

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

¹Human Papillomavirus = HPV

²adjuvanted by AS04 containing:

3-*O*-desacyl-4'-monophosphoryl lipid A (MPL)³ 50 micrograms

³adsorbed on aluminium hydroxide, hydrated (Al(OH)₃) 0.5 milligrams Al³⁺ in total

⁴L1 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 cervical lesions and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types. See sections 4.4 and 5.1 for important information on the data that support this indication.

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

4.2 Posology and method of administration

Posology

The recommended vaccination consists of 3 separate 0.5 ml doses administered according to the schedule: 0, 1, 6 months.

If flexibility in the vaccination schedule is necessary, the second dose can be administered between 1 month and 2.5 months after the first dose and the third dose between 5 and 12 months after the first dose.

The need for a booster dose has not been established (see section 5.1).

It is recommended that subjects who receive a first dose of Cervarix complete the 3-dose vaccination course with Cervarix (see section 4.4).

Paediatric population

Cervarix is not recommended for use in girls below 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).

4.3 Contraindications

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

Administration of Cervarix should be postponed in subjects suffering from an acute severe febrile illness. However, the presence of a minor infection, such as a cold, is not a contraindication for immunisation.

4.4 Special warnings and precautions for use

The decision to vaccinate an individual woman should take into account her risk for previous HPV exposure and her potential benefit from vaccination.

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.

Cervarix 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.

Cervarix is for prophylactic use only and has no effect on active HPV infections or established clinical disease. Cervarix 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.

There are no data on the use of Cervarix in subjects with impaired immune responsiveness such as HIV infected patients or 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 $\geq 10\text{mIU/ml}$ was 98.3% for concomitant vaccination and 100% for Twinrix given alone. Similar results were observed when Cervarix was given concomitantly with Engerix B with 97.9% of subjects reaching anti-HBs $\geq 10\text{mIU/ml}$ compared to 100% for Engerix B given alone.

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

Use with hormonal contraceptive

In clinical efficacy studies, approximately 60% of women who received Cervarix used hormonal contraceptives. There is no evidence that the use of hormonal contraceptives has an impact on the efficacy of Cervarix.

Use with systemic immunosuppressive medicinal products

As with other vaccines it may be expected that, in patients receiving immunosuppressive treatment, an adequate response may not be elicited.

4.6 Fertility, pregnancy and lactation

Pregnancy

Specific studies of the vaccine in pregnant women were not conducted. 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).

These data are insufficient to recommend use of Cervarix during pregnancy.
Vaccination should, therefore, be postponed until after 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.

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 subjects whilst 13,811 subjects received control. These subjects were followed for serious adverse events over the entire study period. In a pre-defined subset of subjects (Cervarix = 8,130 versus control = 5,786), adverse events were followed for 30 days after each injection.

The most common adverse reaction observed after vaccine administration was injection site pain which occurred after 78% of all doses. The majority of these reactions were of mild to moderate severity and were not long lasting.

List of adverse reactions

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

Frequencies are reported as:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

- *Clinical trial data*

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 ($\geq 38^{\circ}\text{C}$)

Uncommon: other injection site reactions such as induration, local paraesthesia

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

- *Post marketing data*

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

Blood and lymphatic system disorders

Lymphadenopathy

Immune system disorders

Allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema

Nervous system disorders

Syncope or vasovagal responses to injection, sometimes accompanied by tonic-clonic movements (see section 4.4)

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. Other oncogenic HPV types can also cause cervical cancer (approximately 30%). HPV 45, -31 and -33 are the 3 most common non-vaccine HPV types identified in squamous cervical carcinoma (12.1%) and adenocarcinoma (8.5%).

The term “pre-malignant cervical lesions” in section 4.1 corresponds to high-grade Cervical Intraepithelial Neoplasia (CIN2/3).

Clinical studies

Clinical efficacy in women aged 15 to 25 years

The efficacy of Cervarix was assessed in two controlled, double-blind, randomised Phase II and III clinical trials that included a total of 19,778 women aged 15 to 25 years.

