ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cervarix suspension for injection
Human Papillomavirus vaccine [Types 16, 18] (Recombinant, adjuvanted, adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml) contains:

Human Papillomavirus[1] type 16 L1 protein[2,3,4]	20 micrograms
Human Papillomavirus[1] type 18 L1 protein[2,3,4]	20 micrograms

[1]Human Papillomavirus = HPV

[2]adjuvanted by AS04 containing:

3-*O*-desacyl-4'- monophosphoryl lipid A (MPL)[3]	50 micrograms
[3]adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$)	0.5 milligrams Al^{3+} in total

[4]L1 protein in the form of non-infectious virus-like particles (VLPs) produced by recombinant DNA technology using a Baculovirus expression system which uses Hi-5 Rix4446 cells derived from *Trichoplusia ni*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.
Turbid white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cervarix is a vaccine for use from the age of 9 years for the prevention of premalignant ano-genital lesions (cervical, vulvar, vaginal and anal) and cervical and anal cancers 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 use of Cervarix should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

The vaccination schedule depends on the age of the subject.

Age at the time of the first injection	Immunization and schedule
9 to and including 14 years*	Two doses each of 0.5 ml. The second dose given between 5 and 13 months after the first dose
From 15 years and above	Three doses each of 0.5 ml at 0, 1, 6 months**

*If the second vaccine dose is administered before the 5th month after the first dose, a third dose should always be administered.
**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 vaccination course with Cervarix (see section 4.4).

Paediatric population (children < 9 years of age)

Cervarix is not recommended for use in children below 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).

Cervarix should under no circumstances be administered intravascularly or intradermally. No data are available on subcutaneous administration of Cervarix (see section 4.4).

If Cervarix is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic reaction following the administration of the vaccine.

Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

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.

The vaccine should under no circumstances be administered intravascularly or intradermally.
No data are available on subcutaneous administration of Cervarix.

As with other vaccines administered intramuscularly, Cervarix should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

Cervarix will only protect against diseases that are caused by HPV types 16 and 18 and to some extent against diseases caused by certain other oncogenic related HPV types (see section 5.1). Therefore, appropriate precautions against sexually transmitted diseases should continue to be used.

The vaccine is for prophylactic use only and has no effect on active HPV infections or established clinical disease. The vaccine has not been shown to have a therapeutic effect. The vaccine is therefore not indicated for treatment of cervical cancer or cervical intraepithelial neoplasia (CIN). It is also not intended to prevent progression of other established HPV-related lesions or existing HPV infections with vaccine or non-vaccine types (see section 5.1 “Efficacy in women with evidence of HPV-16 or HPV-18 infection at study entry.”).

Vaccination is not a substitute for routine cervical screening. Since no vaccine is 100% effective and Cervarix will not provide protection against every HPV type, or against existing HPV infections, routine cervical screening remains critically important and should follow local recommendations.

Duration of protection has not fully been established. Timing and need of booster dose(s) has not been established.

Except for asymptomatic human immunodeficiency virus (HIV) infected subjects for whom limited immunogenicity data are available (see section 5.1), there are no data on the use of Cervarix in subjects with impaired immune responsiveness such as patients receiving immunosuppressive treatment. As with other vaccines, an adequate immune response may not be elicited in these individuals.

There are no safety, immunogenicity or efficacy data to support interchangeability of Cervarix with other HPV vaccines.

4.5 Interaction with other medicinal products and other forms of interaction

In all clinical trials individuals who had received immunoglobulin or blood-derived 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 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 $\geq$ 10mIU/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 $\geq$ 10mIU/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 contraceptive

In clinical 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

See section 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy

Specific studies of the vaccine in pregnant women were not conducted. Data in pregnant women collected as part of pregnancy registries, epidemiological studies and inadvertent exposure during clinical trials are insufficient to conclude whether or not vaccination with Cervarix affects the risk of adverse pregnancy outcomes including spontaneous abortion.
However, during the clinical development program, a total of 10,476 pregnancies were reported including 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 between treatment groups.

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).

As a precautionary measure, it is preferable to avoid the use of Cervarix during pregnancy. Women who are pregnant or trying to become pregnant, are advised to postpone or interrupt vaccination until completion of pregnancy.

Breast-feeding

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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed. However, some of the effects mentioned under section 4.8 “Undesirable effects” may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

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 enrolment), Cervarix was administered to 16,142 females whilst 13,811 females received control. These subjects were followed for serious adverse events over the entire study period. In a pre-defined subset of subjects (Cervarix = 8,130 versus control = 5,786), adverse events were followed for 30 days after each injection. In two clinical studies that enrolled males aged 10 to 18 years, 2,617 males received Cervarix and were followed-up with active safety surveillance.

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.

Tabulated list of adverse reactions

Adverse reactions considered as being at least possibly related to vaccination have been categorised by frequency.

Frequencies are reported as:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)

System Organ Class	Frequency	Adverse reactions
Clinical trials		
Infections and infestations	Uncommon	Upper respiratory tract infection
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness
Gastrointestinal disorders	Common	Gastrointestinal symptoms including nausea, vomiting, diarrhoea and abdominal pain
Skin and subcutaneous tissue disorders	Common	Itching/pruritus, rash, urticaria
Musculoskeletal and connective tissue disorders	Very common	Myalgia
	Common	Arthralgia
General disorders and administration site conditions	Very common	Injection site reactions including pain, redness, swelling; fatigue
	Common	Fever (≥38°C)
	Uncommon	Other injection site reactions such as induration, local paraesthesia
Post-marketing experience		
Blood and lymphatic system disorders	Not known*	Lymphadenopathy
Immune system disorders	Not known*	Allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema
Nervous system disorders	Not known*	Syncope or vasovagal responses to injection, sometimes accompanied by tonic-clonic movements (see section 4.4)

*Because these events were reported spontaneously, it is not possible to reliably estimate their frequency

In clinical trials 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 HPV-16 and HPV-18 antibodies.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic 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 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, 90% of anal cancers, 70% of HPV-related high grade vulvar and vaginal intraepithelial neoplasia and 78% of HPV related high-grade anal (AIN 2/3) intraepithelial neoplasia.
Other oncogenic HPV types can also cause ano-genital cancers (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 ano-genital lesions” in section 4.1 corresponds to high-grade Cervical Intraepithelial Neoplasia (CIN2/3), high-grade vulvar intraepithelial neoplasia (VIN2/3), high-grade vaginal intraepithelial neoplasia (VaIN2/3) and high-grade anal intraepithelial neoplasia (AIN 2/3).

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
- Had normal cytology

The primary efficacy endpoint was incident infection with HPV-16 and/or HPV-18. Twelve-month persistent infection was evaluated as 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+ 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 in women aged 15 to 25 years.

Prophylactic efficacy against HPV-16/18 infection in a population naïve to oncogenic HPV types

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.

Prophylactic efficacy against HPV-16/18 in women naïve to HPV-16 and/or HPV-18

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 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).
Two analyses of study HPV-008 have been performed: an event-triggered analysis performed once at least 36 CIN2+ cases associated with HPV-16/18 were accrued in the ATP cohort and an end-of study analysis.

Vaccine efficacy against the primary endpoint CIN2+at the end of study is presented in Table 1. In a supplemental analysis, the efficacy of Cervarix was evaluated against HPV-16/18-related CIN3+.

Table 1: Vaccine efficacy 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 = 7338)	**Control (N = 7305)**	**% Efficacy (95% CI)**
	n[(2)]	**n**	
CIN2+	5	97	94.9% (87.7;98.4)
CIN3+	2	24	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, were DNA negative and seronegative at month 0 and DNA negative at month 6 to the relevant HPV type (HPV-16 or HPV-18)
[(2)] including 4 cases of CIN2+ and 2 cases of CIN3+ in which another oncogenic HPV type was identified in the lesion, concomitantly with HPV-16 or HPV-18. These cases are excluded in the HPV type assignment analysis (see under Table).
[(3)] mean follow-up of 40 months post dose 3

At the event-triggered analysis the 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 HPV-16 and HPV-18 individually was demonstrated.

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 to be causally associated with HPV-16 or HPV-18 infections acquired during the trial.
Based on the HPV type assignment post-hoc analysis, there was 1 CIN2+ case in the vaccine group versus 92 cases in the control group (Efficacy 98.9% (95% CI: 93.8;100)) and no CIN3+ case in the vaccine group versus 22 cases in the control group (Efficacy 100% (95% CI: 81.8;100)) at the end of study analysis.

In the event-triggered 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+ 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).

At end of study analysis, there were 2 cases of VIN2+ or VaIN2+ in the vaccine group and 7 cases in the control group in the ATP cohort associated with HPV-16 or HPV-18. The study was not powered to demonstrate a difference between the vaccine and the control group for these endpoints.

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 study is presented in Table 2.

Table 2: Vaccine efficacy against virological endpoints associated with HPV-16/18 (ATP cohort)

HPV-16/18 endpoint	**ATP cohort[(1)]**		
	End of study analysis[(2)]		
	Cervarix (N = 7338)	**Control (N = 7305)**	**% Efficacy (95% CI)**
	n/N	**n/N**	
6-month persistent infection	35/7182	588/7137	94.3% (92.0;96.1)
12-month persistent infection	26/7082	354/7038	92.9% (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 to the relevant HPV type (HPV-16 or HPV-18)
(2) mean follow-up of 40 months post dose 3

The efficacy results at the event-triggered 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.
The efficacy estimates are lower in the TVC as this cohort includes women with pre-existing infections/lesions, which are not expected to be impacted by Cervarix.
The TVC may approximate to the general population of women in the age range of 15-25 years.

Vaccine efficacy against high grade cervical lesions associated with HPV-16/18 observed in TVC at end of study is presented in Table 3.

Table 3: Vaccine efficacy against high grade cervical lesions associated with HPV-16/18 (TVC)

HPV-16/18 endpoint	**TVC**[1]		
	End of study analysis[2]		
	Cervarix (N = 8694)	**Control (N = 8708)**	**% Efficacy (95% CI)**
	n	**n**	
CIN2+	90	228	60.7% (49.6;69.5)
CIN3+	51	94	45.7% (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 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

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

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

HPV-16/18 endpoint	**TVC**[1]		
	End of study analysis[2]		
	Cervarix	**Control**	**% Efficacy (95% CI)**
	n/N	**n/N**	
6-month persistent infection	504/8863	1227/8870	60.9% (56.6;64.8)
12-month persistent infection	335/8648	767/8671	57.5% (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 vaccine) irrespective of HPV DNA status, cytology and serostatus at baseline.
[2] mean follow-up of 44 months post dose 1

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 at end of study (Table 5).
The TVC-naïve 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

	End of study analysis[3]				
	Cervarix		**Control**		**% Efficacy (95% CI)**
	N	**Cases**	**N**	**Cases**	
CIN2+					
TVC-naïve[1]	5466	61	5452	172	64.9% (52.7;74.2)
TVC[2]	8694	287	8708	428	33.1% (22.2;42.6)
CIN3+					
TVC-naïve[1]	5466	3	5452	44	93.2% (78.9;98.7)
TVC[2]	8694	86	8708	158	45.6% (28.8;58.7)

N = number of subjects included in each group
[1] TVC naïve: includes all vaccinated subjects (who received at least one dose of vaccine) who had normal cytology, 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 vaccine) irrespective of HPV DNA status, cytology and serostatus at baseline.
[3] mean follow-up of 44 months post dose 1

At the end of study analysis, Cervarix reduced definitive cervical therapy procedures (includes loop electrosurgical excision procedure [LEEP], cold-knife Cone, and laser procedures) by 70.2% (95% CI: 57.8;79.3) in TVC-naïve and 33.2% (95% CI: 20.8;43.7) 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.

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

End of study vaccine efficacy against 6-month persistent infection and CIN2+ associated with individual non-vaccine oncogenic HPV types is presented in Table 6 (ATP cohort).

