

# DATASHEET

## 1. NAME OF THE MEDICINAL PRODUCT

Cervarix Human Papillomavirus vaccine Types 16 and 18 (Recombinant, AS04 adjuvanted).

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Suspension for injection

1 dose (0.5 ml) contains:

Human Papillomavirus type 16 L1 protein <sup>1</sup>	20 micrograms
Human papillomavirus type 18 L1 protein <sup>1</sup>	20 micrograms
3-O-desacyl-4'- monophosphoryl lipid A (MPL) <sup>2</sup>	50 micrograms
aluminium hydroxide, hydrated (Al(OH) <sub>3</sub> ) <sup>2</sup>	0.5 milligrams Al <sup>3+</sup>

<sup>1</sup>L1 protein in the form of non-infectious virus-like particles (VLPs) produced by recombinant DNA technology using a Baculovirus expression system.

<sup>2</sup>The GlaxoSmithKline proprietary AS04 adjuvant system is composed of aluminium hydroxide and 3-O-desacyl-4'- monophosphoryl lipid A (MPL) (see section 5.2)

For a full list of excipients, see section 7.1.

## 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 indicated in females from 10 to 45 years of age for the prevention of persistent infection, premalignant cervical lesions and cervical cancer caused by oncogenic human papillomavirus (HPV). Immunogenicity studies have been conducted in females aged 10 to 14 years and 26 to 45 years to link efficacy in females aged 15 to 25 years to other populations. (see Section 4.4 and 5.2) .

### 4.2 Posology and method of administration

#### Posology

The primary vaccination course consists of three doses.

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.

Although the necessity for a booster dose has not been established an anamnestic response has been observed after the administration of a challenge dose (see section 5.2).

## **Method of Administration**

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

### **4.3 Contraindications**

Cervarix should not be administered to subjects with known hypersensitivity to any component of the vaccine (see also sections 2 and 7.1)

### **4.4 Special warnings and precautions for use**

It is good clinical practice to precede vaccination by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

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 as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

As with other vaccines, the administration of Cervarix should be postponed in subjects suffering from acute severe febrile illness. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

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

As for 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 responses may not be elicited in all vaccinees.

Cervarix is a prophylactic vaccine. It is not intended to prevent progression of HPV-related lesions present at the time of vaccination.

CERVARIX does not provide protection against all oncogenic HPV types (see Section 5.2).

Vaccination is primary prevention and is not a substitute for regular cervical screening (secondary prevention) or for precautions against exposure to HPV and sexually transmitted diseases.

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. For these individuals an adequate immune response may not be elicited.

Duration of protection has not been established. Sustained protective efficacy has been observed for at least 9.4 years after the first dose. Long-term studies are ongoing to establish the duration of protection (see section 5.2).

## **4.5 Interaction with other medicinal products and other forms of interaction**

### **Use with other vaccines**

Cervarix can be given concomitantly with any of the following vaccines: reduced antigen diphtheria-tetanus-acellular pertussis vaccine (dTpa), inactivated poliovirus vaccine (IPV) and the combined dTpa-IPV vaccine; hepatitis A (inactivated) vaccine (HepA), hepatitis B (rDNA) vaccine (HepB) and the combined HepA-HepB vaccine.

Administration of Cervarix at the same time as Twinrix (combined HepA-HepB vaccine) has shown no clinically relevant interference in the antibody response to the HPV and hepatitis A antigens. Anti-HBs geometric mean antibody titres were lower on co-administration, but the clinical significance 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 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 medications**

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

## **4.6 Pregnancy and lactation**

### **Fertility**

See Section 6.1

### **Pregnancy**

Specific studies of the vaccine in pregnant women were not conducted. During the prelicensure clinical development program, pregnancies have been reported. These data are insufficient to recommend use of Cervarix during pregnancy. Vaccination should, therefore, be postponed until after completion of pregnancy.

The effect of Cervarix on embryo-foetal, peri-natal and post-natal survival and development has been assessed in rats. Such animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development.

### **Lactation**

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.

Serological data suggest a transfer of anti-HPV16 and anti-HPV18 antibodies via the milk during the lactation period in rats. However, it is unknown whether vaccine-induced antibodies are excreted in human breast milk.

#### **4.7 Ability to perform tasks that require judgement, motor or cognitive skills**

No studies on the effects on the ability to drive or use machines have been performed.

#### **4.8 Undesirable effects**

In clinical studies, a total of approximately 45,000 doses of Cervarix were administered to approximately 16,000 subjects aged 10-68 years. These subjects were followed to assess the safety of the vaccine.

The most common 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  $\leq 1/100$ )

Rare ( $\geq 1/10,000$  to  $\leq 1/1,000$ )

##### Infections and infestations:

Uncommon: upper respiratory tract infection

##### Blood and lymphatic system disorders:

Uncommon: lymphadenopathy

##### Nervous system disorders:

Very common: headache

Uncommon: dizziness

##### Gastrointestinal disorders:

Common: gastrointestinal including nausea, vomiting, diarrhoea and abdominal pain

##### Skin and subcutaneous tissue disorders:

Common: itching/pruritus, rash, urticaria

##### Musculoskeletal and connective tissue and bone 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

## Post Marketing Data

### Immune system disorders

Rare: allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema

### Nervous system disorders

Rare: syncope or vasovagal responses to injection, sometimes accompanied by tonic-clonic movements.

## 4.9 Overdose

Insufficient data are available.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Mechanism of Action

Persistent infection with oncogenic HPV types has been demonstrated to be responsible for virtually all cases of cervical cancer worldwide.

Cervarix is a 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 an humoral immune response and cell-mediated immune memory.

Cervarix is adjuvanted with AS04 which has been shown in clinical trials to induce a higher and long lasting immune response compared to the same antigens adjuvanted with aluminium salt [Al(OH)<sub>3</sub>] alone.

