

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).

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.

CLINICAL TRIALS

Vaccine Efficacy

Clinical efficacy in women aged 15 to 25 years

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

Clinical trial HPV-001/007 was a study 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 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. Studies HPV-001/007/023 – Vaccine efficacy against HPV-16/18 in women naïve to oncogenic HPV types

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

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

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

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

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

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

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

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

Table 2: Population Cohorts analysed in Study HPV-008

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 Vaccinated Cohort of HPV naïve women	TVC naïve	Women who received at least one dose of study vaccine, and had normal cytology at Month 0, were HPV DNA negative for all oncogenic types at Month 0 and seronegative for HPV-16 and HPV-18, at Month 0.	Exploratory analyses

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

In study HPV-008, approximately 26% of women had evidence of current and/or prior HPV-16/18 infection and less than 1% of women were HPV DNA positive for both HPV-16

and HPV-18 types at baseline. An event triggered analysis of study HPV-008 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).

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

Table 3: Vaccine efficacy from the end of study analysis against CIN3+, CIN2+ and CIN1+ associated with HPV-16 and HPV-18 - (ATP and TVC-1)

HPV 16/18 endpoint		End of study analysis				
		Cervarix		Control		% Efficacy (95% CI)
		N	n	N	n	
CIN3+	ATP ⁽¹⁾	7338	2	7305	24	91.7% (66.6;99.1)
	TVC-1 ⁽²⁾	8068	2	8103	40	95.0% (80.7;99.4)
CIN2+	ATP ⁽¹⁾	7338	5	7305	97	94.9% (87.7;98.4)
	TVC-1 ⁽²⁾	8068	6	8103	135	95.6% (90.1;98.4)
CIN1+	ATP ⁽¹⁾	7338	12	7305	165	92.8% (87.1;96.4)
	TVC-1 ⁽²⁾	8068	15	8103	210	92.9% (88.0;96.1)

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)

At the event-triggered analysis the efficacy against HPV types 16/18 for the ATP cohort was 92.9% (96.1% CI:79.9;98.3) against CIN2+ and 80% (96.1% CI: 0.3;98.1) against CIN3+. The efficacy against HPV types 16/18 for the TVC-naïve cohort was 98.4% (90.4;100) against CIN2+ and 100% (64.7;100) against CIN3+.

Further investigation identified that several CIN3+, CIN2+ and CIN1+ cases had multiple

oncogenic HPV types in the lesion. In order to distinguish between the HPV type(s) most likely to be responsible for a lesion from the HPV type(s) only temporally associated, an HPV type assignment was applied (exploratory analysis). The HPV type assignment considered the HPV types detected by Polymerase Chain Reaction (PCR) in at least one of the two preceding cytologic samples, in addition to types detected in the lesion. Based on this HPV type assignment, the analysis excluded cases (in the vaccine group and in the control group) which were not considered to be causally associated with HPV-16 or HPV-18 infections acquired during the trial (see Table 4 below).

Table 4: Vaccine efficacy from the end of study analysis against CIN3+, CIN2+ and CIN1+ associated with HPV-16 and HPV-18 - HPV type assignment (ATP and TVC-1)

HPV 16/18 endpoint		End of study analysis				% Efficacy (95% CI)
		Cervarix		Control		
		N	n	N	n	
CIN3+	ATP ⁽¹⁾	7338	0	7305	22	100% (81.8;100)
	TVC-1 ⁽²⁾	8068	0	8103	38	100% (89.8;100)
CIN2+	ATP ⁽¹⁾	7338	1	7305	92	98.9% (93.8;100)
	TVC-1 ⁽²⁾	8068	2	8103	128	98.4% (94.3;99.8)
CIN1+	ATP ⁽¹⁾	7338	3	7305	154	98.1% (94.3;99.6)
	TVC-1 ⁽²⁾	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)						

At the event-triggered analysis the efficacy for the ATP cohort for the HPV type assignment was 98.1% (96.1% CI:88.4;100) against CIN2+ and 100% (96.1% CI: 36.4;100) against CIN3+.

In addition, statistically significant vaccine efficacy against CIN2+ and CIN1+ associated with HPV-16 and HPV-18 individually was demonstrated for both the ATP and TVC-1 cohorts.

