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TRANSPARENCY COMMITTEE

OPINION

20 March 2013

CERVARIX suspension for injection, Human Papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed) – pre-filled syringe 0.5 ml + needle

B/1 (CIP: 3400 381 642 3 7)

Applicant: GLAXOSMITHKLINE

INN	Papillomavirus (type 16, 18), recombinant
ATC Code (2012):	J07BM02
Reason for the review	**Renewal of inclusion** ***In addition, see the Committee's Opinion of 20 March 2013 on the new populations recommended by the HCSP (High Council for Public Health)***
List concerned	**National Health Insurance** (French Social Security Code L.162-17)
Indication(s) concerned	"Prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types. The use of CERVARIX should be in accordance with official recommendations."

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Date initiated: 20 September 2007 (centralised procedure)
Prescribing and dispensing conditions / special status	List I

ATC Classification	2012	
	J:	Antiinfectives for systemic use
	J07:	Vaccines
	J07B:	Viral vaccines
	JO7BM:	Papillomavirus vaccines
	J07BM01:	Papillomavirus (types 6, 11, 16, 18), recombinant

02 BACKGROUND

Examination of the dossier for the proprietary medicinal product included for a five-year period starting on 17 June 2008 (JO [Official Gazette] of 8 July 2008).

CERVARIX is the second vaccine made available in France since 2008 for the prevention of premalignant lesions of the cervix and cervical cancer causally related to certain oncogenic types of Human Papillomavirus (HPV).
Since the examination of the dossier for the request for inclusion (Transparency Committee Opinion of 5 March 2008), in February 2012 CERVARIX was the subject of a reassessment by the Committee (Opinion of 1 February 2008) on the basis of new available data.
In the various Opinions, the Committee believed that the actual benefit provided by CERVARIX was substantial only in the indications of the Marketing Authorisation recommended by the HCSP in the current vaccination schedule. In the February 2012 reassessment, the Committee believed that "CERVARIX, *just like the GARDASIL vaccine, provides a moderate improvement in actual benefit (level III) in the strategy for preventing premalignant genital lesions of the cervix due to certain oncogenic types of Human Papillomavirus."*

All the variations to the Marketing Authorisation since 21 February 2011 (revision in force when the reassessment dossier was submitted in April 2011) are described in the table in the appendix. The initial indication, limited to no earlier than the age of 10 years, was expanded to girls aged 9 years on the basis of a pooled analysis of three immunogenicity studies (studies HPV-029, HPV-030 and HPV-048), the results of which were incorporated in the SPC (see appendix). This extension of indication is not the subject of a request for inclusion because the population in question is not included in the French anti-HPV vaccination guidelines.

The new data available on CERVARIX are not likely to change the conclusions of the Transparency Committee in the CERVARIX reassessment in February 2012.

At the same time, the Committee is looking into the justification for the reimbursement of CERVARIX in the new populations recommended by the HCSP (High Council for Public Health) in 2012 (see Committee Opinion of 20 March 2013 on the change in the target population).

03 CHARACTERISTICS OF THE MEDICINAL PRODUCT

03.1 Therapeutic indications

"CERVARIX is a vaccine for use from the age of 9 years for the prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types.

See sections 4.4 and 5.1 of the SPC for important information on the data that support this indication.

The use of CERVARIX should be in accordance with official recommendations."

03.2 Dosage

See SPC.

04 ANALYSIS OF THE NEW DATA AVAILABLE

Since the CERVARIX vaccine was the subject of a very recent (February 2012) reassessment by the Transparency Committee, the current guidelines contain few new data since the previous Opinion (TC Opinion of 1 February 2012).

04.1 Efficacy

Reiteration of the conclusion of the previous Opinion on efficacy:

"The efficacy of the CERVARIX vaccine versus placebo after 15 months against premalignant CIN 2/3 or AIS lesions related to HPV 16 and/or HPV 18 in the interim analysis population (90.4% CI to 97.9%: [53.4-99.3]) was confirmed and maintained in the final analysis after 48 months in all analysed populations:
- in the according to protocol (ATP) population: 94.9% (95% CI: [87.7 – 98.4])
- in the total vaccinated population (TVC): 60.7% (95% CI: [49.6 – 69.5])
- in the TVC naive population: 99.9% (95% CI: [94.2 - 100]);
In addition, the efficacy of the vaccine was demonstrated against CIN 2/3 or AIS individually related to HPV 16 and HPV 18 (ATP population).

In the TVC naive population, overall efficacy against of CIN2+ type premalignant lesions, independently of the HPV oncogene contained in the lesion, was 64.9% (95% CI: [52.7 – 74.2] and 93.2% (95% CI: [78.9-98.7]; against CIN 3+ type premalignant lesions, which are immediate precursors of cervical cancer.

It was shown that infection persisting for at least six months is a relevant surrogate marker for cervical cancer.
Cross-protection was demonstrated vis-à-vis the criteria, infection persisting for six months and CIN2+ in all study cohorts for HPV 31, 33 and 45.
These HPV types 31, 33 and 45 could be involved in 10 to 12% of cervical cancers.

In light of these data, the Committee emphasises the small reduction in the relative risk of occurrence:

- *of CIN2/3 or AIS vis-à-vis HPV 16/18 observed in the total vaccinated population with or without infection (TVC); the relative risk of occurrence was 60.7% (95% CI: [49.6-69.5]), while that found in the according to protocol populatio was: 94.9% (95% CI: [87.7-98.4])*
- *CIN 2/3 or AIS, regardless of the HPV type observed in the lesion compared with that found in the CIN 2/3 vis-à-vis HPV 16/18; in the total vaccinated population, whether infected or not (TVC), the relative risk of occurrence was 33.1% (95% CI: [22.2-42.6]) versus 60.7% (95% CI: [49.6-69.5]).*

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

A 70.2% (95% CI: [57.8; 79.3]) reduction in the number of conisations performed was observed in the TVC-naïve population ; this reduction was 33.2% (95% CI: [20,8: 43.7]) in the total vaccinated population.

In study 023 (follow-up and subgroup of study 001/007), the immune response was assessed 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 HPV 16 and HPV 18 were at least 10 times greater than the GMTs observed in women who had cleared a natural HPV infection.

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

Given the current dossier, the following data have not been obtained:
- *efficacy in terms of preventing cervical cancer, even though additional data on premalignant CIN 3 and AIS lesions, immediate precursors of cervical cancer, had been presented*
- *the duration of cross-protection beyond 48 months*
- *immunogenicity in immunodeficient populations (study in progress in South Africa)*
- *an assessment of a possible change in the viral ecology associated with the introduction of the vaccination"*

New clinical data

Since the reassessment of the CERVARIX data by the Transparency Committee in February 2012, no new data on vaccine efficacy in the populations mentioned in the official guidelines have been submitted by the applicant.

The new results of clinical studies were:

- persistence of the immune response for up to 113 months (study 023): the stability of immunogenicity up to 101 months (median follow-up 7.9 years) had been assessed in the Transparency Committee's last opinion. This stability is confirmed at 113 months (median follow-up 8.9 years). These data were incorporated in the SPC (see appendix: comparative table of revisions to Marketing Authorisations since 21 February 2011).

- immunogenicity in immunocompromised populations: the initial results (12-month follow-up) of study HPV-020 conducted in South Africa in HIV+ women were presented. However, since these data are currently being assessed by the regulatory authorities, they cannot be taken into account in this assessment.

04.2 Adverse effects

Reiteration of the conclusion of the previous safety opinion
"The safety data obtained in the clinical studies did not show any significant increase in adverse events in the group of women vaccinated with CERVARIX compared with the placebo group.

CERVARIX is not indicated in the prevention of premalignant genital lesions of the vulva and the vagina due to certain oncogenic types of Human Papillomavirus (HPV) or for external genital warts (condylomata acuminata) due to specific HPV types.

A similar frequency of newly diagnosed autoimmune diseases (0,8%) and newly diagnosed chronic diseases (2.7% versus 2.9%) – asthma, urticaria, hypersensitivity reactions, hypothyroidism and seasonal allergy – was observed.

A first report on the European and French risk management plan was published by AFSSAPS on 11 July 2011.[1] The report states that the benefit/risk ratio of this vaccine remains favourable and that its safety of use profile is close to that identified at the time it received its Marketing Authorisation. This is confirmed by the absence of any particular pharmacovigilance reports (Bordeaux CRPV regional PV centre report, mid-September 2011)".

In addition, in view of the reported cases of narcolepsy with cataplexy that were attributed to the AS03 lipid adjuvant (composition: vitamin E and squalene in an oil-in-water emulsion) in the context of influenza vaccine, the National Medicines and Health Products Safety Agency (ANSM) was consulted and confirmed that no similar report was made with any of the anti-HPV vaccines with a different adjuvant.

These new data, obtained from ongoing clinical studies and in connection with post-marketing surveillance, are insufficient to change the Committee's previous conclusions.

04.3 Requests for studies

Requests for studies were reissued by the Committee in its reassessment opinion of 1 February 2012.
As a reminder:
"Request for further data:
In 2008, the Transparency Committee and the CEPS (Economic Committee for Health Products) expressed the wish for the applicant to proceed with all the public health impact studies in France mentioned in the 14 December 2007 opinion of the HCSP.
These studies were intended to document the impact on infection and morbidity (especially CIN 2 and 3) of the spread of vaccination in light of the changed attitudes to cervical cancer screening through cervical smears, as well as the possible resultant ecological impact. Epidemiological studies, which are necessary to monitor and estimate, where applicable, the risk of occurrence of autoimmune diseases or any other pathology that might emerge following CERVARIX vaccination, should also be conducted. Likewise, the impact of vaccination on the risk of contracting an STI and on recourse to screening for cervical cancer was to be investigated specifically.

Independently of the safety studies conducted by AFSSAPS, the Committee finds that no relevant and rigorous research programme has been proposed to provide an answer to these questions.
The study proposed by the applicant to study the impact of vaccination on sexual behaviour and screening was an opinion poll and did not answer all of the questions asked.

Consequently, the Committee is asking the applicant to answer the question put to it both by CEPS and by the Committee on the impact of the vaccination programme conducted in France on morbidity (CIN 2/3 lesions).

The applicant will have to put together an up-to-date inventory of French epidemiological data available from public organisations involved in the cervical cancer prevention policy in France (epidemiology of premalignant and malignant lesions, use of screening, etc.).

[1] http://ansm.sante.fr/content/download/34613/452664/version/2/file/cervarix-bilanPGR.pdf

The impact of vaccination could be estimated from individual data collected indirectly by the applicant from patients, prescribers or national health insurance offices (vaccination status) and from bodies running mass screening campaigns or CRISAPs (regional centres for the collection of electronic and statistical data on pathological anatomy and cytology) or from cancer registries.

