Cervarix

1. Name of the medicinal product

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

2. Qualitative and quantitative composition

1 dose (0.5 ml) contains:

Human Papillomavirus type 16 L1 protein[1]	20 micrograms
Human Papillomavirus type 18 L1 protein[1]	20 micrograms
3-*O*-desacyl-4'-monophosphoryl lipid A (MPL)[2]	50 micrograms
Aluminium hydroxide, hydrated[2]	0.5 milligrams Al^{3+}

[1]L1 protein in the form of non-infectious virus-like particles (VLPs) produced by recombinant DNA technology using a Baculovirus expression system
[2]The GlaxoSmithKline proprietary AS04 adjuvant system is composed of aluminium hydroxide and 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL) *(see section 4.1)*

3. Clinical information

3.1 Therapeutic indications

Cervarix is a vaccine indicated in females from 9 to 25 years of age for the prevention of persistent infection, premalignant cervical lesions and cervical cancer caused by Human Papillomavirus (HPV) Types 16 & 18. See sections 3.4 and 4.1 for important information on the data regarding HPV-16 and/or HPV-18, and other oncogenic HPV types that support this indication.

The indication is based on the demonstration of efficacy in women aged 15 to 25 years following vaccination with Cervarix and on the immunogenicity of the vaccine in girls and women aged 9 to 25 years.

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

3.2 Posology and method of administration

The vaccination schedule depends on the age of the subject.

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

*If the second vaccine dose is administered before the 5th month after the first dose, a third dose should always be administered.

**If flexibility in the vaccination schedule is necessary, the second dose can be administered between

1 month and 2.5 months after the first dose and the third dose between 5 and 12 months after the first dose.

The necessity for a booster dose has not been established *(see section 4.1).*

Cervarix is for intramuscular injection in the deltoid region. Cervarix should under no circumstances be administered intravascularly or intradermally. No data are available on subcutaneous administration of Cervarix.

Paediatric population: Cervarix is not recommended for use in children below 9 years of age.

3.3 Contraindications

Cervarix should not be administered to subjects with known hypersensitivity to any component of the vaccine *(see sections 2 and 5.1)*.

Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of Cervarix should not receive further doses of Cervarix.

3.4 Special warnings and special 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.

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 response may not be elicited in all vaccinees.
Cervarix is a prophylactic vaccine. The vaccine is therefore not indicated for treatment of cervical cancer or cervical dysplastic lesions. It is also not intended to prevent progression of other HPV-related lesions present at the time of vaccination. HPV-16 and HPV-18 are not responsible for all cervical cancers *(see section 4.1)*. Other oncogenic HPV types can also cause cervical cancer. HPV infections and related clinical outcomes due to these other oncogenic types may not be prevented by vaccination. Cervarix does not provide protection against all oncogenic HPV types *(see section 4.1)*.

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. Women who receive Cervarix should continue to undergo cervical cancer screening as per standard of care. Except for asymptomatic human immunodeficiency virus (HIV) infected subjects for whom data are available *(see section 4.1)*, there are no data on the use of Cervarix in subjects with impaired immune responsiveness such as patients receiving immunosuppressive treatment. As with other vaccines, an adequate immune response may not be elicited in these individuals.

Duration of protection has not fully been established. Sustained protective efficacy has been observed for up to 9.4 years after the first dose. Long-term studies are ongoing to establish the duration of protection *(*see *section 4.1)*.

3.5 Interaction with other medicaments 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; meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate vaccine (MenACWY-TT); hepatitis A (inactivated) vaccine (HepA), hepatitis B (rDNA) vaccine (HepB) and the combined HepA-HepB 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.

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.

3.6 Use during pregnancy and lactation

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.

Data in pregnant women collected as part of clinical trials, pregnancy registries, and epidemiological studies do not suggest that vaccination with Cervarix alters the risk of abnormal outcomes in neonates including birth defects. Data are insufficient to conclude whether or not vaccination with Cervarix affects the risk of spontaneous abortion.