Table 6: Vaccine efficacy for non-vaccine oncogenic HPV types

ATP[(1)]						
HPV type	**6-month persistent infection**			**CIN2+**		
	Cervarix	**Control**	**% Efficacy (95% CI)**	**Cervarix**	**Control**	**% Efficacy (95% CI)**
	n	**n**		**n**	**n**	
HPV-16 related types (A9 species)						
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)
HPV-18 related types (A7 species)						
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 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

(1) ATP: includes women who received 3 doses of vaccine, were DNA negative at month 0 and at month 6 to the relevant HPV type.

The limits of the confidence interval 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 5778 women aged 26-72 years (median: 37.0 years). The study was conducted in North America, Latin America, Asia Pacific and Europe. Final analysis was performed at study conclusion, 7 years after 1st vaccination.

The primary endpoint was a combination of a virological and a histopathological endpoint: HPV-16/18 related 6-month persistence infection and/or CIN1+. The primary analyses of efficacy were performed on the ATP cohort for efficacy and the TVC which included a subset of up to 15% of women with a history of HPV-associated infection or disease (defined as two or more abnormal smears in sequence, abnormal colposcopy, or biopsy or treatment of the cervix after abnormal smear or colposcopy findings). Inclusion of this subset allowed assessment of prophylactic efficacy in a population that is thought to reflect a real-world setting, as adult women are the age group generally targeted for cervical screening.

Vaccine efficacy at study conclusion is summarised in the following table.

There is no evidence whether prevention of persistent infection that lasts for at least 6 months is a relevant surrogate marker for cervical cancer prevention in women aged 26 years and above.

Table 7 - Vaccine efficacy at study conclusion in study HPV-015

Endpoint	ATP[(1)]			TVC[(2)]		
	Cervarix n/N	Control n/N	% Efficacy (96.2% CI)	Cervarix n/N	Control n/N	% Efficacy (96.2% CI)
HPV-16/18						
6M PI and/or CIN1+	7/1852	71/1818	90.5% (78.6; 96.5)	93/2768	209/2778	56.8% (43.8; 67.0)
6M PI	6/1815	67/1786	91.4% (79.4; 97.1)	74/2762	180/2775	60% (46.4; 70.4)
CIN2+	1/1852	6/1818	83.7% (<0; 99.7)	33/2733	51/2735	35.8% (<0; 61.0)
ASC-US+	3/1852	47/1818	93.8% (79.9; 98.9)	38/2727	114/2732	67.3% (51.4; 78.5)
6M PI in subjects seropositive at baseline only	3/851	13/837	78% (15.0; 96.4)	42/1211	65/1192	38.7% (6.3; 60.4)
Cross protective efficacy						
HPV-31 6MPI	10/2073	29/2090	65.8% (24.9; 85.8)	51/2762	71/2775	29% (<0; 52.5)
HPV-45 6MPI	9/2106	30/2088	70.7% (34.2; 88.4)	22/2762	60/2775	63.9% (38.6; 79.6)
HPV-31 ASC-US+	5/2117	23/2127	78.4% (39.1; 94.1)	34/2727	55/2732	38.7% (2.0; 62.3)
HPV-45 ASC-US+	5/2150	23/2125	78.7% (40.1; 94.1)	13/2727	38/2732	66.1% (32.7; 84.1)

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
ASC-US= Atypical Cells of Undetermined Significance (abnormal cytology)
(1) 3 doses of vaccine, DNA negative and seronegative at month 0 (unless specified) and DNA negative at month 6 for the relevant HPV type (HPV-16 and/or HPV-18)
(2) at least one dose of vaccine, irrespective of HPV DNA and serostatus (unless specified) at month 0. Includes 15% of subjects with previous history of HPV disease/infection

Efficacy against ≥ASC-US (abnormal cytology) associated with oncogenic non-vaccine types was 37.2% (96.2% CI [21.3; 50.1]) (ATP).

Efficacy against CIN1+ irrespective of the HPV type detected in the lesion was 22.9% (96.2% CI [4.8; 37.7]) (TVC).

There was no evidence of protection from disease caused by HPV in subjects aged 25 years and above who were DNA positive and/ or with abnormal cytology at study entry.

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 5,465 female subjects from 9 to 55 years of age and over 800 male subjects aged 10 to 18 years.

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 113 months. 92 subjects in the vaccine group had immunogenicity data at the [M107-M113] interval after the first vaccine dose with a median follow-up of 8.9 years. Of these subjects, 100% (95% CI: 96.1;100) remained seropositive for HPV-16 and HPV-18 in 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 [M107-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 cleared a natural HPV infection.
In study 008, immunogenicity up to month 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. 470 subjects (142 aged 15-25 years, 172 aged 26-45 years and 156 aged 46-55 years) who completed study HPV-014 and received the 3 dose schedule were followed-up for up to 10 years in the extension study HPV-060. Ten years after administration of the first dose, 100% of subjects in the 15-25 years group, 99.2% in the 26-45 years group and 96.3% in the 46-55 years group were still seropositive for HPV-16, and 99.2%, 93.7% and 83.8% for HPV-18, respectively. In all age groups, GMTs remained at least 5- to 32-fold for HPV-16 and 3- to 14-fold for HPV-18 above those elicited in women who cleared a natural infection for both antigens.

Evidence 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 administration of 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.

Bridging the efficacy of Cervarix from young adult women to adolescents

In a pooled analysis (HPV-029,-30 & -48), 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 15 to 25 years, respectively.

In two clinical trials (HPV-012 & -013) performed in girls 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.

In clinical trials (HPV-070 and HPV-048) performed in girls aged 9 to 14 years receiving a 2-dose schedule (0, 6 months or 0, 12 months) and young women aged 15-25 years receiving Cervarix

according to the standard 0, 1, 6 months schedule, all subjects seroconverted to both HPV types 16 and 18 one month after the second dose. The immune response after 2 doses in females aged 9 to 14 years was non-inferior to the response after 3 doses in women aged 15 to 25 years.

On the basis of these immunogenicity data, the efficacy of Cervarix is inferred from 9 to 14 years of age.

Duration of the immune response in women aged 26 years and older

In the Phase III study (HPV-015) in women 26 years and older all subjects seroconverted one month after the third dose. At the 84-month time point, i.e. 78 months after completion of the full vaccination course, 99.3% and 95.9% of initially seronegative women remained 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 titers peaked at month 7 then gradually declined up to month 18 and stabilized to reach a plateau up to month 84.

Immunogenicity in males aged 10 to 18 years

Immunogenicity in males was assessed in 2 clinical trials HPV-011 (N=173) and HPV-040 (N=556). The data showed comparable immunogenicity in males and females. In study HPV-011, all subjects seroconverted to both HPV-16 and 18 and GMT levels were non inferior to those observed in females aged 15 to 25 years in study HPV-012.

Bridging of clinical efficacy against anal lesions and cancers

No efficacy study against anal premalignant lesions has been conducted with Cervarix. However, studies conducted in girls aged 9 to 14 years (study HPV-071) and in women aged 18 to 45 years (study HPV-010) have consistently shown a higher immune response with Cervarix than with the comparator for which efficacy data against anal premalignant lesions are conclusive and have shown protection.

Immunogenicity in HIV infected women

In study HPV-020, conducted in South Africa, 22 HIV uninfected and 42 HIV infected subjects (WHO clinical stage 1; ATP cohort for immunogenicity) received Cervarix. All subjects were seropositive in the ELISA assay to both HPV 16 and 18 one month after the third dose (at Month 7) and the seropositivity for HPV 16 and 18 was maintained up to Month 12. The GMTs appeared to be lower in the HIV infected group (non overlapping 95% confidence interval). The clinical relevance of this observation is unknown. Functional antibodies were not determined. No information exists about protection against persistent infection or precancerous lesions among HIV infected women.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, acute and repeated dose toxicity, local tolerance, fertility, embryo-foetal and postnatal toxicity (up to the end of the lactation period).

Serological data suggest a transfer of anti-HPV-16 and anti-HPV-18 antibodies via the milk during the lactation period in rats. However, it is unknown whether vaccine-induced antibodies are excreted in human breast milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride (NaCl)
Sodium dihydrogen phosphate dihydrate ($NaH_2PO_4.2\ H_2O$)
Water for injections

For adjuvants, see section 2.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years.

Cervarix should be administered as soon as possible after being removed from the refrigerator.

However, stability has been demonstrated when stored outside the refrigerator for up to 3 days at temperatures between 8°C and 25°C or for up to 1 day at temperatures between 25°C and 37°C. If not used at the end of this period the vaccine should be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

0.5 ml of suspension in a vial (type I glass) for 1 dose with a stopper (rubber butyl).

Pack sizes of 1, 10 and 100 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

A fine white deposit with a clear colourless supernatant may be observed upon storage of the vial. This does not constitute a sign of deterioration.

The content of the vial should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to administration.
In the event of either being observed, discard the vaccine.

The vaccine should be well shaken before use.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89

B-1330 Rixensart, Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/419/001
EU/1/07/419/002
EU/1/07/419/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2007.
Date of latest renewal: 17 September 2012.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Cervarix suspension for injection, multidose
Human Papillomavirus vaccine [Types 16, 18] (Recombinant, adjuvanted, adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml) contains:

Human Papillomavirus[1] type 16 L1 protein[2,3,4]	20 micrograms
Human Papillomavirus[1] type 18 L1 protein[2,3,4]	20 micrograms

[1]Human Papillomavirus = HPV

[2]adjuvanted by AS04 containing:

3-*O*-desacyl-4'- monophosphoryl lipid A (MPL)[3]	50 micrograms
[3]adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$)	0.5 milligrams Al^{3+} in total

[4]L1 protein in the form of non-infectious virus-like particles (VLPs) produced by recombinant DNA technology using a Baculovirus expression system which uses Hi-5 Rix4446 cells derived from *Trichoplusia ni*.

This is a multidose container. See section 6.5 for the number of doses per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.
Turbid white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cervarix is a vaccine for use from the age of 9 years for the prevention of premalignant ano-genital lesions (cervical, vulvar, vaginal and anal) and cervical and anal cancers 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 use of Cervarix should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

The vaccination schedule depends on the age of the subject.

Age at the time of the first injection	Immunization and schedule
9 to and including 14 years*	Two doses each of 0.5 ml. The second dose given between 5 and 13 months after the first dose
From 15 years and above	Three doses each of 0.5 ml at 0, 1, 6 months**

*If the second vaccine dose is administered before the 5th month after the first dose, a third dose should always be administered.
**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 vaccination course with Cervarix (see section 4.4).

Paediatric population (children < 9 years of age)

Cervarix is not recommended for use in children below 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).

Cervarix should under no circumstances be administered intravascularly or intradermally. No data are available on subcutaneous administration of Cervarix (see section 4.4).

If Cervarix is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic reaction following the administration of the vaccine.

Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

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.

The vaccine should under no circumstances be administered intravascularly or intradermally.
No data are available on subcutaneous administration of Cervarix.

As with other vaccines administered intramuscularly, Cervarix should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

Cervarix will only protect against diseases that are caused by HPV types 16 and 18 and to some extent against diseases caused by certain other oncogenic related HPV types (see section 5.1). Therefore, appropriate precautions against sexually transmitted diseases should continue to be used.

The vaccine is for prophylactic use only and has no effect on active HPV infections or established clinical disease. The vaccine has not been shown to have a therapeutic effect. The vaccine is therefore not indicated for treatment of cervical cancer or cervical intraepithelial neoplasia (CIN). It is also not intended to prevent progression of other established HPV-related lesions or existing HPV infections with vaccine or non-vaccine types (see section 5.1 "Efficacy in women with evidence of HPV-16 or HPV-18 infection at study entry.").

Vaccination is not a substitute for routine cervical screening. Since no vaccine is 100% effective and Cervarix will not provide protection against every HPV type, or against existing HPV infections, routine cervical screening remains critically important and should follow local recommendations.

Duration of protection has not fully been established. Timing and need of booster dose(s) has not been established.

Except for asymptomatic human immunodeficiency virus (HIV) infected subjects for whom limited immunogenicity data are available (see section 5.1), there are no data on the use of Cervarix in subjects with impaired immune responsiveness such as patients receiving immunosuppressive treatment. As with other vaccines, an adequate immune response may not be elicited in these individuals.

