinical trial, which was performed in female subjects aged 15 to 55, all subjects seroconverted for both HPV types 16 and 18 after the third dose (at month 7).

The GMTs were, however, lower in subjects over 25 years of age. Nevertheless, all subjects remained seropositive for both types up to month 18 and maintained antibody levels that were clearly above those encountered after natural infection.

Extrapolation of the efficacy of Cervarix from young adult women to adolescents
HPV 012 study (phase III, N=770 females aged 15-25 and girls aged 10-14)
HPV 013 study (phase III, N=2067 girls aged 10-14)
In two clinical trials performed in girls and adolescents aged 10 to 14, all subjects seroconverted for HPV type 16 and 18 after the third dose (at month 7) with GMTs at least twice as high as in females aged 15 to 25.
The efficacy of CERVARIX in girls aged 10 to 14 was deduced from this data.

Additional studies:

- Modelling at 50 years of the persistence of HPV-16 and HPV-18 antibodies (unpublished)

This model needs to be validated using real data and several supplementary sensitivity analyses are required.
The model does not take into account the risk of immunosenescence, the possibility that antibody levels may slowly decline later in life, the role of T lymphocytes and their interaction with B lymphocytes.
In addition, the relationship between residual antibody levels, vaccine efficacy and time remains hypothetical. As a result, the Committee cannot take this model into account.

HPV-010 Study:

Interim results from the 7th month of a study (HPV-010) comparing the immune responses induced by CERVARIX and GARDASIL were issued by the manufacturer on the 1st of February 2008. The Committee cannot take these interim results into account.

- Unpublished modelling (epidemiological and medico-economic impact):

The manufacturer has submitted the results of modelling, for which the aim was to estimate the expected impact across the population of CERVARIX vaccination associated with screening on morbidity and mortality related to precancerous and cancerous cervical lesions caused by oncogenic HPV. This model also contains a medico-economic comparison of screening associated with HPV vaccination using CERVARIX versus GARDASIL. This model cannot be considered completely reliable given the methodological limits (inadequate documentation on the internal and external validity of the model; failure to take into account uncertainty as to how values for model parameters are determined; sensitivity analysis on too few variables without justification for the variation intervals used; presentation of the model that does not enable easy identification of all of the hypotheses). Therefore, the Committee considers that the results of this modelling exercise are exploratory in scope, and do not provide the means with which to confidently estimate the impact of CERVARIX vaccination on morbidity and mortality and the vaccine's medico-economic ramifications.

3.3 Safety

In clinical studies of female subjects aged 10 to 72 (of whom 79.2% were aged 10-25 at the time of enrolment), Cervarix was administered to 16,142 subjects whilst 13,811 subjects received a placebo. These subjects were followed for serious adverse events over the entire study period.

In a pre-defined subset of subjects (Cervarix = 8,130 versus placebo = 5,786), adverse events were followed for 30 days after each injection.
The most common adverse reaction observed after vaccine administration was injection site pain, which occurred after 78% of all doses. The majority of these reactions were of mild to moderate intensity and of short duration.

In the subjects who received CERVARIX, adverse effects linked to the vaccine are given below in order of frequency (very common ≥ 1/10, common ≥ 1/100 and < 1/10 and uncommon ≥ 1/1 000 and < 1/100)

Nervous system disorders:
Very common: headache
Uncommon: dizziness

Gastrointestinal disorders:
Common: gastrointestinal symptoms including nausea, vomiting, diarrhoea and abdominal pain

Skin and subcutaneous tissue disorders:
Common: itching/pruritus, rash, urticaria

Musculoskeletal and connective tissue disorders:
Very common: myalgia
Common: arthralgia

Infections and infestations:
Uncommon: upper respiratory tract infection

General disorders and administration site anomalies:
Very common: injection site reactions including pain, redness, swelling; fatigue
Common: fever (≥38℃)
Uncommon: other injection site reactions such as induration and local paraesthesia

Clinical trial data have shown a satisfactory safety profile.
Local injection site reactions, myalgia and arthralgia were observed more frequently in the CERVARIX arm than in the placebo arm.
No specific studies on pregnant women have been carried out, and use of the vaccine is not recommended during pregnancy. Few subjects (0.2%) left the study because of adverse effects.

