HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

1 February 2012

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

Applicant: GLAXOSMITHKLINE

vaccine against the Papillomavirus
ATC code: J07BM02

List I

Date of Marketing Authorisation: 20 September 2007 (Centralised Procedure) – Amendment 21 August 2011
Reimbursement rate: 65% - Approved for hospital use

Reason for request:
Following the submission of new data (immunogenicity, preventative efficacy, safety) and the new vaccination recommendations from the *Haut Conseil de la Sante Publique* (High Council of Public Health, HCSP), reassessment of the improvement in actual benefit in accordance with article R163-12 of the Social Security Code.

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 16 L1 protein, 20 micrograms
Human Papillomavirus type 18 L1 protein, 20 micrograms

L1 protein in the form of non-infectious virus-like particles produced by recombinant DNA technology, adsorbed on aluminium hydroxide, hydrated with adjuvant AS04 (containing 3-*O*-desacyl-4'- monophosphoryl lipid A)

1.2. Indication

“Cervarix is a vaccine for use for the prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types.

The indication is based on the demonstration of efficacy in women aged 15 to 25 years of age vaccinated with Cervarix and on the immunogenicity of the vaccine in girls and women aged 10 to 25 years of age.
Cervarix should be used in accordance with official recommendations.”

1.3. Dosage

“The recommended vaccination schedule includes 3 doses administered as follows: 0, 1, 6 months.
If flexibility in the vaccination schedule is necessary, the second dose can be administered between 1 month and 2.5 months after the first dose and the third dose between 5 and 12 months after the first dose.
The need for a booster dose has not been established.
It is recommended that subjects who receive a first dose of Cervarix complete the 3-dose vaccination course with Cervarix.
Cervarix is not recommended for use in girls below 10 years of age due to lack of data on safety and immunogenicity in this age group.”

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

J:	Anti-infectives for systemic use
J07:	Vaccines
J07B:	Viral vaccines
J07BM:	Vaccines against the Papillomavirus
J07BM02:	Papillomavirus (type 16, 18) recombinant

2.2. Medicines in the same therapeutic category

Not-strictly-comparator medicines:

GARDASIL, Human Papillomavirus vaccine, types 6, 11, 16 and 18, recombinant, adsorbed (substantial ACB, IACB III, opinion dated 18 April 2007)

2.3. Medicines with a similar therapeutic aim

Not applicable

3 REMINDER OF THE PREVIOUS TRANSPARENCY COMMITTEE CONCLUSIONS

Improvement in actual benefit (IAB) (opinion dated 5 March 2008)
"CERVARIX is a primary prevention aimed at preventing, in the short and medium terms, the morbidity linked to high grade cervical intraepithelial neoplasia (CIN grades 2 and 3).
Its preventative effect on the occurrence of cervical cancers, is not currently proven and only including around 70% of them (Human Papillomavirus types 16 and 18 are only involved in approximately 70% of cervical cancers), and will only be manifested in the long term since it is estimated that the period between infection with Human Papillomavirus and onset of invasive cancer is around 15 to 25 years.

Given, on the one hand:
- the efficacy of this vaccine in the prevention of premalignant cervical lesions (high grade cervical intraepithelial neoplasia, CIN 2 and 3) caused by the Human Papillomavirus of genotype 16 and/or 18 and genotype 16.
- its satisfactory safety profile in the clinical studies
- maintenance of the immune response induced by this vaccine up to 64 months after the first dose

On the other hand:
- the evidence level is less than GARDASIL's in the prevention of premalignant cervical lesions (high grade cervical intraepithelial neoplasia, CIN 2 and 3) caused by the Human Papillomavirus genotype 18.
- uncertainties about the long term safety profile, not established for adjuvant AS04

The Committee considered that the CERVARIX vaccine does not provide improvement in actual benefit (IACB V) compared to the GARDASIL vaccine in the strategy of preventing premalignant cervical lesions caused by Human Papillomavirus (HPV) types 16 and 18 in populations recommended by the HCSP (opinion dated 14 December 2007) and by the Technical vaccination Committee and the Superior Council of Public Hygiene of France (*Comité Technique des Vaccinations and Conseil Supérieur d'Hygiène Publique de France*) (opinion dated 9 March 2007) relating to vaccination against Human Papillomaviruses.

In addition, as with the GARDASIL vaccine, the Committee highlights that:
- the duration of protection provided by the vaccine is unknown
- the safety profile will be confirmed under actual conditions of use
- potential adverse effects could be caused by the vaccination:
    - a decrease in the use of condoms; the vaccination could be perceived as a protection against all sexually transmitted diseases
    - a decrease in attending cervical smear screening with the risk of seeing an increase in the number of cervical cancers caused by types of oncogenic HPVs other than 16 and 18
    - a shift in the incidence of cervical cancer towards an older age if a booster would be required and if some women neglect to come back for this
    - selection of other types of oncogenic HPVs.

In any event, the Committee highlights that it would be desirable that organisation and implementation of screening for premalignant and malignant cervical lesions with cervical smears (secondary prevention) is performed throughout the country.

In addition, it specifies that the explanations given to girls and women by the physician before the vaccination should be included in a written document validated by the relevant authorities."

4 ANALYSIS OF NEW AVAILABLE DATA

4.1. Preventative efficacy

New data available from the follow-up data from 2 double-blind, randomised, placebo-controlled clinical studies in young women between 15 and 25 years of age:

- A phase II study (study HPV 001 and its follow-up HPV 007) in young women not infected[1] at inclusion. The objective of this study was to evaluate the preventative efficacy of the vaccine particularly for the prevention of incident[2] and persistent[3] infections associated with Human Papillomavirus (HPV) type 16 and/or 18.
  A total of 1113 women (560 in the vaccinated group – 553 in the placebo group) were included and followed in the HPV 001 study and 776 women were followed in the HPV 007 study.

- a phase III study (HPV 008 study) in young women not previously selected for the presence or absence of HPV infection and having had a normal or low grade abnormal cervical smear. The objective of this study was to evaluate the preventative efficacy of the vaccine on cervical intraepithelial neoplasia (CIN 2 lesions or higher: CIN 2, CIN 3) and AIS (adenocarcinoma *in situ*) and invasive cancers associated with HPV type 16 and/or 18.
  A total of 18,644 women were included, 9319 in the vaccinated group and 9325 in the placebo group.

- Study HPV 001 and its follow-up HPV 007

The new data cover the results of follow-up up at 6.4 years. An interim analysis was carried out at 5 years.
A sub-group of women in the HPV 007 study (N=776) vaccinated in study 001 was followed up for 6.4 years (approximately 77 months) after the initial dose (mean follow-up 5.9 years).
The efficacy of Cervarix against 12-month persistent HPV 16/18 infection was 100% (95% CI: [80.5; 100]) at 6.4 years compared to 100% (95% CI: [66.5; 100]) in the interim analysis. There were sixteen cases of persistent HPV 16 infection, and five cases of persistent HPV 18 infection, all in the placebo group.