Meanwhile, the Committee is asking that up-to-date, real-life epidemiological data be built into a model of a quality suited to the French context in order to be able to answer questions about the economic impact and influence on the population of the HPV vaccination programme.

At the request of the Directorate-General for Health (DGS), the Committee would like to receive, within three months of receipt of the final opinion, a new study protocol drawn up by the applicant to estimate the vaccine's impact on morbidity, as well as a proposal for the structure of the model that could answer the questions about the economic impact and influence on the population of the HPV vaccination programme."

Replies provided by the applicant (currently being analysed by the ISPEP group)
In response to the Transparency Committee's request for studies, the applicant submitted, within the specified deadlines:

- a programme of studies of the impact of vaccination with CERVARIX in France
- a protocol and the results of a medico-economic model adapted to the French situation that can be used to document the economic and population impact of the HPV vaccination programme.

These protocols are currently being assessed by HAS and are currently the subject of discussions with the applicant.

04.4 Prescribing data

According to IMS data (CMA November 2012), the CERVARIX proprietary medicinal product was the subject of 56,111 prescriptions (9.8% of which were prescriptions for anti-HPV vaccines). The small number of prescriptions is insufficient to allow a qualitative analysis of the data to be performed.

04.5 Therapeutic use

This proprietary medicinal product keeps its therapeutic use, according to the HCSP's 28 September 2012 opinion (published on 15 January 2013) on the revision of the age for vaccination against human papillomavirus (HPV) infections in girls.[2,3]

[2] High Council for Public Health (HCSP). Opinion on the revision of the age for vaccination against human papillomavirus infections in girls. 28 September 2012.
[3] See Transparency Committee Opinion of 20 March 2013. Extension of the target population for CERVARIX following the 28 September 2012 opinion of the High Council for Public Health (HCSP) on the revision of the age for vaccination against human papillomavirus (HPV) infections in girls.

05 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee believes that the conclusions of its previous 1 February 2012 opinion do not need to be changed.

05.1 Actual benefit

CERVARIX is a vaccine against human papillomaviruses 16 and 18 for the prevention of premalignant lesions of the cervix and cancer of the cervix due to certain oncogenic types of Human Papillomavirus (HPV) which can be life threatening.

This medicinal product falls into the category of a preventive therapy (primary prevention).

The vaccine's efficacy/adverse events ratio for the new population is high.

Public health benefit:

The incidence of invasive cervical cancer in France is estimated to be 2810 new cases a year (InVS projections 2011[4]). It is therefore the 10th most common cancer in women. The number of deaths from cancer was estimated at 998 in 2011, which puts cervical cancer in 13th place as the cause of cancer deaths among women in 2011.
The public health burden of cervical cancer (corresponding to about 135,000 DALYs[5]) is therefore considered to be moderate.

Reducing the incidence of cervical cancer is an established public health priority (objective 48 of the Law of 9 August 2004 relating to public health policy "to continue reducing the incidence of cervical cancer by 2.5% a year, and in particular by hitting the target of 80% screening coverage among women aged from 25 to 69 years", 2009-2013 Cancer Plan "Measure 15: To improve the structuring of the action plan for national cancer screening programmes").

Vaccination against oncogenic human papillomavirus (HPV) types could constitute a response to this need, and could optimise nationwide cervical cancer screening. Even though improvements in the screening coverage have have continued to be made since 1995, coverage was only 58.5% in 2007-2009,[6] which is still far from the target of 80%, especially in certain more disadvantaged social and occupational categories.[7,8]

In France, the vaccination coverage rate (full vaccination schedule) was estimated on the basis of the national health insurance system's general sample of beneficiaries (CNAM-TS/InVS) on 31 December 2011.[9] It was on average 36.9% in girls born in 1993 (18 years), 39.0% in girls born in 1994 (17 years), 31.2% in girls born in 1995 (16 years) and 20.2% in girls born in 1996 (15 years).
Follow-up of the coverage rates according to the girls' age indicates a downward trend in the vaccination coverage rate for one dose between 2010 and 2011 in cohorts of girls who were 16 years of age in the year in question (49.9% versus 46.8% respectively), 15 years of

[4] Hospices civils de Lyo / National Health Monitoring Institute / National Cancer Institute / Francim / National Institute of Health and Medical Research. Projections of the incidence and mortality from cancer in France in 2011. Technical report. June 2011. http://www.invs.sante.fr/surveillance/cancers [Retrieved 21.10.2011].
5 Regional burden of disease estimates for 2004. Standard DALYs for Zone EURO A. World Health Organization. http://www.who.int/healthinfo/global_burden_disease/DALY14_2004.xls [retrieved 25.02.2013]
[6] DRESS. L'état de santé de la population en France – State of health of the population in France – Follow-up of objectives related to the Public Health Law - 2011 Report http://www.sante.gouv.fr/IMG/pdf/Etat_sante-population_2011.pdf [retrieved 26 02 2013]
[7] Public health objectives. Assessment of the objectives of the Law of 9 August 2004. Proposals. High Council for Public Health (HCSP). April 2010
[8] Public health guidelines: "Situation and recommendations for cervix cancer screening in France". Haute Autorité de santé. July 2010.
[9] Opinion on the revision of the age for vaccination against human papillomavirus infections in girls. High Council for Public Health (HCSP). 28 September 2012.

age in the year in question (39.4% versus 35.8% respectively) and 14 years of age in the year in question (22.5% versus 15.8% respectively).
The majority of girls start vaccination at age 15 years or later. The vaccination coverage of girls aged 14 years is therefore still insufficient today.

In view of the low rate of vaccination coverage achieved in France, especially in girls aged 14 years, as well as the inadequate level of individual screening, the public health need remains.

Considering only the immunogenicity data available for girls aged 11-14 years and in the absence of any new data making it possible to document the impact of the vaccine on morbidity in other age groups, the impact of CERVARIX is still considered substantial in reducing short-term morbidity (CIN2+), especially in girls who have not yet been infected with oncogenic HPVs, irrespective of the age of vaccination.

Nevertheless, the four year's experience with the vaccination in girls aged 15 to 25 years remains insufficient given the changing natural history of HPV infections, to assess the impact of CERVARIX in terms of morbidity and mortality (CIN 3 and carcinoma *in situ*).
In addition, the previously raised doubts (cross-protection not demonstrated for each of the oncogenic HPV types, duration of vaccination protection unknown, consequences of vaccination on the distribution and viral ecology of HPV forms, consequences of the vaccination for screening practices) remain.

Consequently, given that the present level of vaccination coverage in France is unlikely to guarantee group immunity, and despite the expected potentially considerable public health benefit of vaccinating against papillomavirus, the public health benefit of CERVARIX at the present time, with the scant retrospective information at our disposal, is regarded as low.

In order to optimise the public health impact of this vaccine and to meet the public health needs, the Committee in its Opinion of 2 February 2012 considered it necessary to put in place measures designed to:

- stimulate the vaccination programme and increase the vaccination coverage rate especially among HPV-naïve girls, amongst whom vaccination efficacy is greatest,
- and to improve access to, information about and interest in cervical smear screening, particularly among young women in disadvantaged neighbourhoods.

The new recommendations of the HCSP on lowering the age of vaccination to 11-14 years are intended to promote an increase in vaccination coverage by making it possible:

- to promote the vaccination of girls who have not yet been exposed to the risk of HPV infection and in whom vaccination efficacy is maximal;
- to use the vaccination appointment for 11-14 year-olds (booster of tetravalent vaccine against diphtheria-tetanus-pertussis-polio or vaccine against hepatitis B) to start vaccination or to complete an incomplete vaccination schedule.

In addition, the withdrawal of the concept of the age at which sexual activity starts in the target population aged 15-19 years could also limit the obstacles to vaccination. However, in terms of public health, the greatest benefit of vaccination is in girls or young women who have not yet been exposed to papillomaviruses.

Even though it does not specifically pertain to HPV vaccination, the national programme for the 2012-2017[10] vaccination policy improvement programme implemented by the Directorate-General for Health in October 2012 will, in coming years, also aim to facilitate access to vaccines and encourage preventive actions using vaccination.

Finally, since the vaccination does not protect against all oncogenic HPV types, it cannot be a substitute for screening for premalignant and malignant lesions of the cervix. Rather, it should be a complement. Thus, improving access, information and the benefit of screening by means of cervical smears recommended every three years (after two normal cervical smears carried out one year apart) in all women aged 25 to 65 years remains necessary,

[10] National programme for the improvement of vaccination policy 2012 – 2017. http://www.sante.gouv.fr/IMG/pdf/Programme_national_damelioration_de_la_politique_vaccinale.pdf retrieved 25.02.2013.

particularly in young women from disadvantaged neighbourhoods who may not enjoy optimal conditions of regular screening.
To this end, the organisation of screening by means of nationwide cervical smears is still essential.

There is an alternative to vaccination for the prevention of premalignant cervical lesions and cervical cancer.
Screening, which relies on a cytological test – the cervical smear – is an effective secondary means of preventing cervical cancer.

Consequently, the Committee believes that the actual benefit of CERVARIX remains substantial only the Marketing Authorisation indications recommended by the HCSP in the current vaccination schedule.

05.2 Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance in the new population recommended by the HCSP in the current vaccination schedule.

◗ Proposed reimbursement rate: 65%

◗ Packaging:
Appropriate for the prescription conditions.

◗ Other requests
In addition to the recommendations already given in its Opinion of 1 February 2012, the Committee stresses that the effectiveness of this strategy of prevention by vaccination against HPV depends on achieving the highest possible vaccination coverage rate.
It finds that, since the implementation of vaccination in 2007, only a small proportion of the eligible population is currently vaccinated against HPV, and that there was even a slight drop in the vaccination rate between 2010 and 2011.
Consequently, if this coverage did not achieve the objective despite the new guidelines issued, the Committee might have cause to reconsider, in the medium term (in a period of three years), the assessment of the actual benefit of anti-HPV vaccines.

In addition, the Committee points out that the prevention of cancers of the cervix and uterus, regardless of the type of HPV is involved, has for decades been based on screening for premalignant/malignant lesions using the cervical smear test, which has largely proved its efficacy when correctly organised, and that vaccines for preventing infection with oncogenic HPV 16 and 18 complement screening and cannot replace it.
In any event, the Committee confirms its previous opinion and believes that it remains vital for cervical smear screening for premalignant and malignant cervical lesions to be organised nationwide.

Appendix: Comparative table, SPC of 21.02.2011 and SPCs of 26.08.2011, 05.12.2011 and 17.09.2012

Only sections with a major change are shown (see SPC for the other sections).

