Cervarix™

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

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 Pharmacodynamics)

PHARMACEUTICAL FORM

Suspension for injection.

CLINICAL PARTICULARS

Indications

Cervarix™ is indicated from the age of 9 years for the prevention of persistent infection, premalignant ano-genital lesions (cervical, vulvar, vaginal and anal) and cervical, vulvar, vaginal and anal cancers (squamous-cell carcinoma and adenocarcinoma) caused by oncogenic Human Papillomaviruses (HPV) (see Warnings and Precautions and Pharmacodynamics).

Dosage and 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.

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 Pharmacodynamics). ***Cervarix™*** is for intramuscular injection in the deltoid region (see Warnings and Precautions and Interactions).

Contraindications

Cervarix™ should not be administered to subjects with known hypersensitivity to any component of the vaccine (see Qualitative and Quantitative Composition and List of Excipients).

Warnings and Precautions

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 response 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 Pharmacodynamics). 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.
Except for asymptomatic human immunodeficiency virus (HIV) infected subjects for whom limited data are available (see Pharmacodynamics), there are no data on the use of ***Cervarix™*** in subjects with impaired immune responsiveness such as patients receiving immunosuppressive treatment. For these individuals an adequate immune response may not be elicited.

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 Pharmacodynamics).

Interactions

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 titers 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 ≥ 10mIU/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.

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 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.

Effects on Ability to Drive and Use Machines

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

Adverse Reactions

Clinical Trial Data

In clinical studies, a total of approximately 45,000 doses of ***Cervarix™*** were administered to approximately 16,000 female subjects aged 9-72 years and approximately 7,800 doses were administered to approximately 2,600 male subjects aged 10-18 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 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 (≥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.

Overdose
Insufficient data are available

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics
Pharmaco-therapeutic group: Papillomavirus vaccines, J07BM02

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 [$Al(OH)_3$] 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, 80% of vulvar and vaginal cancers, 90% of anal cancers, 70% of HPV related high-grade vulvar (VIN 2/3) and vaginal intraepithelial neoplasia (VaIN 2/3) and 78% of HPV related high-grade anal (AIN 2/3) intraepithelial neoplasia across all regions worldwide.
Other oncogenic HPV types (HPV-31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, -68) can also cause ano-genital cancers. HPV-16, -18, -45 and -31 are the 4 most common types identified in squamous cervical carcinoma (approximately 76%) and adenocarcinoma (approximately 91%).
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.
An anamnestic response was also observed for the related types HPV-31 and HPV-45 by ELISA.
Prophylactic Efficacy
Clinical efficacy in women aged 15 to 25 years
The efficacy of ***Cervarix™*** was assessed in 2 controlled, double-blind, randomised clinical studies (HPV-001/007 and HPV-008) that included a total of 19,778 women aged 15 to 25 years at enrolment.

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. 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 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.
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 months has also been shown to be a relevant surrogate marker for cervical cancer. Although CIN grade 1 is not a surrogate marker for cervical cancer, these lesions require medical follow-up.

1. Vaccine efficacy against HPV-16/18 in women naïve to oncogenic HPV types (studies HPV-001/007/023)

Efficacy results for histological endpoints associated with HPV-16 and/or HPV-18 (HPV-16/18) observed in study HPV-001/007 (Total Cohort i.e. women who received at least one vaccine dose) are presented in Table 1.

Table 1: Vaccine efficacy against CIN2+ and CIN1+ associated with HPV-16/18

HPV-16/18 endpoint	***Cervarix*™ N = 481**	**Control (Aluminium salt) N = 470**	**% Efficacy (95% CI)**
	Number of cases		
CIN2+(1)	**0**	**9**	**100% (51.3;100)**
CIN1+(2)	**0**	**15**	**100% (73.4;100)**

(1) cervical intraepithelial neoplasia grade 2 and higher grade lesions
(2) cervical intraepithelial neoplasia grade 1 and higher grade lesions

