

**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 <sup>1</sup> type 16 L1 protein <sup>2,3,4</sup>	20 micrograms
Human Papillomavirus <sup>1</sup> type 18 L1 protein <sup>2,3,4</sup>	20 micrograms

<sup>1</sup>Human Papillomavirus = HPV

<sup>2</sup>adjuvanted by AS04 containing:

3-*O*-desacyl-4'-monophosphoryl lipid A (MPL)<sup>3</sup> 50 micrograms

<sup>3</sup>adsorbed on aluminium hydroxide, hydrated (Al(OH)<sub>3</sub>) 0.5 milligrams Al<sup>3+</sup> in total

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

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Suspension for injection.

Turbid white suspension. Upon storage, a fine white deposit with a clear colourless supernatant may be observed.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Cervarix is a vaccine for the prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types. See sections 4.4 and 5.1 for important information on the data that support this indication.

The indication is based on the demonstration of efficacy in women aged 15-25 years following vaccination with Cervarix and on the immunogenicity of the vaccine in girls and women aged 10-25 years.

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

### 4.2 Posology and method of administration

#### Posology

The recommended vaccination schedule is 0, 1, 6 months.

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

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

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

#### *Paediatric population*

Cervarix is not recommended for use in girls below 10 years of age due to lack of data on safety and immunogenicity in this age-group.

#### Method of administration

Cervarix is for intramuscular injection in the deltoid region (see also sections 4.4 and 4.5).

### **4.3 Contraindications**

Hypersensitivity to the active substances or to any of the excipients.

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

### **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 event 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  $\geq 10$ 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  $\geq 10$ 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**

Specific studies of the vaccine in pregnant women were not conducted. However, during the clinical development program, a total of 3,993 pregnancies were reported including 2,009 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.

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.

#### **4.7 Effects on the 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**

##### *Clinical trials*

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.

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  $< 1/100$ )

##### 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 surveillance*

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: 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*

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+ (CIN2/3 or AIS) associated with HPV-16 and/or HPV-18 (HPV-16/18). Cervical Intraepithelial Neoplasia (CIN) grade 2 and 3 (CIN2/3) and cervical adenocarcinoma in situ (AIS) were used in the clinical trials as surrogate markers for cervical cancer. The secondary endpoints included 6- and 12-month persistent infection.

Persistent infection that lasts for at least 6 months has also been shown to be a relevant surrogate marker for cervical cancer.

#### 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.

#### 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).

The mean follow-up for women included in study HPV-008 was approximately 39 months post dose 1 in TVC and 35 months post dose 3 in the ATP cohort.

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

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

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

N = number of subjects included in each group  
n = number of cases  
<sup>(1)</sup> 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)  
<sup>(2)</sup> including 3 cases of CIN2/3 or AIS and 2 cases of CIN3 or AIS in which another oncogenic HPV type was identified in the lesion, concomitantly with HPV-16 or HPV-18. These cases are excluded in the HPV type assignment analysis (see under Table).

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 were 1 CIN2/3 or AIS case in the vaccine group versus 53 cases in the control group (Efficacy 98.1% (96.1% CI: 88.4; 100)) and 0 CIN3 or AIS cases in the vaccine group versus 8 cases in the control group (Efficacy 100% (96.1% CI: 36.4; 100)).

In addition, statistically significant vaccine efficacy against CIN2/3 or AIS associated with HPV-16 and HPV-18 individually was demonstrated.

Vaccine efficacy against CIN1 associated with HPV 16/18 observed in the ATP cohort was 94.1% (96.1% CI: 83.4;98.5). Vaccine efficacy against CIN1/2/3 or AIS associated with HPV 16/18 observed in the ATP cohort was 91.7% (96.1% CI: 82.4;96.7).

Vaccine efficacy against virological endpoints (6-month and 12-month persistent infection) associated with HPV-16/18 observed in the ATP cohort is presented in Table 2.

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

HPV-16/18 endpoint	ATP <sup>(1)</sup>		
	Cervarix	Control	% Efficacy (96.1% CI)
	n/N	n/N	
6-month persistent infection	29/7177	488/7122	94.3% (91.5;96.3)
12-month persistent infection	20/7035	227/6984	91.4% (86.1;95.0)

N = number of subjects included in each group  
n = number of cases  
<sup>(1)</sup> 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)

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 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 <sup>(1)</sup>		
	Cervarix (N = 8667)	Control (N = 8682)	% Efficacy (96.1% CI)
	n	n	
CIN2/3 or AIS	82	174	52.8% (37.5;64.7)
CIN3 or AIS	43	65	33.6% (<0;56.9)

N = number of subjects included in each group  
n = number of cases  
<sup>(1)</sup> 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

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

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

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

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

Overall impact of the vaccine on cervical HPV disease burden

In study HPV-008, the incidence of high grade cervical lesions was compared between the placebo and vaccine group irrespective of the HPV DNA type in the lesion. In the TVC and TVC-naïve cohorts, the vaccine's efficacy was demonstrated against high-grade cervical lesions (Table 5). The TVC-naïve 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**

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

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.

Cervarix reduced definitive cervical therapy procedures (includes loop electrosurgical excision procedure [LEEP], cold-knife Cone, and laser procedures) by 68.8% (96.1% CI: 50.0;81.2) in TVC naïve and by 24.7% (96.1% CI: 7.4;38.9) in TVC.

### Cross-protective efficacy

The cross-protective efficacy of Cervarix against histopathological and virological endpoints (persistent infection) has been evaluated in study HPV-008 for 12 non-vaccine oncogenic HPV types. The study was not powered to assess efficacy against disease caused by individual HPV types. The analysis against the primary endpoint was confounded by multiple co-infections in the CIN2+ lesions. Unlike histopathological endpoints, virological endpoints are less confounded by multiple infections. Only HPV-31 showed consistent cross-protection for all endpoints (6m and 12m persistent infection, CIN2/3 or AIS) and all study cohorts. Vaccine efficacy against 6 months persistent infection has also been shown for HPV-33 and HPV-45 in all study cohorts.

Vaccine efficacy against 6-month persistent infection and CIN2/3 or AIS associated with individual non-vaccine oncogenic HPV types is presented in Table 6 (ATP cohort).