Changes made to the SPC dated 26.08.2011
Changes made to the SPC dated 05.12.2011
Changes made to the SPC dated 17.09.2012

Text added: Shaded in the colour of the SPC making the change
~~Text deleted~~: lettering and strike-through in the colour of the SPC which deletes the text with the colour of the associated correction: ~~26/08/2011~~, ~~05/12/2012~~ or ~~17/09/2012~~

CERVARIX – SPC of 21.02.2011	CERVARIX - changes: SPC of 26.08.2011, 05.12.2011, 17.09.2012	*[COMMENTS]*
APPENDIX I **SUMMARY OF PRODUCT CHARACTERISTICS**	**APPENDIX I** **SUMMARY OF PRODUCT CHARACTERISTICS**	
3. PHARMACEUTICAL FORM	**3. PHARMACEUTICAL FORM**	3. PHARMACEUTICAL FORM
Suspension for injection in prefilled syringe. Turbid white suspension. During storage a fine white deposit with a colourless and clear supernatant may be observed.	Suspension for injection in prefilled syringe. Turbid white suspension. ~~During storage a fine white deposit with a colourless and clear supernatant may be observed.~~	Five-yearly renewal (variation No. 35): simplification of the SPC since information already provided in section 6.6
4. CLINICAL PARTICULARS	**4. CLINICAL PARTICULARS**	4. CLINICAL PARTICULARS
4.1 Therapeutic indications	**4.1 Therapeutic indications**	4.1 Therapeutic indications
CERVARIX is a vaccine for the prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types. See sections 4.4 and 5.1 for important information on the data that support this indication. The indication is based on the demonstration of efficacy in women aged 15 to 25 years vaccinated with CERVARIX and on the immunogenicity of the vaccine in girls and women aged 10 to 25 years.	CERVARIX is a vaccine for use from the age of 9 years for the prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types. See sections 4.4 and 5.1 for important information on the data that support this indication. ~~The indication is based on the demonstration of efficacy in women aged 15 to 25 years vaccinated with CERVARIX and on the immunogenicity of the vaccine in girls and women aged 10 to 25 years.~~	Incorporation of the results of the pooled analysis of studies HPV-029/030/048 *(Marketing Authorisation variation No. 21).* Extension of indication outside the French vaccination guidelines

CERVARIX – SPC of 21.02.2011	CERVARIX - changes: SPC of 26.08.2011, 05.12.2011, 17.09.2012	*[COMMENTS]*
CERVARIX should be administered in accordance with official recommendations.	CERVARIX should be administered in accordance with official recommendations.	
4.2 Posology and method of administration	**4.2 Posology and method of administration**	4.2 Posology and method of administration
Dosage The recommended vaccination schedule consists of 3 doses administered according to the following schedule: 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 (see section 5.1). It is recommended that subjects who receive a first dose of CERVARIX complete the 3-dose vaccination course with CERVARIX (see section 4.4). *Paediatric population* 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. Method of administration CERVARIX is for intramuscular injection in the deltoid region (see also sections 4.4 and 4.5).	Dosage ~~The recommended vaccination schedule consists of~~ The recommended vaccination consists of 3 separate 0.5 ml doses administered according to the following schedule: 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 (see section 5.1). It is recommended that subjects who receive a first dose of CERVARIX complete the 3-dose vaccination course with CERVARIX (see section 4.4). *Paediatric population* CERVARIX is not recommended for use in girls below ~~10~~ 9 years of age due to lack of data on safety and immunogenicity in this age-group. Method of administration CERVARIX is for intramuscular injection in the deltoid region (see also sections 4.4 and 4.5).	Five-yearly renewal, improvement of the wording *(Marketing Authorisation variation No. 35)* For consistency with the change in age for the indication *(Marketing Authorisation variation No. 21)*
4.3 Contraindications	**4.3 Contraindications**	4.3 Contraindications
Hypersensitivity to the active substances or to any of the excipients. Administration of CERVARIX should be postponed in subjects suffering from an acute severe febrile illness. However, the presence of a minor infection, such as a cold, is not a contraindication for immunisation.	Hypersensitivity to the active substances or to any of the excipients listed in section 6.1. Administration of CERVARIX should be postponed in subjects suffering from an acute severe febrile illness. However, the presence of a minor infection, such as a cold, is not a contraindication for immunisation.	Five-yearly renewal, for consistency with the EMA template *(Marketing Authorisation variation No. 35)*
4.5 Interaction with other medicinal products and other forms of interaction	**4.5 Interaction with other medicinal products and other forms of interaction**	4.5 Interactions

CERVARIX – SPC of 21.02.2011	CERVARIX - changes: SPC of 26.08.2011, 05.12.2011, 17.09.2012	*[COMMENTS]*
In all clinical trials individuals who had received immunoglobulin or blood products within 3 months prior to the first vaccine dose were excluded. *Use with other vaccines* CERVARIX may be administered concomitantly with a combined booster vaccine containing diphtheria (d), tetanus (T) and pertussis [acellular] (pa) with or without inactivated poliomyelitis (IPV), (dTpa, dTpa-IPV vaccines), with no clinically relevant interference with antibody response to any of the components of either vaccine. The sequential administration of combined dTpa-IPV followed by CERVARIX one month later tended to elicit lower anti-HPV-16 and anti-HPV-18 GMTs as compared to CERVARIX alone. The clinical relevance of this observation is not known. CERVARIX may be administered concomitantly with a combined hepatitis A (inactivated) and hepatitis B (rDNA) vaccine (Twinrix) or with hepatitis B (rDNA) vaccine (Engerix B). Administration of CERVARIX at the same time as Twinrix (hepatitis A/hepatitis B vaccine) has shown no clinically relevant interference in the antibody response to the HPV and hepatitis A antigens. Anti-HBs geometric mean antibody concentrations were significantly lower on co-administration, but the clinical relevance of this observation is not known since the seroprotection rates remain unaffected. The proportion of subjects reaching anti-HBs ≥ 10 mIU/ml was 98.3% for concomitant vaccination and 100% for Twinrix given alone. Similar results were observed when CERVARIX was given concomitantly with Engerix B with 97.9% of subjects reaching anti-HBs ≥ 10 mIU/ml compared to 100% for Engerix B given alone. If CERVARIX is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites. *Use with hormonal contraceptives* In clinical efficacy studies, approximately 60% of women who received CERVARIX used hormonal contraceptives There is no evidence that the use of hormonal contraceptives has an impact on the efficacy of CERVARIX. *Use with systemic immunosuppressive medicinal products* As with other vaccines it may be expected that, in patients receiving immunosuppressive treatment an adequate response may not be elicited.	In all clinical trials individuals who had received immunoglobulin or ~~blood~~ blood-derived products within 3 months prior to the first vaccine dose were excluded. <u>*Use with other vaccines*</u> CERVARIX may be administered concomitantly with a combined booster vaccine containing diphtheria (d), tetanus (T) and pertussis [acellular] (pa) with or without inactivated poliomyelitis (IPV), (dTpa, dTpa-IPV vaccines), with no clinically relevant interference with antibody response to any of the components of either vaccine. The sequential administration of combined dTpa-IPV followed by CERVARIX one month later tended to elicit lower anti-HPV-16 and anti-HPV-18 GMTs as compared to CERVARIX alone. The clinical relevance of this observation is not known. CERVARIX may be administered concomitantly with a combined hepatitis A (inactivated) and hepatitis B (rDNA) vaccine (Twinrix) or with hepatitis B (rDNA) vaccine (Engerix B). Administration of CERVARIX at the same time as Twinrix (hepatitis A/hepatitis B vaccine) has shown no clinically relevant interference in the antibody response to the HPV and hepatitis A antigens. Anti-HBs geometric mean antibody concentrations were significantly lower on co-administration, but the clinical relevance of this observation is not known since the seroprotection rates remain unaffected. The proportion of subjects reaching anti-HBs ≥ 10 mIU/ml was 98.3% for concomitant vaccination and 100% for Twinrix given alone. Similar results were observed when CERVARIX was given concomitantly with Engerix B with 97.9% of subjects reaching anti-HBs ≥ 10 mIU/ml compared to 100% for Engerix B given alone. If CERVARIX is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites. <u>Use with hormonal contraceptives</u> In clinical efficacy studies, approximately 60% of women who received CERVARIX used hormonal contraceptives There is no evidence that the use of hormonal contraceptives has an impact on the efficacy of CERVARIX. <u>Use with systemic immunosuppressive medicinal products</u> As with other vaccines it may be expected that, in patients receiving immunosuppressive treatment an adequate response may not be elicited.	Five-yearly renewal, improvement of the wording *(Marketing Authorisation variation No. 35)*

CERVARIX – SPC of 21.02.2011	CERVARIX - changes: SPC of 26.08.2011, 05.12.2011, 17.09.2012	*[COMMENTS]*
4.6 Fertility, pregnancy and lactation	**4.6 Fertility, pregnancy and lactation**	4.6 Fertility, pregnancy and lactation
Specific studies of the vaccine in pregnant women were not conducted. However, during the clinical development program, a total of 3993 pregnancies were reported including 2009 in women who had received CERVARIX. Overall, the proportions of pregnant subjects who experienced specific outcomes (e.g., normal infant, abnormal infants including congenital anomalies, premature birth, and spontaneous abortion) were similar, regardless of whether the group was vaccinated with CERVARIX or another vaccine. Animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development (see section 5.3). These data are insufficient to recommend use of CERVARIX during pregnancy. Vaccination should, therefore, be postponed until after completion of pregnancy. The effect on breast-fed infants of the administration of CERVARIX to their mothers has not been evaluated in clinical studies. CERVARIX should only be used during breastfeeding when the possible advantages outweigh the possible risks.	Pregnancy Specific studies of the vaccine in pregnant women were not conducted. However, during the clinical development program, a total of ~~3993~~ 10,476 pregnancies were reported including ~~2009~~ 5,387 in women who had received CERVARIX. Overall, the proportions of pregnant subjects who experienced specific outcomes (e.g., normal infant, abnormal infants including congenital anomalies, premature birth, and spontaneous abortion) were similar, regardless of whether the group was vaccinated with CERVARIX or another vaccine. Animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development (see section 5.3). These data are insufficient to recommend use of CERVARIX during pregnancy. Vaccination should, therefore, be postponed until after completion of pregnancy. Breastfeeding The effect on breast-fed infants of the administration of CERVARIX to their mothers has not been evaluated in clinical studies. CERVARIX should only be used during breast-feeding when the possible advantages outweigh the possible risks. Fertility No fertility data are available.	Incorporation of knowledge provided by study HPV-015 conducted in women over 25 years of age *(Marketing Authorisation variation No. 34)* Renewal (variation 35), for consistency with the EMA template
4.7 Effects on ability to drive and use machines	**4.7 Effects on ability to drive and use machines**	4.7 Effects on ability to drive
No studies on the effects on the ability to drive or use machines have been performed.	No studies on the effects on the ability to drive or use machines have been performed.	
4.8 Undesirable effects	**4.8 Undesirable effects**	4.8 Undesirable effects
Clinical studies In clinical studies that enrolled girls and women aged from 10 up to 72 years (of which 79.2% were aged 10-25 years at the time of	~~*Clinical studies*~~ ***Summary of safety profile*** In clinical studies that enrolled girls and women aged from 10 up to 72 years (of which 79.2% were aged 10-25 years at the time of	Five-yearly renewal, improvement of the wording *(Marketing Authorisation variation No. 35)*

