

CERVARIX[®] PRODUCT INFORMATION

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

DESCRIPTION

CERVARIX contains recombinant C-terminally truncated L1 proteins from human papillomavirus (HPV) type-16 and type-18 each assembled as virus-like particles (VLPs). The HPV-16 and HPV-18 L1 antigens are prepared by recombinant DNA technology using a Baculovirus expression system in *Trichoplusia ni* cells.

HPV-16 and HPV-18 L1 antigens in CERVARIX are adjuvanted with AS04. This AS04 adjuvant system comprises aluminium hydroxide (Al(OH)₃) and 3-O-desacyl-4'-monophosphoryl lipid A (MPL). The MPL within AS04 enhances the initiation of the immune response through the activation of innate immunity, leading to an improved cellular and humoral adaptive immune response.

Each 0.5ml dose of CERVARIX contains 20 micrograms each of HPV-16 L1 and HPV-18 L1 proteins, 0.5 milligrams of Al(OH)₃ and 50 micrograms of MPL. CERVARIX also contains sodium chloride (NaCl) 4.4 mg, sodium phosphate - monobasic (NaH₂PO₄·2 H₂O) 624 micrograms and water for injection as excipients. CERVARIX does not contain a preservative.

PHARMACOLOGY

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).

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

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

Mechanism of action

CERVARIX is a recombinant vaccine prepared from VLPs of the major L1 protein of HPV types 16 and 18. Since VLPs contain no viral DNA, they cannot infect cells or reproduce. Animal studies suggest that the efficacy of VLPs is largely mediated by the development of a humoral immune response and cell-mediated immunity.

Transudation of anti-HPV IgG antibodies from the serum to the cervical mucosa is thought to be the primary mechanism of protection against persistent oncogenic HPV infection, the necessary cause of cervical cancer.

CERVARIX is adjuvanted with AS04. In clinical trials CERVARIX adjuvanted with AS04 compared to the same antigens adjuvanted with aluminium hydroxide alone showed:

- significantly higher antibody titres at least 2 fold higher (at all time points analysed up to 4 years after first dose);
- significantly higher functional antibody titres (analysed up to 4 years after first dose);
- B cell memory frequency approximately 2 fold higher (at all time points analysed up to 2 years after first dose).

CLINICAL STUDIES

Vaccine Efficacy

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

Clinical trial HPV-001/007 was a study conducted in North America and Latin America. 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 is an on-going study conducted in North America, Latin America, Europe, Asia Pacific and Australia. Pre-vaccination samples were collected for oncogenic HPV DNA (HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) testing and serum testing for HPV-16 and HPV-18 antibodies. Women were vaccinated regardless of baseline cytology and HPV serological and DNA status. These characteristics are representative of a population which includes women with or without evidence of past and/or current HPV infection.

Subjects initially infected with a particular HPV type were not eligible for the efficacy assessment of that type.

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

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

In both studies the following endpoints were evaluated:

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

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

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

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

1. Study HPV-001/007 – Vaccine efficacy against HPV-16/18 in women naïve to oncogenic HPV types

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

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

Endpoint	Cervarix n/N	Control (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 summary, sustained efficacy of the vaccine was demonstrated against HPV-16 and/or HPV-18 persistent infections, as well as against cytological abnormalities and histopathological lesions.

In study HPV-001/007, high efficacy of CERVARIX was maintained for up to 6.4 years (approximately 77 months) after dose one. Despite evidence of continuous exposure to HPV infections as observed in the control group, there is no evidence of waning protection in vaccinated women.

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

In study HPV-008, the primary analyses of efficacy were performed on the According to Protocol cohort (ATP cohort: including women who received 3 vaccine doses and were naïve to the respective HPV type at month 0 and month 6) and the Total Vaccinated Cohort-1 (TVC-1 cohort: including women who received at least one vaccine dose and were naïve to the respective HPV type at month 0). Both cohorts included women with normal or low-grade cytology at baseline and excluded only women with high-grade cytology (0.5%).

In addition, analyses of efficacy were performed on the broader Total Vaccinated Cohort (TVC) which included all vaccinated women.