Table 5: Vaccine efficacy from the end of study analysis against CIN2+ and CIN1+ associated with HPV-16 and HPV-18 - HPV type assignment

	Vaccine Efficacy (%), 95% CI	
	End of Study Analysis	
	HPV 16	HPV 18
CIN2+		
ATP	100 (95.3;100)	94.8 (67.2;99.9)
TVC-1	99.1 (94.7;100)	96.6 (79.2;99.9)
CIN1+		
ATP	99.2 (95.3;100)	95.7 (83.5;99.5)
TVC-1	98.0 (94.0;99.6)	94.9 (84.4;99.0)

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

Table 6: Vaccine efficacy from the end of study analysis against virological and cytological endpoints associated with HPV-16 and HPV-18 (ATP and TVC-1)

<i>HPV 16/18 endpoint</i>		<i>End of study analysis</i>				
		<i>Cervarix</i>		<i>Control</i>		<i>% Efficacy (95% CI)</i>
		<i>N</i>	<i>n</i>	<i>N</i>	<i>n</i>	
<i>Virological endpoints</i>						
<i>6 month persistent infection</i>	<i>ATP⁽¹⁾</i>	7182	35	7137	588	94.3% (92.0;96.1)
	<i>TVC-1⁽²⁾</i>	7976	73	7999	770	91.0% (88.5;93.0)
<i>12-month persistent infection</i>	<i>ATP⁽¹⁾</i>	7082	26	7038	354	92.9% (89.4;95.4)
	<i>TVC-1⁽²⁾</i>	7864	58	7880	478	88.2% (84.5;91.2)
<i>Cytological endpoint</i>						
<i>Cytological abnormalities (ASC-US+)</i>	<i>ATP⁽¹⁾</i>	7334	55	7305	575	90.7% (87.8;93.1)
	<i>TVC-1⁽²⁾</i>	8068	84	8103	714	88.6% (85.6;91.0)
<i>N = number of subjects included in each group</i> <i>n = number of cases</i> ⁽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)						

At the event triggered analysis the efficacy for the ATP cohort for the HPV type assignment was 94.3% (96.1% CI:91.5;96.3) against 6 month persistent infection, 91.4% (96.1% CI: 86.1;95.0) against 12 month persistent infection and 89.0% (96.1% CI: 84.9;92.1) for cytological abnormalities.

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

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

Prophylactic Efficacy against oncogenic HPV genotypes 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, HPV-33, HPV-52 and HPV-58 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 oncogenic HPV types other than HPV-16 and HPV-18. The vaccine efficacy results for the various cohorts studied for the three most prevalent oncogenic HPV types after HPV types 16 and 18 are provided in Table 7.

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

	Vaccine Efficacy (%)		
	95% CI		
	HPV Type		
	HPV-31	HPV-33	HPV-45
CIN2+			
<i>ATP</i>	87.5 68.3;96.1	68.3 39.7;84.4	81.9 17.0;98.1
<i>TVC1</i>	71.0 47.8;84.9	64.5 37.2;80.9	84.6 32.0;98.3
<i>TVC naive</i>	89.4 65.5;97.9	82.3 53.4;94.7	100 41.7;100
6 month persistent infection			
<i>ATP</i>	76.8 69.0;82.9	44.8 14.6;59.9	73.6 58.1;83.9
<i>TVC1</i>	66.7 58.5;73.5	42.0 24.8;55.7	69.7 55.6;79.7
<i>TVC naive</i>	77.1 67.2;84.4	43.1 19.3;60.2	79.0 61.3;89.4

At the event triggered analysis, statistically significant vaccine efficacy against 6-month persistent infection was observed for HPV types 31, 33 and 45 in the ATP cohort and for HPV types 31, 33, 45 and 51 in the TVC-1 cohort. Statistically significant vaccine efficacy against CIN2+ was observed for HPV types 31, 51 and 58 in the ATP cohort and for HPV types 31, 33, 35 and 51 in the TVC-1 cohort.

At the end of study analysis, statistically significant vaccine efficacy was 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+, statistically significant vaccine efficacy was observed for HPV type 39 in the ATP cohort and HPV type 66 in the TVC-1 cohort.