There are no safety, immunogenicity or efficacy data to support interchangeability of Cervarix with other HPV vaccines.

4.5 Interaction with other medicinal products and other forms of interaction

In all clinical trials individuals who had received immunoglobulin or blood-derived 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 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 $\geq$ 10mIU/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 $\geq$ 10mIU/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 contraceptive

In clinical 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

See section 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy

Specific studies of the vaccine in pregnant women were not conducted. Data in pregnant women collected as part of pregnancy registries, epidemiological studies and inadvertent exposure during clinical trials are insufficient to conclude whether or not vaccination with Cervarix affects the risk of adverse pregnancy outcomes including spontaneous abortion.
However, during the clinical development program, a total of 10,476 pregnancies were reported including 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 between treatment groups.

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).

As a precautionary measure, it is preferable to avoid the use of Cervarix during pregnancy. Women who are pregnant or trying to become pregnant, are advised to postpone or interrupt vaccination until completion of pregnancy.

Breast-feeding

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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed. However, some of the effects mentioned under section 4.8. “Undesirable effects” may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

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 enrolment), Cervarix was administered to 16,142 females whilst

13,811 females received control. These subjects were followed for serious adverse events over the entire study period. In a pre-defined subset of subjects (Cervarix = 8,130 versus control = 5,786), adverse events were followed for 30 days after each injection. In two clinical studies that enrolled males aged 10 to 18 years, 2,617 males received Cervarix and were followed-up with active safety surveillance.

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.

Tabulated list of adverse reactions

Adverse reactions considered as being at least possibly related to vaccination have been categorised by frequency.

Frequencies are reported as:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)

System Organ Class	Frequency	Adverse reactions
Clinical trials		
Infections and infestations	Uncommon	Upper respiratory tract infection
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness
Gastrointestinal disorders	Common	Gastrointestinal symptoms including nausea, vomiting, diarrhoea and abdominal pain
Skin and subcutaneous tissue disorders	Common	Itching/pruritus, rash, urticaria
Musculoskeletal and connective tissue disorders	Very common	Myalgia
	Common	Arthralgia
General disorders and administration site conditions	Very common	Injection site reactions including pain, redness, swelling; fatigue
	Common	Fever (≥38°C)
	Uncommon	Other injection site reactions such as induration, local paraesthesia
Post-marketing experience		
Blood and lymphatic system disorders	Not known*	Lymphadenopathy
Immune system disorders	Not known*	Allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema
Nervous system disorders	Not known*	Syncope or vasovagal responses to injection, sometimes accompanied by tonic-clonic movements (see section 4.4)

*Because these events were reported spontaneously, it is not possible to reliably estimate their frequency

In clinical trials 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 HPV-16 and HPV-18 antibodies.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic 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 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, 90% of anal cancers, 70% of HPV-related high grade vulvar and vaginal intraepithelial neoplasia and 78% of HPV related high-grade anal (AIN 2/3) intraepithelial neoplasia.
Other oncogenic HPV types can also cause ano-genital cancers (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 ano-genital lesions” in section 4.1 corresponds to high-grade Cervical Intraepithelial Neoplasia (CIN2/3), high-grade vulvar intraepithelial neoplasia (VIN2/3), high-grade vaginal intraepithelial neoplasia (VaIN2/3) and high-grade anal intraepithelial neoplasia (AIN 2/3).

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
- Had normal cytology

The primary efficacy endpoint was incident infection with HPV-16 and/or HPV-18. Twelve-month persistent infection was evaluated as 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+ 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 in women aged 15 to 25 years.

Prophylactic efficacy against HPV-16/18 infection in a population naïve to oncogenic HPV types

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.

Prophylactic efficacy against HPV-16/18 in women naïve to HPV-16 and/or HPV-18

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 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).
Two analyses of study HPV-008 have been performed: an event-triggered analysis performed once at least 36 CIN2+ cases associated with HPV-16/18 were accrued in the ATP cohort and an end-of study analysis.

Vaccine efficacy against the primary endpoint CIN2+ at the end of study is presented in Table 1. In a supplemental analysis, the efficacy of Cervarix was evaluated against HPV-16/18-related CIN3+.

Table 1: Vaccine efficacy 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 = 7338)	**Control (N = 7305)**	**% Efficacy (95% CI)**
	n[(2)]	**n**	
CIN2+	5	97	94.9% (87.7;98.4)
CIN3+	2	24	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, were DNA negative and seronegative at month 0 and DNA negative at month 6 to the relevant HPV type (HPV-16 or HPV-18)
[(2)] including 4 cases of CIN2+ and 2 cases of CIN3+ in which another oncogenic HPV type was identified in the lesion, concomitantly with HPV-16 or HPV-18. These cases are excluded in the HPV type assignment analysis (see under Table).
[(3)] mean follow-up of 40 months post dose 3

At the event-triggered analysis the 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 HPV-16 and HPV-18 individually was demonstrated.

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 to be causally associated with HPV-16 or HPV-18 infections acquired during the trial.
Based on the HPV type assignment post-hoc analysis, there was 1 CIN2+ case in the vaccine group versus 92 cases in the control group (Efficacy 98.9% (95% CI: 93.8;100)) and no CIN3+ case in the vaccine group versus 22 cases in the control group (Efficacy 100% (95% CI: 81.8;100)) at the end of study analysis.

In the event-triggered 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+ 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).

At end of study analysis, there were 2 cases of VIN2+ or VaIN2+ in the vaccine group and 7 cases in the control group in the ATP cohort associated with HPV-16 or HPV-18. The study was not powered to demonstrate a difference between the vaccine and the control group for these endpoints.

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 study is presented in Table 2.

Table 2: Vaccine efficacy against virological endpoints associated with HPV-16/18 (ATP cohort)

HPV-16/18 endpoint	**ATP cohort[(1)]**		
	End of study analysis[(2)]		
	Cervarix (N = 7338)	**Control (N = 7305)**	**% Efficacy (95% CI)**
	n/N	**n/N**	
6-month persistent infection	35/7182	588/7137	94.3% (92.0;96.1)
12-month persistent infection	26/7082	354/7038	92.9% (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 to the relevant HPV type (HPV-16 or HPV-18)
[(2)] mean follow-up of 40 months post dose 3

The efficacy results at the event-triggered 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.
The efficacy estimates are lower in the TVC as this cohort includes women with pre-existing infections/lesions, which are not expected to be impacted by Cervarix.
The TVC may approximate to the general population of women in the age range of 15-25 years.

Vaccine efficacy against high grade cervical lesions associated with HPV-16/18 observed in TVC at end of study is presented in Table 3.

Table 3: Vaccine efficacy against high grade cervical lesions associated with HPV-16/18 (TVC)

HPV-16/18 endpoint	**TVC**[1]		
	End of study analysis[2]		
	Cervarix (N = 8694)	**Control (N = 8708)**	**% Efficacy (95% CI)**
	n	**n**	
CIN2+	90	228	60.7% (49.6;69.5)
CIN3+	51	94	45.7% (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 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

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

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

HPV-16/18 endpoint	**TVC**[1]		
	End of study analysis[2]		
	Cervarix	**Control**	**% Efficacy (95% CI)**
	n/N	**n/N**	
6-month persistent infection	504/8863	1227/8870	60.9% (56.6;64.8)
12-month persistent infection	335/8648	767/8671	57.5% (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 vaccine) irrespective of HPV DNA status, cytology and serostatus at baseline.
[2] mean follow-up of 44 months post dose 1

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 at end of study (Table 5).
The TVC-naïve 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

	End of study analysis[3]				
	Cervarix		Control		% Efficacy (95% CI)
	N	Cases	N	Cases	
CIN2+					
TVC-naïve[1]	5466	61	5452	172	64.9% (52.7;74.2)
TVC[2]	8694	287	8708	428	33.1% (22.2;42.6)
CIN3+					
TVC-naïve[1]	5466	3	5452	44	93.2% (78.9;98.7)
TVC[2]	8694	86	8708	158	45.6% (28.8;58.7)

N = number of subjects included in each group
[1] TVC naïve: includes all vaccinated subjects (who received at least one dose of vaccine) who had normal cytology, 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 vaccine) irrespective of HPV DNA status, cytology and serostatus at baseline.
[3] mean follow-up of 44 months post dose 1

At the end of study analysis, Cervarix reduced definitive cervical therapy procedures (includes loop electrosurgical excision procedure [LEEP], cold-knife Cone, and laser procedures) by 70.2% (95% CI: 57.8;79.3) in TVC-naïve and 33.2% (95% CI: 20.8;43.7) 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. HPV-31, 33 and 45 showed consistent cross-protection for 6-month persistent infection and CIN2+ endpoints in all study cohorts.

End of study vaccine efficacy against 6-month persistent infection and CIN2+ associated with individual non-vaccine oncogenic HPV types is presented in Table 6 (ATP cohort).

Table 6: Vaccine efficacy for non-vaccine oncogenic HPV types

	ATP[1]					
HPV type	**6-month persistent infection**			**CIN2+**		
	Cervarix	**Control**	**% Efficacy (95% CI)**	**Cervarix**	**Control**	**% Efficacy (95% CI)**
	n	**n**		**n**	**n**	
HPV-16 related types (A9 species)						
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)
HPV-18 related types (A7 species)						
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%	1	5	80.0%

			(<0;23.8)			(<0;99.6)
HPV-68	165	169	2.6% (<0;21.9)	11	15	26.8% (<0;69.6)
Other 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

(1) ATP: includes women who received 3 doses of vaccine, were DNA negative at month 0 and at month 6 to the relevant HPV type.

The limits of the confidence interval 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 5778 women aged 26-72 years (median: 37.0 years). The study was conducted in North America, Latin America, Asia Pacific and Europe. Final analysis was performed at study conclusion, 7 years after 1st vaccination.

The primary endpoint was a combination of a virological and a histopathological endpoint: HPV-16/18 related 6-month persistence infection and/or CIN1+. The primary analyses of efficacy were performed on the ATP cohort for efficacy and the TVC which included a subset of up to 15% of women with a history of HPV-associated infection or disease (defined as two or more abnormal smears in sequence, abnormal colposcopy, or biopsy or treatment of the cervix after abnormal smear or colposcopy findings). Inclusion of this subset allowed assessment of prophylactic efficacy in a population that is thought to reflect a real-world setting, as adult women are the age group generally targeted for cervical screening.

Vaccine efficacy at study conclusion is summarised in the following table.

There is no evidence whether prevention of persistent infection that lasts for at least 6 months is a relevant surrogate marker for cervical cancer prevention in women aged 26 years and above.

Table 7 - Vaccine efficacy at study conclusion in study HPV-015

Endpoint	**ATP(1)**			**TVC(2)**		
	Cervarix	**Control**	**% Efficacy (96.2% CI)**	**Cervarix**	**Control**	**% Efficacy (96.2% CI)**
	n/N	**n/N**		**n/N**	**n/N**	
HPV-16/18						
6M PI and/or CIN1+	7/1852	71/1818	90.5% (78.6; 96.5)	93/2768	209/2778	56.8% (43.8; 67.0)
6M PI	6/1815	67/1786	91.4% (79.4; 97.1)	74/2762	180/2775	60% (46.4; 70.4)
CIN2+	1/1852	6/1818	83.7% (<0; 99.7)	33/2733	51/2735	35.8% (<0; 61.0)
ASC-US+	3/1852	47/1818	93.8% (79.9; 98.9)	38/2727	114/2732	67.3% (51.4; 78.5)
6M PI in subjects seropositive at baseline only	3/851	13/837	78% (15.0; 96.4)	42/1211	65/1192	38.7% (6.3; 60.4)

Cross protective efficacy						
HPV-31 6MPI	10/2073	29/2090	65.8% (24.9; 85.8)	51/2762	71/2775	29% (<0; 52.5)
HPV-45 6MPI	9/2106	30/2088	70.7% (34.2; 88.4)	22/2762	60/2775	63.9% (38.6; 79.6)
HPV-31 ASC-US+	5/2117	23/2127	78.4% (39.1; 94.1)	34/2727	55/2732	38.7% (2.0; 62.3)
HPV-45 ASC-US+	5/2150	23/2125	78.7% (40.1; 94.1)	13/2727	38/2732	66.1% (32.7; 84.1)

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
ASC-US= Atypical Cells of Undetermined Significance (abnormal cytology)
(1) 3 doses of vaccine, DNA negative and seronegative at month 0 (unless specified) and DNA negative at month 6 for the relevant HPV type (HPV-16 and/or HPV-18)
(2) at least one dose of vaccine, irrespective of HPV DNA and serostatus (unless specified) at month 0. Includes 15% of subjects with previous history of HPV disease/infection

Efficacy against ≥ASC-US (abnormal cytology) associated with oncogenic non-vaccine types was 37.2% (96.2% CI [21.3; 50.1]) (ATP).