Table 2: Population Cohorts analysed in Study HPV-008

Cohort	Abbreviation	Definition	Analysed for
According to Protocol cohort	ATP	Women who received three doses of study vaccine, complied with the study protocol, and had normal or low-grade cytology at Month 0.	Primary and secondary endpoints
Total Vaccinated Cohort -1	TVC-1	Women who received at least one dose of study vaccine and had normal or low-grade cytology at Month 0	Primary and secondary endpoints
Total Vaccinated Cohort	TVC	Women who received at least one dose of study vaccine	Supportive
Total	TVC naïve	Women who received at least one dose of study	Exploratory

Vaccinated Cohort of HPV naïve women		vaccine, and had normal cytology at Month 0, were HPV DNA negative for all oncogenic types at Month 0 and seronegative for HPV-16 and HPV-18, at Month 0.	analyses
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The TVC approximates a general population of women, including those who are sexually active, and may have previous or current HPV infection, cytological abnormalities or precancerous cervical lesions. The TVC-naïve cohort includes women with no evidence of previous or current HPV infection and no cytological abnormalities, and approximates to a population of young women before sexual debut.

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

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

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

Table 3: Vaccine efficacy against CIN2+ and CIN1+ associated with HPV-16/18 - Protocol-specified analysis

HPV-16/18 endpoint	ATP cohort ⁽¹⁾			TVC-1 cohort ⁽²⁾		
	Cervarix (N = 7344)	Control (N = 7312)	% Efficacy (96.1% CI)	Cervarix (N = 8040)	Control (N = 8080)	% Efficacy (96.1% CI)
	n	n		n	n	
CIN2+	4	56	92.9 (79.9;98.3)	5	91	94.5 (86.2;98.4)
CIN1+	8	96	91.7 (82.4;96.7)	11	135	91.8 (84.5;96.2)

N = number of subjects included in each group
n = number of cases
⁽¹⁾ 3 doses of vaccine, DNA negative and seronegative for the corresponding HPV type in the analysis at month 0 and month 6
⁽²⁾ at least one dose of vaccine, DNA negative and seronegative for the corresponding HPV type in the analysis at month 0

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

on this HPV type assignment, the analysis excluded CIN1+ and CIN2+ cases (in the vaccine group and in the control group) which were not considered to be causally associated with HPV-16 or HPV-18 infections acquired during the trial (see Table 4 below).

Table 4: Vaccine efficacy against CIN2+ and CIN1+ associated with HPV-16/18 - HPV type assignment

HPV-16/18 endpoint	ATP cohort ⁽¹⁾			TVC-1 cohort ⁽²⁾		
	Cervarix (N = 7344)	Control (N = 7312)	% Efficacy (96.1% CI)	Cervarix (N = 8040)	Control (N = 8080)	% Efficacy (96.1% CI)
	n	n		n	n	
CIN2+	1	53	98.1% (88.4;100)	2	87	97.7% (91.0;99.8)
CIN1+	2	90	97.8% (91.4;99.8)	5	128	96.1% (90.3;98.8)

N = number of subjects included in each group
n = number of cases
⁽¹⁾ 3 doses of vaccine, DNA negative and seronegative for the corresponding HPV type in the analysis at month 0 and month 6
⁽²⁾ at least one dose of vaccine, DNA negative and seronegative for the corresponding HPV type in the analysis at month 0

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

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

	Vaccine Efficacy (%), 96.1% CI	
	HPV 16	HPV 18
CIN2+		
ATP	100 (91.0;100)	92.3 (45.7;99.9)
TVC-1	98.6 (91.5;100)	95.4 (70.1;99.9)
CIN1+		
ATP	<u>98.5 (91.0;100)</u>	<u>96.6 (78.1;99.9)</u>
TVC-1	96.8 (90.0;99.4)	95.0 (79.7;99.5)

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

Table 6: Vaccine efficacy against virological and cytological endpoints associated with HPV-16/18

