

*For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory*

## **CERVARIX®**

### **Human Papillomavirus Vaccine rDNA Ph Eur**

#### **1. NAME OF THE MEDICINAL PRODUCT**

Human Papillomavirus Vaccine rDNA Ph Eur

#### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

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- <i>O</i> -desacyl-4'-monophosphoryl lipid A (MPL) <sup>2</sup>	50 micrograms
Aluminium hydroxide, hydrated <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 5.1 *Pharmacodynamic Properties*).

#### **3. PHARMACEUTICAL FORM**

Suspension for injection.

Turbid white suspension.

#### **4. CLINICAL PARTICULARS**

##### **4.1 Therapeutic Indications**

*CERVARIX* is indicated in females from 10 to 45 years of age for the prevention of cervical cancer by protecting against incident and persistent infections, cytological abnormalities including atypical squamous cells of undetermined significance (ASC-US) and cervical intraepithelial neoplasia (CIN), CIN 1 and pre-cancerous lesions (CIN 2 and CIN 3) caused by human papillomavirus types 16 and 18.

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.

##### **4.2 Posology and Method of Administration**

### ***Posology***

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

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

The need for a booster dose has not been established (see *5.1 Pharmacodynamic Properties*).

It is recommended that subjects who receive a first dose of *CERVARIX* complete the 3-dose vaccination course with *CERVARIX* (see *4.4 Special Warnings and Precautions for Use*).

### ***Paediatric Population:***

*CERVARIX* is not recommended for use in girls below 9 years of age due to lack of data on safety and immunogenicity in this age-group.

### ***Method of Administration***

*CERVARIX* is for intramuscular injection in the deltoid region (see *4.4 Special Warnings and Precautions for Use* and *4.5 Interaction with other medicinal products and other forms of interaction*).

## **4.3 Contraindications**

Hypersensitivity to the active substances or to any of the excipients listed in section *6.1 List of 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 reaction following the administration of the vaccine.

Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic

limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

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

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

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

*CERVARIX* will only protect against diseases that are caused by HPV types 16 and 18 and to some extent against diseases caused by certain other oncogenic related HPV types (see section 5.1 *Pharmacodynamic Properties*). 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 *Pharmacodynamic Properties* “Efficacy in women with evidence of HPV-16 or HPV-18 infection at study entry.”).

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

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

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

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

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

In all clinical trials individuals who had received immunoglobulin or blood-derived products within 3 months prior to the first vaccine dose were excluded.

##### ***Use with other vaccines***

*CERVARIX* may be administered concomitantly with a combined booster vaccine containing diphtheria (d), tetanus (T) and pertussis [acellular] (pa) with or without inactivated poliomyelitis (IPV), (dTpa, dTpa-IPV vaccines), with no clinically relevant interference with antibody response to any of the components of either vaccine. The sequential administration of combined dTpa-IPV followed by *CERVARIX* one month later tended to elicit lower anti-HPV-16 and anti-HPV-18 GMTs as compared to *CERVARIX* alone. The clinical relevance of this observation is not known.

*CERVARIX* may be administered concomitantly with a combined hepatitis A (inactivated) and hepatitis B (rDNA) vaccine (*TWINRIX*) or with hepatitis B (rDNA) vaccine (*ENGERIX B*).

Administration of *CERVARIX* at the same time as *TWINRIX* has shown no clinically relevant interference in the antibody response to the HPV and hepatitis A antigens. Anti-HBs geometric mean antibody concentrations were significantly lower on co-administration, but the clinical relevance of this observation is not known since the seroprotection rates remain unaffected. The proportion of subjects reaching anti-HBs  $\geq 10$ 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 Pregnancy and Lactation**

### ***Pregnancy***

Specific studies of the vaccine in pregnant women were not conducted. However, during the clinical development program, a total of 10,476 pregnancies were reported including 5,387 in women who had received *CERVARIX*. Overall, the proportions of pregnant subjects who experienced specific outcomes (e.g., normal infant, abnormal infants including congenital anomalies, premature birth, and spontaneous abortion) were similar between treatment groups.