Women who are pregnant or trying to become pregnant, are advised to postpone vaccination until completion of pregnancy.

Lactation

The effect on breast-fed infants due to 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-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.

3.7 Effect on ability to drive and use machines

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

3.8 Undesirable effects

Clinical Trial Data

In clinical studies, a total of approximately 45,000 doses of Cervarix were administered to approximately 16,000 subjects aged 9 to 72 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 (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <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 disorders:
Very common: myalgia
Common: arthralgia
General disorders and administration site conditions:
Very common: injection site reactions including pain, redness, swelling, fatigue
Common: fever (≥38°C)
Uncommon: other injection site reactions such as induration, local paraesthesia

Post Marketing 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

3.9 Overdose

Insufficient data are available.

4. Pharmacological particulars

4.1 Pharmacodynamic properties

Pharmacotherapeutic group: Papillomavirus vaccines, ATC code: J07BM02

Mechanism of action

Epidemiological evidence confirms that persistent infection with oncogenic (high-risk) HPV types is the primary cause of cervical cancer and most precursor lesions. Persistent infection with at least one oncogenic HPV type is a necessary causal factor for pre-cancerous high-grade cervical epithelial abnormalities, for example, cervical intraepithelial neoplasia (CIN).

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 and 70% of HPV-related high-grade vulvar (VIN2/3) and vaginal intraepithelial neoplasia (VaIN2/3). Other oncogenic HPV types can also cause genital cancers. HPV -45, -31 and -33 are the 3 most common non-vaccine HPV types identified in squamous cervical carcinoma (12.1%) and adenocarcinoma (8.5%).

The term “premalignant cervical lesions” in section 3.1 corresponds to high-grade Cervical Intraepithelial Neoplasia (CIN2/3).

Clinical studies

Clinical efficacy in women aged 15 to 25 years

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

The phase II trial (study 001/007) enrolled only women who:
- Were tested negative for oncogenic HPV DNA of types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
- Were seronegative for HPV-16 and HPV-18 and
- Had normal cytology

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

Clinical trial HPV-001/007 was conducted in North America and Latin America. Study HPV-023 followed-up subjects from the Brazilian cohort of study 001/007.

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.

Prophylactic efficacy against HPV-16/18 infection in a population naïve to oncogenic HPV types (Studies HPV-001/007/023)

Efficacy results in the "oncogenic HPV-naïve" population (seronegative by ELISA and HPV DNA negative by PCR in cervical samples at baseline) for virological, cytological and histological endpoints in study HPV-007 through 6.4 years following the first vaccine dose are presented in the tables below.

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

Endpoint	Cervarix n/N	Control (Al 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 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.

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 2. In a supplemental analysis, the efficacy of Cervarix was evaluated against HPV-16/18-related CIN3+.

Table 2: Vaccine efficacy against high grade cervical lesions associated with HPV-16/18 (ATP cohort)

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

N = number of subjects included in each group
n = number of cases
(1) ATP: includes women who received 3 doses of vaccine, were DNA negative and seronegative at month 0 and DNA negative at month 6 to the relevant HPV type (HPV-16 or HPV-18)
(2) including 4 cases of CIN2+ and 2 cases of CIN3+ in which another oncogenic HPV type was identified in the lesion, concomitantly with HPV-16 or HPV-18. These cases are excluded in the HPV type assignment analysis (see under Table).
(3) mean follow-up of 40 months post dose 3

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

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

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

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

At the time of the final study analysis, vaccine efficacy against VIN1+ (vulvar intraepithelial neoplasia grade 1 and higher grade lesions) or VaIN1+ (vaginal intraepithelial neoplasia grade 1 and higher grade lesions) associated with HPV-16/18 was observed in both cohorts: 80.0% (96.1% CI: 0.3;98.1) in ATP cohort and 83.2% (96.1% CI: 20.2;98.4) in TVC-1 cohort. At the end of study analysis, vaccine efficacy against VIN1+ or VaIN1+ 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 were 2 cases of VIN2+ or VaIN2+

associated with HPV-16 or HPV-18 in the vaccine group and 7 cases in the control group in the ATP cohort. The study was not powered to demonstrate a difference between the vaccine and the control group for these endpoints.