HPV-16/18 endpoint	ATP cohort ⁽¹⁾			TVC-1 cohort ⁽²⁾		
	Cervarix	Control	% Efficacy (96.1% CI)	Cervarix	Control	% Efficacy (96.1% CI)
	n/N	n/N		n/N	n/N	
Virological endpoints						
6 month persistent infection	29/7177	488/7122	94.3 (91.5;96.3)	67/7941	661/7964	90.2 (87.3;96.2)
12 month persistent	20/7035	227/6984	91.4	51/7812	340/7823	85.3

infection			(86.1;95.0)			(79.9;89.4)
Cytological endpoint						
Cytological abnormalities (≥ASCUS)	48/7340	427/7312	89.0 (84.9;92.1)	75/8040	553/8080	86.7 (82.8;89.8)
N = number of subjects included in each group n = number of cases (¹) 3 doses of vaccine, DNA negative and seronegative for the corresponding HPV type in the analysis at month 0 and month 6 (²) at least one dose of vaccine, DNA negative and seronegative for the corresponding HPV type in the analysis at month 0						

Statistically significant vaccine efficacy against VIN1+ or VaIN1+ associated with HPV-16/18 was observed in the ATP cohort, 80.0% (96.1% CI: 0.3;98.1) and in the TVC-1 cohort 83.2% (96.1% CI: 20.2;98.4).

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

Prophylactic Efficacy against oncogenic HPV genotypes other than HPV-16 and HPV-18

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

High levels of vaccine efficacy for both the virological and histopathological endpoints were also seen for the other HPV oncogenic types. Statistical significance was seen for the 3 most prevalent (after HPV 16 and HPV 18) HPV types 31, 33 and 45 for the 6 month and 12 month persistent infections.

The vaccine efficacy results for the various cohorts studied for the three most prevalent HPV types after HPV types 16 and 18 are provided in Table 7.

Table 7: Vaccine efficacy results from Study HPV-008 against non-vaccine oncogenic HPV types

	Vaccine Efficacy (%) 96.1% CI		
	HPV 31	HPV 33	HPV 45
CIN2+			
<i>ATP</i>	92.0 66.0;99.2	51.9 -2.9;78.9	100 -67.8;100
<i>TVC1</i>	67.4 32.0;85.7	49.8 2.9;75.2	100 -20.2;100
<i>TVC naive</i>	100	72.3	100

	78.3;100	19.1;92.5	-19.5;100
CIN1+			
<i>ATP</i>	87.7 70.2;95.9	38.1 -13.0;66.9	91.7 39.9;99.9
<i>TVC1</i>	69.0 46.9;82.8	38.9 -2.3;64.2	93.3 53.8;99.9
<i>TVC naive</i>	90.0 66.5;98.2	62.0 7.2;86.2	90.0 25.1;99.8
Persistent infection 12 month			
<i>ATP</i>	80.5 66.1;89.5	41.0 -4.0;67.3	60.0 1.5;85.5
<i>TVC1</i>	60.6 43.6;72.9	37.0 2.5;59.8	51.4 8.3;75.3
<i>TVC naive</i>	70.6 46.5;84.8	31.9 -21.0;62.4	82.5 36.3;97.0
Persistent infection 6 month			
<i>ATP</i>	77.5 68.3;84.4	45.1 21.7;61.9	76.1 59.1;86.7
<i>TVC1</i>	64.9 54.8;72.9	41.6 21.8;56.6	72.0 56.9;82.4
<i>TVC naive</i>	75.3 62.7;84.2	41.8 13.9;61.1	82.3 63.9;92.3

Statistically significant vaccine efficacy against 6-month persistent infection, 12-month persistent infection and CIN1+ associated with HPV-45 was observed in all cohorts. In the broader Total Vaccinated Cohort (TVC), vaccine efficacy against CIN2+ associated with HPV-45 was also statistically significant with 0 cases in the vaccine group versus 6 cases in the control group [vaccine efficacy: 100% (96.1% CI: 7.0;100)].