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

ATP <sup>(1)</sup>						
HPV type	6-month persistent infection			CIN2/3 or AIS		
	Cervarix	Control	% Efficacy (96.1% CI)	Cervarix	Control	% Efficacy (96.1% CI)
	n	n		n	n	
<b>HPV-16 related types (A9 species)</b>						
HPV-31	45	199	77.5% (68.3;84.4)	2	25	92.0% (66.0;99.2)
HPV-33	55	100	45.1% (21.7;61.9)	12	25	51.9% (<0;78.9)
HPV-35	55	43	-28.4% (<0;17.2)	1	6	83.3% (<0;99.7)
HPV-52	293	315	7.4% (<0;22.0)	12	14	14.3% (<0;65.4)
HPV-58	111	101	-10.3% (<0;17.7)	6	17	64.5% (1.5;89.2)
<b>HPV-18 related types (A7 species)</b>						
HPV-39	147	149	1.0% (<0;22.7)	3	10	69.8% (<0;95.2)
HPV-45	19	79	76.1% (59.1;86.7)	0	4	100% (<0;100)
HPV-59	56	59	4.8% (<0;36.4)	1	4	74.9% (<0;99.6)
HPV-68	138	134	-3.1% (<0;20.3)	5	11	54.4% (<0;88.4)
<b>Other types</b>						
HPV-51	304	354	14.5% (<0;27.4)	10	27	62.9% (18.0;84.7)
HPV-56	182	174	-5.0% (<0;16.1)	4	10	59.9% (<0;91.5)
HPV-66	168	178	5.7% (<0;24.9)	4	10	60.0% (<0;91.6)
n= number of cases						
<sup>(1)</sup> ATP: includes women who received 3 doses of vaccine, were DNA negative and seronegative at month						

0 and DNA negative at month 6 to the relevant HPV type.

The limits of the confidence interval 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.

### *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 5,303 female subjects from 10 to 55 years of age.

In clinical trials, more than 99% of initially seronegative subjects had seroconverted to both HPV types 16 and 18 one month after the third dose. Vaccine-induced IgG Geometric Mean Titres (GMT) were well above titres observed in women previously infected but who cleared HPV infection (natural infection). Initially seropositive and seronegative subjects reached similar titres after vaccination.

#### *Persistence of Immune Response to Cervarix*

Study 001/007, which included women from 15 to 25 years of age at the time of vaccination, evaluated the immune response against HPV-16 and HPV-18 up to 76 months after administration of the first vaccine dose. In study 023 (a subset of study 001/007), the immune response continued to be evaluated up to 101 months. 87 subjects in the vaccine group had immunogenicity data at the [M95-M101] interval after the first vaccine dose with a median follow-up of 7.9 years. Of these subjects, 100% (95% CI: 95.8;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 [M95-M101] interval with ELISA GMTs for both HPV-16 and HPV-18 at least still 10-fold higher than the ELISA GMTs observed in women who cleared a natural HPV infection.

In study 008, immunogenicity up to month 36 was similar to the response observed in study 001. A similar kinetic profile was observed with the neutralising antibodies.

In another clinical trial (study 014) performed in women aged 15 to 55 years, all subjects seroconverted to both HPV types 16 and 18 after the 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 two clinical trials performed in girls and adolescents aged 10 to 14 years, all subjects seroconverted to both HPV types 16 and 18 after the third dose (at month 7) with GMTs at least 2-fold higher as compared to women aged 15 to 25 years. On the basis of these immunogenicity data, the efficacy of Cervarix is inferred from 10 to 14 years of age.

## **5.2 Pharmacokinetic properties**

Evaluation of pharmacokinetic properties is not required for vaccines.

## **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, stability data generated indicate that Cervarix presented in monodose containers remains stable and can be administered in case it has been stored outside the refrigerator up to three days at temperatures between 8°C and 25°C or up to one 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) in pack sizes of 1, 10 and 100.

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 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.

## **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 <sup>1</sup> type 16 L1 protein <sup>2,3,4</sup>	20 micrograms
Human Papillomavirus <sup>1</sup> type 18 L1 protein <sup>2,3,4</sup>	20 micrograms

<sup>1</sup>Human Papillomavirus = HPV

<sup>2</sup>adjuvanted by AS04 containing:

3-*O*-desacyl-4'-monophosphoryl lipid A (MPL)<sup>3</sup> 50 micrograms

<sup>3</sup>adsorbed on aluminium hydroxide, hydrated (Al(OH)<sub>3</sub>) 0.5 milligrams Al<sup>3+</sup> in total

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

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

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Suspension for injection.

Turbid white suspension. Upon storage, a fine white deposit with a clear colourless supernatant may be observed.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Cervarix is a vaccine for the prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types. See sections 4.4 and 5.1 for important information on the data that support this indication.

The indication is based on the demonstration of efficacy in women aged 15-25 years following vaccination with Cervarix and on the immunogenicity of the vaccine in girls and women aged 10-25 years.

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

### 4.2 Posology and method of administration

#### Posology

The recommended vaccination schedule is 0, 1, 6 months.

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

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

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

#### *Paediatric population*

Cervarix is not recommended for use in girls below 10 years of age due to lack of data on safety and immunogenicity in this age-group.

#### Method of administration

Cervarix is for intramuscular injection in the deltoid region (see also sections 4.4 and 4.5).

### **4.3 Contraindications**

Hypersensitivity to the active substances or to any of the excipients.

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

### **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 event 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  $\geq 10$  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  $\geq 10$  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**

Specific studies of the vaccine in pregnant women were not conducted. However, during the clinical development program, a total of 3,993 pregnancies were reported including 2,009 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.

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.

#### **4.7 Effects on the 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**

##### *Clinical trials*

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.

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  $< 1/100$ )

##### 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 surveillance*

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: 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*

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+ (CIN2/3 or AIS) associated with HPV-16 and/or HPV-18 (HPV-16/18). Cervical Intraepithelial Neoplasia (CIN) grade 2 and 3 (CIN2/3) and cervical adenocarcinoma in situ (AIS) were used in the clinical trials as surrogate markers for cervical cancer. The secondary endpoints included 6- and 12-month persistent infection.

Persistent infection that lasts for at least 6 months has also been shown to be a relevant surrogate marker for cervical cancer.

#### 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.

#### 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).

The mean follow-up for women included in study HPV-008 was approximately 39 months post dose 1 in TVC and 35 months post dose 3 in the ATP cohort.

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

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

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

N = number of subjects included in each group  
n = number of cases  
<sup>(1)</sup> 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)  
<sup>(2)</sup> including 3 cases of CIN2/3 or AIS and 2 cases of CIN3 or AIS in which another oncogenic HPV type was identified in the lesion, concomitantly with HPV-16 or HPV-18. These cases are excluded in the HPV type assignment analysis (see under Table).

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 were 1 CIN2/3 or AIS case in the vaccine group versus 53 cases in the control group (Efficacy 98.1% (96.1% CI: 88.4; 100)) and 0 CIN3 or AIS cases in the vaccine group versus 8 cases in the control group (Efficacy 100% (96.1% CI: 36.4; 100)).

In addition, statistically significant vaccine efficacy against CIN2/3 or AIS associated with HPV-16 and HPV-18 individually was demonstrated.

Vaccine efficacy against CIN1 associated with HPV 16/18 observed in the ATP cohort was 94.1% (96.1% CI: 83.4;98.5). Vaccine efficacy against CIN1/2/3 or AIS associated with HPV 16/18 observed in the ATP cohort was 91.7% (96.1% CI: 82.4;96.7).

Vaccine efficacy against virological endpoints (6-month and 12-month persistent infection) associated with HPV-16/18 observed in the ATP cohort is presented in Table 2.