Invasive cervical cancer includes squamous cervical carcinoma (84%) and adenocarcinoma (16%, up to 20% in developed countries with screening programs). HPV-16 and HPV-18 are responsible for approximately 70% of cervical cancers across all regions worldwide.

Other oncogenic HPV types (HPV-31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, -68) can also cause cervical cancer. The 5 most common types identified in cervical cancer are HPV-16, -18, -33, -45 and -31.

### 5.2 Pharmacodynamic properties

Pharmaco-therapeutic group: J07BM01

#### Evidence of Anamnestic (Immune Memory) Response

The administration of a challenge dose after a mean of 6.8 years following the first vaccination elicited an anamnestic immune response to HPV-16 and HPV-18 (by ELISA and pseudovirion-based neutralizing assay) at day 7. One month after the challenge dose, GMTs exceeded those observed one month after the primary vaccination course.

#### Prophylactic Efficacy

The efficacy of Cervarix was assessed in 2 controlled, double-blind, randomised Phase II and III clinical studies (HPV-001/007 and HPV-008) that included a total of 19,778 women aged 15 to 25 years.

Clinical trial HPV-001/007 was conducted in North America and Latin America. Study HPV-023 followed by subjects from the Brazilian cohort of study 001/007. Study entry criteria were: negative for oncogenic HPV DNA (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) in cervical samples, seronegative for HPV-16 and HPV-18 antibodies and normal cytology. These characteristics are representative of a population presumed naïve to oncogenic HPV types prior to vaccination.

Clinical trial HPV-008 was conducted in North America, Latin America, Europe, Asia Pacific and Australia. Pre-vaccination samples were collected for oncogenic HPV DNA (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) testing and serum testing for HPV-16 and HPV-18 antibodies. Women were vaccinated regardless of baseline cytology and HPV serological and DNA status. These characteristics are representative of a population which includes women with or without evidence of past and/or current HPV infection.

As in any prophylactic efficacy trial, subjects initially infected with a particular HPV type were not eligible for the efficacy assessment of that type.

The primary endpoints in study HPV-001/007 are incident HPV-16 and/or HPV-18 infections.

The primary endpoint in study HPV-008 is HPV-16 or HPV-18 related CIN2+.

In both studies the following endpoints were evaluated:

- CIN2+ (cervical intraepithelial neoplasia grade 2 and higher grade lesions)
- CIN1+ (cervical intraepithelial neoplasia grade 1 and higher grade lesions)
- cytological abnormalities including atypical squamous cells of undetermined significance (ASC-US), low grade squamous intraepithelial lesions (LSIL), high grade squamous intraepithelial lesions (HSIL) and ASC-US of suspected high grade (ASC-H).
- 12 month persistent infection (i.e. at least 2 positive specimens for the same HPV type over a minimum interval of 10 months)
- 6 month persistent infection (i.e. at least 2 positive specimens for the same HPV type over a minimum interval of 5 months)

In study HPV-008, the following endpoints were also evaluated:

- CIN3+ (cervical intraepithelial neoplasia grade 3 and higher grade lesions)
- VIN1+ (vulvar intraepithelial neoplasia grade 1 and higher grade lesions)
- VaIN1+ (vaginal intraepithelial neoplasia grade 1 and higher grade lesions)

Cervical intraepithelial neoplasia (CIN) grade 2 and 3 (CIN2+) was used in the clinical trials as a surrogate marker for cervical cancer. Persistent infection that lasts for at least 6 month has also been shown to be a relevant surrogate marker for cervical cancer. Although CIN1 is not a surrogate marker for cervical cancer, these lesions require medical follow-up.

### **1. Studies HPV-001/007/023 – Vaccine efficacy against HPV-16/18 in women naïve to oncogenic HPV types**

Efficacy results for the endpoints associated with HPV-16 and/or HPV-18 (HPV-16/18) observed in study HPV-001/007 through 6.4 years after the first vaccine dose are presented in Table 1.

**Table 1: Vaccine efficacy results from Study HPV 001/007 associated with HPV-16/18**

Endpoint	Cervarix n/N	Control (AI hydroxide) n/N	% Efficacy	95% CI
Incident Infection*	4/401	70/372	95.3	87.4;98.7
6 month persistent infection*	0/401	34/372	100.0	90.0;100.0
12 month persistent infection*	0/401	20/372	100.0	81.8;100.0
ASC-US**	1/505	31/497	97.3	83.6;99.9
CIN1+**	0/481	15/470	100.0	73.4;100.0
CIN2+**	0/481	9/470	100.0	51.3;100.0

\*ATP cohort = All women in HPV-007 who received three doses of CERVARIX or placebo in HPV-001, and who were negative for high-risk HPV DNA and seronegative for HPV-16 and HPV-18 at month 0, and negative for HPV-16 and HPV-18 DNA at month 6.

\*\* Total cohort = All women who had received at least one dose of CERVARIX or placebo in HPV-001, and who had any data available for outcome measurement in HPV-007.

N = Number of subjects in specific cohort

n = number of cases

In summary, sustained efficacy of the vaccine was demonstrated against HPV-16 and/or HPV-18 persistent infections, as well as against cytological abnormalities and histopathological lesions.

In study HPV-023, subjects (N=437) were followed-up to 9.4 years (approximately 113 months) after dose one. There were no new cases of infection or histopathological lesions associated with HPV-16/18 in the vaccine group. In the placebo group, there were 4 cases of 6-month persistent infection, 1 case of 12-month persistent infection and 1 case of CIN1+ associated with HPV-16/18.

In the descriptive combined analysis of studies HPV-001/007/023, efficacy against HPV-16/18 incident and 6-month persistent infection was 91.0% (95% CI: 80.2;96.5) and 96.8% (95% CI: 80.4;99.9), respectively

Despite evidence of continuous exposure to HPV infections as observed in the control group, there is no evidence of waning protection in vaccinated women.