CERVARIX – SPC of 21.02.2011	CERVARIX - changes: SPC of 26.08.2011, 05.12.2011, 17.09.2012	*[COMMENTS]*
enrolment), CERVARIX was administered to 16,142 subjects whilst 13,811 subjects received control. These subjects were followed for serious adverse events over the entire study period. In a pre-defined subset of subjects (CERVARIX = 8130 versus control = 5786), 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 severity and were not long lasting. Adverse reactions considered as being at least possibly related to vaccination have been categorised by frequency: Frequencies are defined as follows: Very common (≥ 1/10) Common (≥ 1/100 to < 1/10) Uncommon (≥ 1/1000 to < 1/100) <u>Infections and infestations:</u> Uncommon: upper respiratory tract infection <u>Nervous system disorders:</u> Very common: headaches Uncommon: dizziness <u>Gastrointestinal disorders:</u> Common: gastrointestinal symptoms including nausea, vomiting, diarrhoea and abdominal pain <u>Skin and subcutaneous tissue disorders:</u> Common: itching/pruritus, rash, urticaria <u>Musculoskeletal and systemic disorders</u> Very common: myalgia Common: arthralgia <u>General disorders and administration site conditions:</u> Very common: injection site reactions including pain, redness, swelling; fatigue Common: fever (≥ 38 °C) Uncommon: other injection site reactions such as induration, local paraesthesia. A similar safety profile has been observed in subjects with prior or current HPV infection as compared to subjects negative for oncogenic HPV DNA or seronegative for anti-HPV-16 and anti-HPV-18 antibodies. *Post-marketing surveillance* Because these events were reported spontaneously, it is not possible to reliably estimate their frequency.	enrolment), CERVARIX was administered to 16,142 subjects whilst 13,811 subjects received control. These subjects were followed for serious adverse events over the entire study period. In a pre-defined subset of subjects (CERVARIX = 8130 versus control = 5786), 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 severity and were not long lasting. **List of adverse reactions** Adverse reactions considered as being at least possibly related to vaccination have been categorised by frequency: Frequencies are defined as follows: Very common (≥ 1/10) Common (≥ 1/100 to < 1/10) Uncommon (≥ 1/1000 to < 1/100) • Clinical trial data <u>Infections and infestations:</u> Uncommon: upper respiratory tract infection <u>Nervous system disorders:</u> Very common: headaches Uncommon: dizziness <u>Gastrointestinal disorders:</u> Common: gastrointestinal symptoms including nausea, vomiting, diarrhoea and abdominal pain <u>Skin and subcutaneous tissue disorders:</u> Common: itching/pruritus, rash, urticaria <u>Musculoskeletal and systemic disorders</u> Very common: myalgia Common: arthralgia <u>General disorders and administration site conditions:</u> Very common: injection site reactions including pain, redness, swelling; fatigue Common: fever (≥ 38 °C) Uncommon: other injection site reactions such as induration, local paraesthesia. A similar safety profile has been observed in subjects with prior or current HPV infection as compared to subjects negative for oncogenic HPV DNA or seronegative for anti-HPV-16 and anti-HPV-18 antibodies. *Post-marketing ~~surveillance~~ data* Because these events were reported spontaneously, it is not possible to reliably estimate their frequency.	Five-yearly renewal, improvement of the formulation *(Marketing*

CERVARIX – SPC of 21.02.2011	CERVARIX - changes: SPC of 26.08.2011, 05.12.2011, 17.09.2012	*[COMMENTS]*
Blood and lymphatic system disorders Adenopathy Immune system disorders Allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema Nervous system disorders Syncope or vasovagal responses to injection, sometimes accompanied by tonic-clonic movements (see section 4.4).	Blood and lymphatic system disorders Adenopathy Immune system disorders Allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema Nervous system disorders Syncope or vasovagal responses to injection, sometimes accompanied by tonic-clonic movements (see section 4.4).	*Authorisation variation No. 35)*
5. PHARMACOLOGICAL PROPERTIES	**5. PHARMACOLOGICAL PROPERTIES**	
5.1 Pharmacodynamic properties	**5.1 Pharmacodynamic properties**	**5.1 Pharmacodynamic properties**
Pharmacotherapeutic group: Papillomavirus vaccines, ATC code: J07BM02 *Mechanism of action* CERVARIX is an adjuvanted non-infectious recombinant vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid L1 protein of oncogenic HPV types 16 and 18. Since the VLPs contain no viral DNA, they cannot infect cells, reproduce or cause disease. Animal studies have shown that the efficacy of L1 VLP vaccines is largely mediated by the development of a humoral immune response. HPV-16 and HPV-18 are estimated to be responsible for approximately 70% of cervical cancers. Other oncogenic HPV types can also cause cervical cancer (approximately 30%). HPV 45, -31 and -33 are the 3 most common non-vaccine HPV types identified in squamous cervical carcinoma (12.1%) and adenocarcinoma (8.5%). The term “premalignant cervical lesions” in section 4.1 corresponds to high-grade Cervical Intraepithelial Neoplasia (CIN2/3). *Clinical studies* The efficacy of CERVARIX was assessed in two controlled, double-blind, randomised Phase II and III clinical trials that included a total of 19,778 women aged 15 to 25 years. The phase II trial (study 001/007) enrolled only women who: - Were tested negative for oncogenic HPV DNA of types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68	Pharmacotherapeutic group: Vaccines, Papillomavirus vaccines, ATC code: J07BM02 *Mechanism of action* CERVARIX is an adjuvanted non-infectious recombinant vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid L1 protein of oncogenic HPV types 16 and 18. Since the VLPs contain no viral DNA, they can~~not~~ neither infect cells, nor reproduce nor cause disease. Animal studies have shown that the efficacy of L1 VLP vaccines is largely mediated by the development of a humoral immune response. HPV-16 and ~~HPV-~~18 are estimated to be responsible for approximately 70% of cervical cancers. Other oncogenic HPV types can also cause cervical cancer (approximately 30%). HPV 45, -31 and -33 are the 3 most common non-vaccine HPV types identified in squamous cervical carcinoma (12.1%) and adenocarcinoma (8.5%). The term “premalignant cervical lesions” in section 4.1 corresponds to high-grade Cervical Intraepithelial Neoplasia (CIN2/3). *Clinical studies* Clinical efficacy in women aged 15 to 25 years The efficacy of CERVARIX was assessed in two controlled, double-blind, randomised Phase II and III clinical trials that included a total of 19,778 women aged 15 to 25 years. The phase II trial (study 001/007) enrolled only women who: - Were tested negative for oncogenic HPV DNA of types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 - were seronegative for HPV 16 and HPV 18 and	Five-yearly renewal, improvement of the formulation *(Marketing Authorisation variation No. 35)* Incorporation of knowledge provided by study HPV-015 conducted in women over 25 years of age *(Marketing*

CERVARIX – SPC of 21.02.2011	CERVARIX - changes: SPC of 26.08.2011, 05.12.2011, 17.09.2012	*[COMMENTS]*
- were seronegative for HPV 16 and HPV 18 and - had normal cytology The primary efficacy endpoint was incident infection with HPV-16 and/or HPV-18. Twelve-month persistent infection was evaluated as an additional efficacy endpoint. The phase III trial (study 008) enrolled women without pre-screening for the presence of HPV infection, i.e. regardless of baseline cytology and HPV serological and DNA status. The primary efficacy endpoint was CIN2+ (CIN2/3 or AIS) associated with HPV-16 and/or HPV-18 (HPV-16/18). Cervical Intraepithelial Neoplasia (CIN) grade 2 and 3 (CIN2/3) and cervical adenocarcinoma in situ (AIS) were used in the clinical trials as surrogate markers for cervical cancer. The secondary endpoints included 6- and 12-month persistent infection. Persistent infection that lasts for at least 6 months has also been shown to be a relevant surrogate marker for cervical cancer. <u>Prophylactic efficacy against HPV-16/18 infection in a population naïve to oncogenic HPV types</u> Women (N=1,113) were vaccinated in study 001 and evaluated for efficacy up to month 27. A subset of women (N=776) vaccinated in study 001 was followed in study 007 up to 6.4 years (approximately 77 months) after the first dose (mean follow-up of 5.9 years). There were five cases of 12-month persistent HPV-16/18 infection (4 HPV-16; 1 HPV-18) in the control group and one HPV-16 case in the vaccine group in study 001. In study 007 the efficacy of CERVARIX against 12-month persistent HPV-16/18 infection was 100% (95% CI: 80.5; 100).There were sixteen cases of persistent HPV-16 infection, and five cases of persistent HPV-18 infection, all in the control group. <u>Prophylactic efficacy against HPV-16/18 in women naïve to HPV-16 and/or HPV-18</u> In study HPV-008, the primary analyses of efficacy were performed on	- had normal cytology The primary efficacy endpoint was incident infection with HPV-16 and/or HPV-18. Twelve-month persistent infection was evaluated as an additional efficacy endpoint. The phase III trial (study 008) enrolled women without pre-screening for the presence of HPV infection, i.e. regardless of baseline cytology and HPV serological and DNA status. The primary efficacy endpoint was CIN2+ ~~(CIN2/3 or AIS)~~ associated with HPV-16 and/or HPV-18 (HPV-16/18). Cervical Intraepithelial Neoplasia (CIN) grade 2 and 3 (CIN2/3) and cervical adenocarcinoma in situ (AIS) were used in the clinical trials as surrogate markers for cervical cancer. The secondary endpoints included 6- and 12-month persistent infection. Persistent infection that lasts for at least 6 months has also been shown to be a relevant surrogate marker for cervical cancer. <u>Prophylactic efficacy against HPV-16/18 infection in a population naïve to oncogenic HPV types</u> Women (N=1,113) were vaccinated in study 001 and evaluated for efficacy up to month 27. A subset of women (N=776) vaccinated in study 001 was followed in study 007 up to 6.4 years (approximately 77 months) after the first dose (mean follow-up of 5.9 years). There were five cases of 12-month persistent HPV-16/18 infection (4 HPV-16; 1 HPV-18) in the control group and one HPV-16 case in the vaccine group in study 001. In study 007 the efficacy of CERVARIX against 12-month persistent HPV-16/18 infection was 100% (95% CI: 80.5; 100).There were sixteen cases of persistent HPV-16 infection, and five cases of persistent HPV-18 infection, all in the control group. In study HPV-023, subjects from the Brazilian cohort (N=437) of study 001/007 were followed up to a mean of 8.9 years (standard deviation 0.4 years) after the first dose. At study completion, there were no cases of infection or histopathological lesions associated with HPV-16 or HPV-18 in the vaccine group in study HPV-023. In the placebo group, there were 4 cases of 6-month persistent infection and 1 case of 12-month persistent infection. The study was not powered to demonstrate a difference between the vaccine and the placebo group for these endpoints. <u>Prophylactic efficacy against HPV-16/18 in women naïve to HPV-16 and/or HPV-18</u> In study HPV-008, the primary analyses of efficacy were performed on the According to Protocol cohort (ATP cohort: including women who received 3 vaccine doses and were DNA negative and seronegative at	*Authorisation variation No. 34):* reorganisation of paragraphs in the section Incorporation of knowledge provided by the clinical results of the 36-month analysis of study HPV-023 (follow-up to study PHV-001/007) conducted in women over 25 years of age *(Marketing Authorisation variation No. 22)*