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

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

Endpoint	Cervarix n/N	Control n/N	% Efficacy	96.1% CI
6 month persistent infection	1271/7665	1647/7640	25.0	18.9;30.6
12 month persistent infection	585/7509	803/7488	28.4	19.8;36.1
ASC-US	953/7858	1212/7853	22.1	14.8;28.9
CIN1+	151/7863	279/7853	45.9	33.1;56.4
CIN2+	54/7863	142/7853	61.9	46.7;73.2

Overall impact of the vaccine on HPV disease burden

The overall vaccine efficacy irrespective of HPV DNA in lesions and stratified by baseline HPV DNA status and serostatus was evaluated in study HPV-008 (see Table 9). In presumed HPV-naïve women who were HPV DNA negative for the 14 oncogenic HPV

types at baseline and in a general population of women irrespective of HPV DNA status at baseline, statistically significant vaccine efficacy against CIN2+ and CIN1+ was demonstrated in the TVC-1 cohort and in the broader TVC cohort that included all vaccinated women. Similar prophylactic efficacy was seen in women who had normal cytology at Month 0, were HPV DNA negative for all oncogenic types at Month 0 and seronegative for HPV-16 and HPV-18, at Month 0, i.e TVC naïve cohort . The impact of CERVARIX on reduction of local cervical therapy (Loop Electro-Excision Procedure, Cone, Knife or Laser) was also evaluated and was statistically significant in both cohorts.

Table 9: Overall Vaccine efficacy irrespective of HPV DNA in lesions (TVC-1, TVC naïve and TVC cohorts)

			Cervarix		Control		% Efficacy (96.1% CI)
			<i>N</i>	<i>n</i>	<i>N</i>	<i>n</i>	
CIN2+	Prophylactic efficacy in high risk HPV DNA negative women*	TVC-1	6893	51	6962	142	63.8 (49.0;74.7)
		TVC naïve	5449	33	5436	110	70.2 (54.7;80.9)
	Overall efficacy (all women irrespective of baseline HPV DNA status)	TVC-1	8610	204	8630	296	30.9 (16.4;43.0)
		TVC	8667	224	8682	322	30.4 (16.4;42.1)
CIN1+	Prophylactic efficacy in high risk HPV DNA negative women*	TVC-1	6893	157	6962	278	43.1 (29.9;54.0)
		TVC naïve	5449	106	5436	211	50.1 (35.9;61.4)
	Overall efficacy (all women irrespective of baseline HPV DNA status)	TVC-1	8610	422	8630	549	23.0 (11.8;32.8)
		TVC	8667	451	8682	577	21.7 (10.7;31.4)
Local cervical therapy	Overall efficacy (all women irrespective of baseline HPV DNA status)	TVC-1	8610	162	8630	219	25.7 (7.6;40.4)
	Prophylactic efficacy in high risk HPV DNA negative women*	TVC naïve	5449	26	5436	83	68.8 (50.0;81.2)
	Overall efficacy (all women irrespective of baseline HPV DNA status)	TVC	8667	180	8682	240	24.7 (7.4;38.9)

N = number of subjects included in each group

n = number of cases

* HPV DNA negative for 14 oncogenic HPV types (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, -68)

Overall vaccine efficacy against CIN3+ irrespective of the HPV DNA type found in the lesion and irrespective of the subject's baseline HPV DNA and serostatus was statistically significant in both the TVC-1 cohort [with 64 cases in the vaccine group versus 103 cases in the control group (vaccine efficacy: 37.7%, CI: 12.6;55.9)] and TVC cohort [with 77 cases in the vaccine group versus 116 cases in the control group (vaccine efficacy: 33.4%, CI: 9.1;51.5)]

Immunogenicity

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

The immunogenicity induced by three doses of CERVARIX has been evaluated in 5,303 female subjects from 10 to 55 years of age.

In clinical trials, 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

The immune response against HPV-16 and HPV-18 was evaluated up to 76 months post dose 1, in study HPV-001/007 in women aged 15 to 25 years at the time of vaccination. Results are presented in Figures 1 and 2 below:

Figure 1: Evolution of GMT's for anti-HPV-16 IgG antibodies during studies HPV-001 and HPV-007 (ATP cohort for immunogenicity)

