

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).

Of the several known oncogenic HPV types, HPV types-16 and -18 are the two most prevalent; worldwide, they are responsible for approximately 70% of invasive cervical cancers and approximately 50% of CIN grades 2 or 3.

Depending on the geographical region, a further 20% of invasive cervical cancer may be caused by seven HPV-16 or HPV-18 phylogenetically-related types that have similar biological properties. The phylogenetically-related types to HPV-16 are HPV-31, -33, -52, -58, -35, and the related types to HPV-18 are HPV-45 and -59.

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 is being 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 is an ongoing 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 unlikely to have been exposed to oncogenic HPV types prior to vaccination (“oncogenic HPV-naive”).

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 status. These characteristics are representative of a “general population” including women exposed to HPV infection prior to vaccination.

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 approximately a 12-month interval but no negative sample in between)
- 6 month persistent infection (i.e. at least 2 positive specimens for the same HPV type over approximately a 6-month interval but no negative sample in between).

Efficacy against HPV-16/18 in the “oncogenic HPV-naïve” population (Study HPV-001/007)

Efficacy results in the “oncogenic HPV-naïve population” (seronegative by ELISA and HPV DNA negative by PCR in cervical samples at baseline) for virological, cytological and histological endpoints in study HPV-007 (Total Cohort i.e. women who received at least one vaccine dose) through 4.5 years following the first vaccine dose are presented in the tables 1 and 2 below.

Table 1 Vaccine efficacy against incident infection associated with HPV-16 and/or HPV-18 (by PCR, cervical samples) (ATP cohort)

Event type	Group	N	n	% (95% CI)	P-value
Incident infection	CERVARIX	310	1	96.9 (81.3; 99.9)	<0.001
	Placebo	277	28	-	

N = Number of subjects in specific cohort

n = number of cases

Table 2 Vaccine efficacy against persistent infection (by PCR, cervical samples) (ATP cohort), cytological abnormalities (\geq ASC-US), and histological endpoints (CIN1+ and CIN2+) associated with HPV-16 and/or HPV-18 (Total cohort)

Event type	Group	N	n	% (95% CI)	P-value
Persistent infection (6-month)*	CERVARIX	311	1	94.3 (63.2; 99.9)	<0.001
	Placebo	287	16	-	
Persistent infection (12-month)*	CERVARIX	311	0	100 (33.6; 100)	0.006
	Placebo	295	7	-	
\geq ASC-US**	CERVARIX	357	0	100 (77.6; 100)	<0.001
	Placebo	324	17	-	
CIN1+**	CERVARIX	358	0	100 (<0; 100)	0.236
	Placebo	339	2	-	
CIN2+**	CERVARIX	358	0	100 (<0; 100)	0.238
	Placebo	342	2	-	

*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

High efficacy of CERVARIX was maintained for up to 53 months after dose one. With presumed ongoing exposure to HPV infections as observed in the control group, there is no evidence of waning protection in vaccinated women.

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.

Efficacy against HPV-16/18 in the “general population” including women with current or prior oncogenic HPV infection (Interim analysis of Study HPV-008)

A total of 22% of subjects included in the analysis had abnormal low grade cytology and/or evidence of infection with an oncogenic HPV type at baseline.

The efficacy results which follow are taken from the interim analysis available to date. Efficacy results in the “general population” for histological endpoints in the interim analysis of study HPV-008 (Total Vaccinated Cohort i.e. women who received at least one vaccine dose) are presented in Tables 3, 4 and 5 below.

The planned interim efficacy analysis was triggered when an independent endpoint committee validated a requisite number of events of CIN2+, associated with HPV-16 or HPV-18 in the lesion as detected by PCR. In the pre-specified primary endpoint analysis, the observed vaccine efficacy (VE) against CIN2+ associated with HPV-16 or HPV-18 was statistically significant (VE = 90.4% [53.4%; 99.3], $p < 0.0001$), i.e. 2 cases in the vaccine group versus 21 cases in the control group (see Table 3).