The phase II trial (study 001/007) enrolled only women who:

- Were tested negative for oncogenic HPV DNA of types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
- Were seronegative for HPV-16 and HPV-18 and
- 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.

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).

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 5777 women aged 26 years and older. The study was conducted in North America, Latin America, Asia Pacific and Europe, and allowed women with previous history of HPV disease/infection to be enrolled. An interim analysis was performed when all subjects had completed the month 48 study visit.

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

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

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

HPV-16/18 endpoint	ATP ⁽¹⁾			TVC ⁽²⁾		
	Cervarix	Control	% Efficacy (97.7% CI)	Cervarix	Control	% Efficacy (97.7% CI)
	n/N	n/N		n/N	n/N	
6M PI	6/1859	34/1822	82.9% (53.8; 95.1)	71/2767	132/2776	47% (25.4; 62.7)

N= number of subject in each group
n= number of subjects reporting at least one event in each group
6M PI = 6-month persistent infection
CI = Confidence Interval
⁽¹⁾ 3 doses of vaccine, DNA negative and seronegative at month 0 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 at month 0. Includes 15% of subjects with previous history of HPV disease/infection

Vaccine efficacy against 6-month persistent infection was 79.1% (97.7% CI [27.6; 95.9]) for HPV-31 and 76.9% (97.7% CI [18.5; 95.6]) for HPV-45 in the ATP cohort (3 doses of vaccine, DNA negative at months 0 and 6 for the relevant HPV type).

Vaccine efficacy against 6-month persistent infection was 23.2% (97.7% CI [-23.3; 52.5]) for HPV-31 and 67.7% (97.7% CI [35.9; 84.9]) for HPV-45 in the TVC.

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.

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. Nevertheless, all subjects remained seropositive for both

types throughout the follow-up phase (up to month 18) maintaining antibody levels at an order of magnitude above those encountered after natural infection.

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, 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 performed in girls and adolescents aged 10 to 14 years, all subjects seroconverted to both HPV types 16 and 18 after the third dose (at month 7) with GMTs at least 2-fold higher as compared to women aged 15 to 25 years. On the basis of these immunogenicity data, the efficacy of Cervarix is inferred from 9 to 14 years of age.

Immunogenicity in women aged 26 years and older

In the Phase III study (HPV-015) in women 26 years and older, at the 48-month time point, i.e. 42 months after completion of the full vaccination course, 100% and 99.4% of initially seronegative women 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 48.

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 ($\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$)
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, for the monodose containers, the 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.

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:

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

¹Human Papillomavirus = HPV

²adjuvanted by AS04 containing:

3-*O*-desacyl-4'-monophosphoryl lipid A (MPL)³ 50 micrograms

³adsorbed on aluminium hydroxide, hydrated (Al(OH)₃) 0.5 milligrams Al³⁺ in total

⁴L1 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 cervical lesions and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types. See sections 4.4 and 5.1 for important information on the data that support this indication.

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

4.2 Posology and method of administration

Posology

The recommended vaccination consists of 3 separate 0.5 ml doses administered according to the schedule: 0, 1, 6 months.

If flexibility in the vaccination schedule is necessary, the second dose can be administered between 1 month and 2.5 months after the first dose and the third dose between 5 and 12 months after the first dose.

The need for a booster dose has not been established (see section 5.1).

It is recommended that subjects who receive a first dose of Cervarix complete the 3-dose vaccination course with Cervarix (see section 4.4).

Paediatric population

Cervarix is not recommended for use in girls below 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).

4.3 Contraindications

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

Administration of Cervarix should be postponed in subjects suffering from an acute severe febrile illness. However, the presence of a minor infection, such as a cold, is not a contraindication for immunisation.

4.4 Special warnings and precautions for use

The decision to vaccinate an individual woman should take into account her risk for previous HPV exposure and her potential benefit from vaccination.

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.

Cervarix 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.