## **2. Study HPV-008 - Vaccine efficacy in women with/without evidence of past and/or current HPV infection**

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 naïve to the respective HPV type at month 0 and month 6) and the Total Vaccinated Cohort-1 (TVC-1 cohort: including women who received at least one vaccine dose and were naïve to the respective HPV type at month 0). Both cohorts included women with normal or low-grade cytology at baseline and excluded only women with high-grade cytology (0.5%).

In addition, analyses of efficacy were performed on the broader Total Vaccinated Cohort (TVC) which included all vaccinated women. The TVC approximates a general population of women, including those who are sexually active, and may have previous or current HPV infection, cytological abnormalities or precancerous cervical lesions. The TVC-naïve cohort includes women with no evidence of previous or current HPV infection and no cytological abnormalities, and approximates to a population of young women before sexual debut.

**Table 2: Population Cohorts analysed in Study HPV-008**

<b>Cohort</b>	<b>Abbreviation</b>	<b>Definition</b>	<b>Analysed for</b>
According to Protocol cohort	ATP	Women who received three doses of study vaccine, complied with the study protocol, and had normal or low-grade cytology at Month 0.	Primary and secondary endpoints
Total Vaccinated Cohort -1	TVC-1	Women who received at least one dose of study vaccine and had normal or low-grade cytology at Month 0	Primary and secondary endpoints
Total Vaccinated Cohort	TVC	Women who received at least one dose of study vaccine	Supportive
Total Vaccinated Cohort of HPV naïve women	TVC naïve	Women who received at least one dose of study vaccine, and had normal cytology at Month 0, were HPV DNA negative for all oncogenic types at Month 0 and seronegative for HPV-16 and HPV-18, at Month 0.	Exploratory analyses

For the three Total Vaccinated cohorts, case counting began the day after first vaccination. For the According to Protocol cohort, case counting began the day after the third vaccination.

In study HPV-008, approximately 26% of women had evidence of current and/or prior HPV-16/18 infection and less than 1% of women were HPV DNA positive for both HPV-16 and HPV-18 types at baseline. The mean follow-up for women included in study HPV-008 was approximately 39 months post dose one.

End of study analysis was performed at the end of the 4-year follow-up period (i.e. 48 months post dose one) and included all subjects from the Total Vaccinated Cohort (TVC).

Vaccine efficacy against CIN3+, CIN2+ and CIN1+ associated with HPV-16/18 are provided in Table 3.

**Table 3: Vaccine efficacy against CIN3+, CIN2+ and CIN1+ associated with HPV-16/18 - Protocol-specified analysis (ATP and TVC-1)**

HPV 16/18 endpoint		Final study analysis					End of study analysis				
		Cervarix		Control		% Efficacy (96.1% CI)	Cervarix		Control		% Efficacy (95% CI)
		N	n	N	n		N	n	N	n	
CIN3+	ATP <sup>(1)</sup>	7344	2	7312	10	80.0% (0.3;98.1)	7338	2	7305	24	91.7% (66.6;99.1)
	TVC-1 <sup>(2)</sup>	8040	2	8080	22	90.9% (60.8;99.1)	8068	2	8103	40	95.0% (80.7;99.4)
CIN2+	ATP <sup>(1)</sup>	7344	4	7312	56	92.9% (79.9;98.3)	7338	5	7305	97	94.9% (87.7;98.4)
	TVC-1 <sup>(2)</sup>	8040	5	8080	91	94.5% (86.2;98.4)	8068	6	8103	135	95.6% (90.1;98.4)
CIN1+	ATP <sup>(1)</sup>	7344	8	7312	96	91.7% (82.4;96.7)	7338	12	7305	165	92.8% (87.1;96.4)
	TVC-1 <sup>(2)</sup>	8040	11	8080	135	91.8% (84.5;96.2)	8068	15	8103	210	92.9% (88.0;96.1)

N = number of subjects included in each group  
n = number of cases  
<sup>(1)</sup> 3 doses of vaccine, 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> at least one dose of vaccine, DNA negative and seronegative at month 0 to the relevant HPV type (HPV-16 or HPV-18)

Further investigation identified that several CIN3+, CIN2+ and CIN1+ cases had multiple oncogenic HPV types in the lesion. In order to distinguish between the HPV type(s) most likely to be responsible for a lesion, from the HPV type(s) only temporally associated, an HPV type assignment was applied (exploratory analysis). The HPV type assignment considered the HPV types detected by Polymerase Chain Reaction (PCR) in at least one of the two preceding cytologic samples, in addition to types detected in the lesion. Based on this HPV type assignment, the 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 (see Table 4 below).

**Table 4: Vaccine efficacy against CIN3+, CIN2+ and CIN1+ associated with HPV-16/18 - HPV type assignment (ATP and TVC-1)**

HPV 16/18 endpoint		Final study analysis					End of study analysis				
		Cervarix		Control		% Efficacy (96.1% CI)	Cervarix		Control		% Efficacy (95% CI)
		N	n	N	n		N	n	N	n	
CIN3+	ATP <sup>(1)</sup>	7344	0	7312	8	100% (36.4; 100)	7338	0	7305	22	100% (81.8;100)
	TVC-1 <sup>(2)</sup>	8040	0	8080	20	100% (78.1;100)	8068	0	8103	38	100% (89.8;100)
CIN2+	ATP <sup>(1)</sup>	7344	1	7312	53	98.1% (88.4;100)	7338	1	7305	92	98.9% (93.8;100)
	TVC-1 <sup>(2)</sup>	8040	2	8080	87	97.7% (91.0;99.8)	8068	2	8103	128	98.4% (94.3;99.8)
CIN1+	ATP <sup>(1)</sup>	7344	2	7312	90	97.8% (91.4;99.8)	7338	3	7305	154	98.1% (94.3;99.6)
	TVC-1 <sup>(2)</sup>	8040	5	8080	128	96.1% (90.3;98.8)	8068	6	8103	196	97.0% (93.3;98.9)

N = number of subjects included in each group  
n = number of cases  
<sup>(1)</sup> 3 doses of vaccine, 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> at least one dose of vaccine, DNA negative and seronegative at month 0 to the relevant HPV type (HPV-16 or HPV-18)

In addition, at the time of final study analysis, statistically significant vaccine efficacy against CIN2+ and CIN1+ associated with HPV-16 and HPV-18 individually was demonstrated for both cohorts (Table 5).