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

HPV-16/18 endpoint	ATP <sup>(1)</sup>		
	Cervarix	Control	% Efficacy (96.1% CI)
	n/N	n/N	
6-month persistent infection	29/7177	488/7122	94.3% (91.5;96.3)
12-month persistent infection	20/7035	227/6984	91.4% (86.1;95.0)

N = number of subjects included in each group  
n = number of cases  
<sup>(1)</sup> 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)

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 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 <sup>(1)</sup>		
	Cervarix (N = 8667)	Control (N = 8682)	% Efficacy (96.1% CI)
	n	n	
CIN2/3 or AIS	82	174	52.8% (37.5;64.7)
CIN3 or AIS	43	65	33.6% (<0;56.9)

N = number of subjects included in each group  
n = number of cases  
<sup>(1)</sup> 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

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

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

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

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

Overall impact of the vaccine on cervical HPV disease burden

In study HPV-008, the incidence of high grade cervical lesions was compared between the placebo and vaccine group irrespective of the HPV DNA type in the lesion. In the TVC and TVC-naïve cohorts, the vaccine's efficacy was demonstrated against high-grade cervical lesions (Table 5). The TVC-naïve 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**

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

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.

Cervarix reduced definitive cervical therapy procedures (includes loop electrosurgical excision procedure [LEEP], cold-knife Cone, and laser procedures) by 68.8% (96.1% CI: 50.0;81.2) in TVC naïve and by 24.7% (96.1% CI: 7.4;38.9) in TVC.

### Cross-protective efficacy

The cross-protective efficacy of Cervarix against histopathological and virological endpoints (persistent infection) has been evaluated in study HPV-008 for 12 non-vaccine oncogenic HPV types. The study was not powered to assess efficacy against disease caused by individual HPV types. The analysis against the primary endpoint was confounded by multiple co-infections in the CIN2+ lesions. Unlike histopathological endpoints, virological endpoints are less confounded by multiple infections. Only HPV-31 showed consistent cross-protection for all endpoints (6m and 12m persistent infection, CIN2/3 or AIS) and all study cohorts. Vaccine efficacy against 6 months persistent infection has also been shown for HPV-33 and HPV-45 in all study cohorts.

Vaccine efficacy against 6-month persistent infection and CIN2/3 or AIS associated with individual non-vaccine oncogenic HPV types is presented in Table 6 (ATP cohort).

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

ATP <sup>(1)</sup>						
HPV type	6-month persistent infection			CIN2/3 or AIS		
	Cervarix	Control	% Efficacy (96.1% CI)	Cervarix	Control	% Efficacy (96.1% CI)
	n	n		n	n	
<b>HPV-16 related types (A9 species)</b>						
HPV-31	45	199	77.5% (68.3;84.4)	2	25	92.0% (66.0;99.2)
HPV-33	55	100	45.1% (21.7;61.9)	12	25	51.9% (<0;78.9)
HPV-35	55	43	-28.4% (<0;17.2)	1	6	83.3% (<0;99.7)
HPV-52	293	315	7.4% (<0;22.0)	12	14	14.3% (<0;65.4)
HPV-58	111	101	-10.3% (<0;17.7)	6	17	64.5% (1.5;89.2)
<b>HPV-18 related types (A7 species)</b>						
HPV-39	147	149	1.0% (<0;22.7)	3	10	69.8% (<0;95.2)
HPV-45	19	79	76.1% (59.1;86.7)	0	4	100% (<0;100)
HPV-59	56	59	4.8% (<0;36.4)	1	4	74.9% (<0;99.6)
HPV-68	138	134	-3.1% (<0;20.3)	5	11	54.4% (<0;88.4)
<b>Other types</b>						
HPV-51	304	354	14.5% (<0;27.4)	10	27	62.9% (18.0;84.7)
HPV-56	182	174	-5.0% (<0;16.1)	4	10	59.9% (<0;91.5)
HPV-66	168	178	5.7% (<0;24.9)	4	10	60.0% (<0;91.6)
n= number of cases						
<sup>(1)</sup> ATP: includes women who received 3 doses of vaccine, were DNA negative and seronegative at month						

0 and DNA negative at month 6 to the relevant HPV type.

The limits of the confidence interval 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.

### *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 5,303 female subjects from 10 to 55 years of age.

In clinical trials, more than 99% of initially seronegative subjects had seroconverted to both HPV types 16 and 18 one month after the third dose. Vaccine-induced IgG Geometric Mean Titres (GMT) were well above titres observed in women previously infected but who cleared HPV infection (natural infection). Initially seropositive and seronegative subjects reached similar titres after vaccination.

#### *Persistence of Immune Response to Cervarix*

Study 001/007, which included women from 15 to 25 years of age at the time of vaccination, evaluated the immune response against HPV-16 and HPV-18 up to 76 months after administration of the first vaccine dose. In study 023 (a subset of study 001/007), the immune response continued to be evaluated up to 101 months. 87 subjects in the vaccine group had immunogenicity data at the [M95-M101] interval after the first vaccine dose with a median follow-up of 7.9 years. Of these subjects, 100% (95% CI: 95.8;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 [M95-M101] interval with ELISA GMTs for both HPV-16 and HPV-18 at least still 10-fold higher than the ELISA GMTs observed in women who cleared a natural HPV infection.

In study 008, immunogenicity up to month 36 was similar to the response observed in study 001. A similar kinetic profile was observed with the neutralising antibodies.

In another clinical trial (study 014) performed in women aged 15 to 55 years, all subjects seroconverted to both HPV types 16 and 18 after the 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 two clinical trials performed in girls and adolescents aged 10 to 14 years, all subjects seroconverted to both HPV types 16 and 18 after the third dose (at month 7) with GMTs at least 2-fold higher as

compared to women aged 15 to 25 years. On the basis of these immunogenicity data, the efficacy of Cervarix is inferred from 10 to 14 years of age.

## **5.2 Pharmacokinetic properties**

Evaluation of pharmacokinetic properties is not required for vaccines.

## **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**

3 years.

After first opening, immediate use is recommended. If not used immediately, the vaccine should be stored in a refrigerator ( $2^\circ\text{C} - 8^\circ\text{C}$ ). If not used within 6 hours it should be discarded.

## **6.4 Special precautions for storage**

Store in a refrigerator ( $2^\circ\text{C} - 8^\circ\text{C}$ ).  
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) in pack sizes of 1, 10 and 100.

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 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.

## **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 <sup>1</sup> type 16 L1 protein <sup>2,3,4</sup>	20 micrograms
Human Papillomavirus <sup>1</sup> type 18 L1 protein <sup>2,3,4</sup>	20 micrograms

<sup>1</sup>Human Papillomavirus = HPV

<sup>2</sup>adjuvanted by AS04 containing:

3- <i>O</i> -desacyl-4'-monophosphoryl lipid A (MPL) <sup>3</sup>	50 micrograms
---	---------------

<sup>3</sup> adsorbed on aluminium hydroxide, hydrated (Al(OH) <sub>3</sub> )	0.5 milligrams Al <sup>3+</sup> in total
---	--

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

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Suspension for injection in pre-filled syringe.

Turbid white suspension. Upon storage, a fine white deposit with a clear colourless supernatant may be observed.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Cervarix is a vaccine for the prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types. See sections 4.4 and 5.1 for important information on the data that support this indication.