Cervarix is for prophylactic use only and has no effect on active HPV infections or established clinical disease. Cervarix 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.

There are no data on the use of Cervarix in subjects with impaired immune responsiveness such as HIV infected patients or 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 ≥ 10 mIU/ml was 98.3% for concomitant vaccination and 100% for Twinrix given alone. Similar results were observed when Cervarix was given concomitantly with Engerix B with 97.9% of subjects reaching anti-HBs ≥ 10 mIU/ml compared to 100% for Engerix B given alone.

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

Use with hormonal contraceptive

In clinical efficacy studies, approximately 60% of women who received Cervarix used hormonal contraceptives. There is no evidence that the use of hormonal contraceptives has an impact on the efficacy of Cervarix.

Use with systemic immunosuppressive medicinal products

As with other vaccines it may be expected that, in patients receiving immunosuppressive treatment, an adequate response may not be elicited.

4.6 Fertility, pregnancy and lactation

Pregnancy

Specific studies of the vaccine in pregnant women were not conducted. 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).

These data are insufficient to recommend use of Cervarix during pregnancy.
Vaccination should, therefore, be postponed until after 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.

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 subjects whilst 13,811 subjects received control. These subjects were followed for serious adverse events over the entire study period. In a pre-defined subset of subjects (Cervarix = 8,130 versus control = 5,786), adverse events were followed for 30 days after each injection.

The most common adverse reaction observed after vaccine administration was injection site pain which occurred after 78% of all doses. The majority of these reactions were of mild to moderate severity and were not long lasting.

List of adverse reactions

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

Frequencies are reported as:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

- *Clinical trial data*

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 ($\geq 38^{\circ}\text{C}$)

Uncommon: other injection site reactions such as induration, local paraesthesia

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

- *Post marketing data*

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

Blood and lymphatic system disorders

Lymphadenopathy

Immune system disorders

Allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema

Nervous system disorders

Syncope or vasovagal responses to injection, sometimes accompanied by tonic-clonic movements (see section 4.4)

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. Other oncogenic HPV types can also cause cervical cancer (approximately 30%). HPV 45, -31 and -33 are the 3 most common non-vaccine HPV types identified in squamous cervical carcinoma (12.1%) and adenocarcinoma (8.5%).

The term “pre-malignant cervical lesions” in section 4.1 corresponds to high-grade Cervical Intraepithelial Neoplasia (CIN2/3).

Clinical studies

Clinical efficacy in women aged 15 to 25 years

The efficacy of Cervarix was assessed in two controlled, double-blind, randomised Phase II and III clinical trials that included a total of 19,778 women aged 15 to 25 years.

The phase II trial (study 001/007) enrolled only women who:

- Were tested negative for oncogenic HPV DNA of types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
- Were seronegative for HPV-16 and HPV-18 and
- 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.

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).

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 5777 women aged 26 years and older. The study was conducted in North America, Latin America, Asia Pacific and Europe, and allowed women with previous history of HPV disease/infection to be enrolled. An interim analysis was performed when all subjects had completed the month 48 study visit.

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

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

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

HPV-16/18 endpoint	ATP ⁽¹⁾			TVC ⁽²⁾		
	Cervarix	Control	% Efficacy (97.7% CI)	Cervarix	Control	% Efficacy (97.7% CI)
	n/N	n/N		n/N	n/N	
6M PI	6/1859	34/1822	82.9% (53.8; 95.1)	71/2767	132/2776	47% (25.4; 62.7)

N= number of subject in each group
n= number of subjects reporting at least one event in each group
6M PI = 6-month persistent infection
CI = Confidence Interval
⁽¹⁾ 3 doses of vaccine, DNA negative and seronegative at month 0 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 at month 0. Includes 15% of subjects with previous history of HPV disease/infection

Vaccine efficacy against 6-month persistent infection was 79.1% (97.7% CI [27.6; 95.9]) for HPV-31 and 76.9% (97.7% CI [18.5; 95.6]) for HPV-45 in the ATP cohort (3 doses of vaccine, DNA negative at months 0 and 6 for the relevant HPV type).