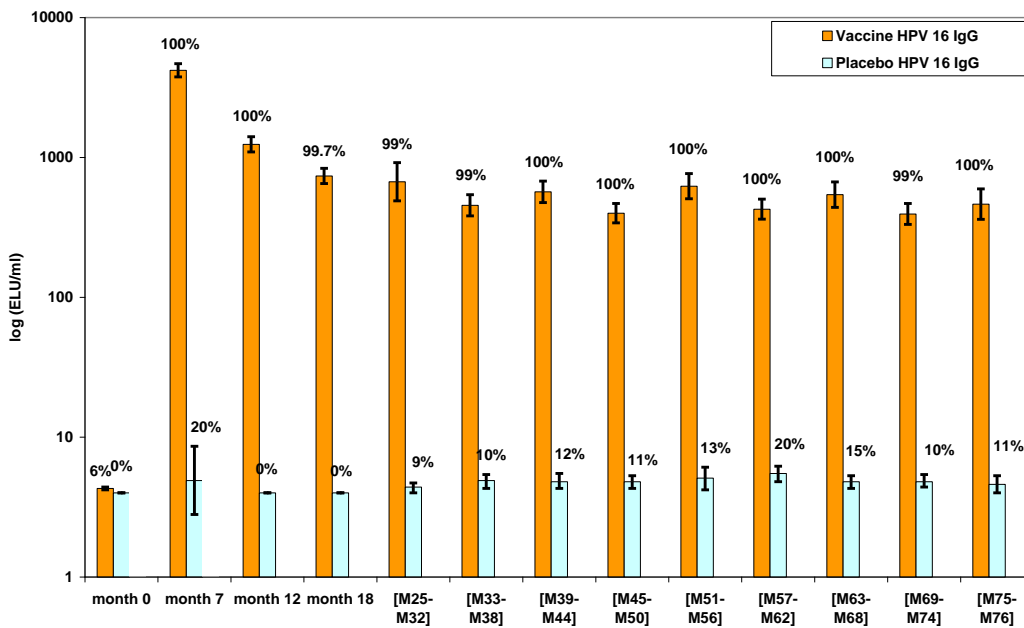
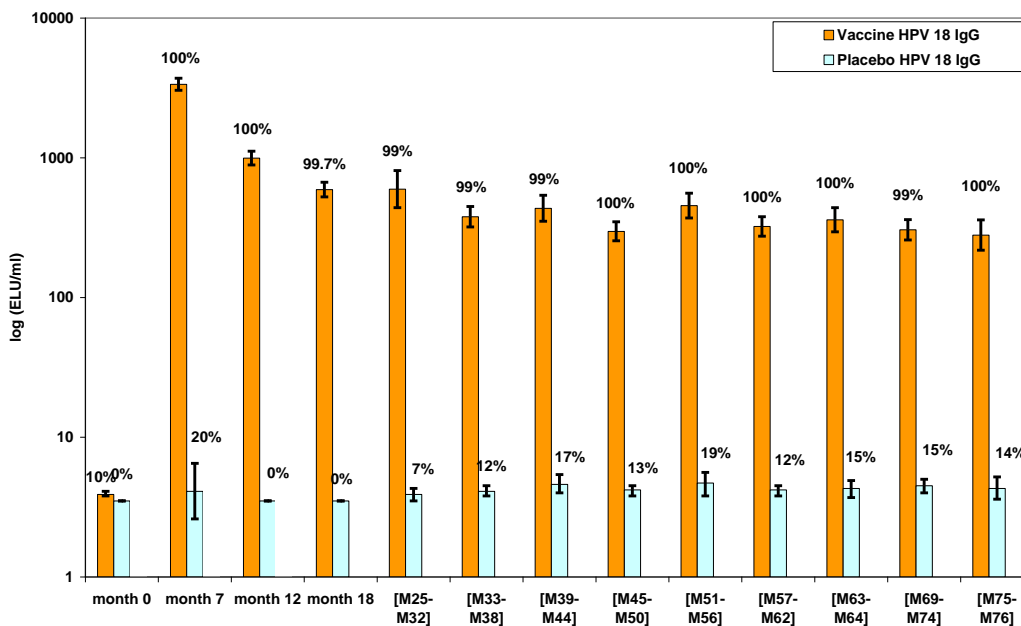


Figure 2: Evolution of GMT's for anti-HPV-18 IgG antibodies during studies HPV-001 and HPV-007 (ATP cohort for immunogenicity)



Vaccine-induced IgG Geometric Mean Titres (GMT) for both HPV-16 and HPV-18 peaked at month 7 and then declined to reach a plateau from month 18 up to end of the follow-up (month 76). At the end of the follow-up period, GMTs for both HPV 16 and 18 were still at least 11-fold higher than titres observed in women previously infected but who cleared HPV infection (natural infection). Nevertheless, natural infection antibody levels may not consistently protect against subsequent infections.