The indication is based on the demonstration of efficacy in women aged 15-25 years following vaccination with Cervarix and on the immunogenicity of the vaccine in girls and women aged 10-25 years.

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

### 4.2 Posology and method of administration

#### Posology

The recommended vaccination schedule is 0, 1, 6 months.

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

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

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

#### *Paediatric population*

Cervarix is not recommended for use in girls below 10 years of age due to lack of data on safety and immunogenicity in this age-group.

#### Method of administration

Cervarix is for intramuscular injection in the deltoid region (see also sections 4.4 and 4.5).

### **4.3 Contraindications**

Hypersensitivity to the active substances or to any of the excipients.

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

### **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 event 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  $\geq 10$ 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  $\geq 10$ 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**

Specific studies of the vaccine in pregnant women were not conducted. However, during the clinical development program, a total of 3,993 pregnancies were reported including 2,009 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.

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.

#### **4.7 Effects on the 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**

##### *Clinical trials*

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.

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  $< 1/100$ )

##### 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 surveillance*

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: 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*

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+ (CIN2/3 or AIS) associated with HPV-16 and/or HPV-18 (HPV-16/18). Cervical Intraepithelial Neoplasia (CIN) grade 2 and 3 (CIN2/3) and cervical adenocarcinoma in situ (AIS) were used in the clinical trials as surrogate markers for cervical cancer. The secondary endpoints included 6- and 12-month persistent infection.

Persistent infection that lasts for at least 6 months has also been shown to be a relevant surrogate marker for cervical cancer.

#### 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.

#### 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).

The mean follow-up for women included in study HPV-008 was approximately 39 months post dose 1 in TVC and 35 months post dose 3 in the ATP cohort.

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

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

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

N = number of subjects included in each group  
n = number of cases  
<sup>(1)</sup> 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)  
<sup>(2)</sup> including 3 cases of CIN2/3 or AIS and 2 cases of CIN3 or AIS in which another oncogenic HPV type was identified in the lesion, concomitantly with HPV-16 or HPV-18. These cases are excluded in the HPV type assignment analysis (see under Table).

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 were 1 CIN2/3 or AIS case in the vaccine group versus 53 cases in the control group (Efficacy 98.1% (96.1% CI: 88.4; 100)) and 0 CIN3 or AIS cases in the vaccine group versus 8 cases in the control group (Efficacy 100% (96.1% CI: 36.4; 100)).

In addition, statistically significant vaccine efficacy against CIN2/3 or AIS associated with HPV-16 and HPV-18 individually was demonstrated.

Vaccine efficacy against CIN1 associated with HPV 16/18 observed in the ATP cohort was 94.1% (96.1% CI: 83.4;98.5). Vaccine efficacy against CIN1/2/3 or AIS associated with HPV 16/18 observed in the ATP cohort was 91.7% (96.1% CI: 82.4;96.7).

Vaccine efficacy against virological endpoints (6-month and 12-month persistent infection) associated with HPV-16/18 observed in the ATP cohort is presented in Table 2.

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

HPV-16/18 endpoint	ATP <sup>(1)</sup>		
	Cervarix	Control	% Efficacy (96.1% CI)
	n/N	n/N	
6-month persistent infection	29/7177	488/7122	94.3% (91.5;96.3)
12-month persistent infection	20/7035	227/6984	91.4% (86.1;95.0)

N = number of subjects included in each group  
n = number of cases  
<sup>(1)</sup> 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)

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 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 <sup>(1)</sup>		
	Cervarix (N = 8667)	Control (N = 8682)	% Efficacy (96.1% CI)
	n	n	
CIN2/3 or AIS	82	174	52.8% (37.5;64.7)
CIN3 or AIS	43	65	33.6% (<0;56.9)

N = number of subjects included in each group  
n = number of cases  
<sup>(1)</sup> 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

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

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

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

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

Overall impact of the vaccine on cervical HPV disease burden

In study HPV-008, the incidence of high grade cervical lesions was compared between the placebo and vaccine group irrespective of the HPV DNA type in the lesion. In the TVC and TVC-naïve cohorts, the vaccine's efficacy was demonstrated against high-grade cervical lesions (Table 5). The TVC-naïve 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**

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

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.

Cervarix reduced definitive cervical therapy procedures (includes loop electrosurgical excision procedure [LEEP], cold-knife Cone, and laser procedures) by 68.8% (96.1% CI: 50.0;81.2) in TVC naïve and by 24.7% (96.1% CI: 7.4;38.9) in TVC.

### Cross-protective efficacy

The cross-protective efficacy of Cervarix against histopathological and virological endpoints (persistent infection) has been evaluated in study HPV-008 for 12 non-vaccine oncogenic HPV types. The study was not powered to assess efficacy against disease caused by individual HPV types. The analysis against the primary endpoint was confounded by multiple co-infections in the CIN2+ lesions. Unlike histopathological endpoints, virological endpoints are less confounded by multiple infections. Only HPV-31 showed consistent cross-protection for all endpoints (6m and 12m persistent infection, CIN2/3 or AIS) and all study cohorts. Vaccine efficacy against 6 months persistent infection has also been shown for HPV-33 and HPV-45 in all study cohorts.

Vaccine efficacy against 6-month persistent infection and CIN2/3 or AIS associated with individual non-vaccine oncogenic HPV types is presented in Table 6 (ATP cohort).

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

HPV type	6-month persistent infection			CIN2/3 or AIS		
	Cervarix	Control	% Efficacy (96.1% CI)	Cervarix	Control	% Efficacy (96.1% CI)
	n	n		n	n	
<b>ATP<sup>(1)</sup></b>						
<b>HPV-16 related types (A9 species)</b>						
HPV-31	45	199	77.5% (68.3;84.4)	2	25	92.0% (66.0;99.2)
HPV-33	55	100	45.1% (21.7;61.9)	12	25	51.9% (<0;78.9)
HPV-35	55	43	-28.4% (<0;17.2)	1	6	83.3% (<0;99.7)
HPV-52	293	315	7.4% (<0;22.0)	12	14	14.3% (<0;65.4)
HPV-58	111	101	-10.3% (<0;17.7)	6	17	64.5% (1.5;89.2)
<b>HPV-18 related types (A7 species)</b>						
HPV-39	147	149	1.0% (<0;22.7)	3	10	69.8% (<0;95.2)
HPV-45	19	79	76.1% (59.1;86.7)	0	4	100% (<0;100)
HPV-59	56	59	4.8% (<0;36.4)	1	4	74.9% (<0;99.6)
HPV-68	138	134	-3.1% (<0;20.3)	5	11	54.4% (<0;88.4)
<b>Other types</b>						
HPV-51	304	354	14.5% (<0;27.4)	10	27	62.9% (18.0;84.7)
HPV-56	182	174	-5.0% (<0;16.1)	4	10	59.9% (<0;91.5)
HPV-66	168	178	5.7% (<0;24.9)	4	10	60.0% (<0;91.6)
n= number of cases						
(1) ATP: includes women who received 3 doses of vaccine, were DNA negative and seronegative at month 0 and DNA negative at month 6 to the relevant HPV type.						