Vaccine efficacy against 6-month persistent infection was 23.2% (97.7% CI [-23.3; 52.5]) for HPV-31 and 67.7% (97.7% CI [35.9; 84.9]) for HPV-45 in the TVC.

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.

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. Nevertheless, all subjects remained seropositive for both types throughout the follow-up phase (up to month 18) maintaining antibody levels at an order of magnitude above those encountered after natural infection.

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, 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 performed in girls and adolescents aged 10 to 14 years, all subjects seroconverted to both HPV types 16 and 18 after the third dose (at month 7) with GMTs at least 2-fold higher as compared to women aged 15 to 25 years. On the basis of these immunogenicity data, the efficacy of Cervarix is inferred from 9 to 14 years of age.

Immunogenicity in women aged 26 years and older

In the Phase III study (HPV-015) in women 26 years and older, at the 48-month time point, i.e. 42 months after completion of the full vaccination course, 100% and 99.4% of initially seronegative women 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 48.

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 ($\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$)
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, for the multidose containers, the 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.

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:

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

¹Human Papillomavirus = HPV

²adjuvanted by AS04 containing:

3-*O*-desacyl-4'-monophosphoryl lipid A (MPL)³ 50 micrograms

³adsorbed on aluminium hydroxide, hydrated (Al(OH)₃) 0.5 milligrams Al³⁺ in total

⁴L1 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 cervical lesions and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types. See sections 4.4 and 5.1 for important information on the data that support this indication.

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

4.2 Posology and method of administration

Posology

The recommended vaccination consists of 3 separate 0.5 ml doses administered according to the schedule: 0, 1, 6 months.

If flexibility in the vaccination schedule is necessary, the second dose can be administered between 1 month and 2.5 months after the first dose and the third dose between 5 and 12 months after the first dose.

The need for a booster dose has not been established (see section 5.1).

It is recommended that subjects who receive a first dose of Cervarix complete the 3-dose vaccination course with Cervarix (see section 4.4).

Paediatric population

Cervarix is not recommended for use in girls below 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).

4.3 Contraindications

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

Administration of Cervarix should be postponed in subjects suffering from an acute severe febrile illness. However, the presence of a minor infection, such as a cold, is not a contraindication for immunisation.

4.4 Special warnings and precautions for use

The decision to vaccinate an individual woman should take into account her risk for previous HPV exposure and her potential benefit from vaccination.

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.

Cervarix 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.

Cervarix is for prophylactic use only and has no effect on active HPV infections or established clinical disease. Cervarix 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.

There are no data on the use of Cervarix in subjects with impaired immune responsiveness such as HIV infected patients or 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 $\geq 10\text{mIU/ml}$ was 98.3% for concomitant vaccination and 100% for Twinrix given alone. Similar results were observed when Cervarix was given concomitantly with Engerix B with 97.9% of subjects reaching anti-HBs $\geq 10\text{mIU/ml}$ compared to 100% for Engerix B given alone.

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

Use with hormonal contraceptive

In clinical efficacy studies, approximately 60% of women who received Cervarix used hormonal contraceptives. There is no evidence that the use of hormonal contraceptives has an impact on the efficacy of Cervarix.

Use with systemic immunosuppressive medicinal products

As with other vaccines it may be expected that, in patients receiving immunosuppressive treatment, an adequate response may not be elicited.

4.6 Fertility, pregnancy and lactation

Pregnancy

Specific studies of the vaccine in pregnant women were not conducted. 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).

These data are insufficient to recommend use of Cervarix during pregnancy.
Vaccination should, therefore, be postponed until after 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.

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 subjects whilst 13,811 subjects received control. These subjects were followed for serious adverse events over the entire study period. In a pre-defined subset of subjects (Cervarix = 8,130 versus control = 5,786), adverse events were followed for 30 days after each injection.