Animal studies do not indicate direct or indirect harmful effects with respect to fertility, pregnancy, embryonal/foetal development, parturition or post-natal development (see section 5.3 *Preclinical safety data*).

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

#### *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.

#### *Fertility*

No fertility data are available.

### **4.7 Effect on Ability to Drive and Use Machines**

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

### **4.8 Undesirable Effects**

#### *Summary of safety profile*

In clinical studies that enrolled girls and women aged from 10 up to 72 years (of which 79.2% were aged 10-25 years at the time of enrolment), *CERVARIX* was administered to 16,142 subjects whilst 13,811 subjects received control. These subjects were followed for serious adverse events over the entire study period. In a pre-defined subset of subjects (*CERVARIX* = 8,130 versus control = 5,786), adverse events were followed for 30 days after each injection.

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

#### *List of adverse reactions*

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

Frequencies are reported as:

Very common ( $\geq 1/10$ )

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

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

- *Clinical trial data*

#### Infections and infestations:

Uncommon: upper respiratory tract infection

Nervous system disorders:

Very common: headache

Uncommon: dizziness

Gastrointestinal disorders:

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

Skin and subcutaneous tissue disorders:

Common: itching/pruritus, rash, urticaria

Musculoskeletal and connective tissue disorders:

Very common: myalgia

Common: arthralgia

General disorders and administration site conditions:

Very common: injection site reactions including pain, redness, swelling; fatigue

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

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

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

- *Post marketing data*

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

Blood and lymphatic system disorders

Lymphadenopathy

Immune system disorders

Allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema

Nervous system disorders

Syncope or vasovagal responses to injection, sometimes accompanied by tonic-clonic movements (see section 4.4 *Special warnings and precautions for use*)

## **4.9 Overdose**

No case of overdose has been reported.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic Properties**

Pharmaco-therapeutic group: Vaccines, Papillomavirus vaccines, ATC code: J07BM02

### ***Mechanism of Action***

*CERVARIX* is an adjuvanted non-infectious recombinant vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid L1 protein of oncogenic HPV types 16 and 18. Since the VLPs contain no viral DNA, they cannot infect cells, reproduce or cause disease. Animal studies have shown that the efficacy of L1 VLP vaccines is largely mediated by the development of a humoral immune response.

HPV-16 and HPV-18 are estimated to be responsible for approximately 70% of cervical cancers. Other oncogenic HPV types can also cause cervical cancer (approximately 30%). HPV 45, -31 and -33 are the 3 most common non-vaccine HPV types identified in squamous cervical carcinoma (12.1%) and adenocarcinoma (8.5%).

The term “pre-cancerous lesions” in section *4.1 Therapeutic indications* corresponds to high-grade Cervical Intraepithelial Neoplasia (CIN2/3).

### ***Clinical studies***

#### *Clinical efficacy in women aged 15 to 25 years*

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

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

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

The primary efficacy endpoint was incident infection with HPV-16 and/or HPV-18. Twelve-month persistent infection was evaluated as additional efficacy endpoint.

The phase III trial (study 008) enrolled women without pre-screening for the presence of HPV infection, i.e. regardless of baseline cytology and HPV serological and DNA status.

The primary efficacy endpoint was CIN2+ associated with HPV-16 and/or HPV-18 (HPV-16/18). Cervical Intraepithelial Neoplasia (CIN) grade 2 and 3 (CIN2/3) and cervical adenocarcinoma in situ (AIS) were used in the clinical trials as surrogate markers for cervical cancer.

The secondary endpoints included 6- and 12-month persistent infection.

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

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

Women (N=1,113) were vaccinated in study 001 and evaluated for efficacy up to month 27. A subset of women (N=776) vaccinated in study 001 was followed in study 007 up to 6.4 years (approximately 77 months) after the first dose (mean follow-up of 5.9 years). There were five cases of 12-month persistent HPV-16/18 infection (4 HPV-16; 1 HPV-18) in the control group and one HPV-16 case in the vaccine group in study 001. In study 007 the efficacy of *CERVARIX* against 12-month persistent HPV-16/18 infection was 100% (95% CI: 80.5; 100). There were sixteen cases of persistent HPV-16 infection, and five cases of persistent HPV-18 infection, all in the control group.