Of the 16,142 subjects who received the CERVARIX vaccine and the 13,811 who received the placebo, 882 had at least one adverse event (459 in the vaccine arm and 423 in the placebo arm). Of the 27 subjects who experienced a serious adverse event that was possibly linked to vaccination, five involved suspected autoimmune disease.

A similar safety profile has been observed in subjects with prior or current HPV infection when compared to subjects negative for oncogenic HPV DNA or seronegative for HPV-16 and HPV-18 antibodies.

Supplementary data:

An unpublished meta-analysis of data from controlled studies included in the development of three vaccines containing the AS04 adjuvant (Fendrix, Simplirix, Cervarix) has been carried out.

The quality of the evidence of the results of this meta-analysis cannot be considered to be optimal, given that the events involved are rare (frequency less than 1%).
As a result, the data would need to be re-analysed, and additional sensitivity analyses would need to be performed.

3.4. Conclusion (efficacy, immunogenicity, safety)

In clinical trials involving youg women aged 15 to 25 whom, at baseline, were not infected by the types of human papillomavirus targeted by the vaccine, and who had normal or low-grade cytology

- CERVARIX was determined to be effective for up to 15 months (following the first dose of vaccine) in the prevention of high-grade (CIN 2 or worse) cervical intraepithelial neoplasias (CIN 2, CIN 3, adenocarcinoma *in situ* and invasive cancer) associated with Human Papillomaviruses:

  . type 16 and/or 18: vaccine efficacy was 90.4% (CI 97.9%: 53.4; 99.3)
  An additional analysis was carried out to determine the efficacy of the vaccine against lesions likely to be caused exclusively by Human Papillomavirus type 16 and/or 18. According to this analysis, vaccine efficacy was 100% (95% CI 74.2%-100%) against CIN 2+ caused by HPV 16 and/or 18

  . type 16: vaccine efficacy was 93.3% (CI 97.9%: 47.0; 99.9)
  According to the supplementary analysis that was done to evaluate the efficacy of the vaccine against lesions likely to be caused solely by Human Papillomavirus type 16, vaccine efficacy was 100% (95% CI 64.5%-100%) for CIN 2+ linked to HPV-16

  (Grade 2 and 3 CIN were used in the clinical trials as surrogate markers for cervical cancer)

- the efficacy of CERVARIX vaccination in preventing high-grade cervical intraepithelial neoplasias of CIN 2+ (CIN 2 and 3, adenocarcinoma *in situ* and invasive cancer) associated with human papillomavirus type 18 or caused exclusively by human papillomavirus type 18 has not been formally established.
It has been established that the vaccine is effective in preventing persistent infection (at 12 months) associated with human papillomavirus type 18 (secondary endpoint) in a sub-population of females aged 15-25 not infected at baseline and who had normal cytology (women with low-grade abnormal cytology were excluded at baseline).

Persistent infection and lesions involving types of oncogenic Human papillomavirus other than types 16 and 18, which were evaluated in other studies, were not included in the indications listed in the marketing authorisation.

There was no evidence of protection from disease caused by the HPV types for which subjects were HPV DNA-positive at study entry. However, females subjects already infected with one of the vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the remaining HPV type.

The efficacy of the vaccine in male subjects has not been evaluated.

At the end of the follow-up period in study HPV-001/007 (up to 64 months after the first dose of the vaccine), GMTs for both HPV-16 and HPV-18 were still at least 11 times higher than titres observed in women previously infected but who had cleared HPV infection. More than 98% of the women were still seropositive for both antigens.

Immune responses observed in these studies have made it possible to extrapolate data on CERVARIX vaccination efficacy observed in adolescent and young adult women to adolescent girls aged 10-15.

Safety data are currently limited to the results of clinical studies.
These data have shown a satisfactory safety profile. Local injection site reactions, myalgia and arthralgia were observed more frequently in the vaccine arm than in the placebo arm. Few individuals (0.2%) left the study because of undesirable effects.

Based on the current state of the dossier, the following data have not been established:
- the efficacy in terms of preventing cervical cancer
- the duration of protection afforded by the vaccine (dosage schedules and the need for booster doses have not been studied)
- immunogenicity in immunocompromised populations that are at high risk for progressive HPV infection
- possible interactions with other vaccines if administered at the same time
- the long-term persistence of immunity after 64 months
- the long-term safety of the AS04 adjuvant.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

CERVARIX is a vaccine used against Human papillomavirus types 16 and 18 to prevent high-grade intraepithelial cervical neoplasias (CIN grades 2 and 3) and cervical cancer caused by human papillomavirus (HPV) types 16 and 18, which can be life threatening.