CERVARIX – SPC of 21.02.2011	CERVARIX - changes: SPC of 26.08.2011, 05.12.2011, 17.09.2012	*[COMMENTS]*
the According to Protocol cohort (ATP cohort: including women who received 3 vaccine doses and were DNA negative and seronegative at month 0 and DNA negative at month 6 for the HPV type considered in the analysis). This cohort included women with normal or low-grade cytology at baseline and excluded only women with high-grade cytology (0.5% of the total population). Case counting for the ATP cohort started on day 1 after the third dose of vaccine. Overall, 74% of women enrolled were naïve to both HPV-16 and HPV-18 (i.e. DNA negative and seronegative at study entry). The mean duration of follow-up for the women in study HPV-008 was approximately 39 months after the first dose of vaccine in the TVC population and 35 months after the third dose in the ATP population.	month 0 and DNA negative at month 6 for the HPV type considered in the analysis). This cohort included women with normal or low-grade cytology at baseline and excluded only women with high-grade cytology (0.5% of the total population). Case counting for the ATP cohort started on day 1 after the third dose of vaccine. Overall, 74% of women enrolled were naïve to both HPV-16 and HPV-18 (i.e. DNA negative and seronegative at study entry). ~~The mean duration of follow-up for the women in study HPV-008 was approximately 39 months after the first dose of vaccine in the TVC population and 35 months after the third dose in the ATP population.~~ Two analyses of study HPV-008 have been performed: the first analysis, defined in the protocol as the primary analysis of the study, was performed once at least 36 CIN2+ cases associated with HPV-16/18 were confirmed in the ATP cohort, and the second analysis was made taking account of all the end-of study data. Vaccine efficacy against the primary endpoint ~~CIN2/3 or AIS~~ CIN2+ at the end of the study is presented in Table 1. In a supplemental analysis, the efficacy of CERVARIX was evaluated against HPV-16/18-related ~~CIN3 or AIS~~ CIN3+.	Incorporation of the end-of-study data from study HPV-008 (48 months). These data included in the dossier for the re-assessment of the IAB of CERVARIX (April 2011) have already been assessed. They are consistent with the final analysis conducted at 39 months and used as principal analysis by the Transparency Committee.

Vaccine efficacy against the primary endpoint CIN2/3 or AIS is presented in Table 1. In a supplemental analysis, the efficacy of CERVARIX was evaluated against HPV-16/18-related CIN3+ or AIS.

Table 1: Vaccine efficiency against high grade cervical lesions associated with HPV-16/18 (ATP cohort)

HPV-16/18 endpoint	ATP[1]		
	CERVARIX (N = 7344)	Control (N = 7312)	% Efficacy (96.1% CI)
	n[2]	n	
CIN2/3 or AIS	4	56	92.9% (79.9;98.3)
CIN3 or AIS	2	10	80.0% (0.3;98.1)

N = number of subjects included in each group
n = number of cases
(1) ATP: includes women who received 3 doses of vaccine and were DNA negative and seronegative at month 0 and DNA negative at month 6 for the HPV type considered in the analysis (HPV-16 or HPV-18).
(2) including 3 cases of CIN2/3 or AIS and 2 cases of CIN3 or AIS in which another oncogenic HPV type was identified in the lesion

Table 1: Vaccine efficiency against high grade cervical lesions associated with HPV-16/18 (ATP cohort)

HPV-16/18 endpoint	ATP cohort[1] End-of-study analysis[3]		
	CERVARIX (N = ~~7344~~ 7338)	Control (N = ~~7312~~ 7305)	% Efficacy (~~96.1~~ 95% CI)
	n[2]	n	
~~CIN2/3 or AIS~~ CIN2+	~~4~~ 5	~~56~~ 97	~~92.9% (79.9;98.3)~~ 94.9% (87.7; 98.4)
~~CIN3 or AIS~~ CIN3+	2	~~10~~ 24	~~80,0% (0,3;98,1)~~ 91.7% (66.6; 99.1)

N = number of subjects included in each group
n = number of cases
(1) ATP: includes women who received 3 doses of vaccine and were DNA negative and seronegative at month 0 and DNA negative at month 6 for the HPV type considered in the analysis (HPV-16 or HPV-18).
(2) including ~~3~~ 4 cases of ~~CIN2/3 or AIS~~ CIN2+ and 2 cases of ~~CIN3 or AIS~~ CIN3+ in which another oncogenic HPV type was identified in the lesion concomitantly with HPV-16 or -18. These cases are excluded from the analysis of the attribution of HPV types (see

CERVARIX – SPC of 21.02.2011	CERVARIX - changes: SPC of 26.08.2011, 05.12.2011, 17.09.2012	*[COMMENTS]*
concomitantly with HPV-16 or -18. These cases are excluded from the analysis of the attribution of HPV types (see under table).	under table). (3) mean follow-up of 40 months post dose 3	
	In the primary analysis, efficacy was 92.9% (96.1% CI: 79.9; 98.3) against CIN2+ and 80% (96.1% CI: 0.3; 98.1) against CIN3+. In addition, statistically significant vaccine efficacy against CIN2+ associated with either HPV-16 or HPV-18 was demonstrated.	Incorporation of the end-of-study data from study HPV-008 (48 months).
Further investigation of the cases with multiple HPV types considered the types of HPV detected by PCR (polymerase chain reaction) in at least one of the two preciding cytological samples, in addition to types detected in the lesion to distinguish the HPV type(s) most likely responsible to the lesion (HPV type assignement). This post-hoc analysis excluded cases (in the vaccine group and in the control group) which were not considered attributable to HPV-16 or HPV-18 infections acquired during the study.	Further investigation of the cases with multiple HPV types considered the HPV types detected by Polymerase Chain Reaction (PCR) in at least one of the two preceding cytology samples, in addition to types detected in the lesion to distinguish the HPV type(s) most likely responsible to the lesion (HPV type assignment). This post-hoc analysis excluded cases (in the vaccine group and in the control group) which were not considered attributable to HPV-16 or HPV-18 infections acquired during the study.	
Based on the HPV type assignment post-hoc analysis, there was 1 CIN2/3 or AIS case in the vaccine group versus 53 cases in the control group (Efficacy 98.1% (96.1% CI: 88.4; 100)) and 0 cases of CIN3 or AIS in the vaccine group versus 8 cases in the control group (Efficacy 100% (96.1% CI: 36.4; 100)) at the end of the study analysis.	Based on the HPV type assignment post-hoc analysis, there was 1 ~~CIN2/3 or AIS~~ CIN2+ case in the vaccine group versus ~~53~~ 92 cases in the control group (Efficacy ~~98.1%~~ 98.9% (~~96.1%~~ 95% CI: ~~88.4~~ 93.8; 100)) and ~~0~~ there were no cases of ~~CIN3 or AIS~~ CIN3+ in the vaccine group versus ~~8~~ 22 cases in the control group (Efficacy 100% (~~96.1%~~ 95% CI: ~~36.4~~ 81.8; 100)) at the end of the study analysis.	
In addition, statistically significant efficacy of the vaccine was demonstrated against CIN 2/3 or AIS individually associated with HPV-16 and HPV-18.	~~In addition, statistically significant efficacy of the vaccine was demonstrated against CIN 2/3 or AIS individually combined with HPV 16 and HPV 18.~~	
Vaccine efficacy against CIN1 associated with HPV 16/18 observed in the ATP cohort was 94.1% (96.1% CI: 83.4; 98.5). Vaccine efficacy against CIN1/2/3 or AIS associated with HPV 16/18 observed in the ATP cohort was 91.7% (96.1% CI: 82.4; 96.7).	In the primary analysis, vaccine efficacy against CIN1 associated with HPV 16/18 observed in the ATP cohort was 94.1% (96.1% CI: 83.4; 98.5). Vaccine efficacy against ~~CIN1/2/3 or AIS~~ CIN1+ associated with HPV 16/18 observed in the ATP cohort was 91.7% (96.1% CI: 82.4; 96.7). At the end of study analysis, vaccine efficacy against CIN1 associated with HPV-16/18 observed in the ATP cohort was 92.8% (95% CI: 87.1; 96.4).	Incorporation of the end-of-study data from study HPV-008 (48 months).
Vaccine efficacy efficacy against virological endpoints (6-month and 12-month persistent infection) associated with HPV-16/18 observed in the ATP cohort is presented in Table 2.	Vaccine efficacy against virological endpoints (6-month and 12-month persistent infection) associated with HPV-16/18 observed in the ATP cohort at the end of the study is presented in Table 2.	
Table 2: Vaccine efficacy against virological endpoints associated with HPV-16/18 (ATP cohort)	*Table 2: Vaccine efficacy against virological endpoints associated with HPV-16/18 (ATP cohort)*	

HPV 16/18 endpoint	**ATP(1)**		
	CERVARIX	**Control**	**% Efficacy (~~96.1%~~ CI)**

HPV-16/18 endpoint	**ATP cohort (1)**		
	End of study analysis (2)		
	CERVARIX (No. = 7338)	**Control (No. = 7305)**	**% Efficacy (~~96.1%~~ 95% CI)**

CERVARIX – SPC of 21.02.2011	CERVARIX - changes: SPC of 26.08.2011, 05.12.2011, 17.09.2012	[COMMENTS]

	n/N	n/N	
6 month persistent infection	29/7177	488/7122	94.3% (91.5;96.3)
12 month persistent infection	20/7035	227/6984	91.4% (86.1; 95.0)

N = number of subjects included in each group
n = number of cases
(1) ATP: includes women who received 3 doses of vaccine, were DNA negative and seronegative at month 0 and DNA negative at month 6 for the relevant HPV type (HPV-16 or HPV-18).