Vaccine efficacy against virological endpoints (6-month and 12-month persistent infection) associated with HPV-16/18 observed in the ATP cohort at the end of the study is presented in Table 3.

Table 3: Vaccine efficacy against virological endpoints associated with HPV-16/18 (ATP cohort)

HPV-16/18 endpoint	**ATP cohort[(1)]**		
	End of study analysis[(2)]		
	Cervarix (N = 7338)	**Control (N = 7305)**	**% Efficacy (95% CI)**
	n/N	**n/N**	
6-month persistent infection	35/7182	588/7137	94.3% (92.0;96.1)
12-month persistent infection	26/7082	354/7038	92.9% (89.4;95.4)

N = number of subjects included in each group
n = number of cases
(1) ATP: includes women who received 3 doses of vaccine, were DNA negative and seronegative at month 0 and DNA negative at month 6 to the relevant HPV type (HPV-16 or HPV-18)
(2) mean follow-up of 40 months post dose 3

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

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

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

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

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

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

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

Vaccine efficacy against high grade cervical lesions associated with HPV-16/18 observed in TVC at end of study is presented in Table 4.

Table 4: Vaccine efficacy against high grade cervical lesions associated with HPV-16/18 (TVC)

HPV-16/18 endpoint	**TVC[(1)]**		
	End of study analysis[(2)]		
	Cervarix (N = 8694)	**Control (N = 8708)**	**% Efficacy (95% CI)**

	n	n	
CIN2+	90	228	60.7% (49.6;69.5)
CIN3+	51	94	45.7% (22.9;62.2)

N = number of subjects included in each group
n = number of cases
(1) TVC: includes all vaccinated subjects (who received at least one dose of vaccine) irrespective of HPV DNA status, cytology and serostatus at baseline. This cohort includes women with pre-existing infections/lesions
(2) mean follow-up of 44 months post dose 1

Vaccine efficacy against virological endpoints (6-month and 12-month persistent infection) associated with HPV-16/18 observed in TVC at end of study is presented in Table 5.

Table 5: Vaccine efficacy against virological endpoints associated with HPV-16/18 (TVC)

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

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

Overall impact of the vaccine on cervical HPV disease burden

In study HPV-008, the incidence of high grade cervical lesions was compared between the placebo and vaccine group irrespective of the HPV DNA type in the lesion. In the TVC and TVC-naïve cohorts, the vaccine's efficacy was demonstrated against high-grade cervical lesions at end of study (Table 6). 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 6: Vaccine efficacy against high-grade cervical lesions irrespective of the HPV DNA type in the lesion

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

N = number of subjects included in each group

(1) TVC naïve: includes all vaccinated subjects (who received at least one dose of vaccine) who had normal cytology, were HPV DNA negative for 14 oncogenic HPV types and seronegative for HPV-16 and HPV-18 at baseline.

(2) TVC: includes all vaccinated subjects (who received at least one dose of vaccine) irrespective of HPV DNA status, cytology and serostatus at baseline.

(3) mean follow-up of 44 months post dose 1

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

Cross-protective efficacy

The cross-protective efficacy of Cervarix against histopathological and virological endpoints (persistent infection) has been evaluated in study HPV-008 for 12 non-vaccine oncogenic HPV types. The study was not powered to assess efficacy against disease caused by individual HPV type. 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 7 (ATP cohort).