In study HPV-023, subjects from the Brazilian cohort (N=437) of study 001/007 were followed up to a mean of 8.9 years (standard deviation 0.4 years) after the first dose. At study completion, there were no cases of infection or histopathological lesions associated with HPV-16 or HPV-18 in the vaccine group in study HPV-023. In the placebo group, there were 4 cases of 6-month persistent infection and 1 case of 12-month persistent infection. The study was not powered to demonstrate a difference between the vaccine and the placebo group for these endpoints.

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

In study HPV-008, the primary analyses of efficacy were performed on the According to Protocol cohort (ATP cohort: including women who received 3 vaccine doses and were DNA negative and seronegative at month 0 and DNA negative at month 6 for the HPV type considered in the analysis) This cohort included women with normal or low-grade cytology at baseline and excluded only women with high-grade cytology (0.5% of the total population). Case counting for the ATP cohort started on day 1 after the third dose of vaccine.

Overall, 74% of women enrolled were naïve to both HPV-16 and HPV-18 (i.e. DNA negative and seronegative at study entry).

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

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

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

HPV-16/18 endpoint	ATP cohort <sup>(1)</sup>		
	End of study analysis <sup>(3)</sup>		
	Cervarix (N = 7338)	Control (N = 7305)	% Efficacy (95% CI)
	n <sup>(2)</sup>	n	
CIN2+	5	97	94.9% (87.7;98.4)
CIN3+	2	24	91.7% (66.6;99.1)



N = number of subjects included in each group

n = number of cases

<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 4 cases of CIN2+ and 2 cases of CIN3+ in which another oncogenic HPV type was identified in the lesion, concomitantly with HPV-16 or HPV-18. These cases are excluded in the HPV type assignment analysis (see under Table).

<sup>(3)</sup> mean follow-up of 40 months post dose 3

At the event-triggered analysis the efficacy was 92.9% (96.1% CI:79.9;98.3) against CIN2+ and 80% (96.1% CI: 0.3;98.1) against CIN3+. In addition, statistically significant vaccine efficacy against CIN2+ associated with HPV-16 and HPV-18 individually was demonstrated.

Further investigation of the cases with multiple HPV types considered the HPV types detected by Polymerase Chain Reaction (PCR) in at least one of the two preceding cytology samples, in addition to types detected in the lesion to distinguish the HPV type(s) most likely responsible to the lesion (HPV type assignment). This post-hoc analysis excluded cases (in the vaccine group and in the control group) which were not considered to be causally associated with HPV-16 or HPV-18 infections acquired during the trial.

Based on the HPV type assignment post-hoc analysis, there was 1 CIN2+ case in the vaccine group versus 92 cases in the control group (Efficacy 98.9% (95% CI: 93.8;100)) and no CIN3+ case in the vaccine group versus 22 cases in the control group (Efficacy 100% (95% CI: 81.8;100)) at the end of study analysis.

In the event-triggered analysis, vaccine efficacy against CIN1 associated with HPV 16/18 observed in the ATP cohort was 94.1% (96.1% CI: 83.4;98.5). Vaccine efficacy against CIN1+ associated with HPV 16/18 observed in the ATP cohort was 91.7% (96.1% CI: 82.4;96.7). At the end of study analysis, vaccine efficacy against CIN1 associated with HPV 16/18 observed in the ATP cohort was 92.8% (95% CI: 87.1;96.4).

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

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

HPV-16/18 endpoint	ATP cohort <sup>(1)</sup>		
	End of study analysis <sup>(2)</sup>		
	Cervarix (N = 7338)	Control (N = 7305)	% Efficacy (95% CI)
6-month persistent infection	n/N 35/7182	n/N 588/7137	

<b>12-month persistent infection</b>	26/7082	354/7038	92.9% (89.4;95.4)
<p>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> mean follow-up of 40 months post dose 3</p>			

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

*Efficacy against HPV-16/18 in women with evidence of HPV-16 or HPV-18 infection at study entry.*

There was no evidence of protection from disease caused by the HPV types for which subjects were HPV DNA positive at study entry. However, individuals already infected (HPV DNA positive) with one of the vaccine-related HPV types prior to vaccination were protected from clinical disease caused by the other vaccine HPV type.