The most common adverse reaction observed after vaccine administration was injection site pain which occurred after 78% of all doses. The majority of these reactions were of mild to moderate severity and were not long lasting.

List of adverse reactions

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

Frequencies are reported as:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

- *Clinical trial data*

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 ($\geq 38^{\circ}\text{C}$)

Uncommon: other injection site reactions such as induration, local paraesthesia

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

- *Post marketing data*

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

Blood and lymphatic system disorders

Lymphadenopathy

Immune system disorders

Allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema

Nervous system disorders

Syncope or vasovagal responses to injection, sometimes accompanied by tonic-clonic movements (see section 4.4)

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. Other oncogenic HPV types can also cause cervical cancer (approximately 30%). HPV 45, -31 and -33 are the 3 most common non-vaccine HPV types identified in squamous cervical carcinoma (12.1%) and adenocarcinoma (8.5%).

The term “pre-malignant cervical lesions” in section 4.1 corresponds to high-grade Cervical Intraepithelial Neoplasia (CIN2/3).

Clinical studies

Clinical efficacy in women aged 15 to 25 years

The efficacy of Cervarix was assessed in two controlled, double-blind, randomised Phase II and III clinical trials that included a total of 19,778 women aged 15 to 25 years.

The phase II trial (study 001/007) enrolled only women who:

- Were tested negative for oncogenic HPV DNA of types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
- Were seronegative for HPV-16 and HPV-18 and
- 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.

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).

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	504/8863	1227/8870	60.9% (56.6;64.8)

infection			
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

the lesion

	End of study analysis ⁽³⁾				% Efficacy (95% CI)
	Cervarix		Control		
	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

HPV type	ATP ⁽¹⁾					
	6-month persistent infection			CIN2+		
	Cervarix	Control	% Efficacy	Cervarix	Control	% Efficacy

	n	n	(95% CI)	n	n	(95% CI)
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 5777 women aged 26 years and older. The study was conducted in North America, Latin America, Asia Pacific and Europe, and allowed women with previous history of HPV disease/infection to be enrolled. An interim analysis was performed when all subjects had completed the month 48 study visit.

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

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

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

HPV-16/18 endpoint	ATP ⁽¹⁾			TVC ⁽²⁾		
	Cervarix	Control	% Efficacy (97.7% CI)	Cervarix	Control	% Efficacy (97.7% CI)
	n/N	n/N		n/N	n/N	
6M PI	6/1859	34/1822	82.9% (53.8; 95.1)	71/2767	132/2776	47% (25.4; 62.7)
N= number of subject in each group n= number of subjects reporting at least one event in each group 6M PI = 6-month persistent infection CI = Confidence Interval ⁽¹⁾ 3 doses of vaccine, DNA negative and seronegative at month 0 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 at month 0. Includes 15% of subjects with previous history of HPV disease/infection

Vaccine efficacy against 6-month persistent infection was 79.1% (97.7% CI [27.6; 95.9]) for HPV-31 and 76.9% (97.7% CI [18.5; 95.6]) for HPV-45 in the ATP cohort (3 doses of vaccine, DNA negative at months 0 and 6 for the relevant HPV type).

Vaccine efficacy against 6-month persistent infection was 23.2% (97.7% CI [-23.3; 52.5]) for HPV-31 and 67.7% (97.7% CI [35.9; 84.9]) for HPV-45 in the TVC.

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.

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. Nevertheless, all subjects remained seropositive for both types throughout the follow-up phase (up to month 18) maintaining antibody levels at an order of magnitude above those encountered after natural infection.

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, 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 performed in girls and adolescents aged 10 to 14 years, all subjects seroconverted to both HPV types 16 and 18 after the third dose (at month 7) with GMTs at least 2-fold higher as compared to women aged 15 to 25 years. On the basis of these immunogenicity data, the efficacy of Cervarix is inferred from 9 to 14 years of age.