The limits of the confidence interval 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.

## *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 5,303 female subjects from 10 to 55 years of age.

In clinical trials, more than 99% of initially seronegative subjects had seroconverted to both HPV types 16 and 18 one month after the third dose. Vaccine-induced IgG Geometric Mean Titres (GMT) were well above titres observed in women previously infected but who cleared HPV infection (natural infection). Initially seropositive and seronegative subjects reached similar titres after vaccination.

### *Persistence of Immune Response to Cervarix*

Study 001/007, which included women from 15 to 25 years of age at the time of vaccination, evaluated the immune response against HPV-16 and HPV-18 up to 76 months after administration of the first vaccine dose. In study 023 (a subset of study 001/007), the immune response continued to be evaluated up to 101 months. 87 subjects in the vaccine group had immunogenicity data at the [M95-M101] interval after the first vaccine dose with a median follow-up of 7.9 years. Of these subjects, 100% (95% CI: 95.8;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 [M95-M101] interval with ELISA GMTs for both HPV-16 and HPV-18 at least still 10-fold higher than the ELISA GMTs observed in women who cleared a natural HPV infection.

In study 008, immunogenicity up to month 36 was similar to the response observed in study 001. A similar kinetic profile was observed with the neutralising antibodies.

In another clinical trial (study 014) performed in women aged 15 to 55 years, all subjects seroconverted to both HPV types 16 and 18 after the 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 two clinical trials performed in girls and adolescents aged 10 to 14 years, all subjects seroconverted to both HPV types 16 and 18 after the third dose (at month 7) with GMTs at least 2-fold higher as

compared to women aged 15 to 25 years. On the basis of these immunogenicity data, the efficacy of Cervarix is inferred from 10 to 14 years of age.

## **5.2 Pharmacokinetic properties**

Evaluation of pharmacokinetic properties is not required for vaccines.

## **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, stability data generated indicate that Cervarix presented in monodose containers remains stable and can be administered in case it has been stored outside the refrigerator up to three days at temperatures between 8°C and 25°C or up to one 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 in pack sizes of 1 and 10.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal and other handling**

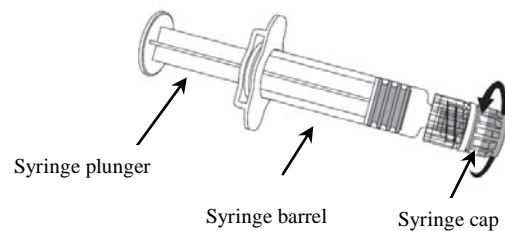
A fine white deposit with a clear colourless supernatant may be observed upon storage of the syringe. This does not constitute a sign of deterioration.

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.

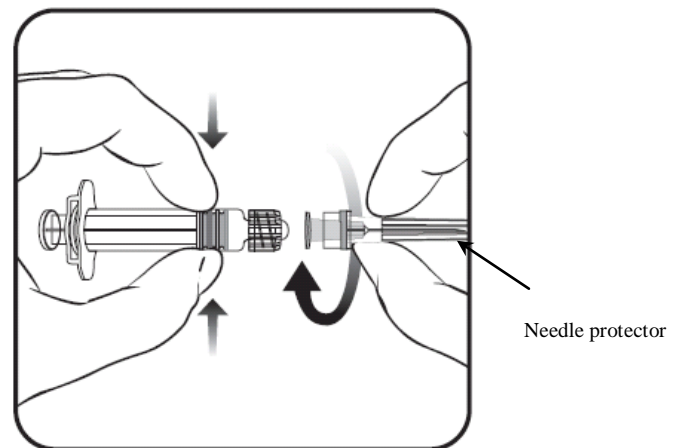
#### Instructions for administration of the vaccine presented in pre-filled syringe

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 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.

**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. MANUFACTURERS OF THE BIOLOGICAL ACTIVE  
SUBSTANCE AND MANUFACTURING AUTHORISATION  
HOLDER RESPONSIBLE FOR BATCH RELEASE**
  
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

**A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturers of the biological active substance

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

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

GlaxoSmithKline Biologicals S.A.  
Les Isnes  
Rue Louis Genonceau, 13  
BE-5023 Gembloux  
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 OF THE MARKETING AUTHORISATION**

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

• **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

• **OTHER CONDITIONS**

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 product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 5 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the 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 EMEA

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

**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 <sup>1,2</sup>	20 micrograms
HPV type 18 L1 protein <sup>1,2</sup>	20 micrograms
<sup>1</sup> adjuvanted by AS04 containing: 3- <i>O</i> -desacyl-4'-monophosphoryl lipid A (MPL) <sup>2</sup>	50 micrograms
<sup>2</sup> adsorbed on aluminium hydroxide, hydrated (Al(OH) <sub>3</sub> )	0.5 milligrams Al <sup>3+</sup> 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 REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight 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 <sup>1,2</sup>	20 micrograms
HPV type 18 L1 protein <sup>1,2</sup>	20 micrograms
<sup>1</sup> adjuvanted by AS04 containing: 3- <i>O</i> -desacyl-4'-monophosphoryl lipid A (MPL) <sup>2</sup>	50 micrograms
<sup>2</sup> adsorbed on aluminium hydroxide, hydrated (Al(OH) <sub>3</sub> )	0.5 milligrams Al <sup>3+</sup> 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 REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight 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**

Justification for not including Braille accepted.



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

**1. NAME OF THE MEDICINAL PRODUCT**

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

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

1 dose (0.5 ml) contains:

HPV type 16 L1 protein <sup>1,2</sup>	20 micrograms
HPV type 18 L1 protein <sup>1,2</sup>	20 micrograms
<sup>1</sup> adjuvanted by AS04 containing: 3- <i>O</i> -desacyl-4'-monophosphoryl lipid A (MPL) <sup>2</sup>	50 micrograms
<sup>2</sup> adsorbed on aluminium hydroxide, hydrated (Al(OH) <sub>3</sub> )	0.5 milligrams Al <sup>3+</sup> 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 REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight 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.**

- 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. Do not pass it on to others.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### **In this leaflet:**

1. What Cervarix is and what it is used for
2. Before you receive Cervarix
3. How Cervarix is given
4. Possible side effects
5. How to store Cervarix
6. Further information

## **1. WHAT CERVARIX IS AND WHAT IT IS USED FOR**

Cervarix is a vaccine intended to protect females 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 15-25 years of age. Cervarix also stimulates production of antibodies in females 10-14 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. BEFORE YOU RECEIVE CERVARIX**

**Cervarix should not be given if**  
the person to be vaccinated:

- is allergic (hypersensitive) to any of the active substances or any of the other ingredients of Cervarix. The active substances and other ingredients of Cervarix are listed at the end of the leaflet (see section 6). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.



- has 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.

### **Take special care with Cervarix**

You should tell the doctor if the person to be vaccinated:

- has a bleeding problem or bruises easily.
- has any disease which reduces her resistance to infection such as HIV infection

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.