Table 7: Vaccine efficacy for non-vaccine oncogenic HPV types

ATP(1)						
HPV type	**6-month persistent infection**			**CIN2+**		
	Cervarix	**Control**	**% Efficacy (95% CI)**	**Cervarix**	**Control**	**% Efficacy (95% CI)**
	n	**n**		**n**	**n**	
HPV-16 related types (A9 species)						
HPV-31	58	247	76.8% (69.0;82.9)	5	40	87.5% (68.3;96.1)
HPV-33	65	117	44.8% (24.6;59.9)	13	41	68.3% (39.7;84.4)
HPV-35	67	56	-19.8% (<0;17.2)	3	8	62.5% (<0;93.6)
HPV-52	346	374	8.3% (<0;21.0)	24	33	27.6% (<0;59.1)
HPV-58	144	122	-18.3% (<0;7.7)	15	21	28.5% (<0;65.7)
HPV-18 related types (A7 species)						
HPV-39	175	184	4.8% (<0;23.1)	4	16	74.9% (22.3;93.9)
HPV-45	24	90	73.6% (58.1;83.9)	2	11	81.9% (17.0;98.1)
HPV-59	73	68	-7.5% (<0;23.8)	1	5	80.0% (<0;99.6)
HPV-68	165	169	2.6% (<0;21.9)	11	15	26.8% (<0;69.6)
Other types						
HPV-51	349	416	16.6%	21	46	54.4%

			(3.6;27.9)			(22.0;74.2)
HPV-56	226	215	-5.3% (<0;13.1)	7	13	46.1% (<0;81.8)
HPV-66	211	215	2.3% (<0;19.6)	7	16	56.4% (<0;84.8)

n = number of cases

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

The limits of the confidence interval around the vaccine efficacy were calculated. When the value zero is included, i.e. when the lower limit of the CI is <0, the efficacy is not considered statistically significant.

The efficacy against CIN3 was only demonstrated for HPV-31 and there was no evidence of protection against AIS for any of the HPV types.

Clinical efficacy in women aged 26 years and older

The efficacy of Cervarix was assessed in a double-blind, randomised Phase III clinical trial (HPV-015) that included a total of 5,778 women aged 26 to 72 years (median: 37.0 years). The study was conducted in North America, Latin America, Asia Pacific and Europe. Final analysis was performed at study conclusion, 7 years after the first Cervarix dose. The primary endpoint was a combination of a virological and a histopathological endpoint: HPV-16/18 related 6-month persistent infection and/or CIN1+. The primary analyses of efficacy were performed on the ATP cohort for efficacy and the TVC which included a subset of up to 15% of women with a history of HPV-associated infection or disease.

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

Table 8: Vaccine efficacy at study conclusion in study HPV-015

Endpoint	**ATP(1)**			**TVC(2)**		
	Cervarix	**Control**	**% Efficacy (96.2% CI)**	**Cervarix**	**Control**	**% Efficacy (96.2% CI)**
	n/N	**n/N**		**n/N**	**n/N**	
HPV-16/18						
6M PI and/or CIN1+	7/1,852	71/1,818	90.5% (78.6; 96.5)	93/2,768	209/2,778	56.8% (43.8; 67.0)
6M PI	6/1,815	67/1,786	91.4% (79.4; 97.1)	74/2,762	180/2,775	60.0% (46.4; 70.4)
ASC-US+	3/1,852	47/1,818	93.8% (79.9; 98.9)	38/2,727	114/2,732	67.3% (51.4; 78.5)
Cross protective efficacy						
HPV-31 6M PI	10/2,073	29/2,090	65.8% (24.9; 85.8)	51/2,762	71/2,775	29.0% (<0; 52.5)
HPV-45 6M PI	9/2,106	30/2,088	70.7% (34.2; 88.4)	22/2,762	60/2,775	63.9% (38.6; 79.6)
HPV-31 ASC-US+	5/2,117	23/2,127	78.4% (39.1; 94.1)	34/2,727	55/2,732	38.7% (2.0; 62.3)