Table 3 Summary of Vaccine Efficacy against CIN2+ associated with HPV-16 or HPV-18 in HPV DNA negative and seronegative subjects at baseline (Total vaccinated cohort*; Pre-specified primary endpoint analysis) – Interim Analysis**

Event Type	Group	N	n	% (97.9% CI*)	P-value
CIN2+	CERVARIX	7788	2	90.4 (53.4; 99.3)	<0.0001
	HAV**	7838	21	-	

*97.9% CI based on Type I error allocated for the interim analysis.

**HAV = Hepatitis A vaccine control group

***Total vaccinated cohort for efficacy included all vaccinated subjects (who received at least one dose) for whom data concerning efficacy endpoint measures were available and who had a normal or low-grade cytology (normal or Atypical Squamous Cells of Undetermined Significance [ASC-US] or low-grade squamous intraepithelial lesions [LSIL]) at month 0. In addition, subjects were to be HPV DNA negative and seronegative at month 0 for the corresponding HPV type in the analysis.

N = Number of subjects in specific cohort

n = number of cases

Further investigation identified that several of the CIN2+ cases had multiple oncogenic types in the lesion. In 3 of the CIN2+ cases (the 2 cases in the vaccine group and 1 in the control group), another oncogenic HPV type was found in the lesion simultaneously with HPV-16 or HPV-18. 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, a clinical case assignment was applied. The clinical case assignment considered the HPV types detected by PCR in preceding cytologic samples, in addition to types detected in the lesion. The 2 cases of CIN2+ in the vaccine group showed a co-infection with HPV-58 without evidence of HPV-16 or HPV-18 in any preceding cytology sample or in subsequent LEEP specimens. In both of these cases, infection with HPV-58 was detected at study entry and repeatedly detected during the follow-up period. This additional analysis confirmed that neither HPV-16 or HPV-18 was present in the samples and therefore not the cause of the lesion in the 2 vaccine cases. These 2 cases of CIN2+ were thus excluded from the analysis of vaccine efficacy. The one case in the control group showed a similar pattern, and was also removed from the analysis (see Tables 4 and 5).

Table 4 Summary of Vaccine Efficacy against CIN2+ associated with HPV-16 or HPV-18 in HPV DNA negative and seronegative subjects at baseline (Total vaccinated cohort*; Clinical Case Assignment) – Interim Analysis**

Event Type	Group	N	n	% (97.9% CI*)	P-value
CIN2+	CERVARIX	7788	0	100 (74.2; 100)	<0.0001
	HAV**	7838	20	-	

*97.9% CI based on Type I error allocated for the interim analysis.

**HAV = Hepatitis A vaccine control group

***Total vaccinated cohort for efficacy included all vaccinated subjects (who received at least one dose) for whom data concerning efficacy endpoint measures were available and who had a normal or low-grade cytology (normal or Atypical Squamous Cells of Undetermined Significance [ASC-US] or low-grade squamous intraepithelial lesions [LSIL]) at month 0. In addition, subjects were to be HPV DNA negative and seronegative at month 0 for the corresponding HPV type in the analysis.

N = Number of subjects in specific cohort

n = number of cases

Table 5 Summary of Vaccine Efficacy against CIN2+ associated with HPV-16/18 in HPV DNA negative subjects at baseline (regardless of initial serostatus) (Total vaccinated cohort, with and without Clinical Case Assignment) – Interim Analysis

Event type	Group	N	n	% (97.9% CI*)	P-value
CIN2+***	CERVARIX	8293	2	91.6 (60.2; 99.4)	<0.0001
	HAV**	8319	24	-	
CIN2+****	CERVARIX	8293	0	100 (78.0; 100)	<0.0001
	HAV**	8319	23	-	

*97.9% CI based on Type I error allocated for the interim analysis.

**HAV = Hepatitis A vaccine control group

N = Number of subjects in specific cohort

n = number of cases

*** = Total Vaccinated cohort without Clinical Case Assignment

**** = Total Vaccinated cohort with Clinical Case Assignment

Since the majority of CIN2+ cases in the control group (14/20) resulted from infections which were initially acquired between the first and the third dose, the absence of cases in the vaccine group reflects the onset of a vaccine effect prior to completion of the full vaccination course (Tables 4 & 5).