The duration of protection after vaccination is currently unknown. In clinical trials, sustained protection has been observed in females aged 15 to 25 years for up to 6.4 years after the first dose. The need for booster dose(s) has not been investigated.

### **Using other medicines**

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.

Please tell the doctor if the person to be vaccinated is taking or has recently taken any other medicines, including medicines obtained without a prescription or has recently received any other vaccine.

### **Pregnancy and breast-feeding**

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.

Ask your doctor for advice about breast-feeding before receiving Cervarix.

### **Driving and using machines**

There is no information on the effect of Cervarix on your ability to drive or use machinery.

## **3. HOW CERVARIX 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 10 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.

**If you forget a return visit for Cervarix:**

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, Cervarix 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 any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE CERVARIX

Keep out of the reach and sight of children.

Do not use Cervarix 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

### What Cervarix contains

- The active substances are:

Human Papillomavirus <sup>1</sup> type 16 L1 protein <sup>2,3,4</sup>	20 micrograms
Human Papillomavirus <sup>1</sup> type 18 L1 protein <sup>2,3,4</sup>	20 micrograms

<sup>1</sup>Human Papillomavirus = HPV

<sup>2</sup>adjuvanted by AS04 containing:

3- <i>O</i> -desacyl-4'-monophosphoryl lipid A (MPL) <sup>3</sup>	50 micrograms
---	---------------

<sup>3</sup> adsorbed on aluminium hydroxide, hydrated (Al(OH) <sub>3</sub> )	0.5 milligrams Al <sup>3+</sup> in total
---	--

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

- The other ingredients are sodium chloride (NaCl), sodium dihydrogen phosphate dihydrate (NaH<sub>2</sub>PO<sub>4</sub>·2 H<sub>2</sub>O) 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.  
Rue de l'Institut 89  
B-1330 Rixensart, Belgium

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

### **België/Belgique/Belgien**

GlaxoSmithKline s.a./n.v.  
Tél/Tel: + 32 2 656 21 11

### **Luxembourg/Luxemburg**

GlaxoSmithKline s.a./n.v.  
Tél/Tel: + 32 2 656 21 11

### **България**

ГлаксоСмитКлайн ЕООД  
ул. Димитър Манов бл.10  
София 1408  
Тел. + 359 2 953 10 34

### **Magyarország**

GlaxoSmithKline Kft.  
Tel.: + 36-1-2255300

### **Česká republika**

GlaxoSmithKline s.r.o.  
Tel: + 420 2 22 00 11 11  
gsk.czmail@gsk.com

### **Malta**

GlaxoSmithKline Malta  
Tel: + 356 21 238131

### **Danmark**

GlaxoSmithKline Pharma A/S  
Tlf: + 45 36 35 91 00  
dk-info@gsk.com

### **Nederland**

GlaxoSmithKline BV  
Tel: + 31 (0)30 69 38 100  
nlinfo@gsk.com

### **Deutschland**

GlaxoSmithKline GmbH & Co. KG  
Tel: + 49 (0)89 360448701  
produkt.info@gsk.com

### **Norge**

GlaxoSmithKline AS  
Tlf: + 47 22 70 20 00  
firmapost@gsk.no

### **Eesti**

GlaxoSmithKline Eesti OÜ  
Tel: +372 667 6900  
estonia@gsk.com

### **Österreich**

GlaxoSmithKline Pharma GmbH.  
Tel: + 43 1 970 75-0  
at.info@gsk.com

### **Ελλάδα**

GlaxoSmithKline A.E.B.E  
Τηλ: + 30 210 68 82 100

### **Polska**

GSK Commercial Sp. z o.o.  
Tel.: + 48 (22) 576 9000

### **España**

GlaxoSmithKline, S.A.  
Tel: + 34 902 202 700  
es-ci@gsk.com

### **Portugal**

GlaxoSmithKline, Produtos Farmacêuticos, Lda.  
Tel: + 351 21 412 95 00  
FI.PT@gsk.com

### **France**

Laboratoire GlaxoSmithKline  
Tél: + 33 (0) 1 39 17 84 44  
diam@gsk.com

### **România**

GlaxoSmithKline (GSK) SRL  
Tel: +40 (0)21 3028 208

### **Ireland**

GlaxoSmithKline (Ireland) Ltd  
Tel: + 353 (0)1 4955000

### **Slovenija**

GlaxoSmithKline d.o.o.  
Tel: + 386 (0) 1 280 25 00  
medical.x.si@gsk.com

**Ísland**

GlaxoSmithKline ehf.  
Sími: +354-530 3700

**Slovenská republika**

GlaxoSmithKline Slovakia s.r.o.  
Tel: + 421 (0)2 48 26 11 11  
receptia.sk@gsk.com

**Italia**

GlaxoSmithKline S.p.A.  
Tel:+ 39 04 59 21 81 11

**Suomi/Finland**

GlaxoSmithKline Oy  
Puh/Tel: + 358 10 30 30 30  
Finland.tuoteinfo@gsk.com

**Κύπρος**

GlaxoSmithKline (Cyprus) Ltd  
Τηλ: + 357 22 39 70 00

**Sverige**

GlaxoSmithKline AB  
Tel: + 46 (0)8 638 93 00  
[info.produkt@gsk.com](mailto:info.produkt@gsk.com)

**Latvija**

GlaxoSmithKline Latvia SIA  
Tel: + 371 67312687  
lv-epasts@gsk.com

**United Kingdom**

GlaxoSmithKline UK  
Tel: + 44 (0)808 100 9997  
customercontactuk@gsk.com

**Lietuva**

GlaxoSmithKline Lietuva UAB  
Tel: +370 5 264 90 00  
info.lt@gsk.com

**This leaflet was last approved in**

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 medical or healthcare professionals only:

Cervarix should be administered as soon as possible after being removed from the refrigerator. However, stability data generated indicate that Cervarix presented in monodose containers remains stable and can be administered in case it has been stored outside the refrigerator up to three days at temperatures between 8°C and 25°C or up to one 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 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.**

- 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. Do not pass it on to others.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### **In this leaflet:**

1. What Cervarix is and what it is used for
2. Before you receive Cervarix
3. How Cervarix is given
4. Possible side effects
5. How to store Cervarix
6. Further information

## **1. WHAT CERVARIX IS AND WHAT IT IS USED FOR**

Cervarix is a vaccine intended to protect females 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 15-25 years of age. Cervarix also stimulates production of antibodies in females 10-14 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. BEFORE YOU RECEIVE CERVARIX**

**Cervarix should not be given if**  
the person to be vaccinated:

- is allergic (hypersensitive) to any of the active substances or any of the other ingredients of Cervarix. The active substances and other ingredients of Cervarix are listed at the end of the leaflet (see section 6). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

- has 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.

### **Take special care with Cervarix**

You should tell the doctor if the person to be vaccinated:

- has a bleeding problem or bruises easily.
- has any disease which reduces her resistance to infection such as HIV infection

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.

The duration of protection after vaccination is currently unknown. In clinical trials, sustained protection has been observed in females aged 15 to 25 years for up to 6.4 years after the first dose. The need for booster dose(s) has not been investigated.