Efficacy against HPV-16/18 cytological abnormalities was 96.7% (95 % CI: 87.3;99.6).
Efficacy against HPV-16/18 persistent infection was 98.2% (95% CI: 89.5;100) and 96.9% (95% CI: 81.4;99.9) when using a 6-month and a 12-month definition, respectively.
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: 80.3;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. Vaccine efficacy in women with evidence of past and/or current HPV infection (study HPV-008)

2.1 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 naïve to the relevant 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 relevant 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) and TVC-naïve.
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 final analysis of study HPV-008 was event-triggered, i.e. was performed when at least 36 CIN2+ cases associated with HPV-16/18 were accrued in the ATP cohort. The mean follow-up 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).
In the protocol-specified analysis, vaccine efficacy against CIN1+ and CIN2+ associated with HPV-16/18 was statistically significant in the ATP and TVC-1 cohorts.
Further investigation identified that several CIN3+, CIN1+ and CIN2+ 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.
The results observed in both analysis (i.e. protocol-specified analysis and HPV type assignment) are presented in Table 2.

Table 2: Vaccine efficacy against CIN1+, CIN2+ and CIN3+ associated with HPV-16/18

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	
Protocol-specified analysis (ATP and TVC-1)											
CIN3+	ATP[(1)]	7344	2	7312	10	80.0% (0.3;98.1)	7338	2	7305	24	91.7% (66.6;99.1)
	TVC-1[(2)]	8040	2	8080	22	90.9% (60.8;99.1)	8068	2	8103	40	95.0% (80.7;99.4)
CIN2+	ATP[(1)]	7344	4	7312	56	92.9% (79.9;98.3)	7338	5	7305	97	94.9% (87.7;98.4)
	TVC-1[(2)]	8040	5	8080	91	94.5% (86.2;98.4)	8068	6	8103	135	95.6% (90.1;98.4)
CIN1+	ATP[(1)]	7344	8	7312	96	91.7% (82.4;96.7)	7338	12	7305	165	92.8% (87.1;96.4)
	TVC-1[(2)]	8040	11	8080	135	91.8% (84.5;96.2)	8068	15	8103	210	92.9% (88.0;96.1)
HPV type assignment (exploratory analysis) (ATP and TVC-1)											
CIN3+	ATP[(1)]	7344	0	7312	8	100% (36.4;100)	7338	0	7305	22	100% (81.8;100)
	TVC-1[(2)]	8040	0	8080	20	100% (78.1;100)	8068	0	8103	38	100% (89.8;100)
CIN2+	ATP[(1)]	7344	1	7312	53	98.1% (88.4;100)	7338	1	7305	92	98.9% (93.8;100)
	TVC-1[(2)]	8040	2	8080	87	97.7% (91.0;99.8)	8068	2	8103	128	98.4% (94.3;99.8)
CIN1+	ATP[(1)]	7344	2	7312	90	97.8% (91.4;99.8)	7338	3	7305	154	98.1% (94.3;99.6)
	TVC-1[(2)]	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
(1) 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)
(2) 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+ associated with HPV-16 and HPV-18 individually was demonstrated in both cohorts for each analysis.

Vaccine efficacy against 6-month and 12-month persistent infection and cytological abnormalities (≥ASCUS) associated with HPV-16/18 was also assessed. The observed vaccine efficacy against each endpoint was statistically significant in both cohorts:
At the time of final study analysis:

- 6-month persistent infection: 94.3% (91.5;96.3) in ATP cohort and 90.2% (87.3;92.6) in TVC-1 cohort,
- 12-month persistent infection: 91.4% (86.1;95.0) in ATP cohort and 85.3% (79.9; 89.4) in TVC-1 cohort,
- cytological abnormalities (≥ASCUS): 89.0% (84.9;92.1) in ATP cohort and 86.7% (82.8; 89.8) in TVC-1 cohort.

At the end of study analysis:

- 6-month persistent infection: 94.3% (92.0;96.1) in ATP cohort and 91.0% (88.5;93.0) in TVC-1 cohort,
- 12-month persistent infection: 92.9% (89.4;95.4) in ATP cohort and 88.2% (84.5%; 91.2%) in TVC-1 cohort,
- cytological abnormalities (≥ASCUS): 90.7% (87.8;93.1) in ATP cohort and 88.6% (85.6; 91.0) in TVC-1 cohort.