Table 6 Vaccine efficacy against persistent infection (by PCR, cervical samples), cytological (\geq ASC-US) and histological (CIN1+) endpoints associated with HPV-16 and/or HPV-18 in HPV DNA negative and seronegative subjects at baseline – Interim Analysis (Total vaccinated cohort)

Event type	Group	N	n	% (97.9% CI*)	P-value
Persistent infection (6-month)	CERVARIX	6344	38	80.4 (70.4; 87.4)	<0.0001
	HAV***	6402	193	-	-
Persistent infection (12-month)	CERVARIX	3386	11	75.9 (47.7; 90.2)	<0.0001
	HAV	3437	46	-	-
\geqASCUS	CERVARIX	7788	30	82.2 (72.0; 89.2)	<0.0001
	HAV	7837	169	-	-
CIN1+**	CERVARIX	7788	1	96.1 (71.6; 100)	<0.0001
	HAV	7838	26	-	-

*97.9% CI based on Type I error allocated for the interim analysis.

** In 1 additional case of CIN1 (in the control group), an oncogenic HPV type was found in the lesion simultaneously with HPV-16 or HPV-18. Based on a case allocation considering that the HPV type causing the lesion must be detected both in the lesion and in at least one of the two immediately preceding cervical samples, this case was excluded from the analysis of vaccine efficacy.

***HAV = Hepatitis A vaccine control group

N = Number of subjects in specific cohort

n = number of cases

In 51% of the ASC-US cases and 93% of the persistent infection cases by a 12 month definition, the onset of infection was before completion of the full vaccination course.

Efficacy against infection by oncogenic HPV types 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 and HPV-31 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 strong association between persistent infection with oncogenic HPV and high grade abnormalities (CIN 2 / CIN 3).

In the “general population” (the interim analysis of study HPV-008), CERVARIX has shown some efficacy against persistent infection caused by oncogenic HPV types other than HPV-16 and HPV-18. The confidence intervals that follow are 97.9% CI associated with the multiple statistical analyses. Vaccine efficacy against persistent infection (6-month definition) was 36.1% (CI: 0.5; 59.5) for HPV type 31, 59.9% (CI: 2.6; 85.2) for HPV type 45 and 31.6 % (CI: 3.5; 51.9) for HPV-52, which supports cross-protection against these types. Vaccine efficacy against persistent infection (6-month definition) for all 12 oncogenic HPV types combined excluding HPV-16 and HPV-18 was not statistically significant (9.0%; [CI: -5.1; 21.2]).

Table 7: Summary of Vaccine Efficacy against persistent infection (6-month definition) for oncogenic types other than HPV-16 or HPV-18 in HPV DNA negative and seronegative subjects at baseline (Total vaccinated cohort) – interim analysis.

Type*	Vaccine Efficacy
	Persistent infection (6 months)
HPV-45	59.9% [CI: 2.6%;85.2%]
HPV-31	36.1% [CI:0.5%;59.5%]
HPV-33	36.5% [CI: <0%; 64.0%]
HPV-52	31.6% [CI: 3.5%;51.9%]
HPV-58	-31.4% [CI: <0%;24.7%]
HPV-HRW**	9.0% [CI: <0%;21.2%]

*The data are presented for the 5 next most prevalent types after HPV-16 and HPV-18 in their decreasing order of prevalence in cervical cancer (with 6.7 % of Cervical Cancer attributed to HPV-45, 2.9 % to HPV-31, 2.6 % to HPV-33; 2.3 % to HPV-52 and 2.2 % to HPV-58)

**HPV-HRW= High-risk (oncogenic) HPV types without HPV-16 or HPV-18: HPV-31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68
CI = 97.9% confidence interval

Furthermore, in the interim analysis of study HPV-008, vaccine efficacy against persistent infection (12-month definition) for all oncogenic HPV types excluding HPV-16 and HPV-18 was 27.1% (CI: 0.5; 46.8). In the majority (92%) of the cases the onset of infection was before completion of the vaccination course. A trend towards higher efficacy was observed in women who received the full vaccination course before being infected (65.1%, CI: <0.0; 92.3).