- Study HPV 008

The new data cover the results from the main analysis at 39 months and the end of study results at an average of 48 months, i.e. 40 months after the third dose. An interim analysis was carried out after a mean follow-up of 15 months.

The populations in the analysis at 39 months and the end of study analysis were as follows:

- According to Protocol cohort (ATP cohort)
- The intention to treat populations:
  - women who received at least one dose of the vaccine, whatever their HPV DNA, cytology and serological status at inclusion (total vaccinated cohort or TVC). This cohort is similar to the general population of women aged 15 to 25 years.
  - women not infected by the 14 types of HPV tested and having received at least 1 injection (TVC-naive). This cohort is similar to the population to be vaccinated.

[1] Not infected includes being seronegative for HPV 16 and 18 (ELISA), viral DNA negative for oncogenic HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 (PCR) and having a normal cervical smear.
[2] Incidental infection: viral DNA PCR detection positive on 1 cervical-uterine sample.
[3] Persistent infections: viral DNA PCR detection positive for the same viral serotype on 2 cervical-uterine samples at 6 month intervals (and 12 months post-hoc)

As a reminder, in study HPV 008 after a mean follow-up of 15 months, the interim analysis included women who had no ongoing infection, were not carriers and did not have anti-HPV 16 or 18 antibodies or DNA of HPV 16 or 18, had normal or low grade abnormal cytology (CIN1) and who had received a single dose of the vaccine (TVC 1).

The primary efficacy end-point was the reduction in the relative risk of occurrence of CIN 2+ (CIN 2/3 or AIS) associated with HPV 16/18 types in the ATP cohort. The 6-month and 12-month persistent infection rates were the secondary end-points.

In the clinical studies, premalignant cervical lesions of grades 2 and 3 (CIN 2/3) and AIS were used as surrogate markers for cervical cancer.

The results of the studies were expressed in terms of reduction of risk of occurrence of premalignant lesions CIN 2+ (CIN 2/3 or AIS) and persistent infections associated with different types of HPV.

Results for HPV 16/18

1-According to protocol (ATP) cohort

This population included women with normal or low grade abnormal cytology at inclusion having received 3 doses of vaccine. For the HPV type considered in the HPV 16 analysis or HPV 18 analysis, women being DNA negative and seronegative at inclusion and DNA negative at 6 months: N = 16,162. Overall, 74% of women included were naive for HPV 16 and 18 i.e. DNA negative and seronegative at inclusion.
The assessment of the number of cases started on day 1 after the third dose of the vaccine.

Table 1: Efficacy against the premalignant cervical lesions (CIN 2/3 or AIS – CIN 3 or AIS) associated with HPV types 16 and/or 18, end of study analysis (ATP cohort).

Efficacy end-points	**Number of lesions CIN2/3 or AIS**		
	Cervarix (N = 7338)	**Placebo (N = 7312)**	**Efficacy % [95% CI], p**
CIN2/3 lesions depending on HPV serotype: HPV 16/18 HPV 16 HPV 18	 5 2 3	 97 81 23	 94.9 [87.7 – 98.4], p<0.05 97.6 [91.0 – 99.7], p<0.05 87.1 [57.2 – 97.5], p<0.05
CIN3 or AIS lesions	2	24	91.7% (66.6; 99.1) p<0.05

N: number of subjects included in each group
n: number of cases

As a reminder, in the main analysis (39 months), the efficacy results on the lesions caused by HPV 16 and HPV 18 were:

- 92.9% (96.1% CI [79.9; 98.3] against the CIN 2/3 or AIS lesions,
- 80% (96.1% CI [0.3; 98.1]) against the CIN3+ lesions.

The efficacy of the vaccine was proven against the CIN2+ lesions associated with HPV 16 or HPV 18.
The results are similar to those observed during the interim analysis at 15 months in TVC 1.
When the cases of premalignant lesions involved several types of HPV, a post-hoc analysis was performed to distinguish the types of HPV which were most likely to be responsible for the lesion (clinical allocation of the cases). This analysis excluded cases which were not considered to be caused by infections by HPV 16 or HPV 18 acquired during the study.
On the basis of this HPV type assignment post-hoc analysis, the efficacy against CIN 2+ lesions was 98.9% (95% CI: [93.8; 100]) p<0.05 for HPV 16 /18 and 100% (95% CI: [81.8; 100]) for the CIN 3+ or AIS lesions.

Table 2: Efficacy against the 6 and 12-month persistent infections associated with HPV types 16 and/or 18 at the end of the study (ATP cohort)

Persistent infections depending on HPV16/18 serotype	Number of infections		
	Cervarix	Placebo	Efficacy
	n/N	n/N	% [95% CI], p
at 6 months HPV 16/18 HPV 16 HPV 18	35 / 7,182 24 / 6,165 11 / 6,649	588 / 7,137 418 / 6,029 212 / 6,581	94.3 [92.0 – 96.1], p<0.05 94.6 [91.8 – 96.6], p<0.05 95.0 [90.8 – 97.5], p<0.05
at 12 months HPV 16/18 HPV 16 HPV 18	26 / 7,082 19 / 6,089 7 / 6,552	354 / 7,038 269 / 5,949 98 / 6,490	92.9 [89.4;95.4], p<0.05 93.3 [89.3;96.0], p<0.05 93.0 [85.0;97.3], p<0.05

N = Number of subjects included in each group
n = Number of cases

As a reminder, in the main analysis, the efficacy results for HPV 16 and HPV 18 were 94.3% (96.1% CI: 91.5; 96.3) against 6-month persistent infection and 91.4% (96.1% CI: 86.1; 95.4) against 12-month persistent infection.

Overall, the vaccine efficacy of CERVARIX has been established up to 48 months on average in the prevention of premalignant lesions of CIN 2 or higher (CIN 2 and CIN 3, adenocarcinoma *in situ* and invasive cancer) and in the prevention of persistent infections associated with HPV 16 and 18. The efficacy was proven for CIN 2/3 or AIS associated individually with HPV 16 and HPV 18.

2- Total vaccinated cohort (TVC)

The total vaccinated cohort included all women who received at least one dose of the vaccine, irrespective of their HPV DNA, cytology and serology status at inclusion.
This population included women with or without ongoing and/or previous HPV infection. The assessment of the number of cases in the TVC cohort started on day 1 after the first dose of the vaccine (N = 18,644).

Table 3: Efficacy of the vaccine against the premalignant cervical lesions (CIN 2/3 or AIS) associated with HPV types 16 and/or 18 at the end of study analysis (TVC cohort).