At the time of the final study analysis, statistically significant 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 also 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.

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.

2.2 Overall impact of the vaccine on HPV disease burden

The overall vaccine efficacy irrespective of HPV DNA type in the lesion and stratified by baseline HPV DNA and serostatus was evaluated in study HPV-008.

In the TVC and TVC-naïve cohorts which included all vaccinated women, vaccine efficacy against CIN3+, CIN2+ and CIN1+ was demonstrated (Table 3). 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 (Table 3).

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 3: Vaccine efficacy irrespective of HPV DNA type in the lesion, 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 (1)**	**5449**	**3**	**5436**	**23**	**87.0% (54.9;97.7)**	**5466**	**3**	**5452**	**44**	**93.2% (78.9;98.7)**
	TVC (2)	**8667**	**77**	**8682**	**116**	**33.4% (9.1;51.5)**	**8694**	**86**	**8708**	**158**	**45.6% (28.8;58.7)**
CIN2+	**TVC naïve (1)**	**5449**	**33**	**5436**	**110**	**70.2% (54.7;80.9)**	**5466**	**61**	**5452**	**172**	**64.9% (52.7;74.2)**
	TVC (2)	**8667**	**224**	**8682**	**322**	**30.4% (16.4;42.1)**	**8694**	**287**	**8708**	**428**	**33.1% (22.2;42.6)**
CIN1+	**TVC naïve (1)**	**5449**	**106**	**5436**	**211**	**50.1% (35.9;61.4)**	**5466**	**174**	**5452**	**346**	**50.3% (40.2;58.8)**
	TVC (2)	**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 (1)**	**5449**	**26**	**5436**	**83**	**68.8% (50.0;81.2)**	**5466**	**43**	**5452**	**143**	**70.2% (57.8;79.3)**
	TVC (2)	**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
(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).

2.3 Prophylactic efficacy against infection by oncogenic HPV types other than HPV-16 and HPV-18

In study HPV-008, vaccine efficacy against 12 non-vaccine oncogenic HPV types (HPV-31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, -68) was evaluated in ATP and TVC-1 cohorts.

At the time of the final study analysis, statistically significant vaccine efficacy against CIN2+ for all HPV types combined (HPV-31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, -68) excluding HPV types 16 and 18 was demonstrated with 54.0% (96.1% CI: 34.0;68.4) in ATP cohort and 46.0% (96.1% CI: 27.0;60.3) in TVC-1 cohort. At the end of study analysis, vaccine efficacy against CIN2+ for all HPV types combined excluding HPV types 16 and 18 was 46.8% (95% CI: 30.7;59.4) in the ATP cohort and 40.8% (95% CI: 25.5;53.1) in the TVC-1 cohort.

At the time of the final study analysis, statistically significant vaccine efficacy against 6-month persistent infection and against CIN2+ has been observed for the following individual HPV types:

- 6-month persistent infection: types 31, 33, 45 in ATP cohort ; types 31, 33, 45, 51 in TVC-1 cohort.
- CIN2+: types 31, 51, 58 in ATP cohort; types 31, 33, 35, 51 in 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.

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 the combined primary endpoint (6-month persistent infection and/or CIN1+) associated with HPV-16/18 is summarised in the following table.

Table 4: Vaccine efficacy against 6M PI and/or CIN1+ associated with HPV 16/18 in ATP and TVC

HPV-16/18 endpoint	ATP[1]			TVC[2]		
	Cervarix™	Control	% Efficacy (97.7% CI)	*Cervarix™*	Control	% Efficacy (97.7% CI)
	N=1898	N=1854		N=2772	N=2779	
	n	n		n	n	
6M PI and/or CIN1+	7	36	81.1% (52.1; 94.0)	90	158	43.9% (23.9; 59.0)
6M PI and/or CIN1+ (HPV TAA)	7	36	81.1% (52.1; 94.0)	89	155	43.5% (23.1; 58.7)