Efficacy against CIN1+ irrespective of the HPV type detected in the lesion was 22.9% (96.2% CI [4.8; 37.7]) (TVC).

There was no evidence of protection from disease caused by HPV in subjects aged 25 years and above who were DNA positive and/ or with abnormal cytology at study entry.

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 5,465 female subjects from 9 to 55 years of age and over 800 male subjects aged 10 to 18 years.

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 113 months. 92 subjects in the vaccine group had immunogenicity data at the [M107-M113] interval after the first vaccine dose with a median follow-up of 8.9 years. Of these subjects, 100% (95% CI: 96.1;100) remained seropositive for HPV-16 and HPV-18 in 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 [M107-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 cleared a natural HPV infection.
In study 008, immunogenicity up to month 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. 470 subjects (142 aged 15-25 years, 172 aged 26-45 years and 156 aged 46-55 years) who completed study HPV-014 and received the 3 dose schedule were followed-up for up to 10 years in the extension study HPV-060. Ten years after administration of the first dose, 100% of subjects in the 15-25 years group, 99.2% in the 26-45 years group and 96.3% in the 46-55 years group were still seropositive for HPV-16, and 99.2%, 93.7% and 83.8% for HPV-18, respectively. In all age groups, GMTs remained at least 5- to 32-fold for HPV-16 and 3- to 14-fold for HPV-18 above those elicited in women who cleared a natural infection for both antigens.

Evidence 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 administration of 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.

Bridging the efficacy of Cervarix from young adult women to adolescents

In a pooled analysis (HPV-029,-30 & -48), 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 15 to 25 years, respectively.

In two clinical trials (HPV-012 & -013) performed in girls 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.

In clinical trials (HPV-070 and HPV-048) performed in girls aged 9 to 14 years receiving a 2-dose schedule (0, 6 months or 0, 12 months) and young women aged 15-25 years receiving Cervarix according to the standard 0, 1, 6 months schedule, all subjects seroconverted to both HPV types 16 and 18 one month after the second dose. The immune response after 2 doses in females aged 9 to 14 years was non-inferior to the response after 3 doses in women aged 15 to 25 years.

On the basis of these immunogenicity data, the efficacy of Cervarix is inferred from 9 to 14 years of age.

Duration of the immune response in women aged 26 years and older

In the Phase III study (HPV-015) in women 26 years and older all subjects seroconverted one month after the third dose. At the 84-month time point, i.e. 78 months after completion of the full vaccination course, 99.3% and 95.9% of initially seronegative women remained 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 titers peaked at month 7 then gradually declined up to month 18 and stabilized to reach a plateau up to month 84.

Immunogenicity in males aged 10 to 18 years

Immunogenicity in males was assessed in 2 clinical trials HPV-011 (N=173) and HPV-040 (N=556). The data showed comparable immunogenicity in males and females. In study HPV-011, all subjects seroconverted to both HPV-16 and 18 and GMT levels were non inferior to those observed in females aged 15 to 25 years in study HPV-012.

Bridging of clinical efficacy against anal lesions and cancers

No efficacy study against anal premalignant lesions has been conducted with Cervarix. However, studies conducted in girls aged 9 to 14 years (study HPV-071) and in women aged 18 to 45 years (study HPV-010) have consistently shown a higher immune response with Cervarix than with the comparator for which efficacy data against anal premalignant lesions are conclusive and have shown protection.

Immunogenicity in HIV infected women

In study HPV-020, conducted in South Africa, 22 HIV uninfected and 42 HIV infected subjects (WHO clinical stage 1; ATP cohort for immunogenicity) received Cervarix. All subjects were seropositive in the ELISA assay to both HPV 16 and 18 one month after the third dose (at Month 7) and the seropositivity for HPV 16 and 18 was maintained up to Month 12. The GMTs appeared to be lower in the HIV infected group (non overlapping 95% confidence interval). The clinical relevance of this observation is unknown. Functional antibodies were not determined. No information exists about protection against persistent infection or precancerous lesions among HIV infected women.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, acute and repeated dose toxicity, local tolerance, fertility, embryo-foetal and postnatal toxicity (up to the end of the lactation period).

Serological data suggest a transfer of anti-HPV-16 and anti-HPV-18 antibodies via the milk during the lactation period in rats. However, it is unknown whether vaccine-induced antibodies are excreted in human breast milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride (NaCl)
Sodium dihydrogen phosphate dihydrate ($NaH_2PO_4.2\ H_2O$)
Water for injections

For adjuvants, see section 2.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years.

Cervarix should be administered as soon as possible after being removed from the refrigerator.

However, stability has been demonstrated when stored outside the refrigerator for up to 3 days at temperatures between 8°C and 25°C or for up to 1 day at temperatures between 25°C and 37°C. If not used at the end of this period the vaccine should be discarded.

After first opening, immediate use is recommended. If not used immediately, the vaccine should be stored in a refrigerator (2°C – 8°C). If not used within 6 hours it should be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.

For storage after first opening, see section 6.3.

6.5 Nature and contents of container

1 ml of suspension in a vial (type I glass) for 2 doses with a stopper (rubber butyl).

Pack sizes of 1, 10 and 100 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

A fine white deposit with a clear colourless supernatant may be observed upon storage of the vial. This does not constitute a sign of deterioration.

The content of the vial should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to administration.
In the event of either being observed, discard the vaccine.

The vaccine should be well shaken before use.

When using a multidose vial, each 0.5 ml dose should be withdrawn using a sterile needle and syringe; precautions should be taken to avoid contamination of the contents.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/419/010
EU/1/07/419/011
EU/1/07/419/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2007.
Date of latest renewal: 17 September 2012.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Cervarix suspension for injection in pre-filled syringe
Human Papillomavirus vaccine [Types 16, 18] (Recombinant, adjuvanted, adsorbed)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 dose (0.5 ml) contains:

Human Papillomavirus[1] type 16 L1 protein[2,3,4]	20 micrograms
Human Papillomavirus[1] type 18 L1 protein[2,3,4]	20 micrograms

[1]Human Papillomavirus = HPV

[2]adjuvanted by AS04 containing:

3-*O*-desacyl-4'- monophosphoryl lipid A (MPL)[3]	50 micrograms
[3]adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$)	0.5 milligrams Al^{3+} in total

[4]L1 protein in the form of non-infectious virus-like particles (VLPs) produced by recombinant DNA technology using a Baculovirus expression system which uses Hi-5 Rix4446 cells derived from *Trichoplusia ni*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection in pre-filled syringe.
Turbid white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cervarix is a vaccine for use from the age of 9 years for the prevention of premalignant ano-genital lesions (cervical, vulvar, vaginal and anal) and cervical and anal cancers 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 use of Cervarix should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

The vaccination schedule depends on the age of the subject.

Age at the time of the first injection	Immunization and schedule
9 to and including 14 years*	Two doses each of 0.5 ml. The second dose given between 5 and 13 months after the first dose
From 15 years and above	Three doses each of 0.5 ml at 0, 1, 6 months**

*If the second vaccine dose is administered before the 5th month after the first dose, a third dose should always be administered.
**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 vaccination course with Cervarix (see section 4.4).

Paediatric population (children < 9 years of age)

Cervarix is not recommended for use in children below 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).

Cervarix should under no circumstances be administered intravascularly or intradermally. No data are available on subcutaneous administration of Cervarix (see section 4.4).

If Cervarix is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic reaction following the administration of the vaccine.

Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

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.

The vaccine should under no circumstances be administered intravascularly or intradermally.
No data are available on subcutaneous administration of Cervarix.

As with other vaccines administered intramuscularly, Cervarix should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

Cervarix will only protect against diseases that are caused by HPV types 16 and 18 and to some extent against diseases caused by certain other oncogenic related HPV types (see section 5.1). Therefore, appropriate precautions against sexually transmitted diseases should continue to be used.

The vaccine is for prophylactic use only and has no effect on active HPV infections or established clinical disease. The vaccine has not been shown to have a therapeutic effect. The vaccine is therefore not indicated for treatment of cervical cancer or cervical intraepithelial neoplasia (CIN). It is also not intended to prevent progression of other established HPV-related lesions or existing HPV infections with vaccine or non-vaccine types (see section 5.1 "Efficacy in women with evidence of HPV-16 or HPV-18 infection at study entry.").

Vaccination is not a substitute for routine cervical screening. Since no vaccine is 100% effective and Cervarix will not provide protection against every HPV type, or against existing HPV infections, routine cervical screening remains critically important and should follow local recommendations.

Duration of protection has not fully been established. Timing and need of booster dose(s) has not been established.

Except for asymptomatic human immunodeficiency virus (HIV) infected subjects for whom limited immunogenicity data are available (see section 5.1), there are no data on the use of Cervarix in subjects with impaired immune responsiveness such as patients receiving immunosuppressive treatment. As with other vaccines, an adequate immune response may not be elicited in these individuals.

There are no safety, immunogenicity or efficacy data to support interchangeability of Cervarix with other HPV vaccines.

4.5 Interaction with other medicinal products and other forms of interaction

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 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 $\geq$ 10mIU/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 $\geq$ 10mIU/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 contraceptive

In clinical 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

See section 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy

Specific studies of the vaccine in pregnant women were not conducted. Data in pregnant women collected as part of pregnancy registries, epidemiological studies and inadvertent exposure during clinical trials are insufficient to conclude whether or not vaccination with Cervarix affects the risk of adverse pregnancy outcomes including spontaneous abortion.
However, during the clinical development program, a total of 10,476 pregnancies were reported including 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 between treatment groups.

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).

As a precautionary measure, it is preferable to avoid the use of Cervarix during pregnancy. Women who are pregnant or trying to become pregnant, are advised to postpone or interrupt vaccination until completion of pregnancy.

Breast-feeding

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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed. However, some of the effects mentioned under section 4.8. “Undesirable effects” may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

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 enrolment), Cervarix was administered to 16,142 females whilst

13,811 females received control. These subjects were followed for serious adverse events over the entire study period. In a pre-defined subset of subjects (Cervarix = 8,130 versus control = 5,786), adverse events were followed for 30 days after each injection. In two clinical studies that enrolled males aged 10 to 18 years, 2,617 males received Cervarix and were followed-up with active safety surveillance.

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.

Tabulated list of adverse reactions

Adverse reactions considered as being at least possibly related to vaccination have been categorised by frequency.

Frequencies are reported as:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)

System Organ Class	Frequency	Adverse reactions
Clinical trials		
Infections and infestations	Uncommon	Upper respiratory tract infection
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness
Gastrointestinal disorders	Common	Gastrointestinal symptoms including nausea, vomiting, diarrhoea and abdominal pain
Skin and subcutaneous tissue disorders	Common	Itching/pruritus, rash, urticaria
Musculoskeletal and connective tissue disorders	Very common	Myalgia
	Common	Arthralgia
General disorders and administration site conditions	Very common	Injection site reactions including pain, redness, swelling; fatigue
	Common	Fever (≥38°C)
	Uncommon	Other injection site reactions such as induration, local paraesthesia
Post-marketing experience		
Blood and lymphatic system disorders	Not known*	Lymphadenopathy
Immune system disorders	Not known*	Allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema
Nervous system disorders	Not known*	Syncope or vasovagal responses to injection, sometimes accompanied by tonic-clonic movements (see section 4.4)

*Because these events were reported spontaneously, it is not possible to reliably estimate their frequency

In clinical trials 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 HPV-16 and HPV-18 antibodies.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic 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 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, 90% of anal cancers, 70% of HPV-related high grade vulvar and vaginal intraepithelial neoplasia and 78% of HPV related high-grade anal (AIN 2/3) intraepithelial neoplasia.
Other oncogenic HPV types can also cause ano-genital cancers (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 ano-genital lesions” in section 4.1 corresponds to high-grade Cervical Intraepithelial Neoplasia (CIN2/3), high-grade vulvar intraepithelial neoplasia (VIN2/3), high-grade vaginal intraepithelial neoplasia (VaIN2/3) and high-grade anal intraepithelial neoplasia (AIN 2/3).