*Efficacy against HPV types 16 and 18 in women with and without prior infection or disease.*

The Total Vaccinated Cohort (TVC) included all subjects who received at least one dose of the vaccine, irrespective of their HPV DNA status, cytology and serostatus at baseline. This cohort included women with or without current and/or prior HPV infection. Case counting for the TVC started on day 1 after the first dose.

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

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

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

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

<b>HPV-16/18 endpoint</b>	<b>TVC<sup>(1)</sup></b>		
	<b>End of study analysis<sup>(2)</sup></b>		
	<b>Cervarix (N = 8694)</b>	<b>Control (N = 8708)</b>	<b>% Efficacy (95% CI)</b>
<b>n</b>	<b>n</b>		
<b>CIN2+</b>	90	228	60.7% (49.6;69.5)
<b>CIN3+</b>	51	94	45.7% (22.9;62.2)

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  
<sup>(2)</sup> mean follow-up of 44 months post dose 1

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

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

HPV-16/18 endpoint	TVC <sup>(1)</sup>		
	End of study analysis <sup>(2)</sup>		
	Cervarix	Control	% Efficacy (95% CI)
n/N	n/N		
<b>6-month persistent infection</b>	504/8863	1227/8870	60.9% (56.6;64.8)
<b>12-month persistent infection</b>	335/8648	767/8671	57.5% (51.7;62.8)

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.  
<sup>(2)</sup> mean follow-up of 44 months post dose 1

Overall impact of the vaccine on cervical HPV disease burden

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

The TVC-naïve is a subset of the TVC that includes women with normal cytology, and who were HPV DNA negative for 14 oncogenic HPV types and seronegative for HPV-16 and HPV-18 at baseline.

**Table 5: Vaccine efficacy against high-grade cervical lesions irrespective of the HPV DNA type in the lesion**

	End of study analysis <sup>(3)</sup>				
	Cervarix		Control		% Efficacy (95% CI)
	N	Cases	N	Cases	
<b>CIN2+</b>					
<b>TVC-naïve<sup>(1)</sup></b>	5466	61	5452	172	64.9% (52.7;74.2)

<b>TVC<sup>(2)</sup></b>	8694	287	8708	428	33.1% (22.2;42.6)
<b>CIN3+</b>					
<b>TVC-naïve<sup>(1)</sup></b>	5466	3	5452	44	93.2% (78.9;98.7)
<b>TVC<sup>(2)</sup></b>	8694	86	8708	158	45.6% (28.8;58.7)
N = number of subjects included in each group					
<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) irrespective of HPV DNA status, cytology and serostatus at baseline.					
<sup>(3)</sup> mean follow-up of 44 months post dose 1					

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

### Cross-protective efficacy

The cross-protective efficacy of *CERVARIX* against histopathological and virological endpoints (persistent infection) has been evaluated in study HPV-008 for 12 non-vaccine oncogenic HPV types. The study was not powered to assess efficacy against disease caused by individual HPV types. The analysis against the primary endpoint was confounded by multiple co-infections in the CIN2+ lesions. Unlike histopathological endpoints, virological endpoints are less confounded by multiple infections.

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

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

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

ATP <sup>(1)</sup>						
HPV type	6-month persistent infection			CIN2+		
	Cervarix	Control	% Efficacy (95% CI)	Cervarix	Control	% Efficacy (95% CI)
	n	n		n	n	
<b>HPV-16 related types (A9 species)</b>						
HPV-31	58	247	76.8% (69.0;82.9)	5	40	87.5% (68.3;96.1)
HPV-33	65	117	44.8% (24.6;59.9)	13	41	68.3% (39.7;84.4)
HPV-35	67	56	-19.8% (<0;17.2)	3	8	62.5% (<0;93.6)
HPV-52	346	374	8.3% (<0;21.0)	24	33	27.6% (<0;59.1)
HPV-58	144	122	-18.3% (<0;7.7)	15	21	28.5% (<0;65.7)
<b>HPV-18 related types (A7 species)</b>						