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.

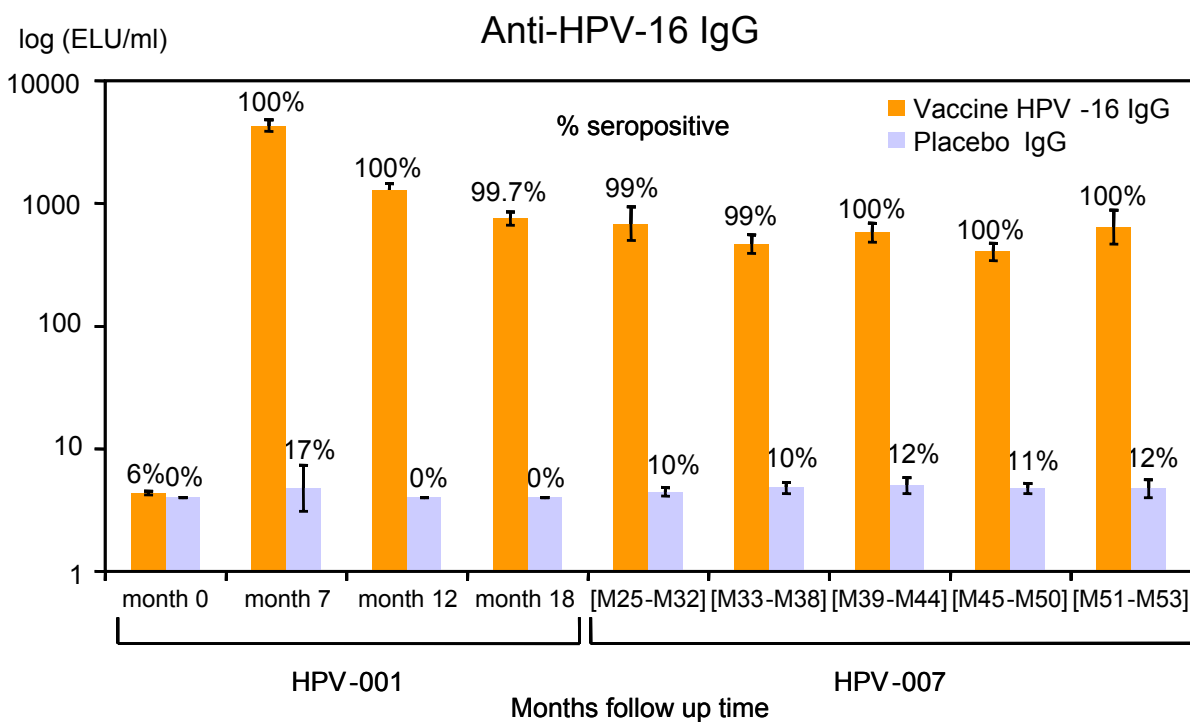
The immunogenicity induced by three doses of CERVARIX has been evaluated in 5,303 female subjects from 10 to 55 years of age.