**Table 5: Vaccine efficacy against CIN2+ and CIN1+ associated with HPV-16 and HPV- 18 - HPV type assignment**

	Vaccine Efficacy (%), 96.1% CI			
	Final Study Analysis		End of Study Analysis	
	HPV 16	HPV 18	HPV 16	HPV 18
<b>CIN2+</b>				
ATP	100 (91.0;100)	92.3 (45.7;99.9)	100 (95.3;100)	94.8 (67.2;99.9)
TVC-1	98.6 (91.5;100)	95.4 (70.1;99.9)	99.1 (94.7;100)	96.6 (79.2;99.9)
<b>CIN1+</b>				
ATP	98.5 (91.0;100)	96.6 (78.1;99.9)	99.2 (95.3;100)	95.7 (83.5;99.5)
TVC-1	96.8 (90.0;99.4)	95.0 (79.7;99.5)	98.0 (94.0;99.6)	94.9 (84.4;99.0)

Statistically significant efficacy against virological and cytological endpoints associated with HPV16/18 was demonstrated (Table 6).

**Table 6: Vaccine efficacy against virological and cytological endpoints associated with HPV-16/18 (ATP and TVC-1)**

HPV 16/18 endpoint		Final study analysis					End of study analysis				
		Cervarix		Control		% Efficacy (96.1% CI)	Cervarix		Control		% Efficacy (95% CI)
		N	n	N	n		N	n	N	n	
<b>Virological endpoints</b>											
6 month persistent infection	ATP <sup>(1)</sup>	7177	29	7122	488	94.3% (91.5;96.3)	7182	35	7137	588	94.3% (92.0;96.1)
	TVC-1 <sup>(2)</sup>	7941	67	7964	661	90.2% (87.3;92.6)	7976	73	7999	770	91.0% (88.5;93.0)
12-month persistent infection	ATP <sup>(1)</sup>	7035	20	6984	227	91.4% (86.1;95.0)	7082	26	7038	354	92.9% (89.4;95.4)
	TVC-1 <sup>(2)</sup>	7812	51	7823	340	85.3% (79.9;89.4)	7864	58	7880	478	88.2% (84.5;91.2)
<b>Cytological endpoint</b>											
Cytological abnormalities (≥ASCUS)	ATP <sup>(1)</sup>	7340	48	7312	427	89.0% (84.9;92.1)	7334	55	7305	575	90.7% (87.8;93.1)
	TVC-1 <sup>(2)</sup>	8040	75	8080	553	86.7% (82.8;89.8)	8068	84	8103	714	88.6% (85.6;91.0)
<i>N = number of subjects included in each group</i> <i>n = number of cases</i> <sup>(1)</sup> 3 doses of vaccine, 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> at least one dose of vaccine, DNA negative and seronegative at month 0 to the relevant HPV type (HPV-16 or HPV-18)											

At the time of the final study analysis, statistically significant vaccine efficacy against VIN1+ or VaIN1+ associated with HPV-16/18 was observed in the ATP cohort, 80.0% (96.1% CI: 0.3;98.1) and in the TVC-1 cohort 83.2% (96.1% CI: 20.2;98.4). At the end of study analysis, vaccine efficacy against V1N1+ or Va1N1+ associated with HPV-16/18 was 75.1% (95%CI: 22.9;94.0) in ATP cohort and 77.7% (95% CI: 32.4;94.5) in TVC-1 cohort.

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 with one of the vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the other vaccine HPV type.

### **Prophylactic efficacy against oncogenic HPV genotypes types other than HPV-16 and HPV-18**

HPV-16 and HPV-18 are not responsible for all cervical cancers. Other oncogenic HPV types can also cause cervical cancer. Study HPV-008 assessed persistent infection with the following oncogenic HPV types by PCR; HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 as a secondary endpoint. Recent studies have shown a strong association between persistent infection with oncogenic HPV and high grade abnormalities (CIN2/CIN3).

High levels of vaccine efficacy for both the virological and histopathological endpoints were also seen for the other HPV oncogenic types.

The vaccine efficacy results for the various cohorts studied are provided in Table 7.

**Table 7: Vaccine efficacy results from Study HPV-008 against non-vaccine oncogenic HPV types for CIN2+ and 6 month persistent infection**