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
- Had normal cytology

The primary efficacy endpoint was incident infection with HPV-16 and/or HPV-18. Twelve-month persistent infection was evaluated as 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+ 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 in women aged 15 to 25 years.

Prophylactic efficacy against HPV-16/18 infection in a population naïve to oncogenic HPV types

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.

Prophylactic efficacy against HPV-16/18 in women naïve to HPV-16 and/or HPV-18

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 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).
Two analyses of study HPV-008 have been performed: an event-triggered analysis performed once at least 36 CIN2+ cases associated with HPV-16/18 were accrued in the ATP cohort and an end-of study analysis.

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

Table 1: Vaccine efficacy 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 = 7338)	**Control (N = 7305)**	**% Efficacy (95% CI)**
	n[(2)]	**n**	
CIN2+	5	97	94.9% (87.7;98.4)
CIN3+	2	24	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, were DNA negative and seronegative at month 0 and DNA negative at month 6 to the relevant HPV type (HPV-16 or HPV-18)
[(2)] including 4 cases of CIN2+ and 2 cases of CIN3+ in which another oncogenic HPV type was identified in the lesion, concomitantly with HPV-16 or HPV-18. These cases are excluded in the HPV type assignment analysis (see under Table).
[(3)] mean follow-up of 40 months post dose 3

At the event-triggered analysis the 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 HPV-16 and HPV-18 individually was demonstrated.

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 to be causally associated with HPV-16 or HPV-18 infections acquired during the trial.
Based on the HPV type assignment post-hoc analysis, there was 1 CIN2+ case in the vaccine group versus 92 cases in the control group (Efficacy 98.9% (95% CI: 93.8;100)) and no CIN3+ case in the vaccine group versus 22 cases in the control group (Efficacy 100% (95% CI: 81.8;100)) at the end of study analysis.

In the event-triggered 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+ 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).

At end of study analysis, there were 2 cases of VIN2+ or VaIN2+ in the vaccine group and 7 cases in the control group in the ATP cohort associated with HPV-16 or HPV-18. The study was not powered to demonstrate a difference between the vaccine and the control group for these endpoints.

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 study is presented in Table 2.

Table 2: Vaccine efficacy against virological endpoints associated with HPV-16/18 (ATP cohort)

HPV-16/18 endpoint	**ATP cohort[(1)]**		
	End of study analysis[(2)]		
	Cervarix (N = 7338)	**Control (N = 7305)**	**% Efficacy (95% CI)**
	n/N	**n/N**	
6-month persistent infection	35/7182	588/7137	94.3% (92.0;96.1)
12-month persistent infection	26/7082	354/7038	92.9% (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 to the relevant HPV type (HPV-16 or HPV-18)
(2) mean follow-up of 40 months post dose 3

The efficacy results at the event-triggered 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.
The efficacy estimates are lower in the TVC as this cohort includes women with pre-existing infections/lesions, which are not expected to be impacted by Cervarix.

The TVC may approximate to the general population of women in the age range of 15-25 years.

Vaccine efficacy against high grade cervical lesions associated with HPV-16/18 observed in TVC at end of study is presented in Table 3.

Table 3: Vaccine efficacy against high grade cervical lesions associated with HPV-16/18 (TVC)

HPV-16/18 endpoint	**TVC[1]**		
	End of study analysis[2]		
	Cervarix (N = 8694)	**Control (N = 8708)**	**% Efficacy (95% CI)**
	n	**n**	
CIN2+	90	228	60.7% (49.6;69.5)
CIN3+	51	94	45.7% (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 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

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

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

HPV-16/18 endpoint	**TVC[1]**		
	End of study analysis[2]		
	Cervarix	**Control**	**% Efficacy (95% CI)**
	n/N	**n/N**	
6-month persistent infection	504/8863	1227/8870	60.9% (56.6;64.8)
12-month persistent infection	335/8648	767/8671	57.5% (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 vaccine) irrespective of HPV DNA status, cytology and serostatus at baseline.
[2] mean follow-up of 44 months post dose 1

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 at end of study (Table 5).
The TVC-naïve 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

	End of study analysis[3]				
	Cervarix		**Control**		**% Efficacy (95% CI)**
	N	**Cases**	**N**	**Cases**	
CIN2+					
TVC-naïve[1]	5466	61	5452	172	64.9% (52.7;74.2)
TVC[2]	8694	287	8708	428	33.1% (22.2;42.6)
CIN3+					
TVC-naïve[1]	5466	3	5452	44	93.2% (78.9;98.7)
TVC[2]	8694	86	8708	158	45.6% (28.8;58.7)

N = number of subjects included in each group
[1] TVC naïve: includes all vaccinated subjects (who received at least one dose of vaccine) who had normal cytology, 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 vaccine) irrespective of HPV DNA status, cytology and serostatus at baseline.
[3] mean follow-up of 44 months post dose 1

At the end of study analysis, Cervarix reduced definitive cervical therapy procedures (includes loop electrosurgical excision procedure [LEEP], cold-knife Cone, and laser procedures) by 70.2% (95% CI: 57.8;79.3) in TVC-naïve and 33.2% (95% CI: 20.8;43.7) 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. HPV-31, 33 and 45 showed consistent cross-protection for 6-month persistent infection and CIN2+ endpoints in all study cohorts.
End of study vaccine efficacy against 6-month persistent infection and CIN2+ associated with individual non-vaccine oncogenic HPV types is presented in Table 6 (ATP cohort).

Table 6: Vaccine efficacy for non-vaccine oncogenic HPV types

ATP[(1)]						
HPV type	**6-month persistent infection**			**CIN2+**		
	Cervarix	**Control**	**% Efficacy (95% CI)**	**Cervarix**	**Control**	**% Efficacy (95% CI)**
	n	**n**		**n**	**n**	
HPV-16 related types (A9 species)						
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)
HPV-18 related types (A7 species)						
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 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

(1) ATP: includes women who received 3 doses of vaccine, were DNA negative at month 0 and at month 6 to the relevant HPV type.

The limits of the confidence interval 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 5778 women aged 26-72 years (median: 37.0 years). The study was conducted in North America, Latin America, Asia Pacific and Europe. Final analysis was performed at study conclusion, 7 years after 1st vaccination.

The primary endpoint was a combination of a virological and a histopathological endpoint: HPV-16/18 related 6-month persistence infection and/or CIN1+. The primary analyses of efficacy were performed on the ATP cohort for efficacy and the TVC which included a subset of up to 15% of women with a history of HPV-associated infection or disease (defined as two or more abnormal smears in sequence, abnormal colposcopy, or biopsy or treatment of the cervix after abnormal smear or colposcopy findings). Inclusion of this subset allowed assessment of prophylactic efficacy in a population that is thought to reflect a real-world setting, as adult women are the age group generally targeted for cervical screening.

Vaccine efficacy at study conclusion is summarised in the following table.

There is no evidence whether prevention of persistent infection that lasts for at least 6 months is a relevant surrogate marker for cervical cancer prevention in women aged 26 years and above.

Table 7 - Vaccine efficacy at study conclusion in study HPV-015

Endpoint	ATP[(1)]			TVC[(2)]		
	Cervarix n/N	Control n/N	% Efficacy (96.2% CI)	Cervarix n/N	Control n/N	% Efficacy (96.2% CI)
HPV-16/18						
6M PI and/or CIN1+	7/1852	71/1818	90.5% (78.6; 96.5)	93/2768	209/2778	56.8% (43.8; 67.0)
6M PI	6/1815	67/1786	91.4% (79.4; 97.1)	74/2762	180/2775	60% (46.4; 70.4)
CIN2+	1/1852	6/1818	83.7% (<0; 99.7)	33/2733	51/2735	35.8% (<0; 61.0)
ASC-US+	3/1852	47/1818	93.8% (79.9; 98.9)	38/2727	114/2732	67.3% (51.4; 78.5)
6M PI in subjects seropositive at baseline only	3/851	13/837	78% (15.0; 96.4)	42/1211	65/1192	38.7% (6.3; 60.4)
Cross protective efficacy						
HPV-31 6MPI	10/2073	29/2090	65.8% (24.9; 85.8)	51/2762	71/2775	29% (<0; 52.5)
HPV-45 6MPI	9/2106	30/2088	70.7% (34.2; 88.4)	22/2762	60/2775	63.9% (38.6; 79.6)
HPV-31 ASC-US+	5/2117	23/2127	78.4% (39.1; 94.1)	34/2727	55/2732	38.7% (2.0; 62.3)
HPV-45 ASC-US+	5/2150	23/2125	78.7% (40.1; 94.1)	13/2727	38/2732	66.1% (32.7; 84.1)

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
ASC-US= Atypical Cells of Undetermined Significance (abnormal cytology)
(1) 3 doses of vaccine, DNA negative and seronegative at month 0 (unless specified) and DNA negative at month 6 for the relevant HPV type (HPV-16 and/or HPV-18)
(2) at least one dose of vaccine, irrespective of HPV DNA and serostatus (unless specified) at month 0. Includes 15% of subjects with previous history of HPV disease/infection

Efficacy against ≥ASC-US (abnormal cytology) associated with oncogenic non-vaccine types was 37.2% (96.2% CI [21.3; 50.1]) (ATP).

Efficacy against CIN1+ irrespective of the HPV type detected in the lesion was 22.9% (96.2% CI [4.8; 37.7]) (TVC).

There was no evidence of protection from disease caused by HPV in subjects aged 25 years and above who were DNA positive and/ or with abnormal cytology at study entry.

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 5,465 female subjects from 9 to 55 years of age and over 800 male subjects aged 10 to 18 years.

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 113 months. 92 subjects in the vaccine group had immunogenicity data at the [M107-M113] interval after the first vaccine dose with a median follow-up of 8.9 years. Of these subjects, 100% (95% CI: 96.1;100) remained seropositive for HPV-16 and HPV-18 in 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 [M107-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 cleared a natural HPV infection.
In study 008, immunogenicity up to month 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. 470 subjects (142 aged 15-25 years, 172 aged 26-45 years and 156 aged 46-55 years) who completed study HPV-014 and received the 3 dose schedule were followed-up for up to 10 years in the extension study HPV-060. Ten years after administration of the first dose, 100% of subjects in the 15-25 years group, 99.2% in the 26-45 years group and 96.3% in the 46-55 years group were still seropositive for HPV-16, and 99.2%, 93.7% and 83.8% for HPV-18, respectively. In all age groups, GMTs remained at least 5- to 32-fold for HPV-16 and 3- to 14-fold for HPV-18 above those elicited in women who cleared a natural infection for both antigens.

Evidence 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 administration of 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.

Bridging the efficacy of Cervarix from young adult women to adolescents

In a pooled analysis (HPV-029,-30 & -48), 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 15 to 25 years, respectively.

In two clinical trials (HPV-012 & -013) performed in girls 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.

In clinical trials (HPV-070 and HPV-048) performed in girls aged 9 to 14 years receiving a 2-dose schedule (0, 6 months or 0, 12 months) and young women aged 15-25 years receiving Cervarix

according to the standard 0, 1, 6 months schedule, all subjects seroconverted to both HPV types 16 and 18 one month after the second dose. The immune response after 2 doses in females aged 9 to 14 years was non-inferior to the response after 3 doses in women aged 15 to 25 years.