Efficacy end-points	Number of lesions CIN2/3 or AIS		
	Cervarix (N = 8694)	Placebo (N = 8708)	Efficacy % [95% CI]
	n	n	
CIN2/3 or AIS	90	228	60.7 [49.6;69.5]
CIN3 or AIS	51	94	45.7 [22.9;62.2]

N = Number of subjects included in each group n = number of cases

Table 4: Efficacy of the vaccine against 6 and 12-month persistent infections associated with HPV types 16 and/or 18 at the end of the study (TVC cohort)

Persistent infections	Number of infections		
	Cervarix	Placebo	Efficacy
	n/N	n/N	% [95% CI]
at 6 months	504/ 8,863	1,227 / 8,870	60.9 [56.6;64.8]
at 12 months	335/ 8,648	767 / 8,671	57.5 [51.7;62.8]

N = Number of subjects included in each group, n = number of cases

As a reminder, in the main analysis, the efficacy results against CIN2+ or AIS lesions associated with HPV 16 and/or HPV 18 were 52.8% (96.1% CI [37.5 – 64.7]).
The efficacy observed in the TVC was less than that observed in the ATP cohort. The TVC included women with pre-existing infections and lesions on which CERVARIX cannot have an impact.

3- Naïve cohort (TVC-naïve)

The TVC-naïve, population, which is similar to the population of girls to be vaccinated according to the HCSP recommendations, included all the vaccinated subjects having received at least one dose of vaccine. At inclusion these subjects had normal cytology, HPV DNA negative for the 14 types of oncogenic HPVs (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) and were seronegative for HPV 16 and HPV 18 (N=11,641).

Table 5: Efficacy of the vaccine against the high grade cervical lesions associated with HPV types 16 and/or 18 at the end of study (TVC-naïve).

Efficacy end-points	Cervarix (N = 5,466)	Placebo (N = 5,452)	Efficacy % [95% CI], p
	n	n	
CIN2/3 or AIS	1	97	99.0 [94.2 - 100], p<0.05

N = Number of subjects included in each group
n = Number of cases

As a reminder, in the main analysis, the efficacy results against CIN2+ or AIS lesions associated with HPV 16 and HPV 18 were 98.4% (96.1% CI: [90.4; 100]).

Results for the non-vaccine oncogenic HPVs

The efficacy of CERVARIX in terms of cross-protection was evaluated for the 12 types of non-vaccine oncogenic HPVs. The study was not powerful enough to evaluate efficacy against the diseases caused by individual HPV types. The analysis regarding the main criteria was confounded by multiple co-infections in the CIN 2+ lesions. Unlike the histopathological criteria, the virological criteria are less confounded by multiple infections.

Persistent infection was used as an intermediate marker of risk of developing cervical cancer for the non-vaccine types provided that efficacy values obtained were elevated, statistically significant and consistent with those obtained on clinical cervical lesions.

Table 6: Efficacy of the vaccine on the persistent infections and the CIN 2/3 or AIS lesions depending on the types of non-vaccine oncogenic HPVs in the ATP cohort at the end of the study

HPV type	6-month persistent infection			CIN 2/3 or AIS		
	Cervarix	Control	Efficacy % [95% CI]	Cervarix	Control	Efficacy % [95% CI]
	n	n		n	n	
Types related to HPV type 16 (species A9)						
HPV 31	58	247	76,8 [69.0;82.9]	5	40	87.5 [68.3;96.1)
HPV 33	65	117	44,8 [24.6;59.9]	13	41	68.3 [39.7;84.4)
HPV 35	67	56	-19.8 [<0;17.2]	3	8	62.5 [<0;93.6)
HPV 52	346	374	8.3 [<0;21.0]	24	33	27.6 [<0;59.1)
HPV 58	144	122	-18.3 [<0; 7.7]	15	21	28.5 [<0;65.7)
Types related to HPV type 18 (species A7)						
HPV 39	175	184	4.8 [<0;23.1]	4	16	74.9 [22.3;93.9]
HPV 45	24	90	73,6 [58.1;83.9]	2	11	81.9 [17.0;98.1]
HPV 59	73	68	-7.5 [<0;23.8]	1	5	80.0 [<0;99.6]
HPV 68	165	169	2.6 [<0;21.9]	11	15	26.8 [<0;69.6]
Other HPV types						
HPV 51	349	416	16.6 [3.6;27.9]	21	46	54.4 [22.0;74.2)
HPV 56	226	215	-5.3 [<0;13.1]	7	13	46.1 [<0;81.8)
HPV 66	211	215	2.3 [<0;19.6]	7	16	56.4 [<0;84.8)

n = Number of cases

HPV 31, 33 and 45 showed consistent cross-protection for 6-month persistent infection and CIN2+ criteria in all study cohorts.

Depending on the different epidemiological data, HPV 31, 33 and 45 could be involved in 10 to 14% of cervical cancers.

Results regarding global preventative efficacy

The overall efficacy of the vaccine on cervical diseases caused by HPVs irrespective of HPV type in the lesion is shown below.

Table 7: Efficacy of the vaccine against high grade cervical lesions irrespective of the HPV DNA type in the lesion (TVC and TVC-naïve cohort) at the end of the study

	Cervarix		Placebo		Efficacy in % [95% CI], p
	N	Cases	N	Cases	
CIN2/3 or AIS					
TVC-naïve	5,466	61	5,452	172	64.9 [52.7;74.2], p<0.05
TVC	8,694	287	8,708	428	33.1 [22.2;42.6], p<0.05
CIN3 or AIS					
TVC-naïve	5,466	3	5,452	44	93.2 [78.9;98.7], p<0.05
TVC	8,694	86	8,708	158	45,6 [28.8;58.7], p<0.05

N = Number of subjects included in each group

The efficacy of the vaccine was demonstrated for high grade cervical lesions in the TVC-naïve (non-infected population) and the TVC (total vaccinated cohort), irrespective of the HPV DNA type in the lesion.
As a reminder, in the main analysis and the TVC-naïve, the efficacy result against CIN2+ or AIS lesions irrespective of the HPV type was 70.2% (96.1% CI [54.7-80.9]).

4.2. Impact on the cervical therapy procedures

The impact of the vaccine on the number of cervical therapy procedures irrespective of the causal HPV types was evaluated in the HPV 008 study.
In the CERVARIX group, the number of cervical excision procedures was reduced compared to the placebo group by 70.2% (95% CI: [57.8; 79.3]) in the TVC-naïve group and 33.2% (95% CI: [20.8: 43.7]) in the TVC group at the end of study analysis.

4.3. Immunogenicity

No minimal antibody level associated with protection against CIN of grade 2 or 3 or against persistent infection associated with vaccine HPV types has been identified for HPV vaccines. There is no correlation established between the level of antibodies and preventative efficacy.

Persistence of the immune response to CERVARIX

Reminder:
Study 001/007 (which included women aged 15 to 25 years at the time of vaccination) evaluated the immune response against HPV 16 and 18 up to 76 months after administration of the first vaccine dose.

New data:
- In the sub-group of 87 women (HPV study 023, follow-up of study 001/007) from which the immunogenicity results were collected between the 95th and 101st month after the first dose of vaccine (median follow-up 7.9 years) 100% of women (95% CI [95.8; 100]) remained seropositive for HPV 16 and HPV 18 according to the ELISA test.