A similar kinetic profile was observed with the neutralising antibodies.

In study HPV-008, immunogenicity up to month 36 was similar to the response observed in study HPV-001/007.

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 compared to women aged 15 to 25 years.

In a clinical study performed in women aged 26 to 55 years, after vaccination, 100% of initially seronegative subjects had seroconverted to both HPV-16 and HPV-18 antigens in all age groups (at month 7) and remained seropositive up to month 18. As observed with other vaccines, the immune response elicited by the vaccine decreases with increasing age. This is not unexpected since this reflects the senescence of the immune system. Furthermore, GMTs remained in the same range or higher as those observed in the plateau phase of the long term follow up in the efficacy study HPV-001/007 in women aged 15-25 years.

On the basis of immunogenicity data observed in females aged 10 to 14 years and aged 26 to 45 years, the efficacy of Cervarix is inferred from 10 to 45 years.

Immunogenicity in seropositive women

The vaccination of women who were initially seropositive for HPV-16 or HPV-18 or both types has shown that the presence of anti-HPV-16 and/or anti-HPV-18 antibodies from natural infection does not affect the immune response to the HPV-16/18 vaccine.

Immunogenicity in males

To date, the vaccine has not been evaluated in males.

INDICATIONS

CERVARIX is indicated in females from 10 to 45 years of age for the prevention of persistent infection, premalignant cervical lesions and cervical cancer caused by 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 (*See Precautions and Clinical Trials*).

CONTRAINDICATIONS

CERVARIX should not be administered to subjects with known hypersensitivity to any component of the vaccine (*See Description*).

PRECAUTIONS

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.

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 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.

CERVARIX should under no circumstances be administered intravascularly or intradermally.

No data are available on subcutaneous administration of CERVARIX.

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

CERVARIX is a prophylactic vaccine. CERVARIX is not intended to be a treatment for persistent infection or for HPV-related lesions present at the time of vaccination. CERVARIX is not intended to prevent progression of established HPV-related lesions present at the time of vaccination.

HPV-16 and HPV-18 are not responsible for all cervical cancers (*see Clinical Studies*). 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.

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

There are no data on the use of CERVARIX in subjects with impaired immune responsiveness such as HIV infected patients or patients receiving immunosuppressive treatment. For these individuals an adequate immune response may not be elicited.

Duration of protection has not been established. Limited data support protective efficacy for 6.4 years after the first dose. Long-term studies are ongoing to establish the duration of protection.

Effects on Fertility

Fertility was not affected in female rats given double the clinical dose of CERVARIX by intramuscular administration 30 days prior to mating.

Use in Pregnancy (Category B2)

Specific studies of the vaccine in pregnant women were not conducted. Pregnancy testing was performed prior to each vaccine administration and vaccination was discontinued in case of a positive pregnancy test. In all clinical trials, subjects were instructed to take precautions to avoid pregnancy until 2 months after the last vaccination. During prelicensure clinical development, a total of 1,737 pregnancies (n = 870 for CERVARIX) were reported. 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. Sub-analyses were conducted to describe pregnancy outcomes in 415 women (n = 210 for CERVARIX) who had their last menstrual period within 30 days prior to, or 45 days after a vaccine dose. The majority of subjects gave birth to normal infants (9.4% of pregnancies were ongoing at the time of the analysis). Apart from elective procedures, spontaneous abortion was next in frequency, reported in a total of 8.9% of subjects: 11% for CERVARIX, 5.7% for Hepatitis A Vaccine control, and 13.8% for placebo. The background rate of spontaneous abortion in individuals who are known to be pregnant has been reported to be 13-16%. These data are insufficient to recommend use of CERVARIX during pregnancy. Vaccination should therefore be postponed until after pregnancy.