This product is intended to provide preventative treatment (primary prevention).

It has a high vaccine efficacy/safety ratio.

Public Health Benefit

Cervical cancer still causes significant mortality in France.
It constitutes a moderate public health burden.
Reducing the incidence of cervical cancer is a public health need (a priority identified by the French National Technical Group for Defining Public Health Objectives [GTNDO] and the French Public Health Act). Vaccination against oncogenic Human Papillomavirus (HPV) may be a response to this need, in addition to optimising cervical smear screening throughout the country.
Given the results of studies that demonstrate that the CERVARIX vaccine is effective in preventing high-grade intraepithelial cervical neoplasia of CIN 2 or worse caused by human papillomavirus 16 and/or 18, CERVARIX is expected to have a significant impact on reducing morbidity in the short term. However, we cannot have full confidence that this impact will be extensive, as it has not been formally demonstrated that CERVARIX is effective against CIN of grade 2 or higher caused by HPV type 18.
There is no guarantee that these data may be transposable to the long term, since:
- 30% of cervical cancers are linked to types of oncogenic HPV other than those contained in CERVARIX. If vaccinated women were to be screened less often, the risk the incidence and mortality from such cancer increasing could not be ruled out.
- the duration of the protection provided by the vaccine is not yet known
- the long-term safety of the adjuvant has not been established.

As a result, the expected public health benefit of CERVARIX is moderate at best given the above uncertainties and the assumption that relevant populations are optimally covered by organised screening for precancerous and cancerous cervical lesions.

There is an alternative vaccine.
Screening based on a cytological test – a cervical smear – is an effective secondary means of preventing cervical cancer.

The medical benefit provided by this vaccine is substantial within the marketing authorisation indication, although the Transparency Committee considers that the quality of evidence for this vaccine in terms of preventing precancerous cervical lesions caused by human papillomavirus 18 is not optimal, and that this vaccine has more limited therapeutic indications than the alternative vaccine (see section 4.3 “*Therapeutic use*”).

4.2. Improvement in actual benefit

CERVARIX is a method of primary prevention intended to avoid the short- and medium-term morbidity linked to high-grade intraepithelial cervical neoplasias (CIN grades 2 and 3).

Its preventative effect on the occurrence of cervical cancers, which has not yet been demonstrated and is theoretically limited to 70% of cases (human papillomavirus types 16 and 18 are only involved in 70% of cervical cancers), will only become evident in the long term, as it is estimated that the period between human papillomavirus infection and the emergence of invasive cancer is of the order of 15-25 years.

Bearing in mind on the one hand the fact that:

- this vaccine is effective in preventing precancerous cervical lesions (high-grade intraepithelial neoplasias, CIN 2 and 3) caused by Human Papillomavirus genotypes 16 and/or 18 and genotype 16.
- the vaccine has a satisfactory safety profile in clinical trials
- the immune response induced by this vaccine lasts up to 64 months after the first dose

and on the other hand, the fact that:

- the quality of evidence related to the prevention of precancerous cervical lesions (high-grade intraepithelial neoplasias, CIN grades 2 and 3) caused by human papillomavirus genotype 18 is lower for CERVARIX than for GARDASIL
- there is uncertainty relating to the long-term safety profile (which has not yet been established) of the AS04 adjuvant,

the Committee considers that the CERVARIX vaccine does not provide any improvement in actual benefit (IAB V) in comparison to the GARDASIL vaccine in the strategy for preventing precancerous and cancerous cervical lesions caused by Human Papillomavirus (HPV) types 16 and 18 in the populations recommended by the High Council for Public Health of France (opinion dated 14 December 2007) as well as the French Technical Committee on Vaccination and the French Superior Council for Public Hygiene (opinion dated 9 March 2007) relating to vaccination against human papillomaviruses.

In addition, the Committee wishes to emphasise (as it did for GARDASIL) that:
- the duration of protection provided by the vaccine is not known
- the safety profile would need to be confirmed under conditions of real use
- there may be harmful effects caused by the vaccine:
    - . decreased condom use, since the vaccine may be perceived as protection against all sexually transmitted diseases
    - . reduced use of cervical cancer screening, 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 towards an older age group if a booster were proven to be necessary and some women failed to have it
    - . a selection for other oncogenic HPV types.