Cohort	Vaccine Efficacy (%)					
	96.1% CI					
	Final Study Analysis % Efficacy (96.1% CI) n vaccine group vs n control			End of Study Analysis % Efficacy (96.1% CI) n vaccine group vs n control		
	ATP	TVC1	TVC naive	ATP	TVC1	TVC naive
<b>CIN2+</b>						
<i>HPV-16 related Types</i>						
HPV-31	92.0% (66.0;99.2) 2 vs 25	67.4% (32.0;85.7) 11 vs 34	100% (78.3; 100) 0 vs 20	87.5% (68.3;96.1) 5 vs 40	71.0% (47.8;84.9) 15 vs 52	89.4% (65.5; 97.9) 3 vs 28
HPV-33	51.9% (-2.9;78.9) 12 vs 25	49.8% (2.9;75.2) 16 vs 32	72.3% (19.1; 92.5) 5 vs 18	68.3% (39.7;84.4) 13 vs 41	64.5% (37.2;80.9) 17 vs 48	82.3% (53.4; 94.7) 5 vs 28
HPV-35	83.3% (-49.1;99.7) 1 vs 6	90.0% (24.6;99.8) 1 vs 10	75.1% (- 176.3;99.6) 1 vs 4	62.5% (-56.5;93.6) 3 vs 8	66.6% (-10.2;92.2) 4 vs 12	83.4% (-36.6; 99.6) 1 vs 6
HPV-52	14.3% (-108.1;65.4) 12 vs 14	-0.4% (-117.1;53.6) 17 vs 17	36.5% (-88.4;80.3) 7 vs 11	27.6% (-26.3;59.1) 24 vs 33	18.9% (-35.0;51.6) 30 vs 37	30.4% (-45.0; 67.5) 14 vs 20
HPV-58	64.5% (1.5;89.2) 6 vs 17	49.6% (-17.1;79.9) 10 vs 20	72.8% (-8.9;95.6) 3 vs 11	28.5% (-45.5;65.7) 15 vs 21	18.9% (-49.9;56.6) 21 vs 26	36.1% (-58.6; 75.6) 9 vs 14
<i>HPV-18 related types</i>						
HPV-39	69.8% (-24.2;95.2) 3 vs 10	36.0% (-90.1;80.1) 7 vs 11	66.8% (-41.4;94.8) 3 vs 9	74.9% (22.3;93.9) 4 vs 16	46.9% (-26.0;79.1) 9 vs 17	72.9% (-2.7; 95.1) 3 vs 11
HPV-45	100% (-67.8;100) 0 vs 4	100% (-20.2;100) 0 vs 5	100% (-19.5; 100) 0 vs 5	81.9% (17.0;98.1) 2 vs 11	84.6% (32.0;98.3) 2 vs 13	100% (41.7; 100) 0 vs 8
HPV-59	74.9% (-178.6;99.6) 1 vs 4	39.7% (-23.7;91.5) 3 vs 5	100% (- 514.5;100) 0 vs 2	80.0% (-79.1;99.6) 1 vs 5	57.0% (-88.2;92.8) 3 vs 7	100.0% (-429.6; 100.0) 0 vs 2
HPV-68	54.4% (-49.8;88.4) 5 vs 11	53.2% (-27.6;84.7) 7 vs 15	71.5% (-60.3;97.5) 2 vs 7	26.8% (-70.7;69.6) 11 vs 15	34.9% (-37.5;70.3) 13 vs 20	54.8% (-41.2; 87.7) 5 vs 11
<i>Other HPV types</i>						
HPV-51	62.9% (18.0;84.7) 10 vs 27	69.2% (38.0;85.9) 12 vs 39	88.3% (47.9; 98.9) 2 vs 17	54.4% (22.0;74.2) 21 vs 46	58.3% (32.5;75.0) 25 vs 60	70.2% (35.6; 87.6) 9 vs 30
HPV-56	59.9% (-47.1;91.5) 4 vs 10	61.4% (-21.2;90.0) 5 vs 13	100% (-67.1;100) 0 vs 4	46.1% (-45.2;81.8) 7 vs 13	43.7% (-35.4;78.1) 9 vs 16	100% (31.0; 100.0) 0 vs 7
HPV-66	60.0% (-46.7;91.6) 4 vs 10	66.7% (-15.8;92.8) 4 vs 12	83.4% (-48.0;99.7) 1 vs 6	56.4% (-12.1;84.8) 7 vs 16	61.2% (2.7;86.3) 7 vs 18	72.9% (-2.7; 95.1) 3 vs 11
<b>Persistent Infection 6 months-75.9%</b>						
<i>HPV-16 related Types</i>						
HPV-31	77.5% (68.3;84.4) 45 vs 199	64.9% (54.8;72.9) 93 vs 264	75.3% (62.7; 84.2) 32 vs 128	76.8% (69.0;82.9) 58 vs 247	66.7% (58.5;73.5) 107 vs 309	77.1% (67.2; 84.4) 38 vs 163

HPV-33	45.1% (21.7;61.9) 55 vs. 100	41.6% (21.8;56.6) 83 vs 142	41.8% (13.9; 61.1) 47 vs 80	44.8% (24.6;59.9) 65 vs 117	42 (24.8;55.7) 93 vs 190	43.1% (19.3; 60.2) 53 vs 92
HPV-35	-28.4% (-100.3;17.2) 55 vs 43	-19.2% (-72.0;17.1) 76 vs 64	-27.4% (- 130.8;28.9) 32 vs 25	-19.8% (-74.1;17.2) 67 vs 56	-14.5 (-57.6;16.6) 88 vs 77	-21.8% (-102.5;26.2) 38 vs 31
HPV-52	7.4% (-9.9;22.0) 293 vs 315	11.2% (-2.9;23.3) 386 vs 434	21.0% (3.6;35.3) 202 vs 253	8.3% (-6.5;21.0) 346 vs 374	10.8 (-1.5;21.7) 449 vs 501	18.9% (3.2;32.2) 231 vs 281
HPV-58	-10.3% (-48.0;17.7) 111 vs 101	-8.1% (-39.4;16.1) 145 vs 135	3.7% (-31.7;29.6) 92 vs 95	-18.3% (-51.8;7.7) 144 vs 122	-15.2% (-43.6;7.5) 180 vs 157	-6.2% (-44.0;21.6) 93 vs 87
<i>HPV-18 related types</i>						
HPV-39	1.0% (-26.7;22.7) 147 vs 146	5.2% (-16.5;22.9) 204 vs 216	17.7% (-10.2;38.7) 97 vs 117	4.8% (-17.7;23.1) 175 vs 184	7.4% (-11.0;22.8) 235 vs 254	20.9% (-2.3;38.9) 111 vs 139
HPV-45	76.1% (59.1;86.7) 19 vs 79	72.0% (56.9;82.4) 30 vs 107	82.3% (63.9; 92.3) 10 vs 56	73.6% (58.1;83.9) 24 vs 90	69.7% (55.6;79.7) 36 vs 118	79.0% (61.3; 89.4) 13 vs 61
HPV-59	4.8% (-42.4;36.4) 56 vs 59	-3.0% (-44.9;26.8) 80 vs 78	13.2% (-26.0;40.4) 62 vs 71	-7.5% (-51.8;23.8) 73 vs 68	-15.1% (-55.2;14.5) 100vs87	-3.9% (-61.7;33.1) 45 vs 43
HPV-68	-3.1% (-33.4;20.3) 138 vs 134	1.4% (-22.8;20.8) 185 vs 188)	3.4% (-30.4;28.4) 100 vs 103	2.6% (-21.5;21.9) 165 vs 169	5.3% (-14.7;21.9) 213 vs 225	8.9% (-18.8;30.1) 112 vs122
<i>Other HPV types</i>						
HPV-51	14.5% (-0.8;27.4) 304 vs 354	15.8% (3.0;27.0) 401 vs 475	27.2% (12.1; 39.8) 217 vs 294	16.6% (3.6;27.9) 349 vs 416	17.1% (5.9;26.9) 453 vs 543	25.5% (12.0; 37.0) 253 vs 334
HPV-56	-5.0% (-31.5;16.1) 182 vs 174	1.5% (-20.2;19.2) 225 vs 229	-2.0% (-34.2;22.5) 122 vs 119	-5.3% (-27.5;13.1) 226 vs 215	1.0% (-17.5;16.6) 272 vs 275	1.4% (-24.8;22.0) 147 vs 148
HPV-66	5.7% (-18.4;24.9) 168 vs 178	3.7% (-18.0;21.4) 213 vs 221	2.2% (-29.4;26.1) 115 vs 117	2.3% (-18.7;19.6) 211 vs 215	-0.4% (-19.6;15.7) 263 vs 261	-1.5% (-29.3;20.3) 141 vs 138