The results for vaccine efficacy against the virological and histopathological endpoints were statistically significant for oncogenic HPV types including HPV-16/18, in HPV DNA negative subjects, regardless of initial serostatus, in the ATP cohort and are provided in Table 8.

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

	<i>HR-HPV⁽¹⁾</i>					<i>HRW-HPV⁽²⁾</i>				
	<i>Cervarix</i>		<i>Control</i>		<i>% Efficacy (95% CI)</i>	<i>Cervarix</i>		<i>Control</i>		<i>% Efficacy (95% CI)</i>
	<i>N</i>	<i>n</i>	<i>N</i>	<i>n</i>		<i>N</i>	<i>n</i>	<i>N</i>	<i>n</i>	
<i>6 month persistent infection</i>	7672	1424	7656	1837	25.4% (20.0;30.4)	7672	1399	7656	1556	11.2% (4.5; 17.5)
<i>12-month persistent infection</i>	7560	824	7545	1112	27.8% (20.9;34.1)	7560	804	7545	878	9.0% (-0.2; 17.4)
<i>ASC-US+</i>	7850	1201	7846	1574	25.1% (19.2;30.5)	7850	1180	7846	1400	16.5% (9.7; 22.8)
<i>CIN1+</i>	7855	235	7846	443	47.3% (38.1;55.2)	7855	229	7846	368	38.0% (26.7; 47.7)
<i>CIN2+</i>	7855	92	7846	220	58.3% (46.6;67.7)	7855	88	7846	165	46.8% (30.7; 59.4)
<i>VIN/VaIN2+</i>	7855	9	7846	21	57.2% (2.4; 82.7)	7855	7	7846	18	61.1% (2.4; 86.3)

⁽¹⁾ HR-HPV = High-risk (oncogenic) HPV types: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68

⁽²⁾ HRW-HPV = High-risk (oncogenic) HPV types (excluding HPV-16 and HPV-18): HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68

Overall impact of the vaccine on HPV disease burden

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

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

The TVC-naïve cohort is a subset of the TVC that includes women with normal cytology, and who were HPV DNA negative for 14 oncogenic HPV types (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, -68) and seronegative for HPV-16 and HPV-18 at baseline.

Table 9: Vaccine efficacy from the end of study analysis irrespective of HPV DNA type in the lesions and regardless of initial serostatus

		<i>End of study analysis</i>				
		<i>Cervarix</i>		<i>Control</i>		<i>% Efficacy (95% CI)</i>
		<i>N</i>	<i>n</i>	<i>N</i>	<i>n</i>	
CIN3+	<i>TVC naïve</i> ⁽¹⁾	5466	3	5452	44	93.2% (78.9;98.7)
	<i>TVC</i> ⁽²⁾	8694	86	8708	158	45.6% (28.8;58.7)
CIN2+	<i>TVC naïve</i> ⁽¹⁾	5466	61	5452	172	64.9% (52.7;74.2)
	<i>TVC</i> ⁽²⁾	8694	287	8708	428	33.1% (22.2;42.6)
CIN1+	<i>TVC naïve</i> ⁽¹⁾	5466	174	5452	346	50.3% (40.2;58.8)
	<i>TVC</i> ⁽²⁾	8694	579	8708	798	27.7% (19.5;35.2)
ASC-US+	<i>TVC naïve</i> ⁽¹⁾	5466	1133	15452	1437	23.2% (16.9; 29.0)
	<i>TVC</i> ⁽²⁾	8692	2414	8708	2718	12.2% (7.2; 16.9)
VIN/VaIN2+	<i>TVC naïve</i> ⁽¹⁾	5466	7	5452	15	53.6% (-20.9; 84.0)
	<i>TVC</i> ⁽²⁾	8694	22	8708	29	24.1% (-36.8; 58.4)

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).

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.