N = number of subject in each group
N = number of subjects reporting at least one event in each group
HPV TAA= HPV type assignment algorithm
6M PI = 6-month persistent infection
CIN1+ = CIN1, CIN2, CIN3, AIS or ICC
CI = Confidence Interval
(1) 3 doses of vaccine, DNA negative and seronegative at month 0 and DNA negative at month 6 for the relevant HPV type (HPV-16 and/or HPV-18)
(2) at least one dose of vaccine, irrespective of HPV DNA and serostatus at month 0. Includes 15% of subjects with previous history of HPV disease/infection

Vaccine efficacy against 6-month persistent infection was 79.1% (97.7% CI [27.6; 95.9]) for HPV-31 and 76.9% (97.7% CI [18.5; 95.6]) for HPV-45 in the ATP cohort.

Clinical efficacy against anal prevalent infection in women aged 18-25 years

Study HPV-009 evaluated vaccine efficacy against anal prevalent infection at the 4-year study visit. Vaccine efficacy against HPV-16/18 and against non-vaccine types HPV-31/33/45 is presented in Table 5. Cervical infection in the same women at the same visit was assessed for comparison purpose.

Table 5: Efficacy against anal and cervical prevalent infection associated with HPV-16/18 and HPV-31/33/45 in study HPV-009

		Number of women	Number of HPV-16/18 infections	HPV 16/18 vaccine efficacy (95% CI)		Number of women	Number of HPV-31/33/45 infection	HPV-31/33/45 vaccine efficacy (95% CI)
Full cohort*	Anus							
	HPV group	2103	47	62.0% (47.1; 73.1)	HPV group	2103	55	49.4% (30.3; 63.6)
	Control group	2107	124		Control group	2107	109	
	Cervix							
	HPV group	2103	40	76.4% (67.0; 83.5)	HPV group	2103	76	45.2% (27.7; 58.7)
	Control group	2107	170		Control group	2107	139	
Restricted cohort**	Anus							
	HPV group	1003	8	83.6% (66.7; 92.8)	HPV group	1629	31	61.8% (42.8; 75.0)
	Control group	986	48		Control group	1684	84	
	Cervix							
	HPV group	1003	10	87.9% (77.4; 94.0)	HPV group	1629	49	51.3% (31.9; 65.5)
	Control group	986	81		Control group	1684	104	

HPV group: treatment group vaccinated with Cervarix vaccine
Control group: treatment group vaccinated with modified Havrix vaccine (Hepatitis A vaccine)
*Full cohort included all women with anal specimens available
**Restricted cohort for efficacy against HPV16/18 infection included subjects from the full cohort with no evidence of prevalent cervical HPV 16 and HPV 18 infection or HPV 16 and HPV 18 antibodies before vaccination, who received three doses of the HPV or control vaccines. Restricted cohort for efficacy against HPV-31/33/45 infection included women from the full cohort with no evidence of prevalent cervical HPV 31, 33, or 45 infections before vaccination, and who received three doses of the HPV or control 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 neutralizing assay developed by the US National Cancer Institute). Transudation of antibodies from serum to the cervical mucosa has been demonstrated in clinical trials.
The immunogenicity induced by three doses of ***Cervarix™*** has been evaluated in over 5,000 female subjects from 9 to 55 years of age and over 800 male subjects aged 10 to 18 years. In clinical trials, more than 99% 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

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.

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.

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 10-14 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 as 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.

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. Antibody titers peaked at month 7 then gradually declined up to month 18 and stabilized to reach a plateau up to month 48.

In another clinical 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.

Comparison of immunogenicity of *Cervarix*™ and Gardasil

In girls aged 9 to 14 years

In a comparison trial with Gardasil (study HPV-071) in girls aged 9-14 years, superiority of the immune response elicited by Cervarix administered according to the 2-dose schedule 0, 6 months compared to that of Gardasil administered according to the 2-dose 0, 6 months and the standard 3-dose 0, 2, 6 months schedules was demonstrated for both HPV-16 and HPV-18 by ELISA (Table 6).