At the time of the final study analysis, statistically significant vaccine efficacy against 6-month persistent infection has been observed for HPV types 31, 33 and 45 in the ATP cohort and for HPV types 31, 33, 45 and 51 in the TVC-1 cohort. Statistically significant vaccine efficacy against CIN2+ has been observed for HPV types 31, 51 and 58 in the ATP cohort and for HPV types 31, 33, 35 and 51 in the TVC-1 cohort.

At the end of study analysis, more cases were accrued and a lower limit of the 95% CI above zero has been observed for HPV types 31, 33, 45 and 51 for both 6 month persistent infection and CIN2+ in the ATP and TVC-1 cohorts. For CIN2+, a lower limit of the 95% CI above zero has also been observed for HPV type 39 in the ATP cohort and HPV type 66 in the TVC-1 cohort.

The results for vaccine efficacy against the virological and histopathological endpoints were statistically significant for all oncogenic HPV types including HPV16/18, in HPV DNA negative subjects, regardless of initial serostatus, in the ATP cohort and are provided in Table 8.

**Table 8: Vaccine efficacy associated with oncogenic HPV types in HPV DNA negative subjects at baseline, regardless of initial serostatus (ATP cohort)**

	Final study analysis					End of study analysis				
	Cervarix		Control		% Efficacy (96.1% CI)	Cervarix		Control		% Efficacy (95% CI)
	N	n	N	n		N	n	N	n	
6 month persistent infection	7665	1271	7640	1647	25.0% (18.9;30.6)	7672	1424	7656	1837	25.4% (20.0;30.4)
12-month persistent infection	7509	585	7488	803	28.4% (19.8;36.1)	7560	824	7545	1112	27.8% (20.9;34.1)
ASC-US	7858	953	7853	1212	22.1 (14.8;28.9)	7850	1201	7846	1574	25.1% (19.2;30.5)
CIN1+	7863	151	7853	279	45.9 (33.1;56.4)	7855	235	7846	443	47.3% (38.1;55.2)
CIN2+	7863	54	7853	142	61.9 (46.7;73.2)	7855	92	7846	220	58.3% (46.6;67.7)

Overall impact of the vaccine on HPV disease burden

The overall vaccine efficacy irrespective of HPV DNA in lesions and stratified by baseline HPV DNA status and serostatus was evaluated in study HPV-008 (see Table 9).

In the TVC and TVC-naïve cohorts which included all vaccinated women, vaccine efficacy against CIN3+, CIN2+ and CIN1+ was demonstrated (see Table 9). The impact of Cervarix on reduction of local cervical therapy (Loop Electro-Excision Procedure, Cone, Knife or Laser) was also demonstrated in the same cohorts (see Table 9).

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 (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, -68) and seronegative for HPV-16 and HPV-18 at baseline.

**Table 9: Vaccine efficacy irrespective of HPV DNA type in lesions regardless of initial serostatus**

		Final study analysis					End of study analysis				
		Cervarix		Control		% Efficacy (96.1% CI)	Cervarix		Control		% Efficacy (95% CI)
		N	n	N	n		N	n	N	n	
CIN3+	TVC naïve <sup>(1)</sup>	5449	3	5436	23	87.0% (54.9;97.7)	5466	3	5452	44	93.2% (78.9;98.7)
	TVC <sup>(2)</sup>	8667	77	8682	116	33.4% (9.1;51.5)	8694	86	8708	158	45.6% (28.8;58.7)
CIN2+	TVC naïve <sup>(1)</sup>	5449	33	5436	110	70.2% (54.7;80.9)	5466	61	5452	172	64.9% (52.7;74.2)
	TVC <sup>(2)</sup>	8667	224	8682	322	30.4% (16.4;42.1)	8694	287	8708	428	33.1% (22.2;42.6)
CIN1+	TVC naïve <sup>(1)</sup>	5449	106	5436	211	50.1% (35.9;61.4)	5466	174	5452	346	50.3% (40.2;58.8)
	TVC <sup>(2)</sup>	8667	451	8682	577	21.7% (10.7;31.4)	8694	579	8708	798	27.7% (19.5;35.2)
Local cervical therapy	TVC naïve <sup>(1)</sup>	5449	26	5436	83	68.8% (50.0;81.2)	5466	43	5452	143	70.2% (57.8;79.3)
	TVC <sup>(2)</sup>	8667	180	8682	240	24.7% (7.4;38.9)	8694	230	8708	344	33.2% (20.8;43.7)

N = number of subjects included in each group

n = number of cases

<sup>(1)</sup> 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.