Efficacy against HPV-16/18 in women with evidence of HPV-16 or HPV-18 infection at study entry.
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 (HPV DNA positive) with one of the vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the other vaccine HPV type.
Efficacy against HPV types 16 and 18 in women with and without prior infection or disease.
The total vaccinated cohort (TVC) included all subjects who received at least one dose of the vaccine, irrespective of their HPV DNA status, cytology and serostatus at baseline. This cohort included women with or without current and/or prior HPV infection. Case counting for the TVC started on day 1 after the first dose of vaccine.
The efficacy estimates are lower in the TVC population as this cohort includes women with pre-existing infections/lesions, which are not expected to be impacted by CERVARIX. The TVC population may approximate the general population of women aged from 15 to 25 years.
Vaccine efficacy against high grade cervical lesions associated with HPV-16/18 observed in the TVC is presented in Table 3.
Table 3: Vaccine efficacy against high grade cervical lesions associated with HPV-16/18 (TVC population).

	n/N	n/N	
6-month persistent infection	~~29/7177~~ 35/7182	~~488/7122~~ 588/7137	94.3% ~~(91.5;96.3)~~ (92.0; 96.1)
12-month persistent infection	~~20/7035~~ 26/7082	~~227/6984~~ 354/7038	~~91,4%~~ 92.9% ~~(86.1;95.0)~~ (89.4; 95.4)

N = number of subjects included in each group
n = number of cases
(1) ATP: includes women who received 3 doses of vaccine, were DNA negative and seronegative at month 0 and DNA negative at month 6 for the relevant HPV (HPV-16 or HPV-18).
(2) mean follow-up of 40 months post dose 3

The efficacy results at the primary analysis were 94.3% (96.1% CI: 91.5; 96.3) against 6-month persistent infection and 91.4% (96.1% CI: 89.4; 95.4) against 12-month persistent infection.

Efficacy against HPV-16/18 in women with evidence of HPV-16 or HPV-18 infection at study entry.
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 (HPV DNA positive) with one of the vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the other vaccine HPV type.

Efficacy against HPV types 16 and 18 in women with and without prior infection or disease.
The total vaccinated cohort (TVC) included all subjects who received at least one dose of the vaccine, irrespective of their HPV DNA status, cytology and serostatus at baseline. This cohort included women with or without current and/or prior HPV infection. Case counting for the TVC started on day 1 after the first dose of vaccine.
The efficacy estimates are lower in the TVC population as this cohort includes women with pre-existing infections/lesions, which are not expected to be impacted by CERVARIX. The TVC may approximate the general population of women aged from 15 to 25 years.
Vaccine efficacy against high grade cervical lesions associated with HPV-16/18 observed in the TVC at the end of the study is presented in Table 3.
Table 3: Vaccine efficacy against high grade cervical lesions associated with HPV-16/18 (TVC population).

~~HPV-16/18 endpoint~~	**TVC(1)**
	End of study analysis (2)

CERVARIX – SPC of 21.02.2011	CERVARIX - changes: SPC of 26.08.2011, 05.12.2011, 17.09.2012	*[COMMENTS]*

HPV 16/18 endpoint	TVC[1]		
	CERVARIX (N = 8667)	Control (N = 8682)	% Efficacy (96.1% CI)
	n	n	
CIN2/3 or AIS	82	174	52.8% (37.5; 64.7)
CIN3 or AIS	43	65	33.6% (<0;56.9)

N = number of subjects included in each group
n = number of cases
(1) TVC: includes all vaccinated subjects (who received at least one dose of the vaccine), irrespective of HPV DNA status, cytology and serostatus at baseline. This cohort includes women with pre-existing infections/lesions.

Vaccine efficacy in the TVC population against virological endpoints (6 and 12 month persistent infection) associated with HPV-16/18 is presented in Table 4.

Table 4: Vaccine efficacy against virological endpoints associated with HPV-16/18 (TVC population)

HPV 16/18 endpoint	TVC[1]		
	CERVARIX	Control	% Efficacy (96.1% CI)
	n/N	n/N	
6 month persistent infection	498/8856	1103/8859	56.4% (51.3;61.1)
12 month persistent infection	327/8625	610/8648	47.3% (39.2;54.4)

N = number of subjects included in each group
n = number of cases
(1) TVC: includes all vaccinated subjects (who received at least one dose of the vaccine), irrespective of their HPV DNA status, cytology and serostatus at baseline.

	CERVARIX (N = ~~8667~~ 8694)	Control (N = ~~8682~~ 8708)	% Efficacy (~~96.1%~~ 95% CI)
	n	n	
~~CIN2/3 or AIS~~ CIN2+	~~82~~ 90	~~174~~ 228	~~52.8%~~ 60.7% ~~(37.5;64.7)~~ (49.6; 69.5)
~~CIN3 or AIS~~ CIN3+	~~43~~ 51	~~65~~ 94	~~33.6%~~ 45.7% ~~(<0;56.9)~~ (22.9; 62.2)

N = number of subjects included in each group
n = number of cases
(1) TVC: includes all vaccinated subjects (who received at least one dose of the vaccine), irrespective of HPV DNA status, cytology and serostatus at baseline. This cohort includes women with pre-existing infections/lesions.
(2) mean follow-up of 44 months post dose 1

Incorporation of the end-of-study data from study HPV-008 (48 months).

Vaccine efficacy in the TVC population at the end of the study against virological endpoints (6 and 12 month persistent infection) associated with HPV 16/18 is presented in Table 4.

Table 4: Vaccine efficacy against virological endpoints associated with HPV-16/18 (TVC population)

HPV-16/18 endpoint	TVC[1] End of study analysis [2]		
	CERVARIX	Control	% Efficacy (~~96.1%~~ 95% CI)
	n/N	n/N	
6-month persistent infection	~~498/8856~~ 504/8863	~~1103/8859~~ 1227/8870	~~56.4%~~ 60.9% ~~(51.3;61.1)~~ (56.6;64.8)
12-month persistent infection	~~327/8625~~ 335/8648	~~610/8648~~ 767/8671	~~47.3%~~ 57.5% ~~(39.2;54.4)~~ (51.7;62.8)

N = number of subjects included in each group
n = number of cases
(1) TVC: includes all vaccinated subjects (who received at least one dose of the vaccine), irrespective of their HPV DNA status, cytology and serostatus at baseline.
(2) mean follow-up of 44 months post dose 1

Incorporation of the end-of-study data from study HPV-008 (48 months).

Overall impact of the vaccine on cervical HPV disease burden

CERVARIX – SPC of 21.02.2011	CERVARIX - changes: SPC of 26.08.2011, 05.12.2011, 17.09.2012	*[COMMENTS]*
Overall impact of the vaccine on cervical HPV disease burden In study HPV-008, the incidence of high grade cervical lesions was compared between the placebo and vaccine group irrespective of the HPV DNA type in the lesion. In the TVC and TVC-naïve cohorts, the vaccine's efficacy was demonstrated against high grade cervical lesions (Table 5). The TVC-naïve population is a subset of the TVC that includes women with normal cytology, and who were HPV DNA negative for 14 oncogenic HPV types and seronegative for HPV-16 and HPV-18 at baseline. *Table 5: Vaccine efficacy against high-grade cervical lesions irrespective of the HPV DNA type in the lesion.*	In study HPV-008, the incidence of high grade cervical lesions was compared between the placebo and vaccine group irrespective of the HPV DNA type in the lesion. In the TVC and TVC-naïve cohorts, the vaccine's efficacy was demonstrated against high grade cervical lesions at the end of the study (Table 5). The TVC-naïve population is a subset of the TVC that includes women with normal cytology, and who were HPV DNA negative for 14 oncogenic HPV types and seronegative for HPV-16 and HPV-18 at baseline. *Table 5: Vaccine efficacy against high-grade cervical lesions irrespective of the HPV DNA type in the lesion.*	Incorporation of the end-of-study data from study HPV-008 (48 months).

	CERVARIX		Control		% Efficacy (96.1% CI)
	N	Cases	N	Cases	
CIN2/3 or AIS					
TVC-naïve [1]	5449	33	5436	110	70.2 (54.7;80.9)
TVC [2]	8667	224	8682	322	30.4 (16.4;42.1)
CIN3 or AIS					
TVC-naïve [1]	5449	3	5436	23	87.0 (54.9;97.7)
TVC [2]	8667	77	8682	116	33.4 (9.1;51.5)

N = number of subjects included in each group
n = number of cases
[1] TVC-naïve: includes all vaccinated subjects (who received at least one dose of vaccine) with normal cytology, and who were HPV DNA negative for 14 oncogenic HPV types and seronegative for HPV-16 and HPV-18 at baseline.
[2] TVC: includes all vaccinated subjects (who received at least one dose of the vaccine), irrespective of their HPV DNA status, cytology and serostatus at baseline.

	End of study analysis [3]				
	CERVARIX		Control		% Efficacy (~~96.1%~~ 95% CI)
	N	Cases	N	Cases	
~~CIN2/3 or AIS~~ CIN2+					
TVC-naïve [1]	~~5449~~ 5466	~~33~~ 61	~~5436~~ 5452	~~110~~ 172	~~70.2 (54.7;80.9)~~ 64.9% (52.7; 74.2)
TVC [2]	~~8667~~ 8694	~~224~~ 287	~~8682~~ 8708	~~322~~ 428	~~30.4 (16.4;42.1)~~ 33.1% (22.2; 42.6)
~~CIN3 or AIS~~ CIN3+					
TVC-naïve [1]	~~5449~~ 5466	3	~~5436~~ 5452	~~23~~ 44	~~87.0 (54.9;97.7)~~ 93.2% (78.9; 98.7)
TVC [2]	~~8667~~ 8694	~~77~~ 86	~~8682~~ 8708	~~116~~ 158	~~33.4 (9.1;51.5)~~ 45.6% (28.8; 58.7)

N = number of subjects included in each group
n = number of cases
[1] TVC-naïve: includes all vaccinated subjects (who received at least one dose of vaccine) with normal cytology, and who were HPV DNA negative for 14 oncogenic HPV types and seronegative for HPV-16 and HPV-18 at baseline.
[2] TVC: includes all vaccinated subjects (who received at least one dose of the vaccine), irrespective of their HPV DNA status, cytology and serostatus at baseline.
[3] mean follow-up of 44 months post dose 1

CERVARIX reduced definitive cervical therapy procedures	At the end of study analysis, CERVARIX reduced definitive cervical therapy procedures ~~(consisations)~~ (includes loop electrosurgical excision procedure [LEEP], cold-knife Cone, and laser procedures) by ~~68.8%~~ 70.2% (~~96.1%~~ 95% CI: ~~50.0; 81.2~~ 57.8; 79.3) in TVC-naïve and ~~24.7%~~ 33.2% (~~96.1%~~ 95%CI: ~~7.4; 38.9~~ 20.8; 43.7) in TVC.	Incorporation of the end-of-study data from study HPV-008 (48 months).