Table 6: Superiority assessment of anti-HPV-16 and anti-HPV-18 immune response for Cervarix (2 dose schedule 0, 6 months) over Gardasil (2 dose schedule 0, 6 months and 3-dose schedule 0, 2, 6 months) one month and six months after the last dose (Total Vaccinated Cohort)

	Antibody	N	GMT	N	GMT	GMT ratio (Cervarix / Gardasil) 95% CI (LL; UL)
Month 7		Cervarix 0,6 months		Gardasil 0,6 months		
	Anti-HPV-16	357	8256	353	4886	1.7 (1.5; 1.9)
	Anti-HPV-18	357	5268	353	1166	4.5 (4.0; 5.1)
		Cervarix 0,6 months		Gardasil 0,2,6 months		
	Anti-HPV-16	357	8256	351	4789	1.7 (1.5; 1.9)
	Anti-HPV-18	357	5268	351	1636	3.2 (2.8; 3.7)
Month 12		Cervarix 0,6 months		Gardasil 0,6 months		
	Anti-HPV-16	355	2217	347	1260	1.8 (1.5; 2.0)
	Anti-HPV-18	355	1296	347	261	5.0 (4.3; 5.7)
		Cervarix 0,6 months		Gardasil 0,2,6 months		
	Anti-HPV-16	355	2217	348	1567	1.4 (1.2; 1.6)
	Anti-HPV-18	355	1296	348	469	2.8 (2.4; 3.2)

GMT = geometric mean antibody titre by ELISA
N = Number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMT ratio (Anova model - pooled variance); LL = lower limit, UL = upper limit; p-value = 0.0001
The association between antibody levels and clinical efficacy is not fully understood

In women aged 18 to 45 years

In a non-inferiority comparative trial with Gardasil (study HPV-010) in women aged 18-45 years, non-inferiority of the immune response elicited by ***Cervarix™*** was demonstrated for both HPV-16 and HPV-18 neutralizing antibodies in all age cohorts up to three years after first vaccination (Table 7).

Table 7: Non-inferiority* assessment in terms of neutralizing antibody titers between Cervarix™ and Gardasil for HPV-16 and HPV-18 at Month 7 and Month 60 (ATP) in study HPV-010

			Cervarix™		Gardasil		GMT ratio *Cervarix™*/Gardasil 97.6% CI at Month 7 95% CI at Month 60
		Age (years)	N	GMT (ED_{50})	N	GMT (ED_{50})	
Month 7	HPV-16	18-26	104	36792	103	10053	3.7 (2.6; 5.2)
		27-35	90	23908	85	4958	4.8 (3.3; 7.1)
		36-45	96	17301	83	7634	2.3 (1.5; 3.4)
	HPV-18	18-26	118	16487	131	2258	7.3 (5.1; 10.4)
		27-35	102	9502	101	1043	9.1 (6.0; 13.9)
		36-45	110	9845	91	1439	6.8 (4.6; 10.2)
Month 60	HPV-16	18-26	35	4118	40	530	7.8 (4.3; 14.0)
		27-35	43	1925	29	346	5.6 (3.0; 10.2)
		36-45	46	1784	47	765	2.3 (1.3; 4.3)
	HPV-18	18-26	39	1523	52	126	12.1 (6.6; 22.1)
		27-35	54	967	36	74	13.0 (7.6; 22.2)
		36-45	55	817	51	105	7.8 (4.5; 13.3)

ED_{50} = Estimated Dose = serum dilution giving a 50% reduction of the signal compared to a control without serum GMT = geometric mean antibody titer
N = Number of subjects with post-vaccination results available
Non-inferiority was demonstrated when the lower limit of the 97.6% CI or 95% CI was greater than 0.5
*Superiority of the immune response elicited by ***Cervarix™*** was also demonstrated up to Month 60 for HPV-16 and HPV-18 neutralizing antibodies in all age cohorts. The association between antibody levels and clinical efficacy is not fully understood.