On the basis of these immunogenicity data, the efficacy of Cervarix is inferred from 9 to 14 years of age.

Duration of the immune response in women aged 26 years and older

In the Phase III study (HPV-015) in women 26 years and older all subjects seroconverted one month after the third dose. At the 84-month time point, i.e. 78 months after completion of the full vaccination course, 99.3% and 95.9% of initially seronegative women remained 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 titers peaked at month 7 then gradually declined up to month 18 and stabilized to reach a plateau up to month 84.

Immunogenicity in males aged 10 to 18 years

Immunogenicity in males was assessed in 2 clinical trials HPV-011 (N=173) and HPV-040 (N=556). The data showed comparable immunogenicity in males and females. In study HPV-011, all subjects seroconverted to both HPV-16 and 18 and GMT levels were non inferior to those observed in females aged 15 to 25 years in study HPV-012.

Bridging of clinical efficacy against anal lesions and cancers

No efficacy study against anal premalignant lesions has been conducted with Cervarix. However, studies conducted in girls aged 9 to 14 years (study HPV-071) and in women aged 18 to 45 years (study HPV-010) have consistently shown a higher immune response with Cervarix than with the comparator for which efficacy data against anal premalignant lesions are conclusive and have shown protection.

Immunogenicity in HIV infected women

In study HPV-020, conducted in South Africa, 22 HIV uninfected and 42 HIV infected subjects (WHO clinical stage 1; ATP cohort for immunogenicity) received Cervarix. All subjects were seropositive in the ELISA assay to both HPV 16 and 18 one month after the third dose (at Month 7) and the seropositivity for HPV 16 and 18 was maintained up to Month 12. The GMTs appeared to be lower in the HIV infected group (non overlapping 95% confidence interval). The clinical relevance of this observation is unknown. Functional antibodies were not determined. No information exists about protection against persistent infection or precancerous lesions among HIV infected women.

5.2 Pharmacokinetic properties

Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, acute and repeated dose toxicity, local tolerance, fertility, embryo-foetal and postnatal toxicity (up to the end of the lactation period).

Serological data suggest a transfer of anti-HPV-16 and anti-HPV-18 antibodies via the milk during the lactation period in rats. However, it is unknown whether vaccine-induced antibodies are excreted in human breast milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride (NaCl)
Sodium dihydrogen phosphate dihydrate ($NaH_2PO_4.2\ H_2O$)
Water for injections

For adjuvants, see section 2.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years.

Cervarix should be administered as soon as possible after being removed from the refrigerator.

However, stability has been demonstrated when stored outside the refrigerator for up to 3 days at temperatures between 8°C and 25°C or for up to 1 day at temperatures between 25°C and 37°C. If not used at the end of this period the vaccine should be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

0.5 ml of suspension in a pre-filled syringe (type I glass) with a plunger stopper (rubber butyl) with or without needles.

Pack sizes of 1 and 10 pre-filled syringes with or without needles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

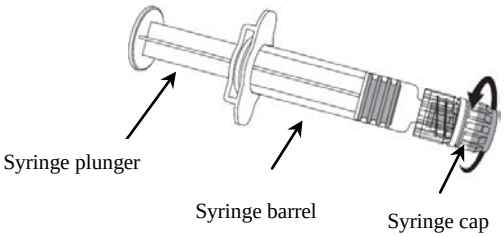
A fine white deposit with a clear colourless supernatant may be observed upon storage of the syringe. This does not constitute a sign of deterioration.

The content of the syringe should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to administration.
In the event of either being observed, discard the vaccine.

The vaccine should be well shaken before use.

<u>Instructions for administration of the vaccine presented in pre-filled syringe</u>

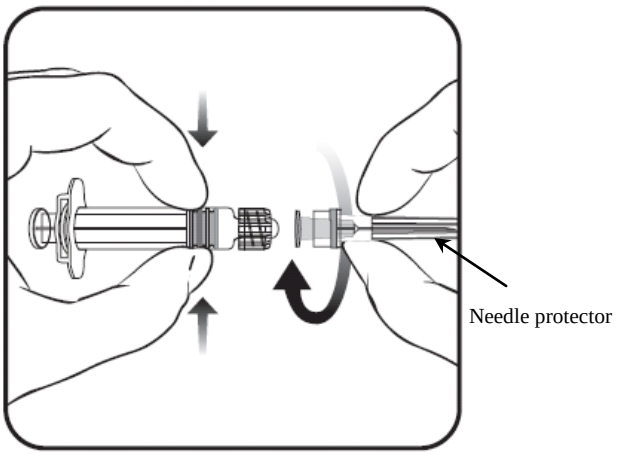
1. Holding the syringe **barrel** in one hand
(avoid holding the syringe plunger),
unscrew the syringe cap by twisting it anticlockwise.



2. To attach the needle to the syringe,
twist the needle clockwise into the syringe
until you feel it lock.

3. Remove the needle protector, which on
occasion can be a little stiff.

4. Administer the vaccine.



Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/419/004
EU/1/07/419/005
EU/1/07/419/006
EU/1/07/419/007
EU/1/07/419/008
EU/1/07/419/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2007.
Date of latest renewal: 17 September 2012.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

GlaxoSmithKline Biologicals SA
Parc de la Noire Epine
rue Flemming
20-1300 Wavre
Belgium

Name and address of the manufacturer responsible for batch release

GlaxoSmithKline Biologicals S.A.
89, rue de l'Institut
BE-1330 Rixensart
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC as amended, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MONODOSE VIAL, PACK OF 1, 10, 100

1. NAME OF THE MEDICINAL PRODUCT

Cervarix suspension for injection
Human Papillomavirus vaccine [Types 16, 18] (Recombinant, adjuvanted, adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml) contains:

HPV type 16 L1 protein[1,2]	20 micrograms
HPV type 18 L1 protein[1,2]	20 micrograms
[1] adjuvanted by AS04 containing:	
3-*O*-desacyl-4'- monophosphoryl lipid A (MPL)[2]	50 micrograms
[2]adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$)	0.5 milligrams Al^{3+} in total

3. LIST OF EXCIPIENTS

Sodium chloride
Sodium dihydrogen phosphate dihydrate
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
1 vial
1 dose (0.5 ml)

10 vials
10 x 1 dose (0.5 ml)

100 vials
100 x 1 dose (0.5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Intramuscular use
Shake before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/419/001 – pack of 1
EU/1/07/419/002 – pack of 10
EU/1/07/419/003 – pack of 100

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
MULTIDOSE VIAL, PACK OF 1, 10, 100

1. NAME OF THE MEDICINAL PRODUCT

Cervarix suspension for injection, multidose
Human Papillomavirus vaccine [Types 16, 18] (Recombinant, adjuvanted, adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml) contains:

HPV type 16 L1 protein[1,2]	20 micrograms
HPV type 18 L1 protein[1,2]	20 micrograms
[1] adjuvanted by AS04 containing:	
3-*O*-desacyl-4'- monophosphoryl lipid A (MPL)[2]	50 micrograms
[2]adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$)	0.5 milligrams Al^{3+} in total

3. LIST OF EXCIPIENTS

Sodium chloride
Sodium dihydrogen phosphate dihydrate
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection
1 vial
2 doses (1 ml)

10 vials
10 x 2 doses (1 ml)

100 vials
100 x 2 doses (1 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Intramuscular use
Shake before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening, use immediately or within 6 hours if stored in a refrigerator

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/419/010 – pack of 1
EU/1/07/419/011 – pack of 10
EU/1/07/419/012 – pack of 100

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PRE-FILLED SYRINGE WITH OR WITHOUT NEEDLE, PACK OF 1, 10

1. NAME OF THE MEDICINAL PRODUCT

Cervarix suspension for injection in pre-filled syringe
Human Papillomavirus vaccine [Types 16, 18] (Recombinant, adjuvanted, adsorbed)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 dose (0.5 ml) contains:

HPV type 16 L1 protein[1,2]	20 micrograms
HPV type 18 L1 protein[1,2]	20 micrograms
[1] adjuvanted by AS04 containing:	
3-*O*-desacyl-4'- monophosphoryl lipid A (MPL)[2]	50 micrograms
[2]adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$)	0.5 milligrams Al^{3+} in total

3. LIST OF EXCIPIENTS

Sodium chloride
Sodium dihydrogen phosphate dihydrate
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension for injection in pre-filled syringe
1 pre-filled syringe
1 dose (0.5 ml)

10 pre-filled syringes
10 x 1 dose (0.5 ml)

1 pre-filled syringe + 1 needle
1 dose (0.5 ml)

10 pre-filled syringes + 10 needles
10 x 1 dose (0.5 ml)

1 pre-filled syringe + 2 needles
1 dose (0.5 ml)

10 pre-filled syringes + 20 needles
10 x 1 dose (0.5 ml)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Intramuscular use
Shake before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator
Do not freeze
Store in the original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local regulations

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/419/008 – pack of 1 without needle
EU/1/07/419/009 – pack of 10 without needle
EU/1/07/419/004 – pack of 1 with 1 needle
EU/1/07/419/006 – pack of 10 with 10 needles
EU/1/07/419/005 – pack of 1 with 2 needles
EU/1/07/419/007 – pack of 10 with 20 needles

13. BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
MONODOSE VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Cervarix
Suspension for injection

I.M.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 ml)

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
MULTIDOSE VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Cervarix
Suspension for injection

I.M.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 doses (1 ml)

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Cervarix
Suspension for injection in pre-filled syringe

I.M.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 dose (0.5 ml)

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Cervarix suspension for injection
Human Papillomavirus vaccine [Types 16, 18] (Recombinant, adjuvanted, adsorbed)

Read all of this leaflet carefully before you start receiving this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Cervarix is and what it is used for

Cervarix is a vaccine intended to protect from the age of 9 years against the diseases caused by infection with Human Papillomaviruses (HPV).

These diseases include:
- cervical cancer (cancer of the cervix i.e. lower part of the uterus or womb) and anal cancer,
- precancerous cervical and anal lesions (changes in cells of the cervix, vulva, vagina and anus that have a risk of turning into cancer).

The Human Papillomavirus (HPV) types contained in the vaccine (HPV types 16 and 18) are responsible for approximately 70% of cervical cancers , 90% of anal cancers, 70% of HPV-related pre-cancerous lesions of the vulva and vagina and 78% of HPV-related pre-cancerous lesions of the anus. Other HPV types can also cause ano-genital cancers. Cervarix does not protect against all HPV types.

When a female is vaccinated with Cervarix, the immune system (the body's natural defence system) will make antibodies against HPV types 16 and 18. In clinical trials Cervarix has been shown to prevent HPV related diseases in women aged 15 years and older. Cervarix also stimulates production of antibodies in females 9-14 years of age.

Cervarix is not infectious and so, it cannot cause HPV related diseases.

Cervarix is not used to treat HPV related diseases already present at the time of vaccination.

Cervarix should be used in accordance with official guidelines.

2. What you need to know before you receive Cervarix

Cervarix should not be given

- if you are allergic to any of the active substances or any of the other ingredients of this vaccine (listed in section 6). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

Warnings and precautions
Talk to your doctor or pharmacist before you are given Cervarix
- if you have a bleeding problem or bruise easily.
- if you have any disease which reduces your resistance to infection such as HIV infection.
- if you have a severe infection with a high temperature. It might be necessary to postpone the vaccination until recovery. A minor infection such as a cold should not be a problem, but talk to the doctor first.

Fainting can occur (mostly in adolescents) following, or even before, any needle injection. Therefore tell the doctor or nurse if you or your child fainted with a previous injection.

As with all vaccines, Cervarix may not fully protect all people who are vaccinated.

Cervarix does not protect people from diseases caused by infection with HPV types 16 or 18 if they are already infected with Human Papillomavirus type 16 or 18 at the time of vaccination.

Although vaccination may protect you against cervical cancer, it is not a substitute for regular cervical screening. You should continue to follow your doctor's advice on cervical smear/Pap test (test to screen for changes in cells of the cervix caused by an HPV infection) and preventative and protective measures.