HPV-45 ASC-US+	5/2,150	23/2,125	78.7% (40.1; 94.1)	13/2,727	38/2,732	66.1% (32.7; 84.1)

N = number of subjects in each group

n = number of subjects reporting at least one event in each group

6M PI = 6-month persistent infection

CI = Confidence Interval

ASC-US = Atypical Cells of Undetermined Significance (abnormal cytology)

(1) 3 doses of vaccine, DNA negative and seronegative at month 0 (unless specified) and DNA negative at month 6 for the relevant HPV type (HPV-16 and/or HPV-18)

(2) at least one dose of vaccine, irrespective of HPV DNA and serostatus (unless specified) at month 0. Includes 15% of subjects with previous history of HPV disease/infection

A minimum anti-HPV level that provides protection against HPV infection and disease has not been identified and immune responses to vaccines are typically lower in older individuals compared to younger individuals. No efficacy was demonstrated against CIN2/3 lesions.

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 over 5,000 female subjects from 9 to 55 years of age.

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

Persistence of Immune Response to Cervarix

In study HPV-001/007, the immune response against HPV-16 and HPV-18 was evaluated up to 76 months post dose one 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 post dose one in a subset of the population from study HPV-001/007.

In study HPV-023, 100% 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.

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 10-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. Natural infection antibody levels may not protect against subsequent infections.

In study HPV-008, immunogenicity up to month 48 was similar to the response observed in study HPV-001/007. A similar kinetic profile was observed with the neutralizing antibodies.

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 a pooled analysis (HPV -029, -030 & -048), 99.7% and 100% of females aged 9 years seroconverted to HPV types 16 and 18, respectively after the third dose (at month 7) with GMTs at least 1.4-fold and 2.4-fold higher as compared to females aged 10 to 14 years and 15 to 25 years, respectively.

In two clinical trials (HPV-012 & -013) performed in girls aged 10 to 14 years, all subjects seroconverted to both HPV type 16 and 18 after the third dose (at month 7) with GMTs at least 2-fold higher compared to women aged 15 to 25 years.

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

The efficacy of Cervarix is inferred on the basis of immunogenicity data observed in girls vaccinated from age 9 to 14 years.

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

In the Phase III study (HPV-015) in women 26 years and older, all subjects seroconverted one month after the third dose. At the 84-month time point, i.e., 78 months after completion of the full vaccination course, 99.3% and 95.9% of initially seronegative women remained seropositive for anti-HPV-16 and anti-HPV-18 antibodies, respectively. Antibody titres peaked at month 7 then gradually declined up to month 18 and stabilized to reach a plateau up to month 84.

In another clinical study (HPV-014) performed in women aged 15 to 55 years (229 aged 15 to 25 years, 226 aged 26 to 45 years and 211 aged 46 to 55 years), all women were seropositive to both HPV type 16 and 18 after the third dose (at month 7). The GMTs were however, lower in the 26 to 55 years old population compared to women aged 15 to 25 years. Subjects (142 aged 15 to 25 years, 172 aged 26 to 45 years and 156 aged 46 to 55 years) who completed study HPV-014 and received the 3-dose schedule were followed-up for up to 10 years in the extension study HPV-060. Ten years after administration of the first dose, 100% of subjects in the 15 to 25 years group, 99.2% in the 26 to 45 years group and 96.3% in the 46 to 55 years group were still seropositive for HPV-16, and 99.2%, 93.7% and 83.8% for HPV-18, respectively. In all age groups, GMTs remained 5- to 32-fold for HPV-16 and 3- to 14-fold for HPV-18 above those elicited in women who cleared a natural infection. However, in the absence of an established immunological correlate for protection, the clinical significance of any GMT comparisons would be difficult to interpret.

Immunogenicity in HIV infected women

Two clinical studies assessed safety and immunogenicity of Cervarix.

1. 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.