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 (including Australia) 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 objectives of HPV-015 were to demonstrate vaccine efficacy in the prevention of:

- (1) Persistent infection (6- month definition) with HPV-16 or HPV-18 (by polymerase chain reaction [PCR]) and/or
- (2) histopathologically confirmed cervical intraepithelial neoplasia (CIN)1+ (defined as CIN1, CIN2, CIN3, adenocarcinoma in-situ [AIS] or invasive cervical cancer) associated with HPV-16 or HPV-18 cervical infection detected by PCR within the lesional component of the cervical tissue specimen, overall and stratified according to initial HPV-16 or HPV-18 serostatus detected by enzyme-linked immunosorbent assay (ELISA).

If efficacy was demonstrated, the primary objectives were assessed sequentially using the HPV type assignment algorithm (HPV TAA), overall and stratified according to initial (Month 0) HPV-16 or HPV-18 serostatus (by ELISA).

The HPV type assignment algorithm (HPV TAA) was developed to detect the causally associated types in case multiple HPV types were detected in the lesions. The following rules applied:

- If more than one HPV type was found in a lesion, the presence of HPV types in the two immediately preceding cytology samples were to be evaluated:
 - The HPV types present in both the lesion and in at least one of the two immediately preceding cytology samples were considered to be associated with that lesion.
 - In case none of the HPV types present in the lesion was found in any of the two immediately preceding cytology samples, then the HPV types present in the lesion was considered to be associated with that lesion.
- If only a single HPV type was found in a lesion, then this type was considered to be associated with the lesion.

Persistent cervical HPV infection (6-month definition) was defined as the detection of the same HPV type by PCR in cervical samples at two consecutive evaluations over

approximately a 6-month interval.

CIN1+ is defined as CIN1, CIN2, CIN3, AIS or invasive cervical cancer.

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 10: Vaccine efficacy at the 48 month time point against 6 month persistent infection and/or CIN1+ associated with HPV 16/18 in ATP and TVC

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

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 at the 48 month time point 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.

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

Immunogenicity

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 neutralising assay developed by the US National Cancer Institute). Due to the high efficacy of the vaccine, it has not been possible to establish minimum anti-HPV-16 and anti-HPV-18 antibody levels that protect against clinical disease caused by HPV-16 and/or 18.

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

In clinical trials, 99% 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.

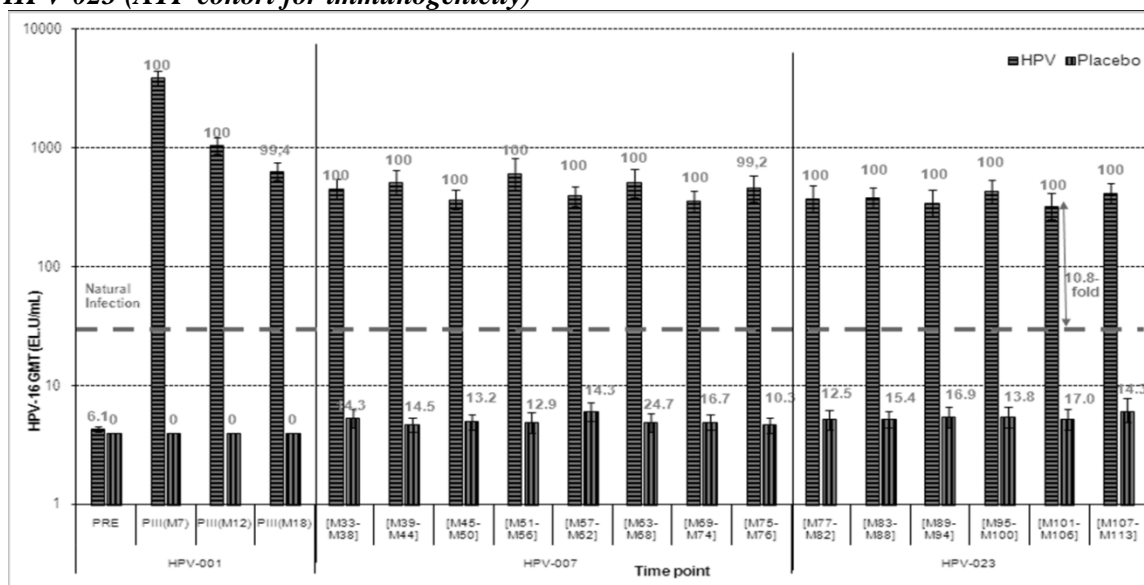
Immunogenicity in women aged 15 to 25 years

The immune response against HPV-16 and HPV-18 was evaluated up to 76 months, after first vaccination in study HPV-001/007 in women aged 15 to 25 years at the time of vaccination. In study HPV-023, this immune response continued to be evaluated up to 9.4 years (113 months) after first vaccination in a subset of the population from study HPV-001/007.