HPV-39	175	184	4.8% (<0;23.1)	4	16	74.9% (22.3;93.9)
HPV-45	24	90	73.6% (58.1;83.9)	2	11	81.9% (17.0;98.1)
HPV-59	73	68	-7.5% (<0;23.8)	1	5	80.0% (<0;99.6)
HPV-68	165	169	2.6% (<0;21.9)	11	15	26.8% (<0;69.6)
<b>Other types</b>						
HPV-51	349	416	16.6% (3.6;27.9)	21	46	54.4% (22.0;74.2)
HPV-56	226	215	-5.3% (<0;13.1)	7	13	46.1% (<0;81.8)
HPV-66	211	215	2.3% (<0;19.6)	7	16	56.4% (<0;84.8)
<p>n= number of cases</p> <p><sup>(1)</sup> ATP: includes women who received 3 doses of vaccine, were DNA negative at month 0 and at month 6 to the relevant HPV type.</p> <p>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 &lt;0, the efficacy is not considered statistically significant.</p> <p>The efficacy against CIN3 was only demonstrated for HPV-31 and there was no evidence of protection against AIS for any of the HPV types.</p>						

#### Clinical efficacy in women aged 26 years and older

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

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

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

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

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

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

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

## ***Immunogenicity***

### ***Immune response to CERVARIX after the primary vaccination course***

No minimal antibody level associated with protection against CIN of grade 2 or 3 or against persistent infection associated with vaccine HPV types has been identified for HPV vaccines.

The antibody response to HPV-16 and HPV-18 was measured using a type-specific direct ELISA (version 2, MedImmune methodology, modified by GSK) which was shown to correlate with the pseudovirion-based neutralisation assay (PBNA).

The immunogenicity induced by three doses of *CERVARIX* has been evaluated in 5,303 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 113 months. 92 subjects in the vaccine group had immunogenicity data at the [M107-M113] interval after the first vaccine dose with a median follow-up of 8.9 years. Of these subjects, 100% (95% CI: 96.1;100) remained seropositive for HPV-16 and HPV-18 in the ELISA assay.

Vaccine-induced IgG GMTs for both HPV-16 and HPV-18 peaked at month 7 and then declined to reach a plateau from month 18 up to the [M107-M113] interval with ELISA GMTs for both HPV-16 and HPV-18 at least still 10-fold higher than the ELISA GMTs observed in women who cleared a natural HPV infection.

In study 008, immunogenicity up to month 48 was similar to the response observed in study 001. A similar kinetic profile was observed with the neutralising antibodies.

In another clinical trial (study 014) performed in women aged 15 to 55 years, all subjects seroconverted to both HPV types 16 and 18 after the third dose (at month 7). The GMTs were, however, lower in women above 25 years. Nevertheless, all subjects remained seropositive for both types throughout the follow-up phase (up to month 18) maintaining antibody levels at an order of magnitude above those encountered after natural infection.

### Evidence of Anamnestic (Immune Memory) Response

In study 024 (a subset of study 001/007), a challenge dose of *CERVARIX* was administered to 65 subjects at a mean interval of 6.8 years after the administration of the first vaccine dose. An anamnestic immune response to HPV-16 and HPV-18 (by ELISA) was observed one week and one month after the challenge dose, GMTs one month after the challenge dose exceeded those observed one month after the primary 3-dose vaccination.

### Bridging the efficacy of *CERVARIX* 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 a clinical study performed in women aged 26 to 55 years, all subjects were seropositive to both HPV type 16 and 18 after the third dose (at month 7) and remained seropositive for both types up to month 18 with GMTs that were still at least in the same range as those observed in the plateau of the long term follow up in the efficacy study HPV-001/007.

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.

### Immunogenicity in women aged 26 years and older

In the Phase III study (HPV-015) in women 26 years and older, at the 48-month time point, i.e. 42 months after completion of the full vaccination course, 100% and 99.4% of initially seronegative women remained seropositive for anti-HPV-16 and anti-HPV-18 antibodies, respectively. All initially seropositive women remained seropositive for both anti-HPV-16 and anti-HPV-18 antibodies. Antibody titers peaked at month 7 then gradually declined up to month 18 and stabilized to reach a plateau up to month 48.