In any case, the Committee reiterates that cervical smear tests to screen for precancerous and cancerous cervical lesions (secondary prevention) should be organised and carried out in all areas of the country.

It also points out that the explanations, which need to be given to girls and young women by doctors prior to vaccination, should be compiled in a written document and validated by the competent authorities.

4.3. Therapeutic use

4.3.1. Opinion of the French High Council for Public Health

Relating to vaccination against human papillomavirus types 16 and 18 with a bivalent vaccine

14 December 2007

"The High Council for Public Health insists on reiterating that data relating to the epidemiology of papillomavirus, cervical cancer, genital warts and cervical cancer screening can be found in the 9 March 2007 opinion of the French Technical Committee on Vaccination and Superior Council for Public Hygiene, in the communicable diseases section in the opinion concerning a quadrivalent vaccine against genotypes 6, 11, 16 and 18[3] and in an appendix to the opinion herein.

Whereas

♦ in addition to a quadrivalent vaccine that provides protection against genital lesions caused by human papillomavirus (HPV) genotypes 6, 11, 16 and 18 (Gardasil®), a bivalent vaccine against HPV genotypes 16 and 18 (Cervarix®) has been granted marketing authorisation

♦ this vaccine has undergone a phase III therapeutic trial involving 18,644 youg women aged 15-25, of whom 9,319 received the bivalent vaccine and 9,325 a hepatitis A vaccine that was used as a placebo

♦ data analysis included 15,626 women (7,788 in the HPV vaccine arm and 7,838 in the "placebo" arm) who, at baseline, had no antibodies to HPV 16 or 18, no HPV 16 or HPV-18 DNA, and normal or low-grade cytology (ASC-US[4] or LSIL[5]), and who received at least one dose of vaccine

♦ the primary endpoint was the occurrence of CIN[6] 2 or worse associated with HPV 16 and/or HPV 18

♦ this analysis was an interim analysis, provided for by the protocol, done after 23 cases of CIN 2+ were confirmed; at the time of analysis, the average follow-up period was 15 months

♦ one case of CIN 2+ linked to HPV 16 occurred in the HPV vaccine arm, versus 15 in the placebo arm,

♦ one case of CIN 2+ linked to HPV 18 occurred in the HPV vaccine arm, versus 6 in the placebo arm,

♦ differences are statistically significant (vaccine efficacy 90.4%, 95% confidence interval[7] (95% CI) 53.4%-99.3%; p<0.0001) for the data relating to CIN 2+ linked to HPV 16 or 18 and for data relating to CIN 2+ linked to HPV 16 (vaccine efficacy 93.3 %, 95% CI 47.0%-99.9%; p=0.0005), but is not statistically significant for CIN 2+ linked to HPV 18 (vaccine efficacy 83.3%, 95% CI 73.8%-99.9%; p=0.125),

♦ additional analyses of biopsy tissue using molecular biology techniques have been carried out on patients with CIN 2+ linked to HPV 16 or HPV 18

♦ in view of the results of these analyses, it was considered that in three cases (two in the HPV vaccine arm and one in the "placebo" arm), it was unlikely that HPV 16 or HPV-18 within the lesions was the cause of these lesions

[3] http://www.hcsp.fr/hcspi/explore.cgi/a_mt_090307_papillomavirus.pdf
[4] Atypical Squamous Cells of Undetermined Significance
[5] Low-Grade Squamous Intraepithelial Lesions
[6] Cervical Intra-epithelial Neoplasia. Opinion relating to the vaccination against human papilloma viruses 16 and 18 using a bivalent vaccine – 14 December 2007
[7] 95% CI adjusted for multiplicity

♦ that by excluding these 3 cases, vaccine efficacy is 100% (95% CI 74.2 %-100 %; p<0.0001) against CIN 2+ linked to HPV 16 or HPV-18, 100% (95% CI 64.5%-100%; p<0.0001) against CIN 2+ linked to HPV 16 and is not statistically significant (vaccine efficacy 100%, 95% CI -49.5%-100%, p=0.0625) against CIN 2+ linked to HPV 18,

♦ these results probably demonstrate that the study lacks statistical power regarding cases of CIN 2+ linked to HPV 18

♦ the vaccine uses AS04 as an adjuvant, and the long-term safety of this product is not well known

♦ the local and systemic safety of this vaccine has been judged to be satisfactory.