Immunogenicity in HIV infected women

In a clinical study performed in 120 HIV positive asymptomatic subjects aged 18 to 25 years (60 subjects received ***Cervarix™***), all subjects were seropositive to both HPV type 16 and 18 after the third dose (at Month 7) and the seropositivity for HPV type 16 and 18 was maintained up to Month 12. The GMTs appear to be lower in this population than observed in HIV negative subjects but were more than fifteen-fold higher than the response to natural HPV infection and equal to or above GMT levels for which sustained efficacy has been demonstrated.

Cervarix™ was shown to be generally well tolerated in women aged 18-25 years infected with HIV up to six months after the last vaccine dose and over the 12 months trial period, the vaccine did not affect the CD4+ cell count, the HIV viral load and the HIV clinical stage.

Immunogenicity in males aged 10 to 18 years

Immunogenicity in males was assessed in 2 clinical trials HPV-011 (N=173) and HPV-040 (N=556). The data showed comparable immunogenicity in males and females. In study HPV-011, all subjects seroconverted to both HPV-16 and 18 and GMT levels were non inferior to those observed in females aged 15 to 25 years in study HPV-012.

Pharmacokinetics

Evaluation of pharmacokinetic properties is not required for vaccines.

Clinical studies

See "Pharmacodynamics"

Pre-clinical 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).

PHARMACEUTICAL PARTICULARS

List of Excipients

Sodium chloride, sodium dihydrogen phosphate dihydrate, water for injections

Incompatibilities

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

Shelf Life

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

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.
Cervarix™ should be administered as soon as possible after being removed from the refrigerator.
However, stability data generated indicate that ***Cervarix™*** presented in monodose containers remains stable and can be administered in case it has been stored outside the refrigerator up to three days at temperatures between 8°C and 25°C or up to one day at temperatures between 25°C and 37°C.
After first opening of the multidose vial, immediate use is recommended. If not used immediately, the vaccine should be stored in a refrigerator (2°C – 8°C). If not used within 6 hours it should be discarded.

Nature and Contents of Container

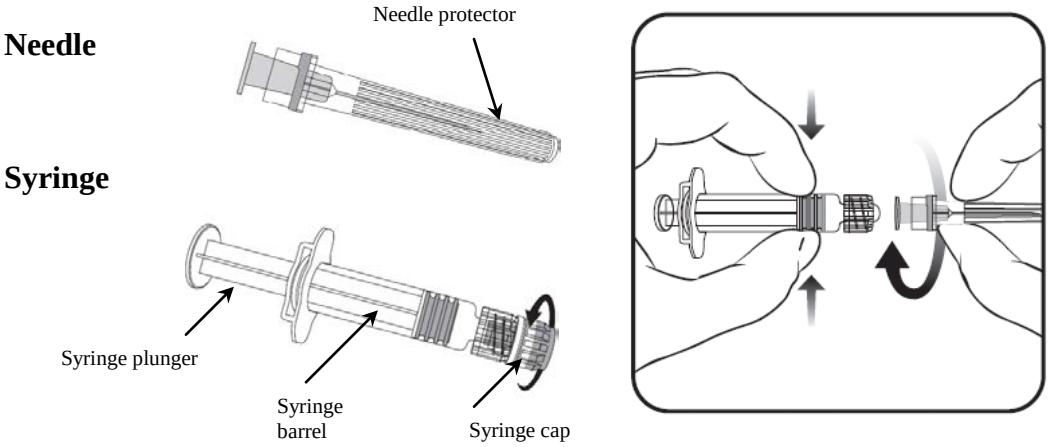
0.5 ml of suspension in a pre-filled syringe (type I glass) with a plunger stopper (rubber butyl) with or without needles.
0.5 ml of suspension in vial (type I glass) with a stopper (rubber butyl).

1 ml of suspension in vial (type I glass) with a stopper (rubber butyl) for 2 doses.
Cervarix^{TM} is presented as a turbid white suspension. Upon storage, a fine white deposit with a clear colourless supernatant can be observed.

Instructions for Use/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.
When using a multidose vial, each 0.5 ml dose should be withdrawn using a sterile needle and syringe; precautions should be taken to avoid contamination of the contents.

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

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

Not all presentations are available in every country.

Cervarix **and** ***Twinrix*** **are trade marks of the GSK group of companies.**

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