Vaccine-induced IgG geometric mean titres (GMT) for both HPV 16 and HPV 18 peaked at month 7 and then declined to reach a plateau from month 18 up to the [M95-M101] interval.
GMTs for both HPV 16 and HPV 18 were at least 10-fold higher than the GMTs observed in women who cleared a natural HPV infection.

- In the sub-group of 65 subjects in which a challenge dose of CERVARIX was administered at a mean interval of 6.8 years after the first vaccine dose, an anamnestic immune response to HPV 16 and HPV 18 (measured by ELISA) was observed one week and one month after this challenge dose; the GMTs one month after this dose exceeded the GMTs observed one month after the primary 3-dose vaccination.

- In the HPV 008 study, immunogenicity up to the 36th month was similar to the response observed in the HPV 001/007 study. A similar kinetic profile was observed for the neutralising antibodies.

- <u>Study HPV 010:</u>
This study compared the immunogenicity of CERVARIX to that of GARDASIL.
In the ATP cohort (evaluable subjects, seronegative and DNA negative at inclusion for the HPV type considered and having received 3 doses of vaccine), this immunogenicity data revealed that in the population of 18-26 year olds, the GMTs induced by CERVARIX for HPV 16 and 18 were 3.7 and 7.3 times higher than those induced by the GARDASIL vaccine.

Table 8: Response in terms of neutralising antibodies for HPV 16 and HPV 18 in subjects aged 18 to 26 (primary efficacy end-point): GMT and GMT ratio in the ATP cohort.

	Cervarix		**Gardasil**		**GMT ratio [97.6% CI]**
Antigen	**N**	**GMT* [95% CI]**	**N**	**GMT* [95% CI]**	
HPV 16	104	36,792 [29,266 – 46,254]	103	10,053 [8,136– 12,422]	**3.7** [2.6 – 5.2]
HPV 18	118	16,487 [13,384 – 20,310]	131	2,258 [1,809 – 2,818]	**7.3** [5.1 – 10.5]

*GMT = geometric mean titre

- Studies of co-administration with other vaccines:
The co-administration studies revealed that the administration of CERVARIX had no significant interference with the antibody response to the components of each vaccine: combined booster vaccine containing diphtheria (d), tetanus (t), pertussis (acellular, ac) with or without inactivated poliomyelitis (P).
CERVARIX can be administered concomitantly with a combined vaccine against hepatitis A (inactivated vaccine) and against hepatitis B (rDNA) (TWINRIX: Hepatitis A/Hepatitis B vaccine) or with a vaccine against hepatitis B (rDNA) (Engerix B).

4.4. Adverse effects

The most common adverse effect observed after vaccine administration was injection site pain, which occurred after 78% of all doses. The majority of these effects was of mild to moderate severity and was not long-lasting.
The additional safety data from the clinical studies did not reveal a significant increase in adverse effects in the group of women vaccinated with CERVARIX compared to the placebo group.

In particular, the safety data from the clinical studies revealed a similar frequency in the vaccinated women and the placebo group:

- newly diagnosed autoimmune diseases (0.8%)
- newly diagnosed chronic diseases (2.7% and 2.9%): asthma, urticaria, hypersensitivity reactions, hypothyroidism and seasonal allergies

During post-marketing surveillance, the reported adverse events were as follows: lymphadenopathy, allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema, syncope or vasovagal reaction to the injection, sometimes accompanied by tonic-clonic movements.

Syncope which can occur following, or even before, any vaccination, particularly in adolescents, can be accompanied by several neurological signs such as transient visual disturbance, paraesthesiae and tonic-clonic limb movements during recovery.

An initial assessment of the European and National risk management plan was released by AFSSAPS on 11 July 2011.[4]
This stated that the benefit/risk ratio of this vaccine remained favourable and close to the safety of use profile established at the time of the Marketing Authorisation, taking account of all of the available data.

An assessment of pharmacovigilance monitoring of the HPV vaccines dated 22 November 2011 (attached in appendix 2) released by the AFSSAPS stated that:
The analysis of pharmacovigilance data reported in mid-September 2011 by the Bordeaux CRPV as well as cases of exposed pregnancy at the end of May 2010 by the Lyon CRPV, have not identified any new signal regarding the safety of these vaccines after administration of more than 4 million doses of the anti-HPV vaccines.
The possibility of an increased risk of occurrence of various autoimmune diseases after anti-HPV vaccination was examined using the data from two epidemiological studies performed in France; one was the “vaccinated/non-vaccinated” cohort performed by the AFSSAPS from the SNIIRAM [National system of National Health Insurance Inter-system information], and the other a case-control study performed by LA SER and conducted from data from the network of PGRx pharmaco-epidemiology studies on autoimmune diseases.
The preliminary results from these studies are consistent and do not reveal a significant association between this vaccination and the risk of these autoimmune diseases. The strength of these two studies has been judged sufficient by the members of the CNPV to validate their relevance.
However, the CNPV has suggested continuing increased pharmacovigilance monitoring targeted at autoimmune diseases and the continuation of pharmaco-epidemiology studies.

[4] http://www.afssaps.fr/content/search?SearchText=CERVARIX&ok=Valider

4.5. Conclusion relating to the new available data

The vaccine efficacy of CERVARIX against placebo evaluated at 15 months on premalignant CIN 2/3 or AIS lesions associated with HPV 16 and/or HPV 18 in the population at the interim analysis (90.4% CI to 97.9%: [53.4 – 99.3]) has been confirmed and maintained at the final analysis at 48 months in all the analysed cohorts, notably:
- in the ATP cohort: 94.9% [95% CI: [87.7 – 98.4])
- in the TVC cohort: 60.7% [95% CI: [49.6 – 69.5])
- in the TVC-naïve cohort: 99.9% [95% CI: [94.2 - 100]);

In addition, the efficacy of the vaccine has been demonstrated for CIN 2/3 or AIS lesions individually associated with HPV 16 and HPV 18 (ATP cohort).

In the TVC-naïve cohort, the overall efficacy against premalignant lesions of CIN2+ type, irrespective of the type of oncogenic HPV contained in the lesion was 64.9% (95% CI: [52.7 – 74.2] and 93.2% (95% CI: [78.9-98.8]; against premalignant lesions of CIN3+ type, the immediate forerunner of cervical cancer.

It was proven that the infection persisting for at least 6 months is a relevant surrogate marker for cervical cancer.
Cross-protection was demonstrated for 6 month persistent infection and CIN 2+ criteria in all the study cohorts for HPV 31, 33 and 45.
These types of HPV 31, 33 and 45 could be involved in 10 to 12% of cervical cancers.