CERVARIX – SPC of 21.02.2011	CERVARIX - changes: SPC of 26.08.2011, 05.12.2011, 17.09.2012	[COMMENTS]
(conisations) (includes loop electrosurgical excision procedure [LEEP], cold-knife Cone, and laser procedures) by 68.8% (96% CI: 50.0; 81.2) in TVC-naïve and 24.7% (96.1% CI: 7.4; 38.9) in TVC. Cross-protective efficacy The cross-protective efficacy of Cervarix against histopathological and virological endpoints (persistent infection) has been evaluated in study HPV-008 for 12 non-vaccine oncogenic HPV types. The study was not powered to assess efficacy against disease caused by individual HPV types. The analysis against the primary endpoint was confounded by multiple co-infections in the CIN2+ lesions. Unlike histopathological endpoints, virological endpoints are less confounded by multiple infections. Cross-protection has been demonstrated as regards all endpoints (6 month and 12 month persistent infection, CIN2/3 or AIS) and in all study cohorts for HPV 31 alone. Vaccine efficacy has also been demonstrated for HPV 33 and HPV 45 as regards 6 month persistent infection in all study cohorts. Vaccine efficacy against 6-month persistent infection and CIN2/3+ or AIS associated with individual non-vaccine oncogenic HPV types is presented in Table 6 (ATP cohort). *Table 6: Vaccine efficacy vis-à-vis for non-vaccine oncogenic HPV types.* **ATP [1]** **HPV type** / **6 month persistent infection** / **CIN2/3 or AIS** **CERV ARIX n** / **Control n** / **% Efficacy (96.1% CI,** / **CERV ARIX n** / **Control n** / **% Efficacy (96.1% CI)** **HPV-16 related types (species A9)** HPV 31: 45 / 199 / 77.5% (68.3;84.4) / 2 / 25 / 92.0% (66.0;99.2) HPV 33: 55 / 100 / 45.1% (21.7;61.9) / 12 / 25 / 51.9% (<0;78.9) HPV 35: 55 / 43 / -28.4% / 1 / 6 / 83.3%	Cross-protective efficacy The cross-protective efficacy of CERVARIX against histopathological and virological endpoints (persistent infection) has been evaluated in study HPV-008 for 12 non-vaccine oncogenic HPV types. The study was not powered to assess efficacy against disease caused by individual HPV types. The analysis against the primary endpoint was confounded by multiple co-infections in the CIN2+ lesions. Unlike histopathological endpoints, virological endpoints are less confounded by multiple infections. HPV 31, 33 and 45 showed consistent cross-protection for 6 ~~and 12~~ month persistent infection~~, CIN2/3 or AIS)~~ and CIN2+ ~~and~~ endpoints in all study cohorts~~only Vaccine efficacy was also demonstrated for HPV 33 and HPV 45 vis-à-vis 6-month persistent infection in all study cohorts.~~ End of the study vaccine efficacy against 6-month persistent infection and ~~CIN2/3 or AIS~~ CIN2+ associated with individual non-vaccine oncogenic HPV types is presented in Table 6 (ATP cohort). *Table 6: Vaccine efficacy ~~vis-à-vis~~ for non-vaccine oncogenic HPV types.* **ATP [1]** **HPV type** / **6 month persistent infection** / **~~CIN2/3 or AIS~~ CIN2+** **CERV ARIX n** / **Control n** / **% Efficacy (~~96.1%~~ 95% CI)** / **CERV ARIX n** / **Control n** / **% Efficacy (~~96.1%~~ 95% CI)** **HPV-16 related types (A9 species)** HPV-31: ~~45~~ 58 / ~~199~~ 247 / ~~77.5%~~ 76.8% ~~(68.3;84.4)~~ (69.0; 82.9) / ~~2~~ 5 / ~~25~~ 40 / ~~92.0%~~ 87.5% ~~(66.0;99.2)~~ (68.3; 96.1) HPV-33: ~~55~~ 65 / ~~100~~ 117 / ~~45.1%~~ 44.8% ~~(21.7;61.9)~~ (24.6; 59.9) / ~~12~~ 13 / ~~25~~ 41 / ~~51.9%~~ 68.3% ~~(<0;78.9)~~ (39.7; 84.4) HPV-35: ~~55~~ 67 / ~~43~~ 56 / ~~-28.4%~~ -19.8% (<0 ; / ~~1~~ 3 / ~~6~~ 8 / ~~83.3%~~ 62.5% ~~(<0;99.7)~~	Incorporation of the end-of-study data from study HPV-008 (48 months).

CERVARIX – SPC of 21.02.2011							CERVARIX - changes: SPC of 26.08.2011, 05.12.2011, 17.09.2012							[COMMENTS]
			(<0;17.2)			(<0;99.7)				17.2)			(<0; 93.6)	
HPV 52	293	315	7.4% (<0;22)	12	14	14.3% (<0;65.4)	HPV-52	~~293~~ 346	~~315~~ 374	~~7.4%~~ 8.3% ~~(<0;22)~~ (<0; 21.0)	~~12~~ 24	~~14~~ 33	~~14.3%~~ 27.6% ~~(<0;65.4)~~ (<0; 59.1)	Incorporation of the end-of-study data from study HPV-008 (48 months).
HPV 58	111	101	-10.3% (<0;17.7)	6	17	64.5% (1.5;89.2)	HPV-58	~~111~~ 144	~~101~~ 122	~~-10.3%~~ -18.3% ~~(<0;17.7)~~ (<0; 7.7)	~~6~~ 15	~~17~~ 21	~~64.5%~~ 28.5% ~~(1.5;89.2)~~ (<0; 65.7)	
HPV-18 related types (species A7)							**HPV-18 related types (A7 species)**							
HPV 39	147	149	1.0% (<0;22.7)	3	10	69.8% (<0;95.2)	HPV-39	~~147~~ 175	~~149~~ 184	~~1.0%~~ 4.8% ~~(<0;22.7)~~ (<0; 23.1)	~~3~~ 4	~~10~~ 16	~~69.8%~~ 74.9% ~~(<0;95.2)~~ (22.3; 93.9)	
HPV 45	19	79	76.1% (59.1;86.7)	0	4	100% (<0;100)	HPV-45	~~19~~ 24	~~79~~ 90	~~76.1%~~ 73.6% ~~(59.1;86.7)~~ (58.1; 83.9)	~~0~~ 2	4 11	~~100%~~ 81.9% ~~(<0;100)~~ (17.0; 98.1)	
HPV 59	56	59	4.8% (<0;36.4)	1	4	74.9% (<0;99.6)	HPV-59	~~56~~ 73	~~59~~ 68	~~4.8%~~ -7.5% ~~(<0;36.4)~~ (<0; 23.8)	1	4 5	~~74.9%~~ 80.0% ~~(<0;99.6)~~ (<0; 99.6)	
HPV 68	138	134	-3.1% (<0;20.3)	5	11	54.4% (<0;88.4)	HPV-68	~~138~~ 165	~~134~~ 169	~~-3.1%~~ 2.6% ~~(<0;20.3)~~ (<0; 21.9)	~~5~~ 11	~~11~~ 15	~~54.4%~~ 26.8% ~~(<0;88.4)~~ (<0; 69.6)	
Other types							**Other types**							
HPV 51	304	354	14.5% (<0;27.4)	10	27	62.9% (18.0;84.7)	HPV-51	~~304~~ 349	~~354~~ 416	~~14.5%~~ 16.6% ~~(<0;27.4)~~ (3.6; 27.9)	~~10~~ 21	~~27~~ 46	~~62.9%~~ 54.4% ~~(18.0;84.7)~~ (22.0; 74.2)	
HPV 56	182	174	-5.0% (<0;16.1)	4	10	59.9% (<0;91.5)	HPV-56	~~182~~ 226	~~174~~ 215	~~-5.0%~~ -5.3%	4 7	~~10~~ 13	~~59.9%~~ 46.1%	
HPV 66	168	178	5.7% (<0;24.9)	4	10	60.0% (<0;91.6)								

CERVARIX – SPC of 21.02.2011	CERVARIX - changes: SPC of 26.08.2011, 05.12.2011, 17.09.2012	[COMMENTS]

n = number of cases
(1) ATP: includes women who received 3 doses of vaccine, were DNA negative and seronegative at month 0 and DNA negative at month 6 to the relevant HPV type.
The limits of the confidence interval (CI) around the vaccine efficacy were calculated. When the value zero is included, i.e., when the lower limit of the CI is <0, the efficacy is not considered statistically significant.

			~~(<0;16.1)~~ (<0; 13.1)			~~(<0;91.5)~~ (<0; 81.8)
HPV-66	~~168~~ 211	~~178~~ 215	~~5.7%~~ 2.3% ~~(<0;24.9)~~ (<0; 19.6)	~~4~~ 7	~~10~~ 16	~~60.0%~~ 56.4% ~~(<0;91.6)~~ (<0; 84.8)

n = number of cases
(1) ATP: includes women who received 3 doses of vaccine, were DNA negative ~~and seronegative~~ at month 0 and ~~DNA negative~~ at month 6 to the relevant HPV type.
The limits of the confidence interval (CI) around the vaccine efficacy were calculated. When the value zero is included, i.e., when the lower limit of the CI is <0, the efficacy is not considered statistically significant.
The efficacy against CIN3 was only demonstrated for HPV-31 and there was no evidence of protection against AIS for any of the HPV types.

Clinical efficacy in women aged 26 years and older

The efficacy of CERVARIX was assessed in a double-blind, randomised Phase III clinical trial (HPV-015) that included a total of 5777 women aged 26 years and older. The study was conducted in North America, Latin America, Asia Pacific and Europe, and allowed women with previous history of HPV disease/infection to be enrolled. An interim analysis was performed when all subjects had completed the month 48 study visit.

The primary analyses of efficacy were performed on the ATP cohort for efficacy and the TVC population.