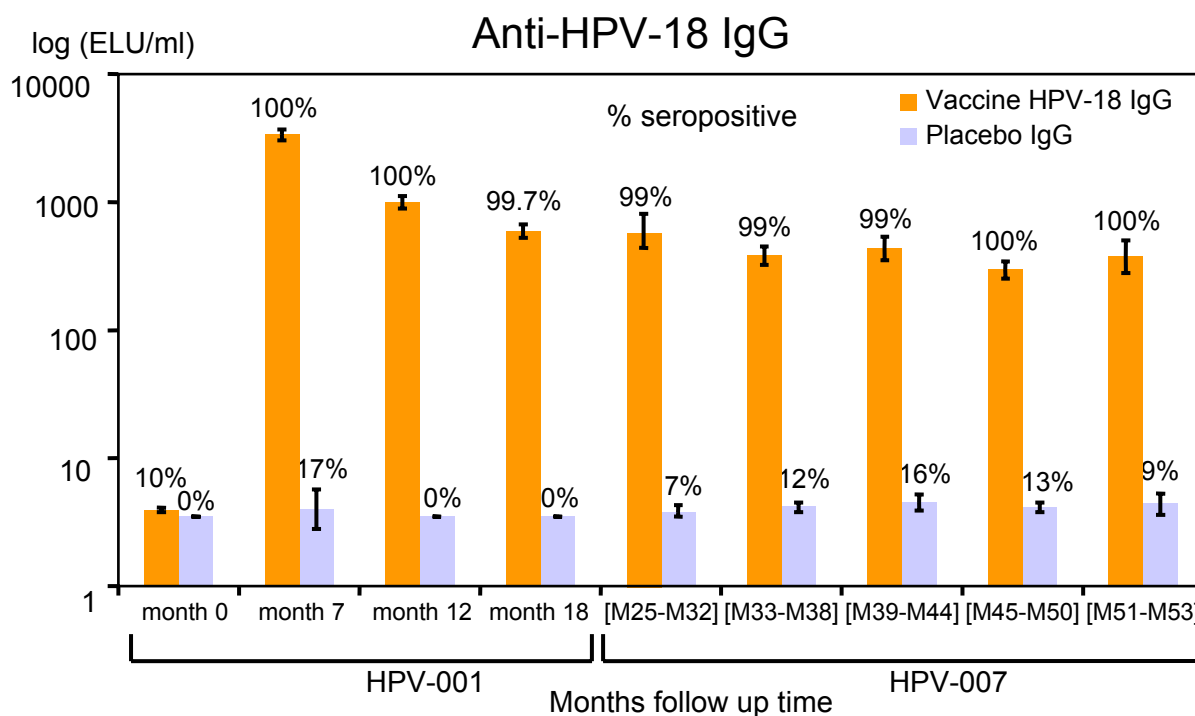
In clinical trials, 99.9% of initially seronegative subjects had seroconverted to both HPV type 16 and 18 one month after the third dose. Vaccine-induced IgG Geometric Mean Titres (GMT) were well above titres observed in women previously infected but who cleared HPV infection (natural infection). Initially 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 53 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 Figure 1 below:

Figure 1 Persistence of Anti-HPV-16 and Anti-HPV-18 Antibodies (Binding ELISA) (According To Protocol 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 53). At the end of the follow-up period, GMTs for both HPV 16 and 18 were still at least 14-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.

In the interim analysis of study HPV-008 (“general population”), immunogenicity at month 7 was similar to the response observed in study HPV-001/007 (“HPV-naive population”).

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 cervical cancer by protecting against incident and persistent infections, cytological abnormalities including atypical squamous cells of undetermined significance (ASC-US) and cervical intraepithelial neoplasia (CIN), CIN 1 and pre-cancerous lesions (CIN 2 and CIN 3) caused by human papillomavirus types 16 and 18. Immunogenicity studies have been conducted in females aged 10 to 14 years and 26 to 45 years to link efficacy in females aged 15 to 25 years to other populations.

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.

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 4.5 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

There are no data on concomitant administration of CERVARIX with hepatitis B vaccine, varicella vaccine and dTpa 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 8 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)	All	22802	5.1	4481	5.2	3058	6.8	8751	4.6

(°C)	>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 (≥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

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

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.

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.

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.

In case of temporary storage of the vaccine outside refrigerator, experimental data have shown that the vaccine is stable when stored at temperatures up to 37°C for 1 week. These data are not recommendations for storage.

The shelf life of CERVARIX is three (3) 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
1061 Mountain Highway
Boronia VIC 3155

This document was approved by the Therapeutic Goods Administration on 16 May 2007.

Issue Number: 1

®CERVARIX is a registered trademark of the GlaxoSmithKline group of companies