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

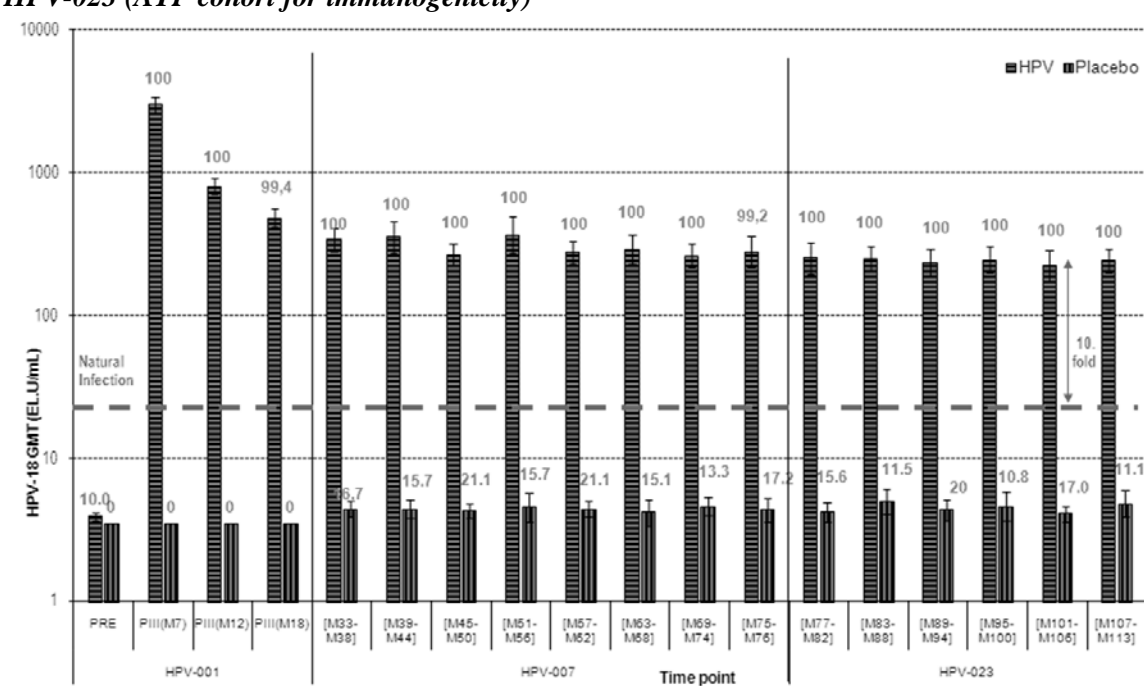
Immunogenicity results by ELISA from studies HPV-001/007/023 are presented in Figures 1 and 2 below:

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



Note: Number above the bar is percentage of subjects that were seropositive for HPV-16 IgG antibodies

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



Note: Number above the bar is percentage of subjects that were seropositive for anti-HPV-18 IgG antibodies

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 d up to the end of the follow-up period (month 113). At (month 113), GMTs for both HPV-16 and HPV-18 were still at least 11-fold higher than titres observed in women previously infected but who cleared HPV infection (natural infection) and 100% of the women were

seropositive by ELISA for both antigens.

A similar kinetic profile was observed with the neutralizing 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 (HPV-012 & HPV-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 study HPV-014 performed in women aged 26 to 55 years (N= 362), after vaccination, 100% of initially seronegative subjects had seroconverted to both HPV-16 and HPV-18 antigens in all age groups after the third dose (at month 7). The GMTs were lower in this population compared to women aged 15 to 25 years. However, all subjects remained seropositive for HPV-16 and all subjects except one remained seropositive for HPV-18 throughout the follow-up phase (up to month 48) maintaining antibody levels at an order of magnitude above those encountered after natural infection.