As Cervarix will not protect against all types of Human Papillomavirus, appropriate precautions against exposure to HPV and sexually transmitted diseases should continue to be used.

Cervarix will not protect against other diseases that are not caused by Human Papillomavirus.

Other medicines and Cervarix
Cervarix can be given with a combined booster vaccine containing diphtheria (d), tetanus (T) and pertussis [acellular] (pa) with or without inactivated poliomyelitis (IPV), (dTpa, dTpa -IPV vaccines), or with a combined hepatitis A and hepatitis B vaccine (Twinrix) or a hepatitis B vaccine (Engerix B), at a separate injection site (another part of your body, e.g. the other arm) during the same visit.

Cervarix may not have an optimal effect if used with medicines that suppress the immune system.

In clinical trials, oral contraceptives (e.g. the pill) did not reduce the protection obtained by Cervarix.

Tell your doctor if you are taking, have recently taken, might take any other medicines, or have recently received any other vaccine.

Pregnancy, breast-feeding and fertility
If you are pregnant, if pregnancy occurs during the course of vaccination or if you are trying to become pregnant it is recommended to postpone or interrupt vaccination until after completion of the pregnancy.

If you are pregnant or breast-feeding, think that you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this vaccine.

Driving and using machines
Cervarix is not likely to affect your ability to drive or use machines. However, do not drive or use any machines if you are feeling unwell.
Cervarix contains sodium chloride.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium-free".

3. How Cervarix is given

How the vaccine is given
The doctor or nurse will give Cervarix as an injection into the muscle of the upper arm.

How much is given
Cervarix is intended for use from 9 years of age onwards.

The total number of injections you will receive depends on your age at the time of the first injection.

<u>If you are between 9 and 14 years old</u>

You will receive 2 injections:

First injection: at chosen date
Second injection: given between 5 and 13 months after first injection

<u>If you are 15 years old or above</u>

You will receive 3 injections:

First injection: at chosen date
Second injection: 1 month after first injection
Third injection: 6 months after first injection

If necessary, the vaccination schedule can be more flexible. Please speak to your doctor for more information.

When Cervarix is given for the first dose, it is recommended that Cervarix (and not another vaccine against HPV) be given for the complete vaccination course.

Cervarix is not recommended for use in girls below 9 years of age.

The vaccine should never be given into a vein.

If you miss a dose
It is important that you follow the instructions of your doctor or nurse regarding return visits. If you forget to go back to your doctor at the scheduled time, ask your doctor for advice.

If you do not finish the complete vaccination course (two or three injections depending on your age at vaccination), you may not get the best response and protection from the vaccination.

4. Possible side effects

Like all medicines, this vaccine can cause side effects, although not everybody gets them.

Side effects that occurred during clinical trials with Cervarix were as follows:

- Very common (side effects which may occur in more than 1 per 10 doses of vaccine):
  - pain or discomfort at the injection site
  - redness or swelling at the injection site
  - headache

- aching muscles, muscle tenderness or weakness (not caused by exercise)
- tiredness

♦ Common (side effects which may occur in less than 1 per 10 but more than 1 per 100 doses of vaccine):
- gastrointestinal symptoms including nausea, vomiting, diarrhoea and abdominal pain
- itching, red skin rash, hives (urticaria)
- joint pain
- fever (≥38°C)

♦ Uncommon (side effects which may occur in less than 1 per 100 but more than 1 per 1,000 doses of vaccine):
- upper respiratory tract infection (infection of the nose, throat or trachea)
- dizziness
- other injection site reactions such as hard lump, tingling or numbness

Side effects that have been reported during marketed use of Cervarix include:

- allergic reactions. These can be recognised by:
  itchy rash of the hands and feet,
  swelling of the eyes and face,
  difficulty in breathing or swallowing,
  sudden drop in blood pressure and loss of consciousness.
  These reactions will usually occur before leaving the doctor's surgery. However, if your child gets any of these symptoms you should contact a doctor urgently.
- swollen glands in the neck, armpit or groin
- fainting sometimes accompanied by shaking or stiffness.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cervarix

Keep this vaccine out of the sight and reach of children.

Do not use this vaccine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Cervarix contains

- The active substances are:

Human Papillomavirus[1] type 16 L1 protein[2,3,4]	20 micrograms
Human Papillomavirus[1] type 18 L1 protein[2,3,4]	20 micrograms

[1]Human Papillomavirus = HPV

[2]adjuvanted by AS04 containing:

3-*O*-desacyl-4'- monophosphoryl lipid A (MPL)[3]	50 micrograms
[3]adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$)	0.5 milligrams Al^{3+} in total

[4]L1 protein in the form of non-infectious virus-like particles (VLPs) produced by recombinant DNA technology using a Baculovirus expression system which uses Hi-5 Rix4446 cells derived from the insect *Trichoplusia ni*.

- The other ingredients are sodium chloride (NaCl), sodium dihydrogen phosphate dihydrate ($NaH_2PO_4.2\ H_2O$) and water for injections.

What Cervarix looks like and contents of the pack

Suspension for injection.

Cervarix is a turbid white suspension.

Cervarix is available in 1 dose vials (0.5 ml) in packs of 1, 10 and 100.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {month YYYY}

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Cervarix should be administered as soon as possible after being removed from the refrigerator. However, stability has been demonstrated when stored outside the refrigerator for up to 3 days at temperatures between 8°C and 25°C or for up to 1 day at temperatures between 25°C and 37°C. If not used at the end of this period the vaccine should be discarded.

A fine white deposit with a clear colourless supernatant may be observed upon storage of the vial. This does not constitute a sign of deterioration.

The content of the vial should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to administration.
In the event of either being observed, discard the vaccine.

The vaccine should be well shaken before use.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Cervarix suspension for injection, multidose
Human Papillomavirus vaccine [Types 16, 18] (Recombinant, adjuvanted, adsorbed)

Read all of this leaflet carefully before you start receiving this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Cervarix is and what it is used for

Cervarix is a vaccine intended to protect from the age of 9 years against the diseases caused by infection with Human Papillomaviruses (HPV).

These diseases include:
- cervical cancer (cancer of the cervix i.e. lower part of the uterus or womb) and anal cancer,
- precancerous cervical and anal lesions (changes in cells of the cervix, vulva, vagina and anus that have a risk of turning into cancer).

The Human Papillomavirus (HPV) types contained in the vaccine (HPV types 16 and 18) are responsible for approximately 70% of cervical cancers , 90% of anal cancers, 70% of HPV-related pre-cancerous lesions of the vulva and vagina and 78% of HPV-related pre-cancerous lesions of the anus. Other HPV types can also cause ano-genital cancers. Cervarix does not protect against all HPV types.

When a female is vaccinated with Cervarix, the immune system (the body's natural defence system) will make antibodies against HPV types 16 and 18. In clinical trials Cervarix has been shown to prevent HPV related diseases in women aged 15 years and older. Cervarix also stimulates production of antibodies in females 9-14 years of age.

Cervarix is not infectious and so, it cannot cause HPV related diseases.

Cervarix is not used to treat HPV related diseases already present at the time of vaccination.

Cervarix should be used in accordance with official guidelines.

2. What you need to know before you receive Cervarix

Cervarix should not be given

- if you are allergic to any of the active substances or any of the other ingredients of this vaccine (listed in section 6). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

Warnings and precautions
Talk to your doctor or pharmacist before you are given Cervarix
- if you have a bleeding problem or bruise easily.
- if you have any disease which reduces your resistance to infection such as HIV infection.
- if you have a severe infection with a high temperature. It might be necessary to postpone the vaccination until recovery. A minor infection such as a cold should not be a problem, but talk to the doctor first.

Fainting can occur (mostly in adolescents) following, or even before, any needle injection. Therefore tell the doctor or nurse if you or your child fainted with a previous injection.

As with all vaccines, Cervarix may not fully protect all people who are vaccinated.

Cervarix does not protect people from diseases caused by infection with HPV types 16 or 18 if they are already infected with Human Papillomavirus type 16 or 18 at the time of vaccination.

Although vaccination may protect you against cervical cancer, it is not a substitute for regular cervical screening. You should continue to follow your doctor's advice on cervical smear/Pap test (test to screen for changes in cells of the cervix caused by an HPV infection) and preventative and protective measures.

As Cervarix will not protect against all types of Human Papillomavirus, appropriate precautions against exposure to HPV and sexually transmitted diseases should continue to be used.

Cervarix will not protect against other diseases that are not caused by Human Papillomavirus.

Other medicines and Cervarix
Cervarix can be given with a combined booster vaccine containing diphtheria (d), tetanus (T) and pertussis [acellular] (pa) with or without inactivated poliomyelitis (IPV), (dTpa, dTpa -IPV vaccines), or with a combined hepatitis A and hepatitis B vaccine (Twinrix) or a hepatitis B vaccine (Engerix B), at a separate injection site (another part of your body, e.g. the other arm) during the same visit.

Cervarix may not have an optimal effect if used with medicines that suppress the immune system.

In clinical trials, oral contraceptives (e.g. the pill) did not reduce the protection obtained by Cervarix.

Tell your doctor if you are taking, have recently taken, might take any other medicines, or have recently received any other vaccine.

Pregnancy, breast-feeding and fertility
If you are pregnant, if pregnancy occurs during the course of vaccination or if you are trying to become pregnant it is recommended to postpone or interrupt vaccination until after completion of the pregnancy.

If you are pregnant or breast-feeding, think that you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this vaccine.

Driving and using machines
Cervarix is not likely to affect your ability to drive or use machines. However, do not drive or use any machines if you are feeling unwell.
Cervarix contains sodium chloride.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium-

free".

3. How Cervarix is given

How the vaccine is given

The doctor or nurse will give Cervarix as an injection into the muscle of the upper arm.

How much is given
Cervarix is intended for use from 9 years of age onwards.

The total number of injections you will receive depends on your age at the time of the first injection.

<u>If you are between 9 and 14 years old</u>

You will receive 2 injections:

First injection: at chosen date
Second injection: given between 5 and 13 months after first injection

<u>If you are 15 years old or above</u>

You will receive 3 injections:

First injection: at chosen date
Second injection: 1 month after first injection
Third injection: 6 months after first injection

If necessary, the vaccination schedule can be more flexible. Please speak to your doctor for more information.

When Cervarix is given for the first dose, it is recommended that Cervarix (and not another vaccine against HPV) be given for the complete vaccination course.

Cervarix is not recommended for use in girls below 9 years of age.

The vaccine should never be given into a vein.

If you miss a dose
It is important that you follow the instructions of your doctor or nurse regarding return visits. If you forget to go back to your doctor at the scheduled time, ask your doctor for advice.

If you do not finish the complete vaccination course (two or three injections depending on your age at vaccination), you may not get the best response and protection from the vaccination.

4. Possible side effects

Like all medicines, this vaccine can cause side effects, although not everybody gets them.

Side effects that occurred during clinical trials with Cervarix were as follows:

- Very common (side effects which may occur in more than 1 per 10 doses of vaccine):
  - pain or discomfort at the injection site
  - redness or swelling at the injection site
  - headache

- aching muscles, muscle tenderness or weakness (not caused by exercise)
- tiredness

♦ Common (side effects which may occur in less than 1 per 10 but more than 1 per 100 doses of vaccine):
- gastrointestinal symptoms including nausea, vomiting, diarrhoea and abdominal pain
- itching, red skin rash, hives (urticaria)
- joint pain
- fever (≥38°C)

♦ Uncommon (side effects which may occur in less than 1 per 100 but more than 1 per 1,000 doses of vaccine):
- upper respiratory tract infection (infection of the nose, throat or trachea)
- dizziness
- other injection site reactions such as hard lump, tingling or numbness.

Side effects that have been reported during marketed use of Cervarix include:

- allergic reactions. These can be recognised by:
  itchy rash of the hands and feet,
  swelling of the eyes and face,
  difficulty in breathing or swallowing,
  sudden drop in blood pressure and loss of consciousness.
  These reactions will usually occur before leaving the doctor's surgery. However, if your child gets any of these symptoms you should contact a doctor urgently.
- swollen glands in the neck, armpit or groin
- fainting sometimes accompanied by shaking or stiffness.