The effect of CERVARIX on embryo-foetal, peri-natal and post-natal survival and development has not been prospectively evaluated in clinical trials.

No adverse effects on embryofetal development, parturition or postnatal development were observed in pregnant rats that received double the clinical dose of vaccine on 4 occasions during gestation.

Use in Lactation

CERVARIX should only be used during breast-feeding when the possible advantages

outweigh the possible risks.

The effect on breastfed infants of the administration of CERVARIX to their mothers has not been evaluated in clinical studies.

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.

Genotoxicity

The genotoxic potential of CERVARIX has not been investigated. The adjuvant substance MPL has been tested for genotoxicity in a series of *in vitro* assays (bacterial mutation and chromosomal aberration) and an *in vivo* rat micronucleus test. Under the condition of these assays, MPL did not cause genetic damage.

Carcinogenicity

The carcinogenic potential of CERVARIX has not been investigated.

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

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

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. 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 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.

ADVERSE REACTIONS

In total approximately 45,000 doses of CERVARIX were administered to approximately 16,000 subjects aged 10 – 68 years. These subjects were followed to assess the safety of the vaccine.

Adverse reactions occurring after vaccination during these studies were reported. 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.

The following table summarises data from seven pivotal studies for solicited local and general symptoms reported during a 7-day follow-up period after vaccination.

Table 10 Pooled safety analysis: Incidence of solicited local and general symptoms reporting during the 7-day (Days 0-6) post-vaccination period following all doses (Total vaccinated cohort)

		CERVARIX		ALU		HAV360		HAV720	
Symptom	Type	N	%	N	%	N	%	N	%
Solicited local symptoms									
Pain	All	22806	78.0	4485	52.5	3059	41.3	8750	58.9
	Grade 3	22806	6.3	4485	3.4	3059	0.8	8750	1.8
Redness (mm)	All	22806	29.6	4485	10.6	3059	13.7	8750	16.0
	>50	22806	0.6	4485	0.0	3059	0.1	8750	0.0
Swelling (mm)	All	22806	25.8	4485	8.2	3059	8.6	8750	10.1
	>50	22806	1.1	4485	0.0	3059	0.2	8750	0.2
Solicited general symptoms									
Fatigue	All	22802	33.1	4481	22.8	3058	24.6	8751	35.3
	Grade 3	22802	1.5	4481	1.2	3058	1.1	8751	1.3
Gastrointestinal symptoms	All	22802	12.9	4481	11.6	3058	11.3	8751	14.0
	Grade 3	22802	0.7	4481	0.7	3058	0.8	8751	0.7
Headache	All	22802	29.5	4481	25.9	3058	25.4	8751	30.8
	Grade 3	22802	1.6	4481	1.2	3058	1.6	8751	1.4
Arthralgia	All	21222	10.2	2916	7.6	3058	9.3	8751	8.6
	Grade 3	21222	0.4	2916	0.2	3058	0.2	8751	0.3
Myalgia	All	21222	28.1	2916	9.9	3058	17.1	8751	26.5
	Grade 3	21222	1.4	2916	0.2	3058	0.5	8751	0.6
Fever (Axillary) (°C)	All	22802	5.1	4481	5.2	3058	6.8	8751	4.6
	>39°C	22802	0.2	4481	0.2	3058	0.6	8751	0.1
Rash	All	22802	3.8	4481	2.7	3058	2.6	8751	3.6
	Grade 3	22802	0.1	4481	0.0	3058	0.1	8751	0.1

CERVARIX group (Studies HPV-001, 008 subset, -012, -013, -014, -015 subset and -016: girls and women 10 years and above)

ALU = Al(OH)₃ control group (Studies HPV-001 and -015 subset; adolescent girls and women 15 years and above)

HAV360 = Hepatitis A control group containing 360 EU hepatitis A antigen per dose (Study HPV-013; girls 10-14 years of age)

HAV720 = Hepatitis A control group containing 720 EU hepatitis A antigen per dose (Study HPV-008 subset; adolescent girls and women 15-25 years of age)