### Immunogenicity in HIV infected women

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

## **5.2 Pharmacokinetic Properties**

Not applicable.

## **5.3 Preclinical safety data**

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

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

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of Excipients**

Sodium chloride, sodium dihydrogen phosphate dihydrate, water for injection

### **6.2 Incompatibilities**

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

### **6.3 Shelf Life**

48 months

The expiry date of the vaccine is indicated on the label and packaging.

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

However, for the monodose containers, the stability has been demonstrated when stored outside the refrigerator 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.

**KEEP OUT OF REACH OF CHILDREN**

### **6.5 Nature and Specifications 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.

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



Not all the presentations may be marketed in India.

## 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/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.

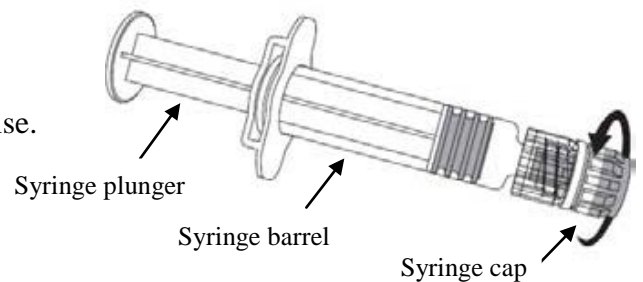
In the event of either being observed, discard the vaccine.

The vaccine should be well shaken before use.

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

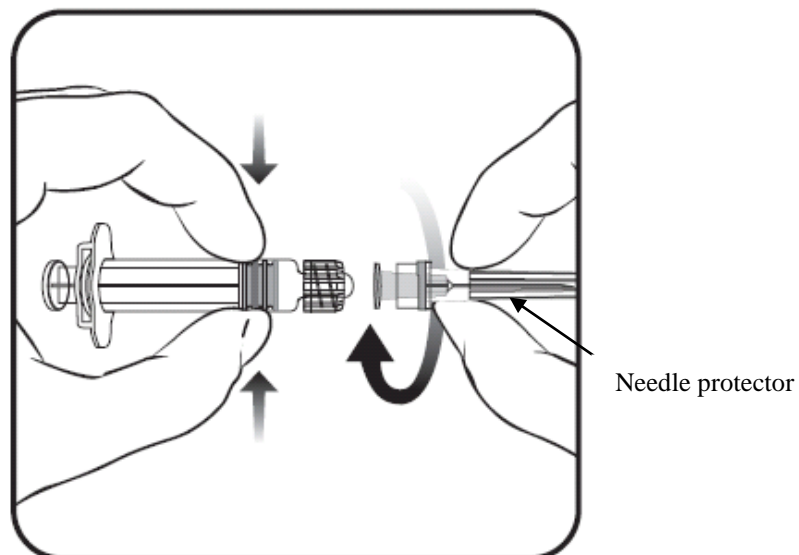
### *Instructions for administration of the vaccine presented in pre-filled syringe*

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.

## 7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Asia Private Limited

Registered Office:  
Patiala Road,  
Nabha (Punjab) 147 201

**8. MARKETING AUTHORISATION NUMBER(S)**

Import Permission No.: Import-955/08

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorization (Form 45): 20<sup>th</sup> September, 2008

<b>Manufactured by:</b>	<b>Imported by:</b>	<b>For further information please contact:</b>
GlaxoSmithKline Biologicals s.a. Rue de l'Institut, 89 B-1330 Rixensart, Belgium.	GlaxoSmithKline Pharmaceuticals Limited. No. 144 (Southern Portion of Ground and First Floor) Poonamallee High Road, Velappanchavadi Chennai - 600077	GlaxoSmithKline Pharmaceuticals Limited, Registered office: Dr. Annie Besant Road, Worli Mumbai 400 030, India

*CERVARIX is a trademark of the GlaxoSmithKline group of companies*

*Version CER-B/PI/IN/2016/01 dated 18<sup>th</sup> April 2016*

*Adapted from EU SPC last updated 27<sup>th</sup> June, 2013 [GDS 19 / IPI 13 dated 14<sup>th</sup> Feb, 2012 and GDS 20 / IPI 15 dated 24<sup>th</sup> May, 2012]*

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