Given this data, the Committee highlights the low reduction of the relative risk of occurrence:
- for CIN2/3 or AIS with HPV 16/18 observed in the total vaccinated cohort with or without infection (TVC); this is actually 60.7% (95% CI: [49.6-69.5]) compared to 94.9% [95% CI: [87.7- 98.4] found in the ATP cohort:
- for CIN2/3 or AIS irrespective of the HPV type observed in the lesion compared to that observed in the CIN2/3 lesions involving HPV 16/18; in the total vaccinated cohort with or without infection (TVC) this is actually 33.1% (95% CI: [22.2-42.6] compared to60.7% (95% CI: [49.6- 69.5]).

No clinical study has compared CERVARIX and GARDASIL in terms of vaccine efficacy in the prevention of premalignant cervical lesions.

A 70.2% (95% CI: [57.8; 79.3]) reduction in cervical therapy procedures was observed in the TVC-naïve and 33.2% (95% CI: [20.8; 43.7]) in the total vaccinated cohort.

In study 023 (follow-up and sub-group of study 001/007), the immune response was evaluated up to 101 months (8.4 years): 100% of women (95% CI: [95.8; 100]) remained seropositive for HPV 16 and HPV 18 according to the ELISA test. The GMTs for both HPV 16 and HPV 18 were at least 10-fold higher than the GMTs observed in women who cleared a natural HPV infection.

In the HPV 008 study, immunogenicity up to the 36th month was similar to the response observed in the HPV 001/007 study.

The safety data from the clinical studies did not reveal a significant increase in adverse effects in the group of women vaccinated with CERVARIX compared to the placebo group.
CERVARIX is not indicated in the prevention of premalignant genital lesions of the vulva and vagina caused by certain oncogenic types of Human Papillomavirus (HPV) and external genital warts (condyloma acuminata) caused by specific types of HPV.

A similar frequency of newly diagnosed autoimmune diseases (0.8%) and newly diagnosed chronic diseases (2.7% vs 2.9%): asthma, urticaria, hypersensitivity reactions, hypothyroidism and seasonal allergies were observed.
An initial assessment of the European and National risk management plan was released by the

AFSSAPS on the 11 July 2011.[5] It reported that the benefit/risk ratio of this vaccine remains favourable and its safety of use profile is close to that established at the time of the Marketing Authorisation. This is confirmed by the absence of a particular pharmacovigilance signal (report by Bordeaux CRPV in mid-September 2011).

In the current state of the dossier, the following data have not been established:
- efficacy in terms of prevention of cervical cancers even though additional data have been provided on CIN3 and AIS premalignant lesions, immediate precursors of cancer
- the duration of the cross-protection is not known beyond 48 months
- the immunogenicity in the immunocompromised populations (ongoing study in South Africa)
- assessment of a possible modification of the viral ecology linked to introduction of vaccination

4.6. Recommendations from the HCSP

On the 21 October 2011[6], the HCSP recommended:
- Continued improvement of cervical cancer screening and rapid generalisation of the organised screening system according to the HAS recommendations.
- In accordance with recommendations from HCSP on 17 December 2010, continued vaccination against Papillomaviruses in 14 year old girls and catch-up in women up to 23 years of age with no previous sexual activity or who started being sexually active less than one year previously. This vaccination can be given with either one or the other of the two existing vaccines.
- It considered that:
  - there was no current data which questioned the efficacy of these vaccines;
  - the monitoring of secondary effects reported following an HPV vaccination, to date had not revealed any pharmacovigilance signal;
  - there was at the time no data suggesting a potentially harmful nature of the vaccine in certain categories of the population, in particular the risk of cancer developing in previously infected women.

It noted that:
- Ultimately, a significant impact of this vaccination on the incidence of cervical cancers could only be expected if vaccination coverage were sufficient
- It was likely that the girls who are vaccinated are most often those who will later participate in screening
- The impact of vaccination would be even better if vaccination involved women who do not participate in screening.

Consequently, they recommended:
- Firstly, improved vaccination coverage through better access to vaccination and optimisation of its organisation as has been achieved in certain European countries which have obtained vaccination coverage rates of 80% or over;

Secondly, implementing any method which reaches the populations in which the screening is less likely to be performed, even though the vaccination does not in any situation replace screening.

[5] http://www.afssaps.fr/content/search?SearchText=GARDASIL
[6] Opinion from the *Haut Conseil de la santé publique* relating to the GARDASIL vaccine and the overall prevention strategy for cervical cancers (21 October 2011)
http://www.hcsp.fr/docspdf/avisrapports/hcspa20111021_gardasil.pdf

On 17 December 2010[7], the HCSP, after recalling the recommendations already made by the *Comité technique des vaccinations* and the *Conseil supérieur d'hygiène publique de France*, transmittable diseases section in their opinion dated 9 March 2007, stated:

- the need to arrange screening for premalignant and malignant lesions of the cervix throughout the country: vaccination against HPV 16 and 18 cannot replace this;
- the need to make it mandatory for companies producing or planning to produce a HPV vaccine to simultaneously promote screening for cervical lesions in their communication on the use of this vaccination and to refer to the lack of efficacy on prevention of all cervical cancers.

and concluded:

- that the two vaccines had demonstrated their protective effect against CIN 2 or higher grade lesions linked to genotypes 16 and 18;
- that the quadrivalent vaccine had been proven to be more effective in the prevention of lesions caused by HPV genotypes 6 and 11 (particularly genital warts and CIN) and grade 2 or higher grade premalignant vulval and vaginal lesions (VIN 2 or higher and VaIN 2 or higher);
- that the data available were in favour of a greater ability of bivalent vaccine to induce cross-protection for some types of oncogenic HPV other than HPV 16 and 18;
- that the clinical safety data for the adjuvant ASO4 contained in the bivalent vaccine was satisfactory.

It considered that in the current state of understanding and there was no longer a need to recommend one of the two vaccines in preference.
as part of the vaccination strategy against the Human Papillomavirus in girls between 14 and 23 years of age, It recalled that the two available vaccines against HPVs are not interchangeable and that any vaccination course initiated with one of them must be completed with the same vaccine.

On the 5 May 2008[8], the HCSP considered that immunocompromised patients (infected by HIV, on immunosuppressive treatment, transplant patients or people or with constitutional immunodeficiency) represent a group at risk of developing cancer linked to HPV. There is no immunogenicity, safety data or protection data on HPV vaccination in patients on immunosuppressant therapy.
The HCSP recommended that the vaccination against HPV could be offered to girls who due to undergo transplantation under 14 years of age while remaining within the age range for the Marketing Authorisation of these vaccines.

[7] Opinion of the *Haut Conseil de la santé publique* relating to the vaccination against infections with Human Papillomavirus in girls between 14 and 23 years old (17 December 2010)
http://www.hcsp.fr/docspdf/avisrapports/hcspa20101217_ppmvjf1423.pdf

[8] Opinion of the *Haut Conseil de la santé publique* on to the age of vaccination against infections with Human Papillomavirus in girls due to undergo transplantation (5 May 2008)
http://www.hcsp.fr/docspdf/avisrapports/hcspa20080505_HPVGreffe.pdf

5 TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Actual benefit

CERVARIX is a vaccine against Human Papillomaviruses 16 and 18 for the prevention of premalignant cervical lesions and cervical cancer caused by certain types of oncogenic Human Papillomavirus (HPV), which can be life-threatening.
This medicinal product is intended as a preventative treatment (primary prevention).