### **Using other medicines**

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.

Please tell the doctor if the person to be vaccinated is taking or has recently taken any other medicines, including medicines obtained without a prescription or has recently received any other vaccine.

### **Pregnancy and breast-feeding**

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.

Ask your doctor for advice about breast-feeding before receiving Cervarix.

### **Driving and using machines**

There is no information on the effect of Cervarix on your ability to drive or use machinery.

## **3. HOW CERVARIX 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 10 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.

**If you forget a return visit for Cervarix:**

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, Cervarix 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 any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE CERVARIX

Keep out of the reach and sight of children.

Do not use Cervarix 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

### What Cervarix contains

- The active substances are:

Human Papillomavirus <sup>1</sup> type 16 L1 protein <sup>2,3,4</sup>	20 micrograms
Human Papillomavirus <sup>1</sup> type 18 L1 protein <sup>2,3,4</sup>	20 micrograms

<sup>1</sup>Human Papillomavirus = HPV

<sup>2</sup>adjuvanted by AS04 containing:

3- <i>O</i> -desacyl-4'- monophosphoryl lipid A (MPL) <sup>3</sup>	50 micrograms
--	---------------

<sup>3</sup> adsorbed on aluminium hydroxide, hydrated (Al(OH) <sub>3</sub> )	0.5 milligrams Al <sup>3+</sup> in total
---	--

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

- The other ingredients are sodium chloride (NaCl), sodium dihydrogen phosphate dihydrate (NaH<sub>2</sub>PO<sub>4</sub>·2 H<sub>2</sub>O) 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  
B-1330 Rixensart, Belgium

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

#### **België/Belgique/Belgien**

GlaxoSmithKline s.a./n.v.  
Tél/Tel: + 32 2 656 21 11

#### **Luxembourg/Luxemburg**

GlaxoSmithKline s.a./n.v.  
Tél/Tel: + 32 2 656 21 11

#### **България**

ГлаксоСмитКлайн ЕООД  
ул. Димитър Манов бл.10  
София 1408  
Тел. + 359 2 953 10 34

#### **Magyarország**

GlaxoSmithKline Kft.  
Tel.: + 36-1-2255300

#### **Česká republika**

GlaxoSmithKline s.r.o.  
Tel: + 420 2 22 00 11 11  
gsk.czmail@gsk.com

#### **Malta**

GlaxoSmithKline Malta  
Tel: + 356 21 238131

#### **Danmark**

GlaxoSmithKline Pharma A/S  
Tlf: + 45 36 35 91 00  
dk-info@gsk.com

#### **Nederland**

GlaxoSmithKline BV  
Tel: + 31 (0)30 69 38 100  
nlinfo@gsk.com

#### **Deutschland**

GlaxoSmithKline GmbH & Co. KG  
Tel: + 49 (0)89 360448701  
produkt.info@gsk.com

#### **Norge**

GlaxoSmithKline AS  
Tlf: + 47 22 70 20 00  
firmapost@gsk.no

#### **Eesti**

GlaxoSmithKline Eesti OÜ  
Tel: +372 667 6900  
estonia@gsk.com

#### **Österreich**

GlaxoSmithKline Pharma GmbH.  
Tel: + 43 1 970 75-0  
at.info@gsk.com

#### **Ελλάδα**

GlaxoSmithKline A.E.B.E  
Τηλ: + 30 210 68 82 100

#### **Polska**

GSK Commercial Sp. z o.o.  
Tel.: + 48 (22) 576 9000

#### **España**

GlaxoSmithKline, S.A.  
Tel: + 34 902 202 700  
es-ci@gsk.com

#### **Portugal**

GlaxoSmithKline, Produtos Farmacêuticos, Lda.  
Tel: + 351 21 412 95 00  
FI.PT@gsk.com

#### **France**

Laboratoire GlaxoSmithKline  
Tél: + 33 (0) 1 39 17 84 44  
diam@gsk.com

#### **România**

GlaxoSmithKline (GSK) SRL  
Tel: +40 (0)21 3028 208

#### **Ireland**

#### **Slovenija**

GlaxoSmithKline (Ireland) Ltd  
Tel: + 353 (0)1 4955000

GlaxoSmithKline d.o.o.  
Tel: + 386 (0) 1 280 25 00  
medical.x.si@gsk.com

**Ísland**

GlaxoSmithKline ehf.  
Sími: +354-530 3700

**Slovenská republika**

GlaxoSmithKline Slovakia s.r.o.  
Tel: + 421 (0)2 48 26 11 11  
repcia.sk@gsk.com

**Italia**

GlaxoSmithKline S.p.A.  
Tel:+ 39 04 59 21 81 11

**Suomi/Finland**

GlaxoSmithKline Oy  
Puh/Tel: + 358 10 30 30 30  
Finland.tuoteinfo@gsk.com

**Κύπρος**

GlaxoSmithKline (Cyprus) Ltd  
Τηλ: + 357 22 39 70 00

**Sverige**

GlaxoSmithKline AB  
Tel: + 46 (0)8 638 93 00  
[info.produkt@gsk.com](mailto:info.produkt@gsk.com)

**Latvija**

GlaxoSmithKline Latvia SIA  
Tel: + 371 67312687  
lv-epasts@gsk.com

**United Kingdom**

GlaxoSmithKline UK  
Tel: + 44 (0)808 100 9997  
customercontactuk@gsk.com

**Lietuva**

GlaxoSmithKline Lietuva UAB  
Tel: +370 5 264 90 00  
info.lt@gsk.com

**This leaflet was last approved in.**

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 medical or 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 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.**

- 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. Do not pass it on to others.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### **In this leaflet:**

1. What Cervarix is and what it is used for
2. Before you receive Cervarix
3. How Cervarix is given
4. Possible side effects
5. How to store Cervarix
6. Further information

### **1. WHAT CERVARIX IS AND WHAT IT IS USED FOR**

Cervarix is a vaccine intended to protect females 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 15-25 years of age. Cervarix also stimulates production of antibodies in females 10-14 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. BEFORE YOU RECEIVE CERVARIX**

**Cervarix should not be given if**  
the person to be vaccinated:

- is allergic (hypersensitive) to any of the active substances or any of the other ingredients of Cervarix. The active substances and other ingredients of Cervarix are listed at the end of the leaflet (see section 6). Signs of an allergic reaction may include itchy skin rash, shortness of breath and swelling of the face or tongue.

- has 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.

### **Take special care with Cervarix**

You should tell the doctor if the person to be vaccinated:

- has a bleeding problem or bruises easily.
- has any disease which reduces her resistance to infection such as HIV infection

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.

The duration of protection after vaccination is currently unknown. In clinical trials, sustained protection has been observed in females aged 15 to 25 years for up to 6.4 years after the first dose. The need for booster dose(s) has not been investigated.

### **Using other medicines**

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.

Please tell the doctor if the person to be vaccinated is taking or has recently taken any other medicines, including medicines obtained without a prescription or has recently received any other vaccine.

### **Pregnancy and breast-feeding**

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.