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

Two dose schedule in girls 9-14 years of age

In a clinical trial (HPV-070) immune response in girls aged 9 to 14 years receiving a 2-dose schedule (0, 6 months or 0, 12 months) was compared with immune response after 3 doses (0, 1, 6 months) in women aged 15 to 25 years.

After Dose 1 (Day 0), the trial protocol allowed some flexibility in the administration of the 2nd dose of the vaccine (180 ± 30 days in 0, 6 months group and 365 ± 60 days in 0, 12 months group). The 2nd and 3rd doses in the 3-dose (0, 1, 6 months) group could be administered at 21-90 days and 180 ± 30 days respectively.

All subjects seroconverted to both HPV types 16 and 18 one month after the completion of respective schedule. 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 2-dose CERVARIX is inferred on the basis of immunogenicity data observed in girls vaccinated from age 9 to 14 years. Immunological correlates of efficacy have not been established.

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)

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.

Specific studies of CERVARIX in pregnant women have not been conducted.

Data in pregnant women collected as part of pregnancy registries, epidemiological studies and inadvertent exposure during clinical trials are insufficient to conclude whether or not vaccination with CERVARIX affects the risk of adverse pregnancy outcomes including spontaneous abortion.

During the clinical development program, a total of 10,476 pregnancies were reported including 5,387 in women exposed to CERVARIX.

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

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), 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 \geq 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 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 11 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)

Data generated on the 2-dose schedule for CERVARIX administered as a 0, 5-13 month in the 9-14 years age group provides a similar safety profile to that observed in 15-25

years age group having received a standard 3-dose schedule (0,1,6 months).

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 vaccination schedule depends on the age of the subject.

Age at the time of the first injection	Immunisation and schedule
10 - 14 years	The vaccination schedule consists of a total of two doses each of 0.5 ml. The second dose given between 5 and 13 months after the first dose* OR The vaccination schedule consists of a total of three doses each of 0.5 ml given at 0, 1, 6 months**
15 - 45 years	The vaccination schedule consists of a total of three doses each of 0.5 ml given 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 yet to be established (see “Clinical Studies”).

Method of administration

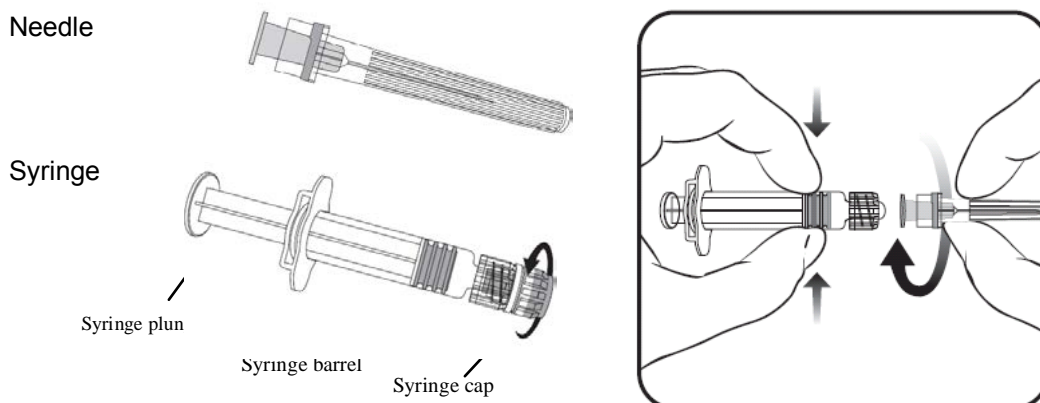
CERVARIX is for intramuscular injection in the deltoid region (see “Precautions”, “Drug Interactions”).

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



1. Holding the syringe barrel in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.
2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock. (see picture)
3. Remove the needle protector, which on occasion can be a little stiff.
4. Administer the vaccine.

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

Overdosage

No case of overdose has been reported. In the event of overdose, 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:

GlaxoSmithKline Biologicals s.a.
Rue de l'Institut, 89
1330 Rixensart
Belgium

DISTRIBUTED IN AUSTRALIA BY:

GlaxoSmithKline Australia Pty Ltd
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Abbotsford, Victoria, 3067

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):

18 May 2007

Date of most recent amendment: 21 September 2015

Version 11

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