The vaccine efficacy/safety ratio of this medicinal product is high.

Public health benefit:
The incidence of invasive cervical cancer in France is estimated at 2,810 new cases per year (InVS projections 2011[9]). It is therefore the 10th most common cancer in women. The number of deaths from cancer was estimated to be 998 in 2011, ranking cervical cancer an 13th for deaths from cancer in women in 2011.
The public health burden represented by cervical cancer is therefore substantial.

Reducing the incidence of cervical cancer constitutes a public health need within the framework of established priorities (objective 48 of the law from 9 August 2004 relating to the public health policy "continued reduction of the incidence of cervical cancer by 2.5% per year and particularly by achieving a screening coverage rate of 80% for women aged 25 to 69", cancer plan 2009-2013 "Measure 15: improve structuring of the national organised cancer screening programmes").

Vaccination against oncogenic Human Papillomaviruses (HPV) can represent a response to this need in addition to optimisation of cervical cancer screening throughout the country. In fact, even though the level of screening cover has been improving since 1995, it was only 58.5% in 2007-2009[10] which remains a long way from the 80% set in the objective[11], particularly in certain social and occupational categories.

In France, the level of vaccination coverage (complete vaccination scheme) has been estimated from the National Health Insurance reimbursement data on the 31 December 2009.[12] This was 33.3% on average in girls born in 1993 and 23.7% in girls born in 1994. The majority of girls started the vaccination at 15 years old or older. The level of coverage in the catch-up population (15-23 years old) on 31 December 2009 was a maximum of 35.6% for the 3 doses in the cohort of girls born in 1992 (15 years of age in 1997) and falls regularly with age (14.6% for 18 year old girls in 2007 and 1.8% for 23 year old women).
Given the low level of vaccination coverage at the launch of the campaign, in particular in 14 year old girls, and the insufficient level of individual screening coverage in the absence of organised screening in the country, the public health need remains.

[9] Lyon civil hospices/Health Monitoring Institute/National Cancer Institute/Francim/National Institute of Health and Medical Research. Projections of the incidence and mortality of cancer in France in 2011. Technical report. June 2011. http://www.invs.sante.fr/surveillance/cancers [Accessed on the 21 10 2011].
[10] DRESS. The state of health of the population in France – Follow-up of the objectives appendiced to the Public health Law – 2011 Report (in press).
[11] Public health objectives. Evaluation of the objectives of the law dated 9 August 2004. HCSP Proposals. . April 2010
[12] Fagot J-P et al. HPV vaccination in France: Uptake, costs and issues for the National Health Insurance. Vaccine 2011; 29(19): 3610-6.

In light of the results from studies demonstrating the vaccine efficacy of CERVARIX in high grade cervical dysplasias linked to Papillomavirus types 16 or 18 and 31 or 33 or 45, it is anticipated that CERVARIX will have a significant impact on the reduction of morbidity in the short term (CIN2+) especially in young girls not infected with HPV.

Nevertheless, the booster at 4 years is insufficient, given the natural history of the progression of HPV infections, to judge the impact of CERVARIX in terms of morbidity and mortality (CIN 3 and carcinomas *in situ*) due to the low numbers of events observed in the trial.
In addition, after three years of monitoring, the updated safety data are reassuring and do not reveal an increase in the risk of autoimmune diseases falling within the long term conditions (LTC), associated with anti-HPV vaccination.[13]

Transferability of study results to practice is not ensured in the long term given that:

- cross-protection has not been demonstrated for each of the oncogenic types of HPV; between 10% (case of simple infections)[14] and 20%[15] of cervical cancers remain linked to other types of oncogenic HPV, for this reason that the screening must be continued even in previously vaccinated girls.
- the duration of vaccination protection is not yet known although we now have longer clinical experience. The need for a booster dose has not been established.
- The consequences of vaccination on the distribution of the virus and ecology of the HPVs is not yet known (risk of emergence phenomena).
- The consequences of vaccination on screening practice will only be known when the first cohorts of vaccinated girls reach screening age particularly as vaccination coverage in the target age range still remains low. If fewer vaccinated women have screening, a risk of increasing the incidence and mortality of these cancers cannot be ruled out. Regular monitoring of screening practices in vaccinated and unvaccinated women should be implemented.

In addition, models[16,17] have been created by the pharmaceutical company to estimate the population impact of CERVARIX vaccination associated with individual screening on the morbidity and mortality linked to premalignant and malignant lesions of the cervix caused by oncogenic HPVs. However, the hypotheses tested are unrealistic, in particular those considered for the level of vaccination coverage in France (70% in the projections) and probably overestimate the effect of cross-protection (protection against the 10 other oncogenic HPVs). Consequently, the hypotheses tested in these models do not allow an estimate to be made of the impact of the vaccination program as it has been implemented in France since 2007.

The public health impact of the Papillomavirus vaccine depends on achieving sufficient vaccination coverage in the recommended populations; in view of the available data, this does not currently appear to be the case in France.

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[13] National monitoring of the adverse effects of Gardasil Human Papillomavirus vaccine. National Committee of pharmacovigilance dated 22 November 2011. Available on http://www.afssaps.fr/var/afssaps_site/storage/original/application/b36f1490dfe7b332d99e10795e76444f.pdf consulted on the 19/01/2012.

[14] Prétet J-L et al. Human Papillomavirus (HPV) genotype distribution in invasive cervical cancers in France: EDITH study. Int. J. Cancer 200; 122: 428-432.

[15] Sanjose S, on behalf of the Retrospective International Survey and HPV Time Trends Study Group. Human Papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010;11(11): 1048-56. Epub 2010 Oct 15.

[16] Demarteau et al. A generally applicable cost-effectiveness model for the evaluation of vaccines against cervical cancer. Int J Public Health. 2010.

[17] Demarteau et al. Modelling the economic value of cross- and sustained-protection in vaccines against cervical cancer. Journal of Medical Economics, 2010; 13(2): 324-338.

In fact, according to the model created by Cresge/InVS[18] in 2007, the epidemiological impact of individual screening combined with vaccinating girls from 14 years of age with 30% vaccination coverage at would allow the incidence of diagnosed cases of cervical cancer to be reduced by 8% mortality to be reduced by 6% compared to individual screening alone. However, these figures do not take the catch-up program into account
According to the same model, the organisation of screening with cervical smears in France (implementation of which throughout the country before the introduction of vaccination against oncogenic Human Papillomavirus was recommended by the Transparency Committee in its opinion of 18 April 2007) would in itself reduce the incidence of diagnosed cases of cervical cancer by 16.1% and the related mortality by 19.5% compared to individual screening alone. According to the Cresge/InVS expert report, at vaccination coverage of under 60%, the vaccination has less of an impact on the number of deaths than the organisation of screening, from the Alsace model.