Vaccine efficacy against 6 month persistent infection with HPV-16/18 (relevant surrogate marker for cervical cancer) is summarised in the following table.

Table 7: Vaccine efficacy against 6M PI with HPV 16/18 in the ATP and TVC cohorts

HPV-16/18 ~~end-~~	ATP[1]			TVC[2]		
	CERVARIX	Control	% Efficacy	CERVARIX	Control	% Efficacy

Incorporation of knowledge provided by study HPV-015 conducted in women over 25 years of age *(Marketing Authorisation variation No. 34)*

CERVARIX – SPC of 21.02.2011	CERVARIX - changes: SPC of 26.08.2011, 05.12.2011, 17.09.2012	[COMMENTS]
Immunogenicity *Immune response to CERVARIX after the primary vaccination course* 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. The antibody response to HPV-16 and HPV-18 was measured using a type-specific direct ELISA (version 2, MedImmune methodology, modified by GSK) which was shown to correlate with the pseudovirion-based neutralisation assay (PBNA). The immunogenicity induced by three doses of CERVARIX has been evaluated in 5303 female subjects from 10 to 55 years of age. In clinical trials, more than 99% of initially seronegative subjects had seroconverted to both HPV types 16 and 18 one month after the third dose. Vaccine-induced IgG Geometric Mean Titres (GMT) were well above titres observed in women previously infected but who cleared HPV infection (natural infection). Initially seropositive and seronegative subjects reached similar titres after vaccination. *Persistence of immune response to CERVARIX* Study 001/007, which included women from 15 to 25 years of age at the time of vaccination, evaluated the immune response against HPV-16 and HPV-18 up to 76 months after administration of the first vaccine dose. In study 023 (a subset of study 001/007), the immune response continued to be evaluated up to 101 months. 87 subjects in the vaccine group had immunogenicity data at the [M95-M101] interval after the first vaccine dose with a median follow-up of 7.9 years. Of these subjects, 100% of women (95% CI: [95.8; 100]) remained seropositive for HPV-16 and HPV-18 according to the ELISA assay. Vaccine-induced IgG GMTs 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 with ELISA GMTs for both HPV-16 and HPV-18 at least still 10-fold higher than the ELISA GMTs observed in women who had cleared a natural HPV infection. In study 008, immunogenicity up to month 36 was similar to the response observed in study 001. A similar kinetic profile was observed with the neutralising antibodies. In another clinical trial (study 014) performed in women aged 15 to 55 years, all subjects seroconverted to both HPV types 16 and 18 after the	<table><tr><td></td><td></td><td></td><td>CI)</td><td></td><td></td><td>CI)</td></tr><tr><td>6M PI</td><td>6/1859</td><td>34/1822</td><td>82.9% (53.8; 95.1)</td><td>71/2767</td><td>132/2776</td><td>47% (25.4; 62.7)</td></tr></table> N = number of subjects in each group n = number of subjects reporting at least one event in each group 6M PI = 6-month persistent infection CI = Confidence interval (1) 3 doses of vaccine, with, DNA negative and seronegative at month 0 and DNA negative at month 6 for the relevant HPV type test and seronegativity in month 0 and a negative DNA test in month 6. (2) at least one dose of vaccine, irrespective of the HPV DNA and serological status at month 0. Includes 15% of subjects with a previous history of HPV disease/infection Vaccine efficacy against 6-month persistent infection was 79.1% (97.7% CI [27.6; 95.9]) for HPV-31 and 76.9% (97.7% CI [18.5; 95.6]) for HPV-45 in the ATP cohort (3 doses of vaccine, negative DNA at months 0 and 6 for the relevant HPV type). Vaccine efficacy against 6-month persistent infection was 23.2% (97.7% CI [-23.3; 52.5]) for HPV-31 and 67.7% (97.7% CI [35.9; 84.9]) for HPV-45 in the TVC cohort. *Immunogenicity* *Immune response to CERVARIX after the primary vaccination course* 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. The antibody response to HPV-16 and HPV-18 was measured using a type-specific direct ELISA (version 2, MedImmune methodology, modified by GSK) which was shown to correlate with the pseudovirion-based neutralisation assay (PBNA). The immunogenicity induced by three doses of CERVARIX has been evaluated in ~~5303~~ 5,465 female subjects from ~~10~~ 9 to 55 years of age. In clinical trials, more than 99% of initially seronegative subjects had seroconverted to both HPV types 16 and 18 after one month after the third dose. Vaccine-induced IgG Geometric Mean Titres (GMT) were well above titres observed in women previously infected but who cleared HPV infection (natural infection). Initially seropositive and seronegative subjects reached similar titres after vaccination. *Persistence of immune response to CERVARIX* Study 001/007, which included women from 15 to 25 years of age at the time of vaccination, evaluated the immune response against HPV-16 and HPV-18 up to 76 months after administration of the first vaccine	Incorporation of the results of the pooled analysis of studies HPV-029/030/048 in girls aged 9-10 years *(Marketing Authorisation variation No. 21).*

CERVARIX – SPC of 21.02.2011	CERVARIX - changes: SPC of 26.08.2011, 05.12.2011, 17.09.2012	*[COMMENTS]*
third dose (at month 7). The GMTs were, however, lower in women above 25 years. Nevertheless, all subjects remained seropositive for both types throughout the follow-up phase (up to month 18) maintaining antibody levels at an order of magnitude clearly above those encountered after natural infection. *Existence of anamnestic (immune memory) response* In study 024 (a subset of study 001/007), a challenge dose of CERVARIX was administered to 65 subjects at a mean interval of 6.8 years after the first vaccine dose. An anamnestic immune response to HPV-16 and HPV-18 (by ELISA) was observed one week and one month after the challenge dose; GMTs one month after the challenge dose exceeded those observed one month after the primary 3-dose vaccination. Extrapolating the efficacy of CERVARIX from young adult women to adolescents. In two clinical trials performed in girls and adolescents aged 10 to 14 years, all subjects seroconverted to both HPV types 16 and 18 after the third dose (at month 7) with GMTs at least 2-fold higher as compared to women aged 15 to 25 years. On the basis of these immunogenicity data, the efficacy of CERVARIX is inferred from 10 to 14 years of age.	dose. In study 023 (a subset of study 001/007), the immune response continued to be evaluated up to ~~101~~ 113 months. ~~87~~ 92 subjects in the vaccine group had immunogenicity data at the [~~M95~~M107-~~M101~~M113] interval after the first vaccine dose with a median follow-up of ~~7.9~~ 8.9 years. Of these subjects, 100% of women (95% CI: ~~95.8~~ 96.1; 100) remained seropositive for HPV 16 and HPV 18 according to the ELISA assay. Vaccine-induced IgG GMTs 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~~M107-~~M101~~M113] interval with ELISA GMTs for both HPV-16 and HPV-18 at least still 10-fold higher than the ELISA GMTs observed in women who had cleared a natural HPV infection. In study 008, immunogenicity up to month ~~36~~ 48 was similar to the response observed in study 001. A similar kinetic profile was observed with the neutralising antibodies. In another clinical trial (study 014) performed in women aged 15 to 55 years, all subjects seroconverted to both HPV types 16 and 18 after the third dose (at month 7). The GMTs were, however, lower in women above 25 years. Nevertheless, all subjects remained seropositive for both types throughout the follow-up phase (up to month 18) maintaining antibody levels at an order of magnitude clearly above those encountered after natural infection. *Existence of anamnestic (immune memory) response* In study 024 (a subset of study 001/007), a challenge dose of CERVARIX was administered to 65 subjects at a mean interval of 6.8 years after the first vaccine dose. An anamnestic immune response to HPV-16 and HPV-18 (by ELISA) was observed one week and one month after the challenge dose; GMTs one month after the challenge dose exceeded those observed one month after the primary 3-dose vaccination. Extrapolating the efficacy of CERVARIX from young adult women to adolescents. In a pooled analysis, 99.7% and 100% of females aged 9 years seroconverted to HPV types 16 and 18, respectively after the third dose (at month 7) with GMTs at least 1.4-fold and 2.4-fold higher as compared to females aged 10-14 years and aged 15 to 25 years, respectively. In two clinical trials performed in girls and adolescents aged 10 to 14 years, all subjects seroconverted to both HPV types 16 and 18 after the third dose (at month 7) with GMTs at least 2-fold higher as compared to women aged 15 to 25 years. On the basis of these immunogenicity data, the efficacy of CERVARIX is inferred from ~~10~~ 9 to 14 years of	Incorporation of the results of the pooled analysis of studies HPV-029/030/048 in girls aged 9-10 years *(Marketing Authorisation variation No. 21).*

CERVARIX – SPC of 21.02.2011	CERVARIX - changes: SPC of 26.08.2011, 05.12.2011, 17.09.2012	*[COMMENTS]*
	age. Immunogenicity in women aged 26 years and older In the Phase III study (HPV-015) in women 26 years and older, at the 48-month time point, i.e. 42 months after completion of the full vaccination course, 100% and 99.4% of initially seronegative women became seropositive for anti-HPV-16 and anti-HPV-18 antibodies, respectively. All initially seropositive women remained seropositive for both anti-HPV-16 and anti-HPV-18 antibodies. Antibody titres peaked at month 7 then gradually declined up to month 18 and stabilized to reach a plateau up to month 48.	Incorporation of knowledge provided by study HPV-015 conducted in women over 25 years of age *(Marketing Authorisation variation No. 34)*
5.2 Pharmacokinetic properties	**5.2 Pharmacokinetic properties**	5.2 Pharmacokinetic properties
The assessment of pharmacokinetic properties is not required for vaccines.	~~The assessment of pharmacokinetic properties is not required for vaccines.~~ Not applicable.	Five-yearly renewal, harmonisation of wording *(Marketing Authorisation variation No. 35)*
6.3 Shelf life	**6.3 Shelf life**	6.3 Shelf life
4 years CERVARIX should be administered as soon as possible after being removed from the refrigerator. However, for CERVARIX in monodose containers, stability has been demonstrated when stored outside the refrigerator for not more than 3 days at temperatures between 8 ℃ and 25 ℃ or for not more than 1 day at temperatures be tween 25 ℃ and 37 ℃.	4 years CERVARIX should be administered as soon as possible after being removed from the refrigerator. ~~However, for CERVARIX in monodose containers, stability has been demonstrated when~~ However, for the monodose containers, the stability has been demonstrated when stored outside the refrigerator for ~~not more than~~ up to 3 days at temperatures between 8 ℃ and 25 ° C, or for ~~not more than~~ up to 1 day at temperatures of between 25 ℃ and 3 7 ℃.	Five-yearly renewal, improvement of the wording *(Marketing Authorisation variation No. 35)*