<sup>(2)</sup> TVC: includes all vaccinated subjects (who received at least one dose of vaccine).

### **Vaccine-Induced Immunogenicity**

The antibody response to HPV-16 and HPV-18 was measured using a type specific ELISA which was shown to strongly correlate with neutralisation assays (including pseudovirion based neutralising assay developed by the US National Cancer Institute). Due to the high efficacy of the vaccine, it has not been possible to establish minimum anti-HPV-16 and anti-HPV-18 antibody levels that protect against clinical disease caused by HPV-16 and/or 18.

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, 99.9% of initially seronegative subjects had seroconverted to both HPV type 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.

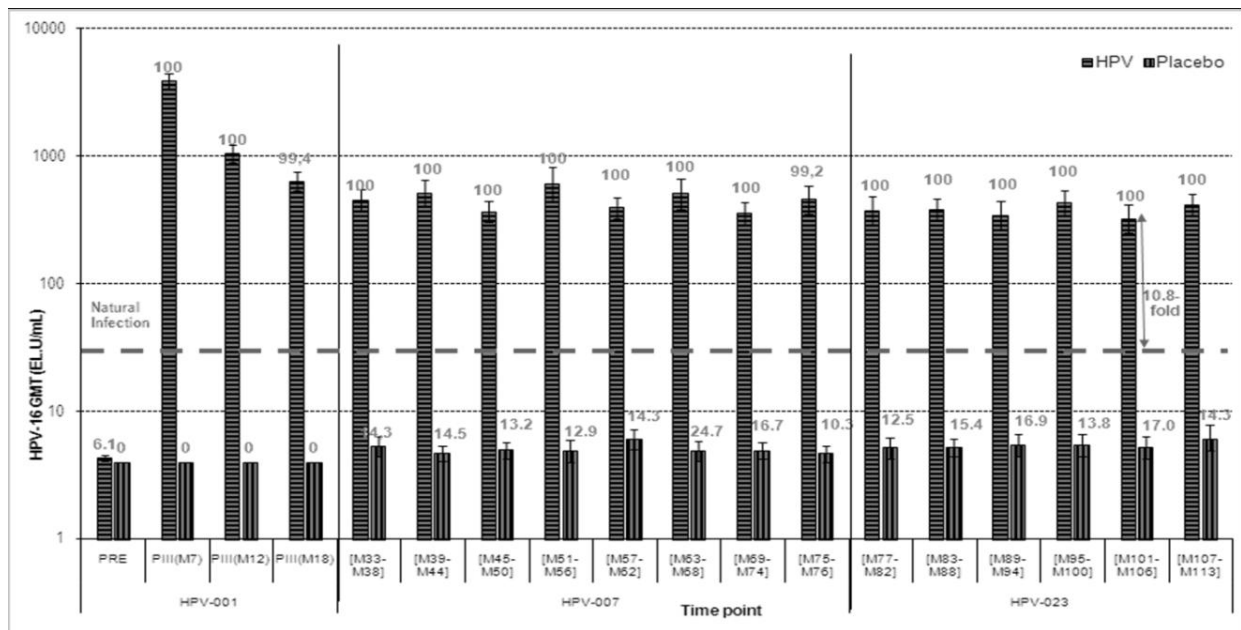
### **Immunogenicity in women aged 15 to 25 years**

The immune response against HPV-16 and HPV-18 was evaluated up to 73 months after first vaccination, in study HPV-001/007 in women 15 to 25 years old at the time of vaccination. In study HPV-023, this immune response continued to be evaluated up to 9.4 years (113 months) after first vaccination in a subset of the population from study HPV-001/007.

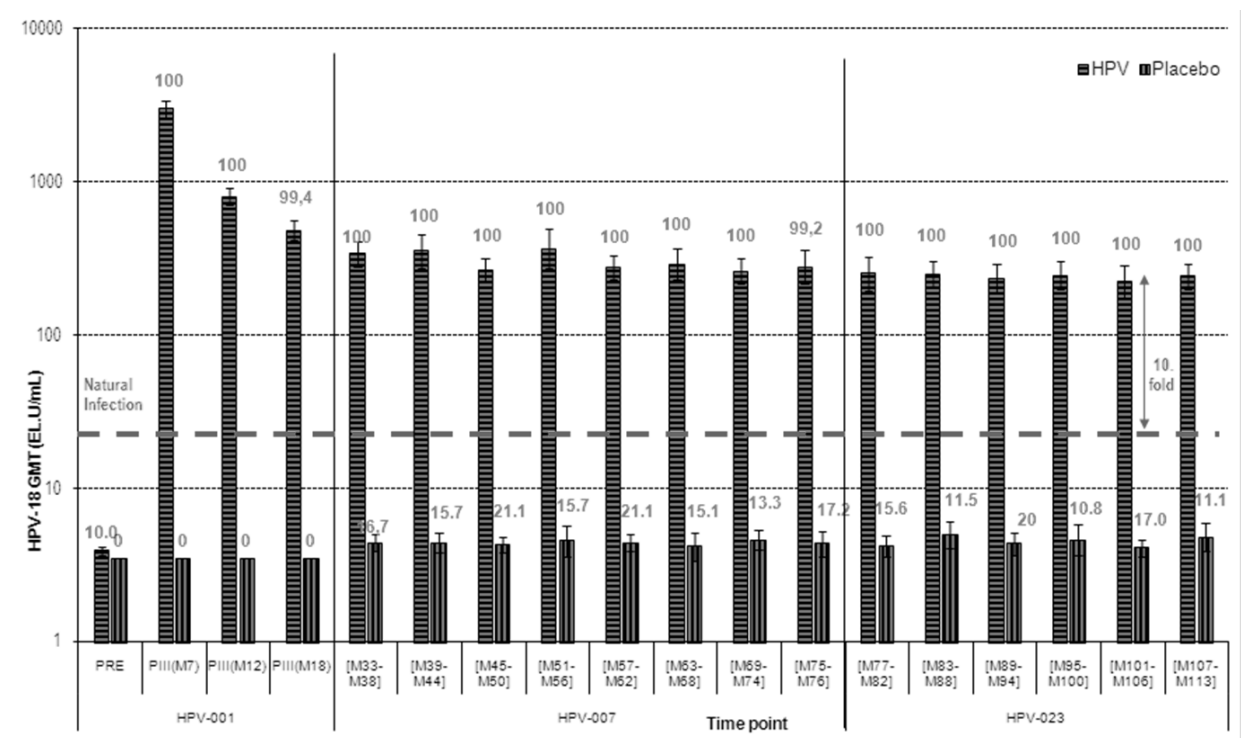
In study HPV-023,  $\geq 96.7\%$  of women were seropositive for both HPV-16 and HPV-18 by ELISA or by pseudovirion-based neutralizing assay (PBNA) up to 9.4 years after first vaccination.