Consequently, in the present state of vaccination coverage in France, and despite an expected potentially significant public health benefit of Papillomavirus vaccination against, the actual benefit for CERVARIX currently, with the limited length of clinical experience we have, is considered to be low.
In order to optimise the public health impact of this vaccine and to respond to the public health need, it appears necessary for measures to be implemented rapidly:
- to boost the vaccination program and increase the vaccination coverage level, particularly in HPV naïve girls in whom vaccine efficacy is greatest
- and also increase the access to, information on and interest in cervical smear screening, particularly in young women from disadvantaged areas.

Based on the updated data, the question of efficiency of the different possible prevention strategies (organised screening, individual screening plus vaccination etc) needs to be reassessed.

There is an alternative vaccine for the prevention of premalignant lesions of the cervix and cervical cancer.
The screening which relies on a cytological test, the cervical smear, is an effective method of secondary prevention for cervical cancers.

The actual benefit of this vaccine **remains substantial** in the only Marketing Authorisation indications recommended by the HCSP in the current vaccination schedule in force.

[18] Dervaux B, Lenne X, Lévy-Bruhl D, Kudjawu Y. Medico-economic modelling of the impact of the organisation of cervical cancer screening and the introduction of the vaccination against HPVs in the vaccination schedule - March 2007. Saint-Maurice (Fra): Health Monitoring Institute, November 2008, 25 p. Available on: www.invs.sante.fr

5.2. Improvement in actual benefit (IAB)

Given the new data, in particular:

- the preventative efficacy data and the reduction in cervical therapy procedures at 48 months of follow-up
- the efficacy demonstrated on CIN2/3 or AIS lesions linked to HPV 18
- the ability to induce cross-protection against HPV 31, HPV 33 and HPV 45
- the persistence of the immune response induced by this vaccine up to 101 months after the first dose
- the reassuring data regarding safety,

the Committee considers that CERVARIX, equivalent to the GARDASIL vaccine, provides a moderate improvement in actual benefit (level III) in the prevention strategy for premalignant genital lesions of the cervix caused by certain types of oncogenic Human Papillomavirus.

In the current state of insufficient vaccine coverage in France, it appears necessary for measures to be implemented to boost the vaccination program and increase the level of vaccination coverage, particularly in HPV 16 and 18-naive girls in whom the vaccine efficacy is greatest.

In any case, the Committee confirms its opinion on 5 March 2008 and considers that it remains essential that cervical smear screening for premalignant and malignant lesions of the cervix (secondary prevention) be organised throughout the country.

5.3. Therapeutic use

GARDASIL and CERVARIX vaccines, which do not have identical indications for prevention, are currently marketed.

Level of vaccination coverage

In France, the level of vaccination coverage (complete vaccination scheme) estimated from the National Health Insurance reimbursement data on 31 December 2009**Erreur ! Signet non défini.** was 33.3% on average in girls born in 1993 and 23.7% in girls born in 1994.
The level of coverage in the catch-up population (15-23 years old) on 31 December 2009 was a maximum of 35.6% for the 3 doses in the cohort of girls born in 1992 (15 years of age in 2007) and falls consistently with age (14.6% for 18 year old girls in 2007 and 1.8% for 23 year old women 2007).

The level of vaccination coverage on 31 December 2010 calculated from the general sample of beneficiaries (EGB) (French national health insurance/InVS) for girls born in 1993 (17 years of age), 1994 (16 years of age) and 1995 (15 years of age) are 52.6%, 50.0% and 38.7% respectively for one dose and 36.0%, 33.4% and 20.3% for 3 doses.
Amongst the European countries, coverage levels of 80% or over have been achieved in the United Kingdom and Portugal, countries which have implemented vaccination in public health facilities or in schools.

Screening coverage for cervical cancer:

The estimate of the level of cervical smear coverage, defined as a smear every three years, is based on data from the general sample of beneficiaries (EGB) from the National Health Insurance system in women between 25 and65 years old.
The latest trend data available[19], released by the InVS before publication by the Directorate-General for Health, show a slight increase in the screening levels between 2004 and2006 and 2005 and2007 for all age groups.

[19] DRESS. The state of health of the population in France – Follow-up of the objectives appended to the Public health Law – 2011 Report (CONFIDENTIAL-in press).

Overall, 58.5% of these women underwent cervical smear screening in 2007-2009 compared to 57% for the period from 2004-2006.

Table 5: Level of screening for cervical cancer using cervical smears in women aged 25 to 65 for the periods 2004-2006 to 2007-2009 (in %) in France.

Age range	**2004-2006**	**2005-2007**	**2006-2008**	**2007-2009**
25-34 years	56.3	58.0	58.4	59.6
35-44 years	65.7	65.3	66.2	67.1
45-54 years	58.5	58.9	59.0	60.1
55-65 years	45.6	46.0	46.0	46.4
25-65 years	**57.0**	**57.4**	**57.7**	**58.5**

Until 2009, only 4 *départements* had an organised cervical screening programme. In Alsace, where screening has been organised since 1994 in the Bas-Rhin and since 2011 in the Haut-Rhin, screening coverage was 71% and 68.5% respectively for the period 2003-2005.[20]

Since 2010, pilot testing of organised screening has been launched in 13 *départements* (Haut-Rhin, Bas-Rhin, Isère, Martinique, Allier, Cantal, Haute-Loire, Puy-de-Dôme, Cher, Indre-et-Loire, Maine-et-Loire, La Réunion, Val-de-Marne).
Data on changes in coverage rates following implementation of these pilot phases are not yet available.

5.4. Transparency Committee recommendations

As part of the prevention strategy for the morbidity and mortality linked to HPV, the Transparency Committee endorses the recommendation of the HCSP, namely that "there is no longer any need to recommend one of the 2 vaccines in preference"

Request for additional data:
In 2008, the Committee and CEPS had hoped that all the studies on public health impact referred to in the HCSP opinion (opinion dated 14 December 2007) would be implemented in France by the pharmaceutical company.
These studies should particularly document the impact on infection and morbidity (particularly CIN 2 and 3) of dissemination of vaccination in light of the behavioural change on cervical cancer screening with smears and environmental impacts which may arise. The epidemiological studies required to monitor and estimate, where appropriate, the risk of onset of autoimmune disease or any other condition which could emerge after vaccination by CERVARIX should also be conducted. Similarly, the vaccination impact on the STI risk-taking and on the use of screening for cervical cancer should be specifically studied.

Regardless of the safety studies monitored by the AFSSAPS, the Committee notes that no program of suitable rigorous studies has been suggested to answer these questions.
The study proposed by the pharmaceutical company to examine the impact of vaccination on sexual and screening behaviours was an opinion survey and did not answer all of the questions raised.

Thus, the Committee requests that the pharmaceutical company answers the question asked both by the CEPS and the Committee itself about the impact of the vaccination program conducted in France on morbidity (CIN 2/3 lesions).