Ask your doctor for advice about breast-feeding before receiving Cervarix.

### **Driving and using machines**

There is no information on the effect of Cervarix on your ability to drive or use machinery.

## **3. HOW CERVARIX 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 10 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.

**If you forget a return visit for Cervarix:**

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, Cervarix 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 any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE CERVARIX

Keep out of the reach and sight of children.

Do not use Cervarix 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

### What Cervarix contains

- The active substances are:

Human Papillomavirus <sup>1</sup> type 16 L1 protein <sup>2,3,4</sup>	20 micrograms
Human Papillomavirus <sup>1</sup> type 18 L1 protein <sup>2,3,4</sup>	20 micrograms

<sup>1</sup>Human Papillomavirus = HPV

<sup>2</sup>adjuvanted by AS04 containing:

3- <i>O</i> -desacyl-4'- monophosphoryl lipid A (MPL) <sup>3</sup>	50 micrograms
--	---------------

<sup>3</sup> adsorbed on aluminium hydroxide, hydrated (Al(OH) <sub>3</sub> )	0.5 milligrams Al <sup>3+</sup> in total
---	--

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

- The other ingredients are sodium chloride (NaCl), sodium dihydrogen phosphate dihydrate (NaH<sub>2</sub>PO<sub>4</sub>·2 H<sub>2</sub>O) 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

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

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

### **België/Belgique/Belgien**

GlaxoSmithKline s.a./n.v.  
Tél/Tel: + 32 2 656 21 11

### **Luxembourg/Luxemburg**

GlaxoSmithKline s.a./n.v.  
Tél/Tel: + 32 2 656 21 11

### **България**

ГлаксоСмитКлайн ЕООД  
ул. Димитър Манов бл.10  
София 1408  
Тел. + 359 2 953 10 34

### **Magyarország**

GlaxoSmithKline Kft.  
Tel.: + 36-1-2255300

### **Česká republika**

GlaxoSmithKline s.r.o.  
Tel: + 420 2 22 00 11 11  
gsk.czmail@gsk.com

### **Malta**

GlaxoSmithKline Malta  
Tel: + 356 21 238131

### **Danmark**

GlaxoSmithKline Pharma A/S  
Tlf: + 45 36 35 91 00  
dk-info@gsk.com

### **Nederland**

GlaxoSmithKline BV  
Tel: + 31 (0)30 69 38 100  
nlinfo@gsk.com

### **Deutschland**

GlaxoSmithKline GmbH & Co. KG  
Tel: + 49 (0)89 360448701  
produkt.info@gsk.com

### **Norge**

GlaxoSmithKline AS  
Tlf: + 47 22 70 20 00  
firmapost@gsk.no

### **Eesti**

GlaxoSmithKline Eesti OÜ  
Tel: +372 667 6900  
estonia@gsk.com

### **Österreich**

GlaxoSmithKline Pharma GmbH.  
Tel: + 43 1 970 75-0  
at.info@gsk.com

### **Ελλάδα**

GlaxoSmithKline A.E.B.E  
Τηλ: + 30 210 68 82 100

### **Polska**

GSK Commercial Sp. z o.o.  
Tel.: + 48 (22) 576 9000

### **España**

GlaxoSmithKline, S.A.  
Tel: + 34 902 202 700  
es-ci@gsk.com

### **Portugal**

GlaxoSmithKline, Produtos Farmacêuticos, Lda.  
Tel: + 351 21 412 95 00  
FI.PT@gsk.com

### **France**

Laboratoire GlaxoSmithKline  
Tél: + 33 (0) 1 39 17 84 44  
diam@gsk.com

### **România**

GlaxoSmithKline (GSK) SRL  
Tel: +40 (0)21 3028 208

### **Ireland**

GlaxoSmithKline (Ireland) Ltd  
Tel: + 353 (0)1 4955000

### **Slovenija**

GlaxoSmithKline d.o.o.  
Tel: + 386 (0) 1 280 25 00  
medical.x.si@gsk.com



**Ísland**

GlaxoSmithKline ehf.  
Sími: +354-530 3700

**Slovenská republika**

GlaxoSmithKline Slovakia s.r.o.  
Tel: + 421 (0)2 48 26 11 11  
repcia.sk@gsk.com

**Italia**

GlaxoSmithKline S.p.A.  
Tel:+ 39 04 59 21 81 11

**Suomi/Finland**

GlaxoSmithKline Oy  
Puh/Tel: + 358 10 30 30 30  
Finland.tuoteinfo@gsk.com

**Κύπρος**

GlaxoSmithKline (Cyprus) Ltd  
Τηλ: + 357 22 39 70 00

**Sverige**

GlaxoSmithKline AB  
Tel: + 46 (0)8 638 93 00  
[info.produkt@gsk.com](mailto:info.produkt@gsk.com)

**Latvija**

GlaxoSmithKline Latvia SIA  
Tel: + 371 67312687  
lv-epasts@gsk.com

**United Kingdom**

GlaxoSmithKline UK  
Tel: + 44 (0)808 100 9997  
customercontactuk@gsk.com

**Lietuva**

GlaxoSmithKline Lietuva UAB  
Tel: +370 5 264 90 00  
info.lt@gsk.com

**This leaflet was last approved in**

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 medical or healthcare professionals only:

Cervarix should be administered as soon as possible after being removed from the refrigerator. However, stability data generated indicate that Cervarix presented in monodose containers remains stable and can be administered in case it has been stored outside the refrigerator up to three days at temperatures between 8°C and 25°C or up to one day at temperatures between 25°C and 37°C.

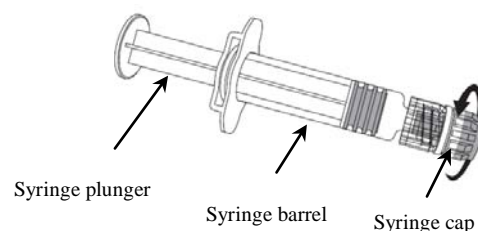
A fine white deposit with a clear colourless supernatant may be observed upon storage of the syringe. This does not constitute a sign of deterioration.

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.

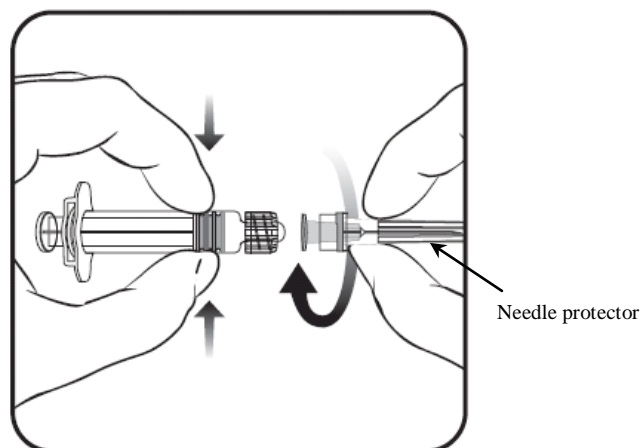
**Instructions for administration of the vaccine presented in pre-filled syringe**

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