N=number of documented doses

% = percentage of doses followed by at least one type of symptom

Grade 3 Pain: Spontaneously painful (HPV-001) or Pain that prevents normal activity (HPV-008, HPV-012, HPV-013, HPV-014, HPV-015 and HPV-016)

Other events

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

Frequencies are reported as:

Very common ($\geq 1/10$)

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

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

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

Infections and infestations:

Uncommon: upper respiratory tract infection

Blood and lymphatic system disorders:

Uncommon: lymphadenopathy

Nervous system disorders:

Very common: headache

Uncommon: dizziness

Gastrointestinal disorders:

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

Skin and subcutaneous tissue disorders:

Common: itching/pruritus, rash, urticaria

Musculoskeletal and connective tissue and bone disorders:

Very common: myalgia

Common: arthralgia

General disorders and administration site conditions:

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

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

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

Post Marketing Data

Immune system disorders:

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

Nervous system disorders:

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

DOSAGE AND ADMINISTRATION

Dosage

The primary vaccination course consists of three doses.

The recommended vaccination schedule is 0, 1, 6 months. If flexibility in the vaccination schedule is necessary, the second dose can be administered between 1 month and 2.5 months after the first dose and the third dose between 5 and 9 months after the first dose.

The necessity for a booster dose has yet to be established (see “*Clinical Studies*”).

Method of administration

CERVARIX is for intramuscular injection in the deltoid region (see “*Precautions*”, “*Drug Interactions*”).

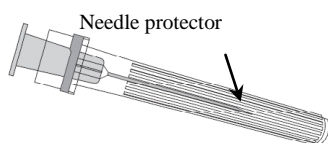
The content of the syringe/vial should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to administration.

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

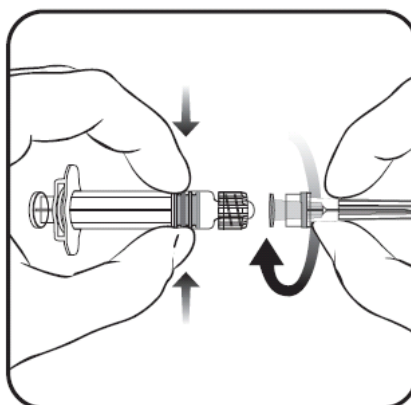
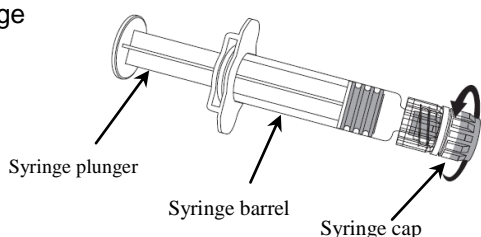
The vaccine should be well shaken before use.

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

Needle



Syringe



1. Holding the syringe barrel in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.
2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock. (see picture)

3. Remove the needle protector, which on occasion can be a little stiff.

4. Administer the vaccine.

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

Overdosage

No case of overdose has been reported. In the event of overdosage, please contact the Poisons Information Centre on 13 11 26.

STORAGE

CERVARIX must be stored at +2°C to +8°C. DO NOT FREEZE, discard if vaccine has been frozen. The vaccine should be stored in the original package in order to protect from light.

CERVARIX should be administered as soon as possible after being removed from refrigeration. CERVARIX can be kept out of refrigeration at temperatures at or below 25°C, for a total time of not more than 72 hours or at temperatures between 25°C and 37°C, for a total time of not more than 24 hours.

The shelf life of CERVARIX is four years from the date of manufacture at temperatures of +2°C to +8°C. The expiry date of the vaccine is indicated on the label and packaging.

PRESENTATIONS

CERVARIX is presented as a turbid white suspension. Upon storage, a fine white deposit with a clear colourless supernatant can be observed. This does not constitute a sign of deterioration.

CERVARIX is presented as

- 0.5 ml of suspension in a pre-filled syringe (type I glass) with a plunger stopper (rubber butyl) with or without needles in pack sizes of 1 and 10, or
- 0.5 ml of suspension in vial (type I glass) with a stopper (rubber butyl) in pack sizes of 1, 10 and 100.

Not all pack sizes may be marketed.

MANUFACTURER:

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