[20] Duport N, Haguenoer K, Ancelle-Park R, Bloch J. Dépistage organisé du cancer du col de l'utérus – Evaluation épidémiologique des quatre départements « pilotes ». InVS, 12 June 2007: 32 pages

An updated overview of the French epidemiological data available from the public facilities involved in the prevention of cancer policy in France (epidemiology of premalignant and malignant lesions, use of screening) should be performed by the pharmaceutical company.

The impact of vaccination could be estimated from individual data indirectly collected by the pharmaceutical company from patients, prescribers or the social security funds (vaccination status) and the structures of organised screening or from the Regional Centres of Data and Statistical Collection of Pathological Anatomy and Cytology (CRISAP) or cancer registries.

At the same time, the Committee requests that the updated epidemiological data and the use in real life be integrated in a model of quality appropriate to the French context, in order to respond to the questions on the economic and population impact of the vaccination against HPV.

At the request of the Directorate-General for Health, the Committee would like to receive, within 3 months of the date of receipt of the definitive opinion, the new study protocol planned by the laboratory to estimate the impact of the vaccine on morbidity as well as the proposed model structure capable of answering the questions on the economic and population impact of the vaccination program against HPV infections.

Appendix 1: Epidemiology
Appendix 2: Assessment of the pharmacovigilance monitoring of the anti-HPV vaccines

Appendix 1: Epidemiology

The incidence of invasive cervical cancer in France is estimated to be 2810 new cases per year (InVS projections 2011[21]). It is therefore the 10th most common cancer in women. The number of deaths from cervical cancer is estimated to be 998 in 2011. This ranks cervical cancer 13th for deaths from cancer in women in 2011.

Data listed in the 2010 European Marketing Authorisation:
HPV types 16 and 18 are estimated to be responsible for around 70% of cervical cancers; they are predominant in severe lesions:
- 80% of the adenocarcinomas in situ (AIS);
- 45-70% of the high grade cervical premalignant lesions (CIN2/3);
- 25% of the low grade cervical malignant lesions (CIN 1).

- Europe: the data from the most recent literature on the distribution of genotypes of HPV, in particular the meta-analysis by Sanjose et al[22] in invasive cancers (2058 patients), reveal the following prevalence in Europe in descending order:
  . HPV 16 (66%),
  . HPV 18 (7%),
  . HPV 33 (6%),
  . HPV 45 (4%),
  . HPV 31 (3%).

- France: according to the publication cited below the distribution of HPV genotypes 16, 18, 33, 45 and 31 in France depending on the type of cervical lesion is as follows [23]:

Cervical cancer (516 cases)	**High grade lesions (CIN 2/3)** (493 cases)	**Low grade lesions** (397 cases)
HPV 16 (73%)	HPV 16 (62%)	HPV 16 (21%)
HPV 18 (19%)	HPV 18 (4%)	HPV 18 (8%)
HPV 33 (4%)	HPV 33 (12%)	-
HPV 45 (3%)	-	-
HPV 31 (7%)	HPV 31 (15%)	HPV 31 (7%)

The proportion of the cancers linked to these genotypes however is moderate due to the number of multiple infections which make it difficult to allocate a particular genotype to a given cancer. The multiple infections are rarely detailed in the published studies.

- France according to the WHO annual statistics[24]:

Cervical cancer	**High grade lesions (CIN 2/3)**	**Low grade lesions**
HPV 16 (60.7%)	HPV 16 (59.2%)	HPV 16 (19.2%)
HPV 18 (14.9%)	HPV 18 (4.2%)	HPV 18 (5.7%)
HPV 33 (3.3%)	HPV 33 (10.7%)	HPV 33 (4%)
HPV 45 (2.9%)	-	-
HPV 31 (3.8%)	HPV 31 (13.3%)	HPV 31 (5.4%)

[21] Lyon civil hospices/Health Monitoring Institute/National Cancer Institute/Francim/National Institute of Health and Medical Research. Projections of the incidence and mortality of cancer in France in 2011. Technical report. June 2011. http://www.invs.sante.fr/surveillance/cancers [Accessed on 21 10 2011].
[22] Sanjose S, on behalf of the Retrospective International Survey and HPV Time Trends Study Group. Human Papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 2010;11(11): 1048-56. Epub 2010 Oct 15.
[23] Jacquard AC, Denis D, Prétet JL et al, Distribution des génotypes de papillomavirus humain (HPV) dans les lésions génitales en France : études EDiTH, BEH 2009:29, 313-7
[24] http://apps.who.int/hpvcentre/statistics/dynamic/ico/DataQuerySelect.cfm

Appendix 2: Assessment of the pharmacovigilance monitoring of the anti-HPV vaccines (CNPV dated 22 November 2011, AFSSAPS)

The National Pharmacovigilance Committee has read the updated assessment of the pharmacovigilance data for the anti-Human Papillomavirus vaccines (anti-HPV) collected as part of the National monitoring provided by the CRPV of Bordeaux and Lyon. In addition, the results of two pharmaco-epidemiology studies evaluating the risk of autoimmune diseases after anti-HPV vaccination have also been presented.

The analysis of pharmacovigilance data reported in mid-September 2011 by the Bordeaux CRPV as well as cases of exposed pregnancy at the end of May 2010 by the Lyon CRPV, have not identified any new signal regarding the safety of these vaccines, after administration of more than 4 million doses of the anti-HPV vaccines.

The possibility of an increases risk of occurrence of various autoimmune diseases after anti-HPV vaccination has been examined using data from two epidemiological studies carried out in France. The preliminary results from these studies are consistent and do not reveal a significant association between the vaccination and a risk of these autoimmune diseases. The strength of these two studies (a study of "vaccinated/unvaccinated" cohort, performed by the AFSSAPS from the SNIIRAM database [National System of National Health Insurance Inter-system information], and a case-control study carried out by the LA SER Company and conducted from data from the network of RMPx pharmaco-epidemiology studies on autoimmune diseases) have been judged sufficient by the members of the CNPV to confirm their relevance.

These results are consistent with the international surveillance data and the results from epidemiological studies performed in other countries.

Given all these data, the members of the CNPV unanimously agreed on the following proposals:

1. Reminder of the practical recommendations to the medical vaccinators to minimise the risk of a traumatic accident occurring as a result of vasovagal syncope after vaccination, a common adverse effect reported in the pharmacovigilance assessment. ***These recommendations mean vaccinating the subject in a lying or relaxed position and monitoring for 15 minutes after the vaccination.***

2. Standardisation of section 4.8 "Adverse effects" for the two vaccines.[25]

3. Maintaining enhanced monitoring of pharmacovigilance ***targeted at autoimmune diseases***.

4. Continuation of the pharmaco-epidemiology "vaccinated/unvaccinated" cohort studies at intervals to be determined.

[25] So that the information in the Summary of Product Characteristics of the two products is presented in a similar manner and is thus made "more readable" for the prescribers.