Immunogenicity in women aged 26 years and older

In the Phase III study (HPV-015) in women 26 years and older, at the 48-month time point, i.e. 42 months after completion of the full vaccination course, 100% and 99.4% of initially seronegative women 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 48.

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 ($\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$)
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, for the monodose containers, the 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.

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.

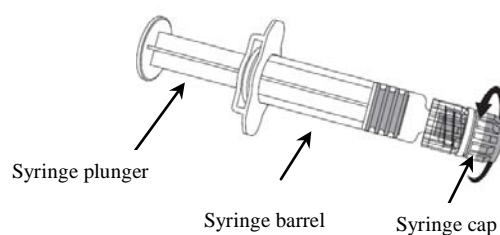
The content of the syringe should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to administration.

In the event of either being observed, discard the vaccine.

The vaccine should be well shaken before use.

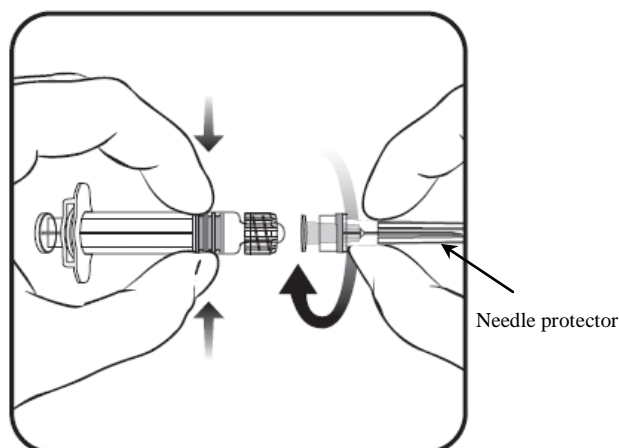
Instructions for administration of the vaccine presented in pre-filled syringe

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.

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:

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**

**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**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
 - Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
 - At the request of the European Medicines Agency.
- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND
EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable

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

²adsorbed on aluminium hydroxide, hydrated (Al(OH)₃) 0.5 milligrams Al³⁺ 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

Medicinal product subject to medical prescription

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- <i>O</i> -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

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

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- <i>O</i> -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

Medicinal product subject to medical prescription

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.

What is in this leaflet:

1. What Cervarix is and what it is used for
2. What you need to know before you receive Cervarix
3. How Cervarix is given
4. Possible side effects
5. How to store Cervarix
6. Contents of the pack and other information

1. What Cervarix is and what it is used for

Cervarix is a vaccine intended to protect females 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),
- precancerous cervical lesions (changes in cells of the cervix 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 cancer cases. Other HPV types can also cause cervical cancer. 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.

- 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.

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.

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

There are insufficient data concerning the use of Cervarix during pregnancy. If pregnancy occurs during the course of vaccination your doctor should be consulted. It is recommended to postpone 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.

3. How Cervarix is given

How much is given

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

Cervarix is intended for females from 9 years of age onwards. A total of three injections will be administered by your doctor or nurse according to the following schedule:

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 3-dose 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 of three injections, 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 ($\geq 38^{\circ}\text{C}$)
- ◆ 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.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

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

¹Human Papillomavirus = HPV

²adjuvanted by AS04 containing:

3- <i>O</i> -desacyl-4'-monophosphoryl lipid A (MPL) ³	50 micrograms
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³ adsorbed on aluminium hydroxide, hydrated (Al(OH) ₃)	0.5 milligrams Al ³⁺ in total
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⁴L1 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 (NaH₂PO₄·2 H₂O) 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 vials for 1 dose (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.
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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 (EMA) 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, for the monodose containers, the 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. 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.

What is in this leaflet:

1. What Cervarix is and what it is used for
2. What you need to know before you receive Cervarix
3. How Cervarix is given
4. Possible side effects
5. How to store Cervarix
6. Contents of the pack and other information

1. What Cervarix is and what it is used for

Cervarix is a vaccine intended to protect females 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),
- precancerous cervical lesions (changes in cells of the cervix 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 cancer cases. Other HPV types can also cause cervical cancer. 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.