Immunogenicity results from studies HPV-001/007/023 are presented in Figures 1 and 2 below:

**Figure 1: Evolution of GMTs for anti-HPV-16 IgG antibodies during studies HPV-001, HPV-007 and HPV-023 (ATP cohort for immunogenicity)**



**Figure 2: Evolution of GMTs for anti-HPV-18 IgG antibodies during studies HPV-001, HPV-007 and HPV-023 (ATP cohort for immunogenicity)**



Vaccine-induced IgG Geometric Mean Titres (GMT) for both HPV-16 and HPV-18 peaked at month 7 and then declined to reach a plateau from month 18 with no substantial decline up to the end of the follow-up period (month 113). At month 113, GMTs for both HPV-16 and HPV-18 were still at least 11-fold higher than titres observed in women previously infected but who cleared HPV infection (natural infection) and 100% of the women were seropositive for both antigens.

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

### **Bridging the efficacy of Cervarix demonstrated in 15 to 25 year olds to other age groups**

In two clinical trials performed in girls and adolescents aged 10 to 14 years, all subjects seroconverted to both HPV type 16 and 18 after the third dose (at month 7) with GMTs at least 2-fold higher as compared to women aged 15 to 25 years.

In study HPV-014 performed in women aged 26 to 55 years (N= 362), all subjects were seropositive to both HPV type 16 and 18 after the third dose (at month 7). The GMTs were lower in this population compared to women aged 15 to 25 years. However, all subjects remained seropositive for HPV-16 and all subjects except one remained seropositive for HPV-18 throughout the follow-up phase (up to month 48) maintaining antibody levels at an order of magnitude above those encountered after natural infection.

On the basis of immunogenicity data observed in females 10 to 14 and 26 to 55 years old, the efficacy of Cervarix is inferred from 10 years of age onwards.

### **5.3 Pharmacokinetic properties**

Evaluation of pharmacokinetic properties is not required for vaccines.

## **6. NON-CLINICAL INFORMATION**

### **6.1 Carcinogenesis, mutagenesis**

No studies were done with Cervarix. However, the MPL adjuvant was not mutagenic in standard mutagenicity tests.

### **6.2 Reproductive toxicology**

Animal studies performed with Cervarix administered to female rats do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or postnatal development.

### **6.3 Animal toxicology and/or pharmacology**

Non-clinical data reveal no special hazard for humans based on conventional studies of acute and repeated dose toxicity, local tolerance and cardiovascular/respiratory safety pharmacology.

## **7. PHARMACEUTICAL PARTICULARS**

### **7.1 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.

## 7.2 Incompatibilities

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

## 7.3 Shelf life

When stored at the recommended temperature of +2°C to +8°C, the shelf life of Cervarix is 4 years.

## 7.4 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.

In case of temporary storage of the vaccine outside refrigerator, experimental data have shown that the vaccine is stable when stored at temperatures up to 37°C for 1 day. These data are not recommendations for storage.

## 7.5 Nature and contents of container

- 0.5mL 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 or 10 or
- 0.5ml of suspension vial (type I glass) with a stopper (rubber butyl) in pack sizes of 1, 10 and 100.

Not all strengths, dose forms, pack sizes, container types may be distributed in New Zealand.

## 7.6 Special precautions for disposal

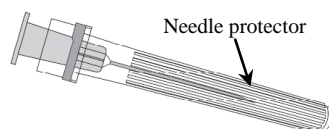
A fine white deposit with a clear colourless supernatant may be observed upon storage of the vial. This does not constitute a sign of deterioration.

The content of the syringe/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.

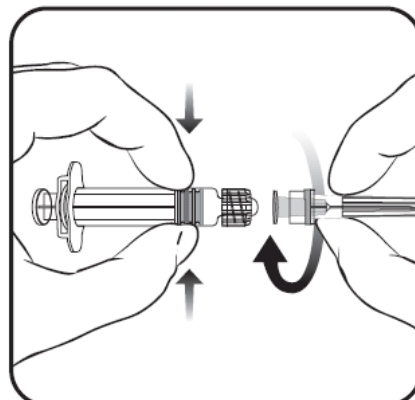
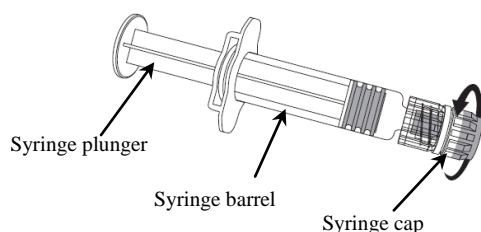
The vaccine should be well shaken before use.

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

*Needle*



*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. (see picture)
3. Remove the needle protector, which on occasion can be a little stiff.
4. Administer the vaccine.

CERVARIX syringe or vials are for single use in a single patient only. Any unused product or waste material should be disposed of in accordance with local requirements.

## **8. MEDICINE CLASSIFICATION**

Prescription medicine.

## **9. MARKETING AUTHORISATION HOLDER**

GlaxoSmithKline NZ Ltd  
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## **10. DATE OF PREPARATION**

21 December 2011

VERSION: 6.0