Reporting of side effects
If you get any side effects , talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cervarix

Keep this vaccine out of the sight and reach of children.

Do not use this vaccine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.

After first opening, immediate use is recommended. If not used immediately, the vaccine should be stored in a refrigerator (2°C – 8°C). If not used within 6 hours it should be discarded.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Cervarix contains

- The active substances are:

Human Papillomavirus[1] type 16 L1 protein[2,3,4]	20 micrograms
Human Papillomavirus[1] type 18 L1 protein[2,3,4]	20 micrograms

[1]Human Papillomavirus = HPV

[2]adjuvanted by AS04 containing:

3-*O*-desacyl-4'- monophosphoryl lipid A (MPL)[3]	50 micrograms
[3]adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$)	0.5 milligrams Al^{3+} in total

[4]L1 protein in the form of non-infectious virus-like particles (VLPs) produced by recombinant DNA technology using a Baculovirus expression system which uses Hi-5 Rix4446 cells derived from the insect *Trichoplusia ni*.

- The other ingredients are sodium chloride (NaCl), sodium dihydrogen phosphate dihydrate ($NaH_2PO_4.2\ H_2O$) and water for injections.

What Cervarix looks like and contents of the pack

Suspension for injection.

Cervarix is a turbid white suspension.

Cervarix is available in 2 dose vials (1 ml) in packs of 1, 10 and 100.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {month YYYY}

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Cervarix should be administered as soon as possible after being removed from the refrigerator. However, stability has been demonstrated when stored outside the refrigerator for up to 3 days at temperatures between 8°C and 25°C or for up to 1 day at temperatures between 25°C and 37°C. If not used at the end of this period the vaccine should be discarded.

A fine white deposit with a clear colourless supernatant may be observed upon storage of the vial. This does not constitute a sign of deterioration.

The content of the vial should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to administration.
In the event of either being observed, discard the vaccine.

The vaccine should be well shaken before use.

When using a multidose vial, each 0.5 ml dose should be withdrawn using a sterile needle and syringe; precautions should be taken to avoid contamination of the contents.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Package leaflet: Information for the user

Cervarix suspension for injection in pre-filled syringe
Human Papillomavirus vaccine [Types 16, 18] (Recombinant, adjuvanted, adsorbed)

Read all of this leaflet carefully before you start receiving this vaccine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Cervarix is and what it is used for

Cervarix is a vaccine intended to protect from the age of 9 years against the diseases caused by infection with Human Papillomaviruses (HPV).

These diseases include:
- cervical cancer (cancer of the cervix i.e. lower part of the uterus or womb) and anal cancer,
- precancerous cervical and anal lesions (changes in cells of the cervix, vulva, vagina and anus that have a risk of turning into cancer).

The Human Papillomavirus (HPV) types contained in the vaccine (HPV types 16 and 18) are responsible for approximately 70% of cervical cancers , 90% of anal cancers, 70% of HPV-related pre-cancerous lesions of the vulva and vagina and 78% of HPV-related pre-cancerous lesions of the anus. Other HPV types can also cause ano-genital cancers. Cervarix does not protect against all HPV types.

When a female is vaccinated with Cervarix, the immune system (the body's natural defence system) will make antibodies against HPV types 16 and 18. In clinical trials Cervarix has been shown to prevent HPV related diseases in women aged 15 years and older. Cervarix also stimulates production of antibodies in females 9-14 years of age.

Cervarix is not infectious and so, it cannot cause HPV related diseases.

Cervarix is not used to treat HPV related diseases already present at the time of vaccination.

Cervarix should be used in accordance with official guidelines.

2. What you need to know before you receive Cervarix

Cervarix should not be given:

- if you are allergic to any of the active substances or any of the other ingredients of this vaccine (listed in section 6). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

Warnings and precautions
Talk to your doctor or pharmacist before you are given Cervarix
- if you have a bleeding problem or bruise easily.
- if you have any disease which reduces your resistance to infection such as HIV infection.
- if you have a severe infection with a high temperature. It might be necessary to postpone the vaccination until recovery. A minor infection such as a cold should not be a problem, but talk to the doctor first.

Fainting can occur (mostly in adolescents) following, or even before, any needle injection. Therefore tell the doctor or nurse if you or your child fainted with a previous injection.

As with all vaccines, Cervarix may not fully protect all people who are vaccinated.

Cervarix does not protect people from diseases caused by infection with HPV types 16 or 18 if they are already infected with Human Papillomavirus type 16 or 18 at the time of vaccination.

Although vaccination may protect you against cervical cancer, it is not a substitute for regular cervical screening. You should continue to follow your doctor's advice on cervical smear/Pap test (test to screen for changes in cells of the cervix caused by an HPV infection) and preventative and protective measures.

As Cervarix will not protect against all types of Human Papillomavirus, appropriate precautions against exposure to HPV and sexually transmitted diseases should continue to be used.

Cervarix will not protect against other diseases that are not caused by Human Papillomavirus.

Other medicines and Cervarix
Cervarix can be given with a combined booster vaccine containing diphtheria (d), tetanus (T) and pertussis [acellular] (pa) with or without inactivated poliomyelitis (IPV), (dTpa, dTpa -IPV vaccines), or with a combined hepatitis A and hepatitis B vaccine (Twinrix) or a hepatitis B vaccine (Engerix B), at a separate injection site (another part of your body, e.g. the other arm) during the same visit.

Cervarix may not have an optimal effect if used with medicines that suppress the immune system.

In clinical trials, oral contraceptives (e.g. the pill) did not reduce the protection obtained by Cervarix.

Tell your doctor if you are taking, have recently taken, might take any other medicines or have recently received any other vaccine.

Pregnancy, breast-feeding and fertility
If you are pregnant, if pregnancy occurs during the course of vaccination or if you are trying to become pregnant it is recommended to postpone or interrupt vaccination until after completion of the pregnancy.

If you are pregnant or breast-feeding, think that you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this vaccine.

Driving and using machines
Cervarix is not likely to affect your ability to drive or use machines. However, do not drive or use any machines if you are feeling unwell.
Cervarix contains sodium chloride.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium-free".

3. How Cervarix is given

How the vaccine is given
The doctor or nurse will give Cervarix as an injection into the muscle of the upper arm.

How much is given
Cervarix is intended for use from 9 years of age onwards.

The total number of injections you will receive depends on your age at the time of the first injection.

<u>If you are between 9 and 14 years old</u>

You will receive 2 injections:

First injection: at chosen date
Second injection: given between 5 and 13 months after first injection

<u>If you are 15 years old or above</u>

You will receive 3 injections:

First injection: at chosen date
Second injection: 1 month after first injection
Third injection: 6 months after first injection

If necessary, the vaccination schedule can be more flexible. Please speak to your doctor for more information.

When Cervarix is given for the first dose, it is recommended that Cervarix (and not another vaccine against HPV) be given for the complete vaccination course.

The vaccine should never be given into a vein.

Cervarix is not recommended for use in girls below 9 years of age.

If you miss a dose
It is important that you follow the instructions of your doctor or nurse regarding return visits. If you forget to go back to your doctor at the scheduled time, ask your doctor for advice.

If you do not finish the complete vaccination course (two or three injections depending on your age at vaccination), you may not get the best response and protection from the vaccination.

4. Possible side effects

Like all medicines, this vaccine can cause side effects, although not everybody gets them.

Side effects that occurred during clinical trials with Cervarix were as follows:

- Very common (side effects which may occur in more than 1 per 10 doses of vaccine):
  - pain or discomfort at the injection site
  - redness or swelling at the injection site
  - headache

- aching muscles, muscle tenderness or weakness (not caused by exercise)
- tiredness

♦ Common (side effects which may occur in less than 1 per 10 but more than 1 per 100 doses of vaccine):
- gastrointestinal symptoms including nausea, vomiting, diarrhoea and abdominal pain
- itching, red skin rash, hives (urticaria)
- joint pain
- fever (≥38°C)

♦ Uncommon (side effects which may occur in less than 1 per 100 but more than 1 per 1,000 doses of vaccine):
- upper respiratory tract infection (infection of the nose, throat or trachea)
- dizziness
- other injection site reactions such as hard lump, tingling or numbness.

Side effects that have been reported during marketed use of Cervarix include:

- allergic reactions. These can be recognised by:
  itchy rash of the hands and feet,
  swelling of the eyes and face,
  difficulty in breathing or swallowing,
  sudden drop in blood pressure and loss of consciousness.
  These reactions will usually occur before leaving the doctor's surgery. However, if your child gets any of these symptoms you should contact a doctor urgently.
- swollen glands in the neck, armpit or groin
- fainting sometimes accompanied by shaking or stiffness.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cervarix

Keep this vaccine out of the sight and reach of children.

Do not use this vaccine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Cervarix contains

- The active substances are:

Human Papillomavirus[1] type 16 L1 protein[2,3,4]	20 micrograms
Human Papillomavirus[1] type 18 L1 protein[2,3,4]	20 micrograms

[1]Human Papillomavirus = HPV

[2]adjuvanted by AS04 containing:

3-*O*-desacyl-4'- monophosphoryl lipid A (MPL)[3]	50 micrograms
[3]adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$)	0.5 milligrams Al^{3+} in total

[4]L1 protein in the form of non-infectious virus-like particles (VLPs) produced by recombinant DNA technology using a Baculovirus expression system which uses Hi-5 Rix4446 cells derived from the insect *Trichoplusia ni*.

- The other ingredients are sodium chloride (NaCl), sodium dihydrogen phosphate dihydrate ($NaH_2PO_4.2\ H_2O$) and water for injections.

What Cervarix looks like and contents of the pack

Suspension for injection in pre-filled syringe.

Cervarix is a turbid white suspension.

Cervarix is available in pre-filled syringes (0,5 ml) with or without needles in packs of 1 and 10.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart, Belgium

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {month YYYY}

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Cervarix should be administered as soon as possible after being removed from the refrigerator. However, stability has been demonstrated when stored outside the refrigerator for up to 3 days at temperatures between 8°C and 25°C or for up to 1 day at temperatures between 25°C and 37°C. If not used at the end of this period the vaccine should be discarded.

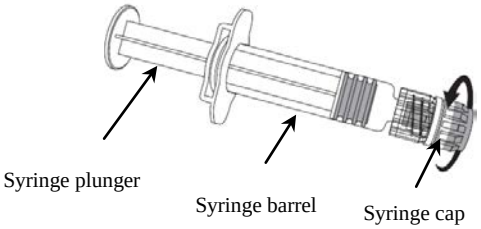
A fine white deposit with a clear colourless supernatant may be observed upon storage of the syringe. This does not constitute a sign of deterioration.

The content of the syringe should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to administration.
In the event of either being observed, discard the vaccine.

The vaccine should be well shaken before use.

Instructions for administration of the vaccine presented in pre-filled syringe

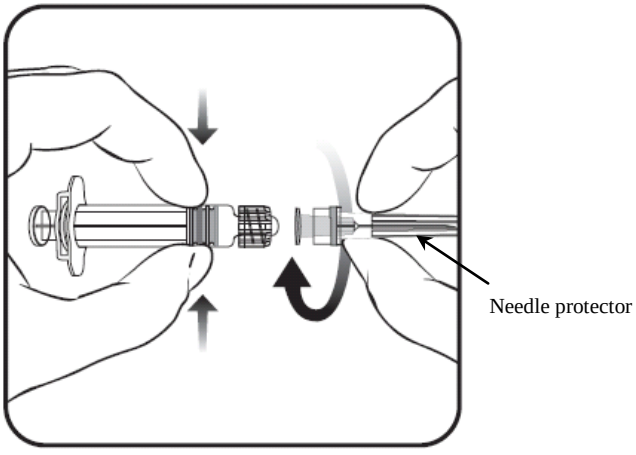
1. Holding the syringe **barrel** in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.



2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock.

3. Remove the needle protector, which on occasion can be a little stiff.

4. Administer the vaccine.



Any unused medicinal product or waste material should be disposed of in accordance with local requirements.