- 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.

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.

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

There are insufficient data concerning the use of Cervarix during pregnancy. If pregnancy occurs during the course of vaccination your doctor should be consulted. It is recommended to postpone 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.

3. How Cervarix is given

How much is given

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

Cervarix is intended for females from 9 years of age onwards. A total of three injections will be administered by your doctor or nurse according to the following schedule:

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 3-dose 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 of three injections, 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 ($\geq 38^{\circ}\text{C}$)
- ◆ 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.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

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

¹Human Papillomavirus = HPV

²adjuvanted by AS04 containing:

3- <i>O</i> -desacyl-4'-monophosphoryl lipid A (MPL) ³	50 micrograms
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³ adsorbed on aluminium hydroxide, hydrated (Al(OH) ₃)	0.5 milligrams Al ³⁺ in total
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⁴L1 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 (NaH₂PO₄·2 H₂O) 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 vials for 2 doses (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
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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 (EMA) web site: <http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

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.

What is in this leaflet:

1. What Cervarix is and what it is used for
2. What you need to know before you receive Cervarix
3. How Cervarix is given
4. Possible side effects
5. How to store Cervarix
6. Contents of the pack and other information

1. What Cervarix is and what it is used for

Cervarix is a vaccine intended to protect females 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),
- precancerous cervical lesions (changes in cells of the cervix 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 cancer cases. Other HPV types can also cause cervical cancer. 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.

- 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.

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.

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

There are insufficient data concerning the use of Cervarix during pregnancy. If pregnancy occurs during the course of vaccination your doctor should be consulted. It is recommended to postpone 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.

3. How Cervarix is given

How much is given

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

Cervarix is intended for females from 9 years of age onwards. A total of three injections will be administered by your doctor or nurse according to the following schedule:

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 3-dose 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 of three injections, 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 ($\geq 38^{\circ}\text{C}$)
- ◆ 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.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

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

¹Human Papillomavirus = HPV

²adjuvanted by AS04 containing:

3- <i>O</i> -desacyl-4'-monophosphoryl lipid A (MPL) ³	50 micrograms
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³ adsorbed on aluminium hydroxide, hydrated (Al(OH) ₃)	0.5 milligrams Al ³⁺ in total
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⁴L1 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 (NaH₂PO₄·2 H₂O) 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 with or without needles in packs of 1 and 10.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency (EMA) 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, for the monodose containers, the 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.

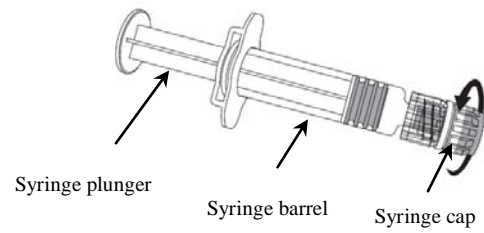
A fine white deposit with a clear colourless supernatant may be observed upon storage of the syringe. This does not constitute a sign of deterioration.

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.

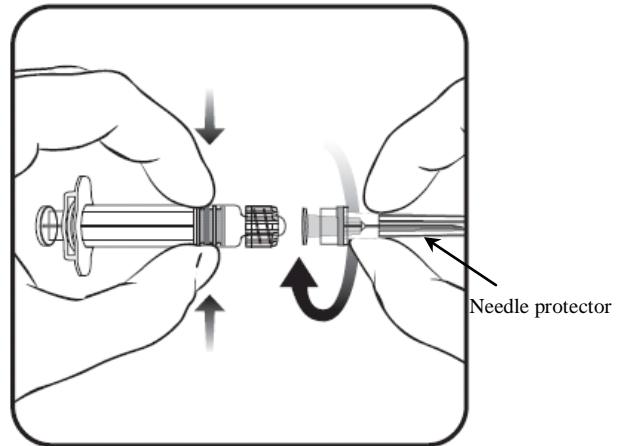
The vaccine should be well shaken before use.

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.