The High Council for Public Health of France,

● in addition to the guidelines already issued by the Technical Committee on Vaccination and the French Superior Council for Public Hygiene, the communicable diseases section, in their opinion dated 9 March 2007, and in particular:

o the need to organise screening for precancerous and cancerous lesions of the cervix throughout the country, as vaccination against papillomavirus 16 and 18 cannot be used as a substitute for this;

o the need to oblige firms that produce or that are led to produce an HPV vaccine to promote, in their communication materials, the use of both this vaccine and the cervical smear screening, and to mention that the vaccine is ineffective in preventing 30% of cancers.

● with the current state of knowledge in the field, recommends the quadrivalent vaccine over the bivalent vaccine as part of the strategy to prevent the morbidity and mortality linked to HPV as defined in the opinion dated 9 March 2007 because of:

o the fact that the bivalent vaccine does not prevent lesions caused by HPV genotypes 6 or 11 (in particular, genital warts and CIN)

o the fact that the bivalent vaccine has not been shown to be effective against precancerous vulvar lesions of grade 2 or higher (VIN 2+)

o the fact that the bivalent vaccine has not been formally demonstrated to be effective (though it is likely to be effective) against CIN 2+ linked to HPV genotype 18

o the lack of data concerning the long-term safety of the AS04 adjuvant

● considers that the current data are too limited to determine whether the lack of protection against genotypes 6 and 11 could be offset by a long period of protection and/or cross-protection against other oncogenic HPV types

● repeats the 9 March 2007 request made by the Superior Council for Public Hygieneof France to have studies carried out on the public health impact, and asks that long-term safety studies be carried out on adjuvant AS04, particularly in France

● will reconsider its opinion based on any new data relating to the above points".

The opinion issued by the Specialist Health Safety Committee based on proposals from the French Technical Committee on Vaccination, dated 14 December 2007 (this opinion must be distributed in its entirety without additions or alterations)
Haut Conseil de la santé publique (High Council for Public Health), 14 avenue Duquesne, 75350 Paris 07 SP
www.hcsp.fr

4.3.2. Transparency Committee Opinion

In the context of the strategy to prevent HPV-linked morbidity and mortality, the Transparency Committee is adopting the guideline to use the quadrivalent vaccine, which has a wider range of indications.

4.4. Target Population

The target population for vaccination against human papillomavirus types 16 and 18 was defined by the French Technical Committee on Vaccination and Superior Council for Public Hygiene of France in an opinion dated 9 March 2007. It corresponds to:

- adolescent girls aged 14, and
- girls and young women 15–23 who have not had sexual relations or who had their first sexual relations under a year ago.

- Population of 14-year-old girls

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

- Population of girls and young women 15–23 years of age (catch-up population) who have not had sexual relations or who had their first sexual relations under a year ago

A study carried out by the French National Prevention and Health Education Institute (INPES)[8] indicates the proportion (%) of young women who have never engaged in sexual activity, broken down by age.

In order to estimate the population by age group of girls and young women 15–23 years of age who have not had sexual relations or who had their first sexual relations under a year ago (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.

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	**Age 15**	**Age 16**	**Age 17**	**Age 18**	**Age 19**	**Age 20**	**Age 21**	**Age 22**	**Age 23**
Total population by age group under consideration (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 relations or who have been sexually active for less than a year is estimated to have been approximately 1,570,000 individuals in 2007.

8 Guilbert P, Gautier A. Baromètre Santé 2005 [Health Barometer 2005]. INPES

4.5. Transparency Committee recommendations

The Committee recommends that this product be included on the list of products reimbursed by French National Insurance and approved for use in hospitals and various public services for the populations recommended in the opinion issued by the High Council for Public Health and the opinion of the Technical Committee on Vaccination and Superior Council for Public Hygiene relating to vaccination against human papillomaviruses (meeting of 9 March 2007).

4.5.1. Packaging

The packaging is appropriate for the prescription requirements.

4.5.2. Reimbursement rate: 65%

The Transparency Committee considers that it is essential to carry out all the public health studies mentioned in the opinion relating to vaccination against human papillomavirus types 16 and 18 (Opinion dated 14 December 2007).

To the extent that the studies that are planned or that are currently being carried out, particularly in the context of the European Risk Management Plan for CERVARIX, could fail to answer all the questions raised in the opinion of the High Council for Public Health, specific studies will need to be conducted.