2. A comparative study (HPV-019) of Cervarix and Gardasil was performed in 257 asymptomatic HIV-infected females aged 15-25 years (129 subjects received Cervarix) in Brazil, Estonia, India and Thailand.

In both studies, seroconversion at Month 7 in HIV-infected subjects receiving Cervarix was 100% for both antigens. In HPV-019, seropositivity rate at Month 24 after Cervarix vaccination was 100% for HPV-16 antibodies and >96% for HPV-18 antibodies with a Geometric Mean Concentration (GMC) level more than 12 times higher than the response to natural HPV infection. In both studies the antibody GMCs in HIV-infected subjects appeared lower than in HIV negative subjects. The clinical relevance of this observation is unknown.

In HPV-019, superiority of immune responses (neutralizing antibodies) to both HPV-16 (GMT ratio = 2.74 [95% CI 1.83; 4.11]) and HPV-18 (GMT ratio = 7.44 [95% CI 4.79; 11.54]) antigens was demonstrated with Cervarix compared to quadrivalent HPV vaccine, at Month 7 in HIV-infected subjects. The clinical relevance of these observations is unknown. No clinical efficacy data exist about protection against persistent infection or precancerous lesions among HIV infected women.

The observed reactogenicity and safety profile of Cervarix in HIV-infected women was in line with the known safety profile in healthy subjects *(see section 3.8)*.

The vaccine did not affect the CD4+ cell count, the HIV viral load and the HIV clinical stage.

4.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

4.3 Non-clinical information

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).

5. Pharmaceutical information

5.1 List of excipients

Sodium chloride, sodium dihydrogen phosphate dihydrate, water for injections

5.2 Shelf life

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

5.3 Storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Store in the original package in order to protect from light.
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 for up to three days at temperatures between 8°C and 25°C or for up to one day at temperatures between 25°C and 37°C.

The storage conditions are detailed on the packaging.

5.4 Nature and contents of container

Cervarix is presented as a turbid white suspension. Upon storage, a fine white deposit with a clear colourless supernatant can be observed.

0.5 ml of suspension in a pre-filled syringe (type I glass) with a plunger stopper (butyl rubber) and with a rubber tip cap, with or without needle.
0.5 ml of suspension in vial (type I glass) for 1 dose with a stopper (butyl rubber).
1 ml of suspension in vial (type I glass) for 2 doses with a stopper (butyl rubber).

The tip cap and rubber plunger stopper of the pre-filled syringe and the stopper of the vial are not made with natural rubber latex.

Not all presentations are available in every country.

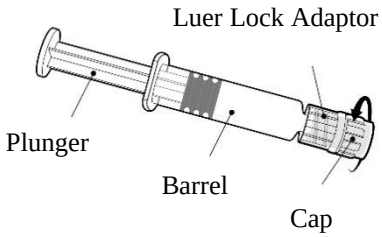
5.5 Incompatibilities

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

5.6 Use and handling

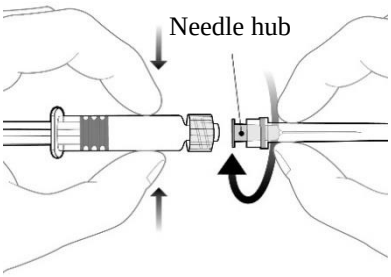
A fine white deposit with a clear colourless supernatant may be observed upon storage of the syringe/vial. This does not constitute a sign of deterioration.
The content of the syringe/vial should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to administration.
In the event of either being observed, discard the vaccine.
The vaccine should be well shaken before use.

<u>Instructions for the pre-filled syringe</u>



Hold the syringe by the barrel, not by the plunger.

Unscrew the syringe cap by twisting it anticlockwise.



To attach the needle, connect the hub to the Luer Lock Adaptor and rotate a quarter turn clockwise until you feel it lock.

Do not pull the syringe plunger out of the barrel. If it happens, do not administer the vaccine.

Disposal

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

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Product Registrant

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[GlaxoSmithKline Logo]